Retrospective cohort study of the efficiency of Sputnik V and EpiVacCorona vaccines against infections and deaths caused by SARS-CoV-2 Delta variant in Moscow (June- July 2021)

Preprint · January 2022

CITATIONS
0

READS
437

2 authors, including:

Olga Matveeva
Sendai Viralytics
57 PUBLICATIONS **866** CITATIONS

SEE PROFILE

Retrospective cohort study of the effectiveness of Sputnik V and EpiVacCorona vaccines against infections and deaths caused by SARS-CoV-2 Delta variant in Moscow (June-July 2021)

Olga Matveeva, Alexander Ershov*

Sendai Viralytics LLC, 23 Nylander Way, Acton, MA 01720, USA
*Medusa Project SIA, Krisjana Barona iela 5-2, Rīga, Latvia, LV-1050

Abstract

Background. The effectiveness of the vaccines used in Russia against COVID-19, caused by Delta variant of SARS-CoV-2 is unknown.

Objective. The goal of the study was to evaluate the epidemiological effectiveness of Sputnik V and EpiVacCorona vaccines against COVID-19 caused predominantly by the SARS-CoV-2 Delta variant. We were interested in the ability of the vaccines to protect against disease of different severity, including lethality, in different age groups.

Method. This work is a retrospective cohort study of COVID-19 patients. The cohort created by the Moscow Health Department included more than 300,000 infected people who sought medical care in Moscow in June and July 2021. The relevant dataset became available in the Telegram group "COVID-19 Vaccine News: 2021" and is in the public domain. The dataset includes patients' vaccination status, specifically whether they were immunized with the Sputnik V or EpiVacCorona vaccine. Reported cases of infection and diseases are also categorized according to age, and severity of COVID-19, including death. We used two control comparison groups in our studies. The first group consisted of unvaccinated Moscow residents and the second group included seronegative city residents, that is, those who had no detectable antibodies to SARS-CoV-2.

Results. Analysis of data using both control groups revealed a tendency for the effectiveness of the Sputnik V vaccine to increase as the severity of the disease the vaccine protects against increases. Protection was lowest for mild disease, it was more pronounced for severe disease, and finally, the vaccine provided maximum protection against COVID-19-related death. At the same time, we observed a decrease in the vaccine effectiveness (VE) with age. The results obtained with the first control group are as follows. For the youngest (18-50 years old), the estimated VE in preventing death in June 2021 was 95% (95% CI 64-100), and for the older generation (50+), it was 74% (95% CI 67-87). Estimated protection against a severe form of the disease in the group of 18-50 years old in June-July 2021 was above 81% (CI 95% 72-93), and in the group over 50 years old it was above 68% (CI 95% 65-82). The VE values were higher with the second comparison control group. According to our analysis, EpiVacCorona proved to be an ineffective vaccine and therefore cannot protect against COVID-19.

Interpretation. Sputnik V vaccine effectiveness against the Delta variant of SARS-CoV-2, was higher for severe disease or death and its protective effect was more pronounced in younger age groups. There may be more people with comorbidities among the vaccinated elderly than among the unvaccinated, so estimates of VE are lower for older age groups. Other biological or social factors may contribute to the observed age bias. EpiVacCorona is an ineffective vaccine for any age group.

Key words

COVID-19; vaccine effectiveness; SARS-CoV-2; Delta variant, Sputnik V vaccine; EpiVacCorona vaccine; medical informatics

Introduction

A wide range of effective vaccines for the prevention of COVID-19 is now available worldwide. The effectiveness of these vaccines has been demonstrated in both clinical and retrospective studies [1-4]. However, the SARS-CoV-2 viral genomes continue to evolve, giving the virus more and more advantages in evading the immune response. In this regard, the effectiveness of vaccines based on antigens of the ancestral variant needs to be re-evaluated for new successful viral variants that can cause new epidemic waves.

COVID-19 vaccine platforms in Russia

There are 4 vaccines that have been approved for use in Russia. Two of them are viral vector vaccines (Sputnik V and Sputnik Light, one is a peptide-based vaccine (EpiVacCorona), and the fourth is an inactivated virus-based vaccine (Covivac).

Sputnik V. Sputnik V (Gam-COVID-Vac) is a viral vector vaccine based on two recombinant replication-defective human adenoviruses: Ad26 (serotype 26) and Ad5 (serotype 5). Both Ad26 and Ad5 are used as vectors for the expression of the SARS-CoV-2 spike protein (S-protein). Immunization with Sputnik V occurs with two doses of the vaccine, one of which is a primer (rAd26) and the other is a booster (rAd5). There is another vaccine Ad26.COV2. S. This vaccine was developed by Janssen/Johnson & Johnson and based on the rAd26 adenovirus vector. It encodes a full length, stabilized S-protein of SARS-CoV-2 and is used in a one-time, single-dose immunization regimen [5].

According to a randomized, double-blind, placebo controlled, multicenter Phase 3 trial that took place in Russia, the protective efficacy of the Sputnik V vaccine is 91.6% [6]. In Hungary, a large retrospective cohort study has been carried out to compare the efficacy of vector-based and mRNA-based vaccines. In this study, almost all the data analysis was done before the Delta variant. Hungarian researchers estimate the protective effectiveness of Sputnik V in preventing symptomatic infection at 86%, and its ability to prevent deaths associated with COVID-19 at 97% [7]. Analysis of data from retrospective case-control studies conducted in Bahrain shows that the ratio of the risks of death in the group of vaccinated and unvaccinated is 1/15. Accordingly, the vaccine's effectiveness in preventing deaths exceeds 90% [8]. Unfortunately, the publication indicates that during the time, which the study was conducted in the country, the dominant variants of the virus changed, so it is not possible to link the estimated vaccine efficiencies to a specific variant of SARS-CoV-2.

Unfortunately, we do not know how long the Sputnik V vaccine has a high degree of protection. How quickly it weakens and how its protection depends on the dominant variant of the coronavirus circulating in the human population. In this regard, a cohort prospective study done in Argentina is of interest. This study analyzed the dynamics of changes in the antibody’s levels in vaccinated. It turned out that the level of antibodies decreases relatively quickly. Six months after vaccination, antibodies to the receptor-binding domain of the S-protein are not detected in 69% of vaccinated [9]. How this relates to the duration of the vaccine's protective effect remains to be studied.

Sputnik Light. Sputnik Light is a single-dose vaccine based on the adenovirus rAd26 [10], that is, the first component of the Sputnik V vaccine. The effectiveness of this vaccine in protecting against COVID-19 caused by the Delta variant of SARS-CoV-2 was evaluated using data from a retrospective cohort study conducted in Moscow in July 2021. A single immunization with the first component of the Sputnik V vaccine demonstrated 86% and 75% efficacy in young and middle-aged people, respectively. The overall average vaccine efficacy was 69.85% (95% CI 64-75). The result is obtained from the analysis of data collected within a period limited to 3 months after vaccination [11].

According to research that took place in Argentina, Sputnik-Light effectiveness for preventing COVID-19 infections was 78% (95% CI 75-83) 78•6% and for the prevention of hospitalizations and deaths - 88% (CI 95% 80 - 92) and 85% (CI 95% 75 - 90), respectively. The study was conducted based on data collected for adults in the 60 - 79 age range within a short time interval limited to 83 days after vaccination, before the Delta viral variant became dominant [12]. It can be assumed that with other dominant viral variants, the vaccine will be less effective.

The efficacy of the similar vaccine Ad26COV2.S (Johnson & Johnson/Janssen) against COVID-19 infection, based on results of phase 3 clinical trials, is like that of Sputnik Light at 67% (95% CI 59-73). The efficacy of the vaccine against severe COVID-19 is slightly higher at 85% (95% CI 54-97) [5]. However, these trials were conducted before the Delta-virus variant became dominant. It can be assumed that in a situation with the dominant viral variant Delta or Omicron, the result would be somewhat worse.

Interestingly, in Venezuela, on a relatively small sample of several dozen people, it was shown that after vaccination with the first dose of Sputnik V, which is equal to the full Sputnik Light vaccination, 42% of those vaccinated did not develop antiviral antibodies. However, complete seroconversion occurred in everyone observed after two doses of the vaccine. At the same time, after the first dose of the vaccine, all previously infected seropositive individuals developed a humoral response with an antibody level ~ 40% higher than previously seronegative individuals who received 2 doses of the vaccine. Thus, a second dose of vaccine in previously seropositive patients does not significantly increase antibody levels [13].

These data from Venezuela demonstrate that Sputnik Light may be a good booster vaccine, but is ineffective in triggering complete seroconversion in most people and therefore is unlikely to provide the same effective immune protection as Sputnik V. In addition, these data show that hybrid immunity, immunity in those who have had COVID-19 and have been vaccinated with at least one dose of the vaccine, may protect better than a complete vaccination with Sputnik V.

However, Sputnik Light as a booster dose of the vaccine is highly valuable for the prevention of the Omicron variant virus infection. A 12-fold decrease in neutralizing antibodies to this variant was demonstrated in the sera of people vaccinated with Sputnik V 6-12 months earlier. Nevertheless, analysis of sera of individuals vaccinated with Sputnik V and then vaccinated with Sputnik Light showed that 2-3 months after revaccination the decrease in the level of neutralizing antibodies against Omicron variant was only 7 times. In addition, boosting dose increases the titer of antibodies capable of neutralizing Omicron by an average of 16 times [14]. Thus, it appears that the protective effectiveness of the Sputnik V vaccine can and should be enhanced by an additional booster dose of Sputnik Light.

EpiVacCorona. The vaccine representing the second platform in Russia is the peptide vaccine EpiVacCorona. It consists of three peptides of SARS-CoV-2 virus' S-protein conjugated to a carrier

protein. The carrier protein in EpiVacCorona is a two-part chimeric protein, one of which is a viral nucleocapsid protein (N-protein) and the other is a bacterial maltose-binding protein. The carrier protein is expressed in E. coli, and peptides are also expressed in E. coli or chemically synthesized. The three peptides of the vaccine are the following amino acid sequences: CRLFRKSNLKPFERDISTEIYQAGS, CKEIDRLNEVAKNLNESLIDLQE, and CKNLNESLIDLQELGKYEQYIK [15]. It is worth noting that these three peptides do not overlap with the mapped antigenic linear epitopes of the S-protein of SARS-CoV-2 [16-21].

EpiVacCorona has been in use in Russia since December 11, 2020. By the time large-scale immunization with this vaccine began, even the first phase of clinical trials had not been completed. So, the representative of the State Research Center "Vector" on January 22, 2021, told the RIA-Novosti correspondent: “Clinical trials of phases I-II have not yet been completed. There are only intermediate results."[22]. Later the trials were finished, and preclinical and clinical Phase I / II trial results have been published [15,23].

However, in the scientific community, these publications, and the design of the vaccine itself have come under serious criticism. For example, the lack of important controls in published experiments [24] was criticized. In addition, the vaccine has been criticized for the lack of overlap between the three peptides and the experimentally determined linear antigenic epitopes of SARS-CoV-2 S-protein B-cells [24].

Only 3,000 participants were enrolled in the EpiVacCorona phase III clinical trial [25]. It was planned that 25% (750 of 3,000) of the participants would receive a placebo. The total number of participants is very small. Therefore, it is difficult to imagine that any statistically significant information can be extracted from the trial data. The trial was registered with ClinicalTrial.gov on March 3, 2021. There have been no updates of the clinical data since that date. We know nothing about the progress of the trial.

After an injection of EpiVacCorona, a vaccinated person can develop antibodies not only to the S-protein peptides of the coronavirus, the protective function of which has not been established, but also to the chimeric protein antigens present in the vaccine. In particular, the viral N-protein and bacterial maltose-binding protein. The antiviral immune-protective function of the latter has not been demonstrated either.

Independent studies, results of which were presented on the preprint server in Russia, did not confirm the presence of neutralizing antibodies in the plasma of those vaccinated with EpiVacCorona [26]. At the time of this writing (December 2021), the results of phase III clinical trials showing the epidemiological efficacy of the vaccine have not been published. Thus, in our work, we present the first, as far as we know, data on vaccine effectiveness.

Covivac. Finally, the vaccine, which represents the third platform in Russia, is inactivated SARS-CoV-2 [27]. Data confirming the epidemiological effectiveness of this vaccine have not yet been published. We did not conduct a retrospective analysis of the effectiveness of this vaccine due to the lack of sufficient data.

Viral variant Delta (B.1.617.2)

The viral variant Delta (B.1.617.2) was first detected in patient samples from India, but quickly spread and became dominant in other countries [28 10]. This viral variant can circulate efficiently at current vaccination levels in most countries [29-31]. In addition, the effectiveness of vaccines against the disease caused by the SARS-CoV-2 Delta variant is reduced [32-34].

In the summer of 2021, in Moscow, the Delta variant replaced all other variants and became dominant [11,32,35]. In June, it averaged more than half of COVID-19 infections, and in July it was already more than 90%. However, most of the cases in June corresponded to the second half of the month, when the Delta variant of the coronavirus became dominant [36 44]. Among the variants of B.1.617.2 the following representatives AY.4, AY.5, AY.6, AY.10, AY.12, AY.20, AY.23, AY.24 were encountered in Moscow, however, two variants prevailed: B.1.617.2 and AY.12 [11,37]. The genomes of these variants have several characteristic mutations in the S-protein, which significantly reduce the neutralizing potential of antiviral antibodies directed to this protein [38]. Variable molecular mechanisms have been described that make the virus-Delta variants easier to overcome the human immune defenses.

The need to evaluate the effectiveness of vaccines against new SARS-CoV-2 variants

It is of interest to conduct retrospective cohort studies that can reveal the vaccine effectiveness against different dominant virus-variants in Moscow. Such an analysis is a new challenge of the time since vaccines were developed against one (Wuhan) ancestral variant of SARS-CoV-2, while they should protect against other rapidly appearing virus-variants with different antigenic properties. It is also important to evaluate the effectiveness of other vaccines registered for use in Russia, especially those with no published results from phase III clinical trials, such as EpiVacCorona and Covivac. One research method that can help answer the question of whether a vaccine against the new dominant variant of SARS-CoV-2 is effective is a retrospective cohort data analysis. It is based on data collected in June and July 2021 in Moscow, Russia. During this period, the viral variant Delta dominated in Moscow [35].

Results

The effectiveness of Sputnik V and EpiVacCorona vaccines against severe COVID-19

The results of the VE analysis of Sputnik V and EpiVacCorona vaccines against severe COVID-19 are shown in Fig. 1 (left panel). The upper left histogram shows the result of the VE estimation with the control group of unvaccinated individuals, and the lower left with the control group of seronegative ones. The *Materials and methods* section below shows how the numbers of Moscow residents constituting both control groups were estimated.

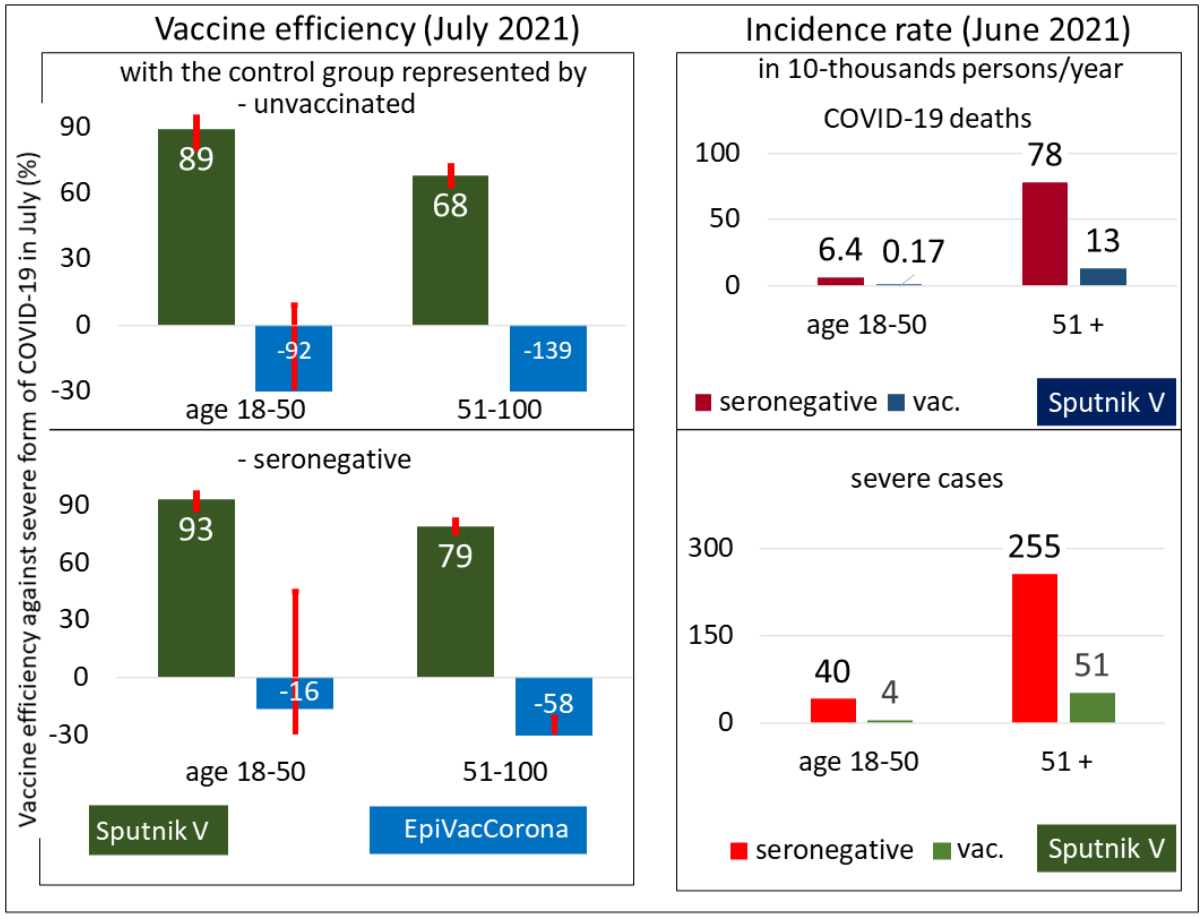

Fig.1: Characterization of immune protection with COVID-19 vaccine. *Data obtained* in *Moscow, summer 2021. The left panel with two histograms shows the effectiveness of Sputnik V and EpiVacCorona vaccines in preventing severe forms of COVID-19. The analysis is based on data from July 2021. The upper histogram in the left panel shows the results of the data analysis performed with a control group represented by unvaccinated Moscow residents, and the lower histogram in the same left panel corresponds to the data analysis performed with a control group represented by seronegative individuals. The VE estimates for Sputnik V vaccine are positive and highly significant ($p<<0.001$) according to the chi-square test, $p<<0.001$. The VE values for EpiVacCorona vaccines are negative, non-significant ($p>0.05$) for the age group 18-50 and negative, significant for the age group 50+ ($p<<0.001$). The right panel shows the number of deaths and severe cases of COVID-19 among fully vaccinated or seronegative Moscow residents, normalized per 10,000 person-years. An estimate of the number of seronegative individuals was obtained in a June 2021 serosurveillance study, the results of which are presented in a recently published preprint [11].*

Comparison of the results in the upper and in the lower left histograms of Fig. 1 suggests that regardless of the definition of the control group, the estimated VE of the Sputnik V to prevent severe COVID-19 is high and its value is statistically significant. The histograms also show the presence of an age-related decrease in the Sputnik V vaccine effectiveness. The older the person is, the lower the estimated VE is.

More detailed information on the age related VE of Sputnik V is presented in Table 1. Because the use of any control group definition is not completely satisfactory in all necessary aspects of VE estimation, it may be appropriate to use a combination of calculated 95% confidence intervals to determine the upper and lower limits of VE. The combination obtained from two control groups is presented in the last column under the title "95% CI of both control groups" in Table 1. Based on this 95% CI combination, we can say that the vaccine protects against severe forms of the disease with an effectiveness of over 81% in the group under 50 years of age and over 32% in the group over 70 years of age.

In Figure 1 (left histograms), instead of positive estimates of EpiVacCorona vaccine effectiveness, we see negative ones. Despite the wide confidence intervals of these negative values, a comparison with the estimates of the VE of the Sputnik V vaccine allows us to say with confidence that the EpiVacCorona vaccine does not protect against the severe form of COVID-19.

Table 1: Effectiveness of the Sputnik V vaccine to prevent severe form of COVID-19 with confidence intervals. *Data obtained in Moscow, in July 2021.*

Age	Control group - unvaccinated			Control group - seronegative			CI 95% of both control groups	
	VE %	CI 95%		VE %	CI 95%			
		lower	upper		lower	upper	lower	upper
18-50	89	81	94	93	88	96	81	96
51-70	76	70	81	84	80	87	70	87
70+	42	32	51	63	56	69	32	69

Comparative effectiveness of the Sputnik V vaccine in preventing COVID-19 of varying severity

In June in Moscow, there were practically no immunizations with two doses of any vaccines other than Sputnik V (at the end of the month, the number of those immunized with other vaccines was less than 3% of the total number). Therefore, the incidence of COVID-19 among all those vaccinated this month coincides with the incidence among those vaccinated with this vaccine. It is interesting to compare the number of Moscow residents in whom COVID-19 resulted in serious illness or death in categories of people differing in age and vaccine status.

Table 2 shows the number of Moscow residents in these different categories per 10,000 person-years. The data were normalized using an estimate of the number of seronegative city residents (control group 2). In addition, the same table demonstrates the calculated odds ratios of COVID-19 outcomes among vaccinated or seronegative individuals. Although all calculations were based on data collected in one month (June or July), we introduced a time parameter into our estimates to compare our results with those of other studies that use time normalization.

Table 2. Estimation of deaths and severe COVID-19 cases. *Data obtained in Moscow, in June 2021.*

Age	Normalized data (10-thousands person per year)				Odds Ratio		95% CI			
	deaths		severe form of COVID-19				deaths		severe form of COVID-19	
	unvacc.	vacc.	unvacc.	vacc.	deaths	severe form	lower	upper	lower	upper
18-50	6.4	0.17	40	4	0.03	0.1	0	0.21	0.07	0.15
51+	78	13	255	51	0.17	0.2	0.13	0.22	0.18	0.23

Estimates of the number of deaths and severe COVID-19 among the vaccinated or seronegative people in Moscow, are plotted on the histograms shown in the right panel of Fig. 1. We clearly see that the risk of either outcome is drastically reduced in vaccinated individuals. At the same time, note that among those who received the vaccine but are older than 51, the number of deaths and serious illnesses is significantly higher compared to those who are younger than 50.

Perhaps in older age groups, vaccinated people may have more people with comorbidities compared to unvaccinated people of the same age group. It is likely that people with chronic diseases are much more motivated to be vaccinated. Thus, the observed difference in estimated VE values across age groups may be the result of a bias in the characteristics of follow-up cohorts.

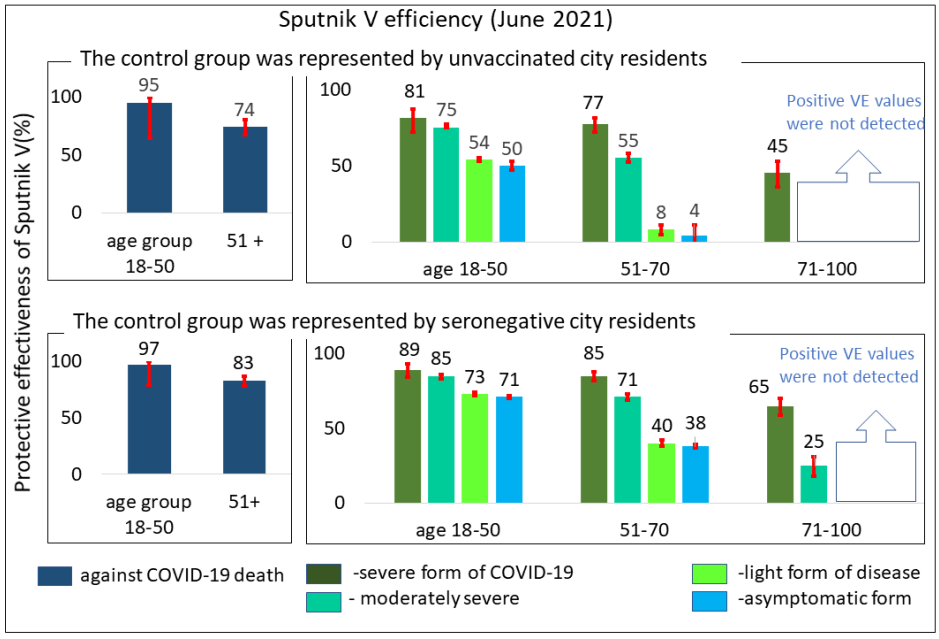

Fig.2: Protective effectiveness of the vaccine (Sputnik V) against COVID-19 disease of varying severity or death (%). *The upper histograms represent calculations with control group 1 and the lower histograms with control group 2. All positive VE estimates in all histograms are highly significant according to the chi-square test, p<< 0.001. Data obtained in Moscow, in June 2021.*

For clarity, we also created histograms showing the VE of the vaccine Sputnik V in preventing COVID-19-related deaths (Fig. 2, left panel). A comparison of the upper, and lower histograms in the left panel of Fig. 2. shows that the estimate of VE in preventing COVID-19 deaths is almost independent of how the control group is defined. More detailed results of the estimated VE of the Sputnik V against COVID-19 disease of varying severity are shown in the right panel of Fig.2.

Both the June and July data shown in the histograms of Fig. 1 and Fig.2 reveal a decreasing trend in estimated VE values as age increases. And this trend is independent of which control group was used for the analysis. According to this estimation breakthrough infections occur more frequently in the older age group.

The trend of decline in estimated VE as age increases also characterizes diseases of varying severity, namely severe, moderately severe, mild, and asymptomatic (Fig.2. right panel). The highest protection is seen in the 18 to 50 age group, regardless of whether we are dealing with a severe or mild form of the disease. In the groups of those over 51, protection is worse. We observe no protection against the milder form of the disease for the group of those over 71 years of age. However, this result must be interpreted with consideration that in older age groups, vaccinated people may have more representatives with comorbidities compared to unvaccinated people of the same age group. It is likely that people with chronic diseases are much more motivated to be vaccinated. Thus, the observed difference in estimated VE values in different age groups may be the result of sampling bias in the number of people with chronic diseases in the observation cohorts.

In addition, the histograms of Fig.2. also reveal a correlation: the more severe the disease, the better the vaccine protection observed. We notice a tendency for vaccine effectiveness to increase as the severity of the disease increases, so that the vaccine protects particularly well against the most severe form of the disease or even death. Conversely, the milder the disease, the weaker the apparent protection.

Assessment of seropositivity levels in Moscow

The number of individuals with antibodies to SARS-CoV-2 can be estimated in different ways. We used three different approaches, which are described in the Materials and Methods section. The results of a comparative analysis of these approaches from February to October 2021 are shown in Fig.3 A. We observe a monotonic, almost linear increase in the number of seropositive city residents over time, which can be seen irrespective of the method of assessing the antibody presence. In January, the number of people with antibodies was estimated to be in the range of 20-30%, and in September, it was already in the range of 60-80%. The Moscow Department of Health (MDH) estimate of 46% seropositivity in June corresponds to the estimate obtained when calculating seropositivity using the Infection Fatality Rate (IFR) [39] for the same month. At the same time, Invitro's ("Invitro" is one of the largest medical companies in Russia, specializing in laboratory diagnostics and medical services) estimates are slightly higher than other estimates [40]. We believe that the reason for this is the general bias of the Invitro sample towards a higher frequency of positive results, arising from the methodology: only those who want to measure antibody levels contact the company and get tested. Accordingly, people after vaccination, or after COVID-19 disease, are more likely to want to determine antibody levels compared to those who did not get disease and/or were not vaccinated.

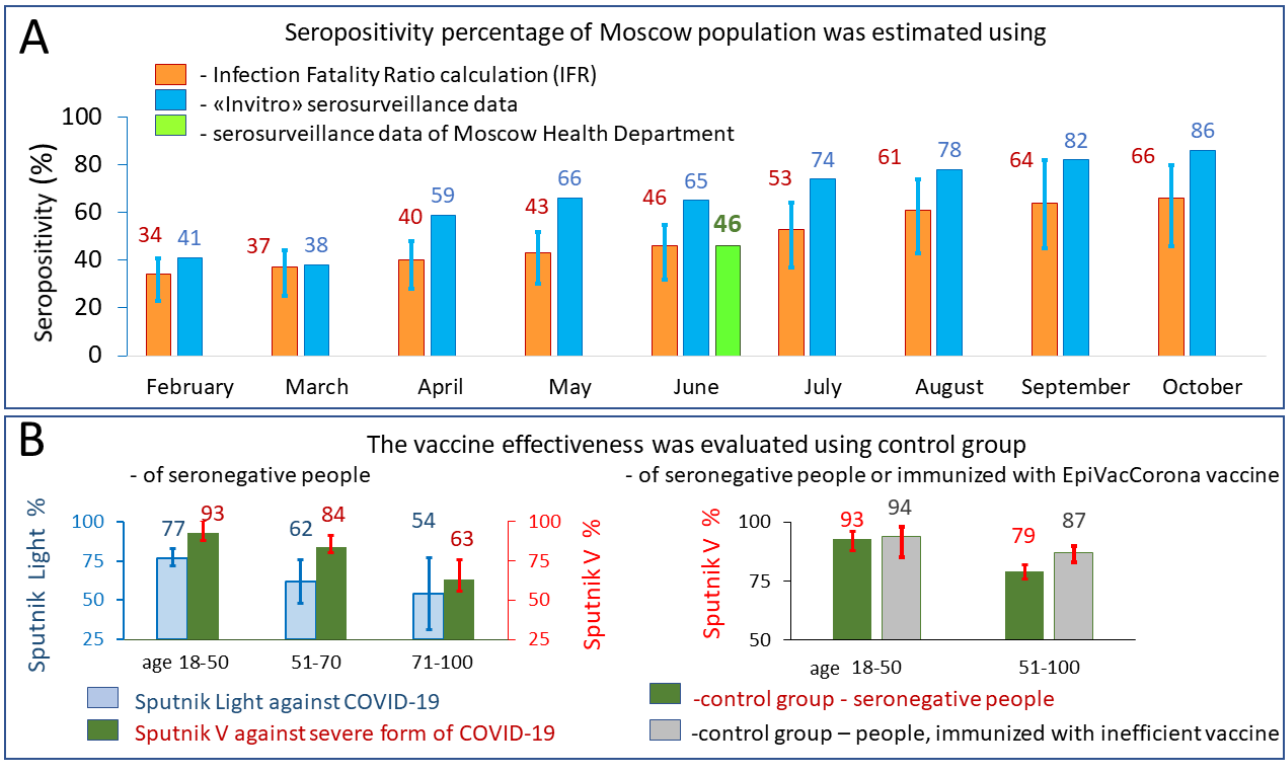

Fig.3: Percentage of Moscow residents with antibodies to SARS-CoV-2, effectiveness of Sputnik V and Sputnik Light vaccines. *A. Percentage of seropositive individuals calculated based on excess mortality data, on "Invitro" data [40], and serosurveillance by the Moscow Department of Health. B. Protective efficiencies of Sputnik V and Sputnik Light vaccines. Left histogram shows VE of Sputnik V and Sputnik Light* [11] *vaccines to prevent COVID-19 that were estimated using seronegative individuals as controls. Right histogram shows the protective effectiveness of Sputnik V estimated by using two different control groups. One of them represented by seronegative city residents, and another one by those who got the EpiVacCorona vaccine. All positive values in the lower histograms are highly significant according to the chi-square test, p<< 0.001. Data obtained in July 2021 in Moscow.*

Comparison with Sputnik Light

It is interesting to compare the VEs of Sputnik V and Sputnik Light vaccines. To estimate the VE of the Sputnik V we considered categories of patients with severe form COVID-19 in Moscow in July 2021. As a control group, we used the number of seropositive individuals estimated at the end of June in the preprint [11]. It should be noted that the calculations of the VE of the Sputnik-Light were made based on the data collected by our colleagues in July and presented recently [11].

We evaluated the effectiveness of the Sputnik V and Sputnik Light vaccines for three age groups. The comparison result shown in Fig. 3B left histogram illustrates a general pattern evident for both vaccines: the estimated effectiveness of protection against COVID-19 weakens as the age of the patients increases. Unfortunately, we cannot directly compare the VEs of Sputnik V and Sputnik Light in our study. This is because we do not have data on the timing of immunization of each vaccine. This timing could significantly affect VE (see below). In addition, we do not know how COVID-19 patients were

defined in the publication describing the effectiveness of Sputnik Light. Were those who were mildly or asymptomatically ill included?

Unfortunately, we cannot directly compare the VE of Sputnik V and Sputnik Light in our study because of the lack of data on the timing of immunization in each case. This timing could significantly affect the calculated VE (see below). In addition, we do not know how COVID-19 cases were defined in the publication describing the efficacy of Sputnik Light and whether cases of mild or asymptomatic infection were included. To emphasize that the VE of Sputnik V and Sputnik Light vaccines cannot be compared directly, we used two different vertical axes in Fig.3B left histogram. The left axis corresponds to the histogram illustrating the Sputnik Light and the right axis to the histogram of Sputnik V.

Evaluation of VE Sputnik V using individuals immunized with an ineffective vaccine as a comparison control group

In our study, we found that those vaccinated with EpiVacCorona had no advantage over unvaccinated or seronegative individuals in their chances of getting COVID-19. Therefore, we used EpiVacCorona-vaccinated individuals as an additional control group to evaluate VE of Sputnik V. The advantage of using this control group is the greater similarity in behavior of those who have been vaccinated with one vaccine or the other compared to those who have not been vaccinated. The proportion of people with chronic diseases or comorbidities among those vaccinated with a particular vaccine should also be more similar compared to the proportion of such people among the unvaccinated.

The comparative results of the VE evaluation using the seronegative control group or the EpiVacCorona vaccinated control group are shown in Fig. 3B, right histogram. The histogram demonstrates that the difference in VE estimates between the two age groups becomes smaller when the EpiVacCorona vaccinated control group is used instead of the seronegative group. Moreover, the CI intervals for VE estimated using the EpiVacCorona control group overlap for the two age groups.

Discussion

Limitations of our study

Our cohort retrospective study has many limitations. We must deal with a dataset that is missing a lot of important information about those who got COVID-19. We don't know the demographics, except for the age of COVID-19 patients, we don't know the timing of vaccination, and we can't connect each vaccinated and unvaccinated person so that their characteristics match each other. Limitations related to the nature of the data analyzed do not allow us to answer many important questions about the vaccines used in Russia, such as: has the effectiveness of Sputnik V changed in the spread of the viral variant Delta? What is the relationship between the effectiveness of the single-dose vaccine (Sputnik Light) and the two-dose Sputnik V vaccine?

EpiVacCorona is inefficient vaccine

So far, the developers of EpiVacCorona have not published the results of their phase III study. This means that we are the first to publish an analysis of the morbidity data of those who have been vaccinated with this vaccine. The results of this analysis indicate a lack of protective VE. Previously,

independent researchers found no neutralizing antibodies in the sera of those vaccinated with EpiVacCorona [26].

Perhaps there are more people with comorbid chronic conditions in the vaccinated elderly groups

Perhaps the vaccinated elderly groups had many more people with comorbid chronic conditions than the other groups, simply because people with chronic conditions were more motivated to get vaccinated and received the vaccine more often. As a result, despite vaccination, groups of older people with more comorbidities had more COVID-19 infections compared to groups that were not vaccinated but had a lower proportion of chronically ill people. This difference can significantly underestimate the VE in certain age groups of people or even make it negative. Perhaps for this reason, and because there are more people with comorbid chronic diseases in the vaccinated elderly groups than in other groups, morbidity after EpiVacCorona is somewhat more common among vaccinated individuals and results in negative vaccine effectiveness values. It is possible that this may also explain the low or even negative effectiveness values of Sputnik V for preventing non severe forms of COVID-19 disease in the older age groups.

This hypothesis is consistent with the results of the VE evaluation for the Sputnik V using those immunized with the ineffective vaccine (EpiVacCorona) as a control group (Figure 3B, right histogram). The histogram demonstrates that the difference in VE estimates between the two age groups becomes smaller if a control group with the EpiVacCorona vaccinated is used instead of a seronegative control group.

Moreover, the CI intervals for VE, estimated using EpiVacCorona data, overlap for two different age groups. These results show that differences in VE estimates between age groups can be minimized by using a more appropriate control group.

Perhaps vaccinated people behave more risky

Is the VE related to the behavior of those who have been immunized? Could there be a decrease in VE due to social rather than biological factors? It is possible that yes. The negative vaccine effectiveness in some age groups in our studies could presumably be partly due to the behavior of those vaccinated who feel more secure after vaccination neglecting social distance, masks, and other means of protection.

Biological factors may be contributing to the decrease in VE in older age groups

In addition to social and behavioral factors, features of the immune system of the elderly may contribute to the age-related decline in VE. Below is a detailed description of the specific functioning of the immune system in the elderly.

Recurrent SARS-CoV-2 infections and their relationship with age

Interestingly, the ability of the human immune system to protect against COVID-19 re-infection also appears to depend on age. For example, a study of 4 million PCR-positive cases in the first and

second wave of infections in Denmark showed that protection against reinfection was stronger in the younger generation: 81% in the under-65 group versus 47% in the over-65 group [41].

USA-UK

Perhaps the weaker protection against the virus even for vaccinated older people and their greater susceptibility to breakthrough infections is related to the level of neutralizing antibodies. After vaccination, it is either immediately lower or falls faster in the elderly than in the younger generation. For example, U.S. researchers observed an inverse correlation between age and the level of virus-neutralizing antibodies after BNT162b2 vaccination [42]. BNT162b2 is BioNTech, a Pfizer vaccine. Notably, in a study by British scientists as well, increased age correlated significantly with decreased neutralizing antibodies in those observed [43].

Germany

Similar effects were observed by scientists in Germany, who studied antibody levels in those immunized with the BNT162b2 vaccine. In their study they found that in those over 75 years of age the vaccination causes a low level of antibodies, on average corresponding to a value of 52 BAU/ml. Many people of this age, however, did not produce any antibodies at all after vaccination [44]. Another study examined antibody levels to SARS-CoV-2 after natural COVID-19 infection. It showed that the rate at which antibody levels fell was related to age. Antibodies disappeared particularly quickly in those over 60 years of age [45].

Argentina

Researchers in Argentina have shown that antibody levels after immunization with Sputnik V first rise, peak between 28 and 60 days after the second dose of vaccine, and then fall. After six months, only 31% of those immunized [9] have antibodies. This decrease in antibody levels to the coronavirus S-protein may correlate with a drop in protection against symptomatic COVID-19 infection.

Correlation of antibody levels with antiviral protection

Several papers have shown that antiviral neutralizing antibody levels correlate with the degree of immune protection against symptomatic SARS-CoV-2 infection [46-50]. Accordingly, it has been found that a drop in the level of antibodies to viral S-protein as time passes after vaccination, correlates with a drop in the protective effectiveness of the vaccine [51,52]. Although there are many other factors besides neutralizing antibody levels that may influence worse protection against viral infection in older people [53]

Protective immunity may decline faster in older people

The decrease in the VE of the Sputnik V with increasing age was not detected in clinical trials [6 6]. Also, such a decrease was not observed in retrospective cohort studies of several vaccines, including BNT162b2 in Israel [54] and Sputnik V, in Hungary [7]. Moreover, in a case-control study of two vaccines BNT162b2 and ChAdOx1 nCoV-19 in Scotland, it was shown that the protective effectiveness of the vaccine even increases with age, but most breakthrough infections leading to death occur in old age among people at risk of comorbidity [55].

Our retrospective cohort analysis revealed a consistent decline in the estimated vaccine effectiveness with age. In the elderly, vaccine-induced protective immunity can weaken more quickly because their antibody levels decrease faster [42,43,45]. A rapid drop in antibody levels has also been reported for Sputnik V in Argentina [9]. Therefore, clinical, or retrospective trials that were carried out at a time close to vaccination did not document such a drop in protection, however, it manifested itself in other retrospective studies, which included categories of vaccinated with a long period of immunization.

The need for a booster dose for everyone, but especially for the elderly

In the U.S., people over the age of 60 or those who are younger but have serious comorbidities were offered a booster third dose of the vaccine earlier than other populations [56,57]. It is worth noting that Israeli scientists have shown that a third booster dose of the vaccine can greatly reduce the likelihood of severe COVID-19, including in the elderly. For example, participants in the Israeli study had tens of times less morbidity after the third vaccination compared to people in the same age group who received only two shots and were followed for a similar period [58-60]. Significant improvements in the protective effectiveness of the same vaccine after a booster dose, including in people over 50 years old, have also been reported in the United Kingdom [61]. Preliminary analysis of the results of booster dose ChAdOx1 nCoV-19 vaccination suggests a relatively low number of side effects and safety of this immunization [62].

Revaccination in a form of the booster dose of the vaccine is especially important for the prevention of COVID-19, which results from infection with the Omicron variant. A 12-fold decrease in neutralizing antibodies towards this virus variant has been demonstrated in the sera of individuals vaccinated with Sputnik V 6-12 months ago. At the same time, analysis of serum of persons vaccinated with Sputnik V and then vaccinated with Sputnik Light showed that 2-3 months after revaccination the decrease in the level of neutralizing antibodies against Omicron variant was only 7 times. Moreover, boosting dose increases the titer of antibodies capable of neutralizing this virus variant by an average of 16 times [14]. Thus, it appears that the protective efficacy of the Sputnik V vaccine can and should be enhanced by additional revaccination.

Comparison with retrospective studies of vaccine effectiveness estimates in different countries

In general, we can say that our VE estimate of the Sputnik V vaccine in preventing COVID-19 related deaths or severe disease is comparable to the VE estimates of vaccines from other developers. However, VE that is estimated by us, decreases as the age of the individual increases. The reasons for this trend may be related to deficiencies in the cohort study design that does not consider large differences in the characteristics of people in the observation groups. In addition, differences in the immunological and behavioral characteristics of people in different age cohorts may be contributing to this effect. Does the same tendency appear in the studies of other authors? In some, yes, and in some, no. Table 3 summarizes the results of the studies.

Table 3. Studies demonstrating the presence or absence of an association between VE and age.

Country of data origin	Type of research	Vaccines	Outcomes of COVID-19	Age dependence of VE	Virus variant	Type of publication	Ref.
Scotland	retrospective case control	BNT162b2, ChAdOx1 nCoV-19	death	not detected	mainly Delta	article	[55]
Israel	retrospective cohort	BNT162b2	death, hospitalizations, symptomatic and asymptomatic	not detected	mainly Alpha	article	[54]
Hungary	retrospective cohort	BNT162b2, mRNA-1273, Sputnik V, Sinofarm, ChAdOx1 nCoV-19	infection	not detected	not specified	article	[7]
Sweden	retrospective cohort	BNT162b2, ChAdOx1 nCoV-19, mRNA-1273	death, hospitalizations, symptomatic and asymptomatic	detected	not specified	preprint	[63]
USA	retrospective cohort	BNT162b2	PCR-positive and hospitalization	detected, but minor	Delta	article	[64]
Qatar	case-negative control	BNT162b2, mRNA-1273	symptomatic or asymptomatic infection	detected	Delta	article	[65]
UK	case-control study	BNT162b2, ChAdOx1 nCoV-20	PCR-positive	detected	Delta	article	[66]

USA	retrospective cohort, controlled by those who got flu vaccine	is not specified	death, ICU hospitalizations, and many other outcomes	detected	not specified	preprint	[67]
UK	case-control study	BNT162b2, ChAdOx1 nCoV-19	mild and severe	detected	Delta	preprint	[68]
Israel	case-control study	BNT162b2	infection and severe form of disease	detected	Delta	preprint	[69]
Russia	retrospective cohort	Sputnik Light	symptomatic infection	detected	Delta	preprint	[11]

Below is more information about some of the studies listed in Table 3.

Sweden

An interesting retrospective cohort study of the duration of vaccine protection against infection was conducted in Sweden [63]. All vaccinated people in the observation cohort were matched for comparison at the individual level with people in the control cohort who were not vaccinated and did not have COVID-19. Comparisons were made using several demographic and medical criteria. It was found that the effectiveness of the vaccine in protecting against COVID-19 infection decreased faster among men and the elderly. The observations of this study, in terms of decreasing vaccine efficacy with age, are consistent with our findings. In the Swedish study, however, special emphasis was placed on examining the duration of the protective effect of the vaccine. It was shown that, on average, over a period slightly longer than six months, vaccine effectiveness in preventing symptomatic COVID-19 for the BNT162b2 vaccine dropped from 92% to zero. Also, over an even shorter period (four months), the effectiveness of the ChAdOx1 nCoV-19 vaccine dropped from 66% to zero. Slightly more stable was the effectiveness of the mRNA-1273 vaccine (Moderna). It dropped from 96% to 59% in half a year [63]. However, the average effectiveness of all vaccines to prevent symptomatic COVID-19 for those under age 50 was still positive, although not high (~34%) even after half a year. On the contrary, for those over 50 years of age, vaccine effectiveness in just over half a year had waned to zero [63].

USA

Interestingly, in a retrospective cohort study in the United States, results were found that showed a slightly slower decline in the effectiveness of the BNT162b2 vaccine compared to the decline found by scientists in Sweden. The protective effectiveness (against infection with the Delta variant of SARS-CoV-2) in the United States fell from 93% to 53% in five months [64], and not to zero as in Sweden [63]. VE was age-dependent; against COVID-19 infection, it decreased from 88% to 47% in those younger than 65 and from 80% to 43% in those older, within five months of vaccination. However, the

VE against Delta-related hospitalizations was overall high 93% and did not decline for at least 6 months [64].

Qatar

Similar information is shared by researchers from Qatar, who performed a case-negative control study [65]. According to their analysis, the VE of BNT162b2 and mRNA-1273 vaccines against the Delta variant was lower, for those over 50 years of age. However, the paper notes that this result should be seen in the context of the fact that people over 50 years of age received the second dose an average of one and a half months earlier than those younger. As a result, the longer period following vaccination may have led to a decrease in VE [65].

UK-USA

Finally, it is worth mentioning a preprint by British researchers that is based on a retrospective cohort study [67] presenting an analysis of a large database obtained mainly from the United States. In this database, the researchers identified more than 10,000 vaccine breakthrough COVID-19 cases, which were matched with those of unvaccinated controls. The work showed that from death and intensive care units' hospitalization, the vaccine protected those under 60 years of age significantly better compared to those who were older. In fact, authors of the study didn't detect any positive effects of vaccination for those over-60s [67]. Unfortunately, the type of vaccine was not specified in the study.

Similar results were obtained in a case-control study in the UK VE against symptomatic disease caused by the Delta viral variant dropped to 70% for BNT162b24 and 47% for ChAdOx1 nCoV-19 over 20 weeks, respectively, but did not fall as much for hospitalizations. The decline in the effectiveness of these vaccines was more noticeable in people over 65. The authors conclude that the VE declines much faster in older people than in younger people [68].

Another already published case-control study done in the UK shows a decrease in vaccine effectiveness when moving from the 18-34 age group to the 35-64 age group. This decrease for the BioNTech mRNA vaccine was 10% and for the adenovirus vector ChAdOx1 nCoV-19 almost 20% [66]. It is worth noting, though, that the study authors are cautious about these kinds of findings, suggesting that young people are more sociable and could be much more likely to be infected with the virus by carrying the disease asymptomatically. Therefore, vaccination in this age group seems to be more effective, but effectiveness is achieved by combining natural immunity with vaccine immunity. This kind of immunity is called hybrid immunity. The authors of the same study show a higher effectiveness of such immunity compared to just vaccine immunity [66]. Thus, the authors of the study are not convinced that the effectiveness of vaccines, per se, declines with age.

Israel

Scientists from Italy, analyzing data from Israel and comparing them with data obtained by mathematical modeling, hypothesized that the main reasons for breakthrough COVID-19 infections in immunized people were a drop in the effectiveness of protection for six months and the low effectiveness of the BNT162b2 vaccine in the elderly [69]. It is possible that the latter, namely the lower VE in the elderly, is a consequence of the former, namely, the drop in vaccine protection over time.

Since older Israelis were vaccinated in the first place, the fact of the poorer protection can be directly related to the earlier time of vaccination compared to young people. The incidence of severe COVID-19 among those over 60 and fully vaccinated in January was 0.34 cases per 1000 people over the study period. It fell to 0.26 cases among those who were fully vaccinated in February. Further, the incidence dropped to 0.15 cases per 1000 people for those who were fully vaccinated in March, and to 0.12 cases for those who received the vaccine between April and May. Thus, the more recently a person was vaccinated, the better the vaccine protected him [70].

Perhaps the very short time interval between vaccination and evaluation of BNT162b2 vaccine effectiveness in Israel is the reason for the lack of detectable differences in VE estimates in different age groups [54].

Concluding remarks

Our research shows that those vaccinated with EpiVacCorona have no advantage over unvaccinated or seronegative individuals in their chances of getting COVID-19. The vaccine was introduced into civilian circulation without sufficient testing, has not proven itself and should therefore be withdrawn from production. At the same time, all those immunized with this pseudo-vaccine should be given the opportunity to be vaccinated with a modern, effective vaccine.

We find that the estimated VE of the Sputnik V vaccine to prevent deaths and severe forms of disease caused by the Delta variant of SARS-CoV-2 is comparable to the estimated VE of this vaccine against COVID-19 caused by other viral variants that have previously appeared in circulation.

Our observations are consistent with those of other scientists who have evaluated the VE of the Sputnik V vaccine in clinical trials or retrospective studies [6,12,39,65]. However, due to several factors, and primarily due to the limitations of the database with which we worked, it was impossible to directly compare the estimated VE values in our work with VE estimates from published papers.

In our study, we found that the estimated VE of the Sputnik V vaccine decreases with age and reaches a minimum in the age cohort over age 70. We do not know the reasons for this decrease in effectiveness, but we discuss several hypotheses in the Discussion section above. Among them are those based on 1) limitation in design of our database, 2) biological factors, and 3) social factors.

Our database does not allow us to normalize the analyzed groups by the number of people with chronic diseases, as well as by other important demographic characteristics. If there are more people with comorbidities among the vaccinated elderly than among the unvaccinated, then the VE calculations will underestimate the effectiveness of the vaccine.

Biological hypotheses relate to the immune characteristics of the elderly. These characteristics may manifest as lower antibody levels that appear after vaccination in the elderly and/or a more rapid decline in antibody levels. The protective effect of the vaccine may be shorter. These hypotheses are partially supported by the literature [42-45].

A hypothesis based on social factors links the decrease in vaccine effectiveness to behaviors leading to additional risks of COVID-19 infection predominantly in the elderly group. Perhaps members of this group feel more protected and spend more time in public places where the risk of infection is

higher, such as on public transportation. The opposite hypothesis can also be considered, which has been proposed by researchers from Great Britain [66]. These researchers believe that young people, because of their busier social lives compared to older people, are more likely to be infected with COVID-19 in an asymptomatic form and after vaccination they develop hybrid immunity, which protects better than just vaccine immunity in older people. Hybrid immunity forms in those who have had the disease and have been vaccinated [66].

In any case, we are not the only researchers who have found a pattern of decreasing estimated VE with increasing age. Similar observations for other vaccines have been made in various countries in Sweden [63], Israel [69], Qatar [65], UK [66,68 86], and the United States [64,67]. Finally, such a pattern is shown for Sputnik Light [11].

No matter how the nature of the detected effect is explained, it might indicate that elderly people get sick more often compared to younger ones, which means they need to protect themselves to a greater extent, e.g., by booster doses of vaccines, in addition, by masks, social distance and all other means.

The value of boosting vaccine doses is especially high during COVID-19 epidemics associated with Omicron. Preliminary data show that additional vaccination with Sputnik Light significantly increases the level of antibodies capable of neutralizing the Omicron variant [14].

Conclusions

Summarizing the results of our analysis, we can state the following:

1) The EpiVacCorona vaccine does not protect against COVID-19.

2) The more severe the COVID-19 disease, the better the vaccine protects against it.

3) The estimated VE of Sputnik V was lower in the elderly compared to the young.

Materials and methods

Dataset of COVID-19 infected individuals

We conducted our analysis using the dataset created by the Moscow Health Department that included people who sought medical care for COVID-19 in Moscow in June and July 2021. The dataset was published in the Telegram group "COVID-19 Vaccine News: 2021" and is in the public domain [71]. In this dataset the number of COVID-19 cases are divided into categories according to patient age and vaccination status. All cases, among those vaccinated, are further divided into subcategories according to the type of vaccine (Sputnik V, EpiVacCorona, and Covivac) and the number of doses (one or two) patients received. In addition, COVID-19 cases are categorized according to the severity of patients' illnesses or deaths.

It should be noted that EpiVacCorona vaccination only began in Moscow in April, and in June there were still few individuals who had already received two doses of the vaccine. Also in June, there were very few people who were fully immunized with Covivac. Therefore, in June, the main contribution to the number of people who received two doses of vaccine and fell ill was made by those who were immunized with Sputnik V. In fact, at the end of the month, the number of those immunized

with other vaccines was less than 3% of the total number. In July, there were more of those immunized with EpiVacCorona or Covivac among those who got COVID-19. In our work, only those vaccinated with two doses of each vaccine were counted.

Therefore, to estimate the VE values of the Sputnik V vaccine, data on the number of COVID-19 cases and deaths for different age groups for June 2021 were used [71]. To compare the VE of the Sputnik V and EpiVacCorona vaccines, data characterizing the number of severe COVID-19 cases for July were employed. These limitations in the use of the data were since the number of people vaccinated with Sputnik V and diagnosed with COVID-19 for July was available only for the severe COVID-19 case category [71]. The rest of the cases in the database, we were given, were not categorized by individual vaccines, so the groups of vaccinated less severe COVID cases included people immunized with different vaccines. It was not possible to separate the protective effect of different vaccines for less severe cases.

Control groups

In our work a few methods were used to count the number of people in a control group. From the total number of city residents in each age group, we subtracted 1) the number of vaccinated ones or 2) the number of seropositive individuals. The first control group was formed by subtracting vaccinated city residents from the total population of the same age group. The second control group was formed by subtracting seropositive city residents from the total population of the same age group.

To calculate the number of fully vaccinated by the time the number of cases was estimated, we used data from the Ministry of Health registry created for the registration and issuance of vaccine certificates in Russia [72]. A representative sample of the registry contents was generated by computer polling of vaccine certificate issuance service url addresses from the space of all possible unique registry record numbers. Data from this registry on those who received Sputnik V or EpiVacCorona vaccines were grouped into the same age categories used to estimate COVID-19 cases.

The 2021 demographics were used to normalize the data and estimate the total number of Moscow residents in different control age groups [73]. The study also used estimates of the total number of vaccinated and COVID-19 infected city residents at various dates in June and July 2021[36,74].

We calculated the number of seropositive city residents in each age group based on Department of Health of Moscow data in the published preprint [11]. The details are below in the section: Estimation of the percentage of city residents with antibodies.

An additional control group, which was used to evaluate the effectiveness of the Sputnik V vaccine, was represented by the group that included immunized with the inefficient vaccine EpiVacCorona. This control group has many advantages because people with similar behavior and people with comorbidities should be equally represented between those who received the Sputnik V and those who got EpiVacCorona vaccine. Therefore, the comparison vaccine group of those that got Sputnik V with such a control group should yield more reliable results.

Estimation of the percentage of Moscow residents with antibodies

The estimate in the preprint [11] is based on monitoring a representative sample of Moscow residents, which evaluates that just under half of them had antibodies to SARS-CoV-2 by the end of June 2021. This number is based on the results of continuous serological studies. For this seroprevalence study, samples were formed among patients from those who were admitted to the hospital for routine treatment, with a disease not related to COVID-19. The average number of patients tested for SARS-CoV-2 antibodies was 10,000 per week. The presence of IgG antibodies in the serum venous blood was evaluated in all patients using a Mindray Medical International Limited (China) immunochemiluminescent analyzer. This estimation was used to form a second control group by subtracting seropositive city residents from the total population.

For comparison we also estimated the percentage of Moscow residents with antibodies based on the city's infection/fatality ratio (IFR) [39]. It is hypothesized that the ratio between the number of COVID-19 cases and excess mortality within an urban metropolitan population is stable over time. For St. Petersburg, those who died were 0.86% of those seropositive in the city (CI 95% 0.66-1.05) according to data published in the preprint [39]. On the hypothesis that Moscow has the same ratio, we calculated the percentage of seropositive individuals for each past month in 2021 based on excess mortality data [75]. To estimate the number of seropositive people in the current month, we took the excess mortality of the previous month and all preceding months, starting in February 2020.

In addition, we estimated this number based on data from “Invitro”, which monitors seroprevalence of antibodies against SARS-CoV-2[40] among the company clients. ("Invitro” is one of the largest medical companies in Russia, specializing in laboratory diagnostics and medical services). However, IFR values and “Invitro” estimates, which are shown in Fig.3 were used only for comparison with estimates presented in the preprint [11].

Calculating the VE of Sputnik Light

The first dose of Sputnik V corresponds to the Sputnik Light vaccination. We evaluated the VE of Sputnik Light regrouping the data from published preprint by other age categories [11]. The study counted the number of people who got the first dose of the Sputnik V vaccine and did not get a second dose by the time they got sick.

Method of VE calculation

The calculations were based on the algorithms described in the literature [76,77]. The significance values for VE estimations were calculated using the chi-square method [78]. In case outcome in the population being studied is rare, as with COVID 19 cases among vaccinated or unvaccinated, Odds Ratio obtained accurately estimates Risk Ratio (RR).

Odds Ratio (OR) was calculated as follows: $OR = \frac{a*d}{b*c}$,

$95\%\ OR = exp\ (ln\ (OR)\ \pm 1.96 * \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}})$

considering:
a- number of COVID-19 cases among vaccinated people in Moscow
b-number of vaccinated in Moscow
c-number of COVID-19 cases among unvaccinated people in Moscow

d-number of Moscow residents in the control group. *To calculate the number of individuals in the control group, two variants of numerical estimation were used for each age group 1) the number of unvaccinated Moscow residents 2) the number of seronegative city residents.*

Vaccine Effectiveness (VE) % was calculated as follows: VE=100*(1-OR)

The data for the calculations were obtained from the following sources:

The total number of Moscow residents in each age group was calculated based on the city's 2021 demographics [73].

a and c- [71] and Supplemental Table 1.

b-register of vaccinations in Moscow, with data aggregated for the same age groups [72] and [74].

d- a numerical estimate of the number of individuals in each age group of the control group was made by subtracting the number of vaccinated or seropositive citizens from the number of Moscow residents in each age group.

Confidence intervals for vaccine effectiveness estimates

In this paper, we estimate vaccine effectiveness using two types of assumptions about the control group. Because of this, we can only estimate a vaccine's effectiveness value as a value within a confidence interval whose width is determined by our assumptions. Thus, the lower end of the interval for estimating effectiveness can be used as the minimum among all estimates derived from assumptions about the size of the control group, and the upper end as the maximum. The confidence intervals for the effectiveness of the Sputnik V vaccine in preventing severe disease, calculated using this algorithm, are shown in the Results section of Table 1 in the last column.

Funding: The work is done without any allocated funding.

Author Contributions: Both authors participated in data analysis, writing, and editing.

Conflict of Interest: The authors of the study have no conflict of interest.

Acknowledgements: The authors of this article would like to thank the organizers of social networks: "*Project V1V2.ru*, *systems of chats about vaccinations"* for constructive discussion of data analysis related to the Sputnik V vaccine. The authors are also grateful to Andrei Krinitsky, the administrator of the Telegram chat room that organized the COVID-19 Grais "epivakorona.com" civic vaccination group, and to the members of this "Grais" group for their help in analyzing data related to the effectiveness of Sputnik V and EpiVacCorona vaccines.

Literature

1. Baden, L.R.; El Sahly, H.M.; Essink, B.; Kotloff, K.; Frey, S.; Novak, R.; Diemert, D.; Spector, S.A.; Rouphael, N.; Creech, C.B., et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* **2021**, *384*, 403-416, doi:10.1056/NEJMoa2035389.
2. Thomas, S.J.; Moreira, E.D., Jr.; Kitchin, N.; Absalon, J.; Gurtman, A.; Lockhart, S.; Perez, J.L.; Perez Marc, G.; Polack, F.P.; Zerbini, C., et al. Safety and Efficacy of the BNT162b2 mRNA

Covid-19 Vaccine through 6 Months. *N Engl J Med* **2021**, 10.1056/NEJMoa2110345, doi:10.1056/NEJMoa2110345.

3. Voysey, M.; Clemens, S.A.C.; Madhi, S.A.; Weckx, L.Y.; Folegatti, P.M.; Aley, P.K.; Angus, B.; Baillie, V.L.; Barnabas, S.L.; Bhorat, Q.E., 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, doi:10.1016/S0140-6736(20)32661-1.
4. Marfe, G.; Perna, S.; Shukla, A.K. Effectiveness of COVID-19 vaccines and their challenges (Review). *Exp Ther Med* **2021**, *22*, 1407, doi:10.3892/etm.2021.10843.
5. Sadoff, J.; Gray, G.; Vandebosch, A.; Cardenas, V.; Shukarev, G.; Grinsztejn, B.; Goepfert, P.A.; Truyers, C.; Fennema, H.; Spiessens, B., et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med* **2021**, *384*, 2187-2201, doi:10.1056/NEJMoa2101544.
6. Logunov, D.Y.; Dolzhikova, I.V.; Shcheblyakov, D.V.; Tukhvatulin, A.I.; Zubkova, O.V.; Dzharullaeva, A.S.; Kovyrshina, A.V.; Lubenets, N.L.; Grousova, D.M.; Erokhova, A.S., 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**, *397*, 671-681, doi:10.1016/S0140-6736(21)00234-8.
7. Vokó, Z.e.a. Nationwide effectiveness of five SARS-CoV-2 vaccines in Hungary - The HUN-VE study. *Clinical Microbiology and Infection* **2021**, 2021DOI:https://doi.org/10.1016/j.cmi.2021.11.011, doi:2021DOI:https://doi.org/10.1016/j.cmi.2021.11.011.
8. AlQahtani, M.; Bhattacharyya, S.; Alawadi, A.; Mahmeed, H.A.; Sayed, J.A.; Justman, J.; El-Sadr, W.M.; and, J.H.; Mukherjee, S. Morbidity and mortality from COVID-19 post-vaccination breakthrough infections in association with vaccines and the emergence of variants in Bahrain. *preprint, researchsquare* **2021**, 10.21203/rs.3.rs-828021/v1, doi:10.21203/rs.3.rs-828021/v1.
9. Chahla, R.E.e.a. Long-term analysis of antibodies elicited by SPUTNIK V: A prospective cohort study in Tucumán, Argentina

   The Lancet Regional Health – Americas **2021**, DOI:https://doi.org/10.1016/j.lana.2021.100123, doi:DOI:https://doi.org/10.1016/j.lana.2021.100123.
10. Tukhvatulin, A.; Dolzhikova, I.; Shcheblyakov, V.; Zubkova, O.e.a. An Open, Non-Randomised, 1/2 Phase Study on the Safety, Tolerability, and Immunogenicity of Single Dose 'Sputnik Light' Vaccine for Prevention of Coronavirus Infection in Healthy Adults. *preprint, Lancet* **2021**.
11. Dolzhikova, I.V.; Gushchin, V.A.; Shcheblyakov, D.V.; Tsybin, A.N.; Shchetinin, A.M.; Pochtovyi, A.A.; Komissarov, A.B.; Kleymenov, D.A.; Kuznetsova, N.A.; Tukhvatulin, A.I., et al. One-shot immunization with Sputnik Light (the first component of Sputnik V vaccine) is effective against SARS-CoV-2 Delta variant: efficacy data on the use of the vaccine in civil circulation in Moscow. *medRxiv* **2021**, 10.1101/2021.10.08.21264715, 2021.2010.2008.21264715, doi:10.1101/2021.10.08.21264715.
12. Gonzalez, S.; Olszevicki, S.; Salazar, M.; Calabria, A.; Regairaz, L.; Marin, L.; Campos, P.; Varela, T.; Martinez, V.V.G.; Ceriani, L., et al. Effectiveness of the first component of Gam-COVID-Vac (Sputnik V) on reduction of SARS-CoV-2 confirmed infections, hospitalisations and mortality in patients aged 60-79: a retrospective cohort study in Argentina. *EClinicalMedicine* **2021**, *40*, 101126, doi:10.1016/j.eclinm.2021.101126.

13. Claro, F.; Silva, D.; Rodriguez, M.; Rangel, H.R.; de Waard, J.H. Immunoglobulin G antibody response to the Sputnik V vaccine: previous SARS-CoV-2 seropositive individuals may need just one vaccine dose. *Int J Infect Dis* **2021**, *111*, 261-266, doi:10.1016/j.ijid.2021.07.070.
14. Dolzhikova, I.; Iliukhina, A.; Kovyrshina, A.; Kuzina, A.; Gushchin, V.; Siniavin, A.; Pochtovyi, A.; Shidlovskaya, E.; Kuznetsova, N.; Megeryan, M., et al. Sputnik Light booster after Sputnik V vaccination induces robust neutralizing antibody response to B.1.1.529 (Omicron) SARS-CoV-2 variant. *medRxiv* **2021**, 10.1101/2021.12.17.21267976, 2021.2012.2017.21267976, doi:10.1101/2021.12.17.21267976.
15. Ryzhikov A.B, R.E.A., Bogryantseva M.P, Danilenko E.D, Imatdinov I.R, Nechaeva E.A, Pyankov O.V, Pyankova O.G, Susloparov I.M, Taranov O.S, Gudymo A.S, Danilchenko N.V, Sleptsova E.S, Bodnev S.A, Onkhonova GS, Petrov V N, Moiseeva A A, TorzhkovaPYu, Pyankov SA, Tregubchak TV, Antonets DV, Gavrilova EV, Maksyutov R A . Immunogenicity and Protectivity of the Peptide Vaccine against SARS-CoV-2. *Annals of the Russian Academy of Medical Sciences* **2021**, *76*, 5–19, doi:https://doi.org/10.15690/vramn1528.
16. Shrock, E.; Fujimura, E.; Kula, T.; Timms, R.T.; Lee, I.H.; Leng, Y.; Robinson, M.L.; Sie, B.M.; Li, M.Z.; Chen, Y., et al. Viral epitope profiling of COVID-19 patients reveals cross-reactivity and correlates of severity. *Science* **2020**, *370*, doi:10.1126/science.abd4250.
17. Farrera-Soler, L.; Daguer, J.P.; Barluenga, S.; Vadas, O.; Cohen, P.; Pagano, S.; Yerly, S.; Kaiser, L.; Vuilleumier, N.; Winssinger, N. Identification of immunodominant linear epitopes from SARS-CoV-2 patient plasma. *PLoS One* **2020**, *15*, e0238089, doi:10.1371/journal.pone.0238089.
18. Yi, Z.; Ling, Y.; Zhang, X.; Chen, J.; Hu, K.; Wang, Y.; Song, W.; Ying, T.; Zhang, R.; Lu, H., et al. Functional mapping of B-cell linear epitopes of SARS-CoV-2 in COVID-19 convalescent population. *Emerg Microbes Infect* **2020**, *9*, 1988-1996, doi:10.1080/22221751.2020.1815591.
19. Poh, C.M.; Carissimo, G.; Wang, B.; Amrun, S.N.; Lee, C.Y.; Chee, R.S.; Fong, S.W.; Yeo, N.K.; Lee, W.H.; Torres-Ruesta, A., et al. Two linear epitopes on the SARS-CoV-2 spike protein that elicit neutralising antibodies in COVID-19 patients. *Nat Commun* **2020**, *11*, 2806, doi:10.1038/s41467-020-16638-2.
20. Li, Y.; Lai, D.Y.; Zhang, H.N.; Jiang, H.W.; Tian, X.; Ma, M.L.; Qi, H.; Meng, Q.F.; Guo, S.J.; Wu, Y., et al. Linear epitopes of SARS-CoV-2 spike protein elicit neutralizing antibodies in COVID-19 patients. *Cell Mol Immunol* **2020**, *17*, 1095-1097, doi:10.1038/s41423-020-00523-5.
21. Li, Y.; Ma, M.L.; Lei, Q.; Wang, F.; Hong, W.; Lai, D.Y.; Hou, H.; Xu, Z.W.; Zhang, B.; Chen, H., et al. Linear epitope landscape of the SARS-CoV-2 Spike protein constructed from 1,051 COVID-19 patients. *Cell Rep* **2021**, *34*, 108915, doi:10.1016/j.celrep.2021.108915.
22. Pichugina, T. What to expect from EpiVacCorona. All about the peptide vaccine against COVID-19. *RIA-Novosti* January 22, 2021, 2021.
23. Ryzhikov A.B., R.E.A., Bogryantseva M.P., Usova S.V., Danilenko E.D., Nechaeva E.A., Pyankov O.V., Pyankova O.G., Gudymo A.S., Bodnev S.A., Onkhonova G.S., Sleptsova E.S., Kuzubov V.I., Ryndyuk N.N., Ginko Z.I., Petrov V.N., Moiseeva A.A., Torzhkova P.Yu., Pyankov S.A., Tregubchak T.V., Antonec D.V., Gavrilova E.V., Maksyutov R.A. . A single blind, placebo-controlled randomized study of the safety, reactogenicity and immunogenicity of the "EpiVacCorona" Vaccine for the prevention of COVID-19, in volunteers aged 18–60 years (phase I–II). . *Russian Journal of Infection and Immunity* **2021**, *11* 283-296., doi:https://doi.org/10.15789/2220-7619-ASB-1699.

24. Matveeva, O. The problem of selecting peptides for EpiVacCorona and a review of the article by the vaccine developers on phase I and phase II clinical trials. *BioMolecule (in Russian) An informative online publication about modern biology.* June 4, 2021.
25. ClinicalTrialNCT04780035. Study of the Tolerability, Safety, Immunogenicity and Preventive Efficacy of the EpiVacCorona Vaccine for the Prevention of COVID-19 ClinicalTrials.gov Identifier NCT04780035. "Vector", S., Ed. March 3, 2021.
26. Krinitsky, A.A. Study of immunogenicity and potential protectiveness of EpiVacCorona vaccine. *COVID19-PREPRINTS.MICROBE.RU* **2021**, https://doi.org/10.21055/preprints-3111948, doi:https://doi.org/10.21055/preprints-3111948.
27. Kozlovskaya, L.I.; Piniaeva, A.N.; Ignatyev, G.M.; Gordeychuk, I.V.; Volok, V.P.; Rogova, Y.V.; Shishova, A.A.; Kovpak, A.A.; Ivin, Y.Y.; Antonova, L.P., et al. Long-term humoral immunogenicity, safety and protective efficacy of inactivated vaccine against COVID-19 (CoviVac) in preclinical studies. *Emerg Microbes Infect* **2021**, *10*, 1790-1806, doi:10.1080/22221751.2021.1971569.
28. Mishra, S.; Mindermann, S.; Sharma, M.; Whittaker, C.; Mellan, T.A.; Wilton, T.; Klapsa, D.; Mate, R.; Fritzsche, M.; Zambon, M., et al. Changing composition of SARS-CoV-2 lineages and rise of Delta variant in England. *EClinicalMedicine* **2021**, *39*, 101064, doi:10.1016/j.eclinm.2021.101064.
29. Rella, S.A.; Kulikova, Y.A.; Dermitzakis, E.T.; Kondrashov, F.A. Rates of SARS-CoV-2 transmission and vaccination impact the fate of vaccine-resistant strains. *Sci Rep* **2021**, *11*, 15729, doi:10.1038/s41598-021-95025-3.
30. Brown, C.M.; Vostok, J.; Johnson, H.; Burns, M.; Gharpure, R.; Sami, S.; Sabo, R.T.; Hall, N.; Foreman, A.; Schubert, P.L., et al. Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings - Barnstable County, Massachusetts, July 2021. *MMWR Morb Mortal Wkly Rep* **2021**, *70*, 1059-1062, doi:10.15585/mmwr.mm7031e2.
31. Chia, P.Y.; Xiang Ong, S.W.; Chiew, C.J.; Ang, L.W.; Chavatte, J.-M.; Mak, T.-M.; Cui, L.; Kalimuddin, S.; Chia, W.N.; Tan, C.W., et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. *medRxiv* **2021**, 10.1101/2021.07.28.21261295, 2021.2007.2028.21261295, doi:10.1101/2021.07.28.21261295.
32. Bian, L.; Gao, Q.; Gao, F.; Wang, Q.; He, Q.; Wu, X.; Mao, Q.; Xu, M.; Liang, Z. Impact of the Delta variant on vaccine efficacy and response strategies. *Expert Rev Vaccines* **2021**, 10.1080/14760584.2021.1976153, 1-9, doi:10.1080/14760584.2021.1976153.
33. Lopez Bernal, J.; Andrews, N.; Gower, C.; Gallagher, E.; Simmons, R.; Thelwall, S.; Stowe, J.; Tessier, E.; Groves, N.; Dabrera, G., et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med* **2021**, *385*, 585-594, doi:10.1056/NEJMoa2108891.
34. Harder, T.; Kulper-Schiek, W.; Reda, S.; Treskova-Schwarzbach, M.; Koch, J.; Vygen-Bonnet, S.; Wichmann, O. Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection with the Delta (B.1.617.2) variant: second interim results of a living systematic review and meta-analysis, 1 January to 25 August 2021. *Euro Surveill* **2021**, *26*, doi:10.2807/1560-7917.ES.2021.26.41.2100920.
35. Mullen J.L.; Tsueng G.; Latif A.A., e.a. outbreak.info. Available online: https://outbreak.info/ (2020). Center for Viral Systems Biology: 2021.
36. https://coronavirus-monitor.info/. Statistics on the spread of coronavirus in Moscow. 2021.

37. Knorre, D.; Nabiyeva, E.; Garushyants, S.K., Bazykin G.A.; . Russian Consortium for Coronavirus Genome Sequencing (CORGI), https://taxameter.ru/ 2021.
38. Mlcochova, P.; Kemp, S.A.; Dhar, M.S.; Papa, G.; Meng, B.; Ferreira, I.; Datir, R.; Collier, D.A.; Albecka, A.; Singh, S., et al. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. *Nature* **2021**, 10.1038/s41586-021-03944-y, doi:10.1038/s41586-021-03944-y.
39. Barchuk, A.; Skougarevskiy, D.; Kouprianov, A.; Shirokov, D.; Dudkina, O.; Tursun-zade, R.; Sergeeva, M.; Tychkova, V.; Komissarov, A.; Zheltukhina, A., et al. COVID-19 pandemic in Saint Petersburg, Russia: combining surveillance and population-based serological study data in May, 2020–April, 2021. *medRxiv* **2021**, 10.1101/2021.07.31.21261428, 2021.2007.2031.21261428, doi:10.1101/2021.07.31.21261428.
40. InVitro. Data on patients who tested positive for IgG antibodies. Availabe online: https://www.invitro.ru/l/invitro_monitor/ (accessed on November 15).
41. Hansen, C.H.; Michlmayr, D.; Gubbels, S.M.; Molbak, K.; Ethelberg, S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet* **2021**, *397*, 1204-1212, doi:10.1016/S0140-6736(21)00575-4.
42. Arunachalam, P.S.; Scott, M.K.D.; Hagan, T.; Li, C.; Feng, Y.; Wimmers, F.; Grigoryan, L.; Trisal, M.; Edara, V.V.; Lai, L., et al. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. *Nature* **2021**, *596*, 410-416, doi:10.1038/s41586-021-03791-x.
43. Wall, E.C.; Wu, M.; Harvey, R.; Kelly, G.; Warchal, S.; Sawyer, C.; Daniels, R.; Hobson, P.; Hatipoglu, E.; Ngai, Y., et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. *Lancet* **2021**, *397*, 2331-2333, doi:10.1016/S0140-6736(21)01290-3.
44. Delbrück, M.; Hoehl, S.; Toptan, T.; Schenk, B.; Grikscheit, K.; Metzler, M.; Herrmann, E.; Ciesek, S. Characterization of the humoral immune response to BNT162b2 in elderly residents of long-term care facilities five to seven months after vaccination. *medRxiv* **2021**, 10.1101/2021.11.09.21266110, 2021.2011.2009.21266110, doi:10.1101/2021.11.09.21266110.
45. Sjaarda, C.P.; Moslinger, E.; Tozer, K.; Colautti, R.I.; Kheitan, S.; Meurant, R.; Cleaf, S.V.; Ardakani, A.; Bosnjak, O.; Ghaffari, A., et al. Distinct age-specific SARS-CoV-2 IgG decay kinetics following natural infection. *medRxiv* **2021**, 10.1101/2021.08.05.21259465, 2021.2008.2005.21259465, doi:10.1101/2021.08.05.21259465.
46. Khoury, D.S.; Cromer, D.; Reynaldi, A.; Schlub, T.E.; Wheatley, A.K.; Juno, J.A.; Subbarao, K.; Kent, S.J.; Triccas, J.A.; Davenport, M.P. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* **2021**, *27*, 1205-1211, doi:10.1038/s41591-021-01377-8.
47. Feng, S.; Phillips, D.J.; White, T.; Sayal, H.; Aley, P.K.; Bibi, S.; Dold, C.; Fuskova, M.; Gilbert, S.C.; Hirsch, I., et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* **2021**, 10.1038/s41591-021-01540-1, doi:10.1038/s41591-021-01540-1.
48. Bergwerk, M.; Gonen, T.; Lustig, Y.; Amit, S.; Lipsitch, M.; Cohen, C.; Mandelboim, M.; Levin, E.G.; Rubin, C.; Indenbaum, V., et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. *N Engl J Med* **2021**, *385*, 1474-1484, doi:10.1056/NEJMoa2109072.
49. Dimeglio, C.; Herin, F.; Martin-Blondel, G.; Miedouge, M.; Izopet, J. Antibody titers and protection against a SARS-CoV-2 infection. *J Infect* **2021**, 10.1016/j.jinf.2021.09.013, doi:10.1016/j.jinf.2021.09.013.

50. Letizia, A.G.; Ge, Y.; Vangeti, S.; Goforth, C.; Weir, D.L.; Kuzmina, N.A.; Balinsky, C.A.; Chen, H.W.; Ewing, D.; Soares-Schanoski, A., et al. SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study. *Lancet Respir Med* **2021**, *9*, 712-720, doi:10.1016/S2213-2600(21)00158-2.
51. Aldridge, R.W.; Yavlinsky, A.; Nguyen, V.G.; Eyre, M.T.; Shrotri, M.; Navaratnam, A.M.D.; Beale, S.; Braithwaite, I.; Byrne, T.E.; Kovar, J., et al. Waning of SARS-CoV-2 antibodies targeting the Spike protein in individuals post second dose of ChAdOx1 and BNT162b2 COVID-19 vaccines and risk of breakthrough infections: analysis of the Virus Watch community cohort. *medRxiv* **2021**, 10.1101/2021.11.05.21265968, 2021.2011.2005.21265968, doi:10.1101/2021.11.05.21265968.
52. Shrotri, M.; Navaratnam, A.M.D.; Nguyen, V.; Byrne, T.; Geismar, C.; Fragaszy, E.; Beale, S.; Fong, W.L.E.; Patel, P.; Kovar, J., et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. *Lancet* **2021**, *398*, 385-387, doi:10.1016/S0140-6736(21)01642-1.
53. Bartleson, J.M.; Radenkovic, D.; Covarrubias, A.J.; Furman, D.; Winer, D.A.; Verdin, E. SARS-CoV-2, COVID-19 and the Ageing Immune System. *Nat Aging* **2021**, *1*, 769-782, doi:10.1038/s43587-021-00114-7.
54. Haas, E.J.; Angulo, F.J.; McLaughlin, J.M.; Anis, E.; Singer, S.R.; Khan, F.; Brooks, N.; Smaja, M.; Mircus, G.; Pan, K., et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet* **2021**, *397*, 1819-1829, doi:10.1016/S0140-6736(21)00947-8.
55. Grange, Z.; Buelo, A.; Sullivan, C.; Moore, E.; Agrawal, U.; Boukhari, K.; McLaughlan, I.; Stockton, D.; McCowan, C.; Robertson, C., et al. Characteristics and risk of COVID-19-related death in fully vaccinated people in Scotland. *The Lancet* **2021**, DOI:https://doi.org/10.1016/S0140-6736(21)02316-3, doi:DOI:https://doi.org/10.1016/S0140-6736(21)02316-3.
56. CDC. CDC Expands Eligibility for COVID-19 Booster Shots. 2021.
57. CDC. CDC Expands Eligibility for COVID-19 Booster Shots to All Adults. 2021.
58. Bar-On, Y.M.; Goldberg, Y.; Mandel, M.; Bodenheimer, O.; Freedman, L.; Kalkstein, N.; Mizrahi, B.; Alroy-Preis, S.; Ash, N.; Milo, R., et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *N Engl J Med* **2021**, *385*, 1393-1400, doi:10.1056/NEJMoa2114255.
59. Barda, N.; Dagan, N.; Cohen, C.; Hernan, M.A.; Lipsitch, M.; Kohane, I.S.; Reis, B.Y.; Balicer, R.D. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* **2021**, 10.1016/S0140-6736(21)02249-2, doi:10.1016/S0140-6736(21)02249-2.
60. Patalon, T.; Gazit, S.; Pitzer, V.E.; Prunas, O.; Warren, J.L.; Weinberger, D.M. Odds of Testing Positive for SARS-CoV-2 Following Receipt of 3 vs 2 Doses of the BNT162b2 mRNA Vaccine. *JAMA Intern Med* **2021**, 10.1001/jamainternmed.2021.7382, doi:10.1001/jamainternmed.2021.7382.
61. Andrews, N.; Stowe, J.; Kirsebom, F.; Gower, C.; Ramsay, M.; Bernal, J.L. Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) COVID-19 booster vaccine against covid-19 related symptoms in England: test negative case-control study. *medRxiv* **2021**, 10.1101/2021.11.15.21266341, 2021.2011.2015.21266341, doi:10.1101/2021.11.15.21266341.
62. Flaxman, A.; Marchevsky, N.G.; Jenkin, D.; Aboagye, J.; Aley, P.K.; Angus, B.; Belij-Rammerstorfer, S.; Bibi, S.; Bittaye, M.; Cappuccini, F., et al. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a

substudy of two randomised controlled trials (COV001 and COV002). *Lancet* **2021**, *398*, 981-990, doi:10.1016/S0140-6736(21)01699-8.
63. Nordström, P.; Ballin, M.; Nordström, A. Effectiveness of Covid-19 Vaccination Against Risk of Symptomatic Infection, Hospitalization, and Death Up to 9 Months: A Swedish Total-Population Cohort Study. *preprint, Lancet* **2021**.
64. Tartof, S.Y.; Slezak, J.M.; Fischer, H.; Hong, V.; Ackerson, B.K.; Ranasinghe, O.N.; Frankland, T.B.; Ogun, O.A.; Zamparo, J.M.; Gray, S., et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* **2021**, *398*, 1407-1416, doi:10.1016/S0140-6736(21)02183-8.
65. Tang, P.; Hasan, M.R.; Chemaitelly, H.; Yassine, H.M.; Benslimane, F.M.; Al Khatib, H.A.; AlMukdad, S.; Coyle, P.; Ayoub, H.H.; Al Kanaani, Z., et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. *Nat Med* **2021**, 10.1038/s41591-021-01583-4, doi:10.1038/s41591-021-01583-4.
66. Pouwels, K.B.; Pritchard, E.; Matthews, P.C.; Stoesser, N.; Eyre, D.W.; Vihta, K.D.; House, T.; Hay, J.; Bell, J.I.; Newton, J.N., et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nat Med* **2021**, *27*, 2127-2135, doi:10.1038/s41591-021-01548-7.
67. Taquet, M.; Dercon, Q.; Harrison, P.J. Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. *medRxiv* **2021**, 10.1101/2021.10.26.21265508, 2021.2010.2026.21265508, doi:10.1101/2021.10.26.21265508.
68. Andrews, N.; Tessier, E.; Stowe, J.; Gower, C.; Kirsebom, F.; Simmons, R.; Gallagher, E.; Chand, M.; Brown, K.; Ladhani, S.N., et al. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. *medRxiv* **2021**, 10.1101/2021.09.15.21263583, 2021.2009.2015.21263583, doi:10.1101/2021.09.15.21263583.
69. De-Leon, H.; Pederiva, F. Using a physical model and aggregate data from Israel to estimate the current (July 2021) efficacy of the Pfizer-BioNTech vaccine. *medRxiv* **2021**, 10.1101/2021.08.10.21261856, 2021.2008.2010.21261856, doi:10.1101/2021.08.10.21261856.
70. Goldberg, Y.; Mandel, M.; Bar-On, Y.M.; Bodenheimer, O.; Freedman, L.; Haas, E.J.; Milo, R.; Alroy-Preis, S.; Ash, N.; Huppert, A. Waning Immunity after the BNT162b2 Vaccine in Israel. *N Engl J Med* **2021**, 10.1056/NEJMoa2114228, doi:10.1056/NEJMoa2114228.
71. https://t.me/COVID19VaccinesNews/9479. Telegram group, COVID-19 Vaccine News: 2021. This group is created for medical professionals and enthusiasts who have something to share about the status of the development and clinical/preclinical trials of the COVID-19 vaccines candidates worldwide. August 24, 2021
72. https://www.gosuslugi.ru/covid-cert/. State Services Portal (https://www.gosuslugi.ru/)

Ministry of Communications of Russia. 2021.
73. https://rosstat.gov.ru/compendium/document/13284. Population of the Russian Federation by gender and age. Federal State Statistics Service. 2021.
74. https://gogov.ru/covid-v-stats/msk. Coronavirus vaccination statistics.

Number of people vaccinated against coronavirus in Moscow. 2021.
75. Kobak, D. Excess mortality in Russia by month. https://github.com/dkobak/excess-mortality/blob/main/russia_excess_deaths.csv. 2021.
76. Weinberg, G.A.; Szilagyi, P.G. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. *J Infect Dis* **2010**, *201*, 1607-1610, doi:10.1086/652404.

77. Tenny, S.; Hoffman, M.R. Odds Ratio. In *StatPearls*, Treasure Island (FL), 2021.
78. McHugh, M.L. The chi-square test of independence. *Biochem Med (Zagreb)* **2013**, *23*, 143-149, doi:10.11613/bm.2013.018.

Supplemental Table 1. COVID-19 cases in Moscow categorized according to age and vaccination status of patients (June-July 2021).

Age	completed vaccination	month	The outcome and form of COVID-19 infection										in Moscow		
			death		severe form		moderately severe		light form		asymptomatic		vaccin.	seronegative	population
			unvac.	vac.	unvac.	vac.	unvac.	vac.	unvac.	vac.	unvac.	vac.	by the 1st of the month		2021
18-50	Sputnik V	June	158	1	974	26	10463	368	88075	5703	14623	1027	711347		5760116
		July			645	13							879731	2947963	
	EpiVacCorona					7							27529		
51-70	Sputnik V	June			2429	103	10009	833	27525	4726	4202	751	512338		3284276
		July			1819	92							580664	1790209	
	EpiVacCorona					24							17910		
71+	Sputnik V	June			3153	174	5151	606	6221	1701	1398	364	129466		1422425
		July			2418	151							138974	831713	
	EpiVacCorona					30							3206		
50+	Sputnik V	June	1700	70	5582	277	15160	1439	33746	6427	5600	1115	879731		4706701