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Review article

Controversy surrounding the Sputnik V vaccine

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ABSTRACT

The Sputnik V COVID-19 vaccine is a member of the so-called vector vaccines and uses two different vectors (Ad26 priming and Ad5 boost) to reduce the risk of a reduction in the effectiveness of the vaccination. Real life data indicate an efficacy of the vaccine above 97%. Low cost and no need for ultra-cold storage temperature temperatures are other pluses of the Sputnik V vaccine. However, there are also several important shortcomings that must be considered such as the possible reduction of its immunogenicity in the presence of very high Ad5 neutralizing antibody titres and the decrease with age of the antibody titres neutralizing the virus. Furthermore, there is emerging documentation that Sputnik V has a reduced neutralizing capacity against the Beta variant and all variants with the spike protein carrying the E484K substitution. Nevertheless, due to its characteristics, Sputnik V could be another useful means of satisfying the need for mass vaccination. However, it is imperative to document the efficacy and safety of the Sputnik V vaccine in individuals with high pre-existing anti-Ad26 and Ad5-neutralizing antibody titres and in those under the age of 18 or older than 60 years and be certain that Sputnik V does not cause the rare development of immune thrombotic thrombocytopenia. It is hoped that the now widespread use of this vaccine will generate a large pragmatic real-world study with data accessible to anyone interested in verifying them.

1. The Sputnik V COVID-19 vaccine

The Sputnik V COVID-19 vaccine or Gam-COVID-Vac has been developed by the Gamaleya National Center of Epidemiology and Microbiology in Russia. It is a two-part adenovirus (Ad) viral vector vaccine designed to trigger the production of antibodies against the spike protein (S) [1]. Ads serve as the delivery vehicle for the DNA instructions to produce the S of the SARS-CoV-2 virus in the body. They are engineered to be able to invade cells but not replicate. Sputnik V is made up of two different Ads, Ad26 and Ad5, both carriers of the gene for the SARS-CoV-2 glycoprotein S, which are given separately, three weeks apart. Ad26 is used in the first dose and Ad5 is used in the second to boost the vaccine's effect. The use of two different vectors is designed to reduce the chance of the body developing antibodies to Ad after the first dose, which could make the second dose ineffective [2]. The manufacturer's information states that only non-replicating Ad vectors of type E1 and E3, which are developed and produced on HEK293 cells, are used in Sputnik V vaccine production [3]. Deletion of the E1 gene prevents the virus from replicating, while deletion of the E3 gene prevents it from interacting with the immune system.

2. Phase 1–3 clinical trials

In two Phase 1/2, non-randomized, open-label studies, the Sputnik V COVID-19 vaccine induced strong humoral responses in all participants, with a 100% seroconversion and geometric mean anti-S IgG titres that were 10-fold higher than those reported in people who have recovered from COVID-19 [4]. Cell-mediated responses were detected in all participants at day 28, with activation of both $CD4^+$ and $CD8^+$ T cells and interferon-γ secretion in peripheral blood mononuclear cells. The safety profile was favourable, with no serious adverse events reported. However, only 38 subjects took part in each of the 2 studies.

An interim analysis of a Phase 3 trial in almost 20,000 subjects, 75% of whom received the vaccine, showed 91·6% efficacy against COVID-19 and reported that the Sputnik V COVID-19 vaccine was well tolerated [5]. In the vaccine group, 98% and 96% of the subjects seroconverted for virus S-specific IgG and for neutralizing antibodies, respectively, compared with 15% and 7% in the placebo group. Secretion of

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interferon-γ by peripheral blood mononuclear cells stimulated with the viral S protein occurred in 98% of the tested vaccinees and in 0% of the placebo recipients. SARS-CoV-2 infection was confirmed from day 21 after the first vaccine dose in 62 (1.3%) of 4,902 people in the placebo group and 16 (0.1%) of 14,964 participants in the vaccine group. The most common adverse events were flu-like illness, injection site reactions, headache, and asthenia. In a second interim analysis, data obtained 42 days after the first dose (corresponding to 21 days after the second dose) showed an efficacy of the vaccine above 95% [6]. Data from 3.8 million Russians who received both components of Sputnik V from 5 December last year to 31 March this year, as part of the mass-scale civil inoculation drive, showed a 97.6% efficacy and an infection rate of 0.027% starting from the 35th day after administration of the first dose [7].

3. Pros

These results are certainly important and place Sputnik V among the vaccines to be considered in the fight against the virus. It is reported to be 100% efficient against serious illness or death and, furthermore, it appears safe [5].

In a study conducted to verify adverse events following immunisation with this vaccine through active surveillance (i.e., solicited reporting) and to present the preliminary data on prevalence and characteristics of adverse events to the Sputnik V vaccine in the San Marino Republic population, local pain, asthenia, headache, and joint pain were the most frequent adverse symptoms [8]. Among those who had received two doses, 76.0% reported some adverse events after one of the two doses of vaccine, and 2.1% experienced serious reactions. In subjects aged 60–89 years, the incidence of adverse events was 70.0%, with 53.0% of subjects describing systemic reactions and 0.8% reporting serious symptoms.

Sputnik V has other two key advantages that make its use potentially popular. Its low cost and the fact that Gamaleya makes its technology available for free, so countries can produce their own supplies [9], are critical aspects that can make this vaccine extremely popular in low- and middle-income countries.

Additionally, Sputnik V is easier to deliver than the mRNA vaccines, which are composed of nucleoside-modified messenger RNA encoding a mutated form of the SARS-CoV-2 S that is encapsulated in lipid nanoparticles. Its lyophilized version only requires refrigeration (2–8 °C), whereas BNT162b2 or tozinameran, sold under the brand name Comirnaty, requires ultracold freezer storage between −80 and −60 °C [10], a need that was being portrayed by the media as a potential 'logistical nightmare' [11]. However, it must be pointed out that mRNA-1273 (Moderna COVID-19 vaccine or Spikevax), the other available mRNA vaccine, requires storage at the temperature of a standard medical refrigerator of 2–8 °C for up to thirty days or −20 °C for up to four months [11]. Furthermore, recently the Europe Medicines Agency (EMA) has recommended extending the storage time for Comirnaty at normal fridge temperatures to 31 days from five days, easing logistical challenges during rollouts in the region [12].

Nevertheless, Sputnik V could fully meet the need to provide equitable access to COVID-19 vaccines for people living in low- and middle-income countries due to the described clinical outcomes and benefits [13]. It has been suggested that cautious pragmatism should therefore be used to overcome concerns about the clinical development of this vaccine and the interpretation of some of the data produced in several clinical trials [14].

4. Cons

Obviously, besides the advantages that Sputnik V can offer, the limitations of this vaccine in view of its global use cannot be overlooked.

First, we must point out that studies on Sputnik V have been questioned due to major inconsistencies [15]. For example, in Phase 1/2 study participants in the test group were not only too few to generate solid information but also appeared to have identical values for several variables. Furthermore, several data patterns repeatedly appeared for the reported experiments [16]. The answer to this important criticism was that suspiciously similar antibody numbers among the participants were likely to have been coincidences because the sample size was too small [17]. In fact, according to the Russian research team behind Sputnik V, the measured titration results could only take discrete values, and since the values tended to plateau after three to four weeks, it was not unlikely that different subjects would show identical results for days 21–28.

There were criticisms also for the Phase 3 trial. They focused mainly on data discrepancies, numerical inconsistencies, and poor communication of the trial results. In addition, concerns were raised that the trial protocol was not made available to the public, which made it impossible to determine whether the primary outcome, the proportion of participants with PCR-confirmed COVID-19 from day 21 after receiving the first dose, was established before or during the trial. In any case, the fact that the data from which the conclusions of the clinical trial were drawn were not made available certainly made an independent assessment impossible [18]. The answer to these criticisms was that "the numerical inconsistencies were simple typing errors that were formally corrected" and, regardless of any dispute, the fact that the vaccine received registration in 51 countries confirms full transparency and compliance with regulatory requirements [19]. However, there was no comment on the absence of approval from the EMA, the U.S. Food and Drug Administration (FDA) or the World Health Organization (WHO).

Apart from these controversies over published trials, there are other issues that are equally or perhaps even more relevant. The majority (65–100% of Africans, 30–80% of Asians, 61% of Europeans, and 37–70% of Americans) of the human population exhibit high pre-existing anti-Ad5 antibodies titres from previous infections, with Ad5 with neutralizing antibodies titres >200 [20], and a substantial fraction (25.1–46.8%) with titres >1000 [21]. Some concerns have been raised about the use of Ad5-based vaccines in populations residing in low- and middle-income countries, especially in Africa and Asia where there is a high prevalence of HIV-1, and in any case a very high Ad seroprevalence [22]. The use of an Ad5 vector for immunisation against SARS-CoV-2 could increase the risk of HIV acquisition among men receiving the vaccine because Ad5 immune complexes activate the dendritic T-cell axis, which could increase HIV-1 replication in CD4 T-cells [23]. Furthermore, this high seroprevalence has the potential to suppress the immunogenicity of Ad5 vector-based vaccines [20]. Furthermore, absolutely not negligible is the trend in virus-neutralizing geometric mean antibody titres. They decline with age, suggesting that the Ad5 encoding the SARS-CoV-2 S vaccine may not offer effective protection in older adults (45–54 years and beyond) [24].

In the developing world, also baseline Ad26 immunity is common. However, baseline Ad26 neutralizing antibody titres remain low and do not appear to suppress Ad26-based vaccines [25]. In sub-Saharan Africa and Southeast Asia, only a minority of individuals (5.4–17.8%) demonstrate Ad26 neutralizing antibodies titres >200 [21]. This eventuality should not be understood as a limitation because Ad26 evades the prevalent Ad5 immunity and induces robust and protective antigen-specific cellular and humoral immune responses [25].

Nevertheless, the main concern is related to the fact that data from the Phase 3 study with Sputnik V, which codes the codon optimized S from the Wuhan Hu-1 isolate (SCoV2), refer to patients treated by November 2020, whereas in December 2020, an unexpected increase in COVID-19 cases attributable to the emergence of the novel SARS-CoV-2 variants B.1.1.7 in the United Kingdom and B.1.351 in South Africa, was reported [26]. The B.1.1.7 variant, now labelled Alpha variant, carries the N501Y mutation in the S receptor-binding domain (RBD) whereas the B.1.351 variant, labelled Beta variant, has three notable mutations in the S RBD, namely, K417 N, E484K, and N501Y [27]. N501Y enhances receptor binding domain/angiotensin-converting enzyme 2 (ACE2)

receptor binding affinity while also disrupting the binding of potent neutralizing antibodies [28] and is the major S determinant driving increased transmission of these variants [29]. However, the S RBD of the Alpha variant binds to ACE2 with 1.98-times greater affinity than the SCoV2 S RBD, whereas the S RBD of the Beta variant binds to ACE2 with 4.62-times greater affinity than the SCoV2 S RBD. The E484K mutation can help virus variants to escape neutralization by serum antibodies from recovered COVID-19 patients [30].

These two variants and P.1, another variant of concern evolved from lineage B.1.1.28, now labelled Gamma variant and circulating in December in Manaus, Brazil, rapidly gained prevalence and spread across borders from late 2020 onwards. Gamma variant has three changes in the S RBD (K417T, E484K, and N501Y) [30]. These three changes are almost identical to the changes in the Beta variant. However, the use of convalescent serum made it possible to ascertain that neutralization titres against the Beta variant were, on average, reduced 13.3-fold compared to those against Victoria, an early Wuhan-related isolate [31], while those against the Gamma variant were only reduced 3.1-fold, a reduction comparable to that against the Alpha variant (2.9-fold) [32]. Similarly, neutralization of Gamma variant by serum collected from individuals who had received Comirnaty or ChAdOx1 nCoV-19 (AZD1222 or Vaxzevria or Covishield in India) was less impacted than neutralization of Beta variant [32]. Vaxzevria is a non-replicating chimpanzee Ad-vectored vaccine to avoid the problem of pre-existing immune responses to the vector neutralizing the inoculum and expresses the full-length SARS-CoV-2 S protein gene. It has been suggested that Gamma variant is significantly less resistant to naturally acquired or vaccine induced antibody responses than Beta variant likely because changes outside the S RBD impact neutralization [32].

The recently designated variant of concern B.1.617.2, labelled Delta variant, and variant of interest B.1.617.1, labelled Kappa variant, have also been gaining attention in India [33]. Delta variant shows four key mutations in sequence encoding S protein: L452R, T478K, D614G, P681R. Also, Kappa variant has four S mutations of interest, L452R, E484Q, D614G, and P681R. E484Q mutation shares antibody-escape features like those of E484K mutation. The L452R mutation is within the S RBD, and thus may be relevant to transmissibility or immune escape [34]. The D614G mutation is the hallmark of all variants, as it promotes viral spread by increasing the number of open S protomers in the homo-trimeric receptor complex [35]. The L452R mutation increases protein stability, viral infectivity, and potentially promotes viral replication [36].

The impact of SARS-CoV-2 variants can be a pivotal modifying factor that can cause loss of neutralization capacity and, consequently, could alter the real clinical impact of Sputnik V vaccine against COVID-19. In this regard, we must highlight that it is believed that the higher the efficacy and level of neutralizing antibodies a vaccine has against the original virus, the more likely it is that it will work against new variants [12]. The available data indicate that Sputnik V induces a very wide effect on the peak level of neutralizing antibodies against SARS-CoV-2 [37].

A small, independent Argentinean study by Ikegame and colleagues has shed light on this fundamental aspect revealing the worrying possibility that the Beta variant, and to a lesser extent, any variant carrying the E484K substitution may escape the neutralizing antibody responses that this immunisation elicits [38,39]. The important information is that 8 out of 12 (67%) serum samples from a cohort of recipients of Sputnik V vaccine showed dose response curve slopes indicative of failure to neutralize Beta variant, but antibodies from people who had received both doses of Sputnik V were effective against the Alpha variant and D614G variant and showed only moderately reduced activity against S carrying the E484K substitution alone. When extrapolated to full serum strength, half of the sera samples failed to achieve an 80% inhibitory concentration (IC) and only 1 out 12 achieved a 90% IC. One serum had little to no detectable neutralizing activity against Beta variant, E484K and even wild type, but neutralized Alpha variant effectively. Ultimately, sera from Sputnik vaccine recipients had a median 6.1-fold and 2.8-fold reduction in neutralizing potency against Beta variant and all variants with the S protein carrying the E484K substitution, respectively, although resistance of the E484K mutant was competitive and was absent at higher serum concentrations.

Also, a Russian study showed that the neutralizing activity of sera from persons vaccinated with Sputnik V against the variants of concern was reduced [40]. For the Beta, Gamma and Delta variants, a statistically significant reduction in neutralizing activity of 3.1, 2.8-, and 2.5-fold, respectively, was observed. In commenting on this finding, the authors concluded that this decrease was lower than that reported in publications for other vaccines. However, they had to honestly admit that this conclusion was not robust due to the lack of direct comparative studies.

In another Argentinean study, 42 days after vaccination, 99.65% of individuals who received both doses within 4 months, had anti-S IgG, but 23.15% had no detectable neutralizing antibodies against SARS-CoV-2 strains [41]. Although the ability of neutralizing antibodies showed significantly higher levels of neutralization against wild type strain B.1 lineage than against the Gamma variant ($p < 0.001$), only a few samples were unable to neutralize this variant.

The Gamaleya Institute has announced that it is working on its own research into Sputnik V's effectiveness against virus mutations [42], but it has not released useful information yet.

5. Differentiation between Sputnik V and some other vaccines

It is necessary to point out that it is difficult to define the clinical significance of the efficacy of different vaccines, especially when comparing different randomized clinical trials (RCTs). In fact, the primary outcome was defined differently depending on the design of each study, so efficacy rates are not comparable, Actually, in Sputnik V trial it was defined as PCR-confirmed COVID-19 starting 21 days after the first dose [5], whereas in Comirnaty trials by the appearance of COVID-19 7 days after the second injection [43], and the primary efficacy analysis of the Vaxzevria trial included symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine [44].

SARS-CoV-2 variants question the efficacy of all commercialized vaccines that encode production of the S protein. Studies based on pseudoviruses and infectious cDNA clones with mutations in S have shown that the neutralizing activity of sera stimulated with different vaccines is decreased and the protective efficacy of some vaccines has also been found to decrease in clinical trials [45].

However, because potentially effective treatment options remain inadequate [46,47], vaccination is the only reliable strategy for preventing COVID-19 and its devastating consequences. Therefore, the WHO, in recommending vaccination against SARS-CoV-2 to mitigate the COVID-19 pandemic, has emphasized that equitable access to safe and effective vaccines is critical to this purpose [48].

A network meta-analysis of phase 3 trials [49] suggests that mRNA-based vaccines, such as Comirnaty and Spikevax, generally are better than Ad-based vaccines, although Sputnik V appears superior to Vaxzevria. However, the inherent weaknesses of the included trials, characterized by differences in study design and reporting of results and, most importantly, the failure to assess the impact of SARS-CoV-2 variants on the efficacy of different vaccines, which is a critical bias, were highlighted. Furthermore, RCTs are considered the "gold standard" for evaluating intervention effects, but they have notable limitations of sample size and subgroup analysis, restrictive inclusion criteria, and a highly controlled setting that may not be replicated in a mass vaccine rollout [50].

A very recent study whose aim was to better illustrate, from a medical point of view, the different efficacy parameters, and not to perform an indirect comparison of the different vaccines, used several validated methods of risk expression, in particular the absolute risk

reduction (ARR), which is the arithmetic difference between the risk in the treatment group and the risk in the control group, and the number needed to treat (NNT) calculated as the reciprocal of the ARR, both considered better from a clinical point of view [51]. ARR was 0.71%, 1.13%, 1.20%, 0.67%, and 1,20%, while NTT was 141, 91, 83, 149, and 83 for Comirnaty, Spikevax, Vaxzevria, Ad26.COV2·S (Janssen COVID-19 Vaccine), which is a recombinant, nonreplicable Ad26 vector that encodes a complete and stabilized SARS-CoV-2 S protein, and Sputnik V, respectively.

The apparent better efficacy of Sputnik V compared to Vaxzevria that emerged, albeit indirectly, from this study is confirmed at least for the Alpha variant in a recent literature review. According to the available data, the efficacy of Sputnik V is comparatively higher (91.6%) than that of Vaxzevria (70.42%) after inoculation of 2 doses as per respective protocol; both vaccines are effective in avoiding the Alpha variant, but in the case of the Beta variant, Sputnik V shows minimal efficacy and Vaxzevria appears even less effective [52]. However, it should be noted that a study that used data on all symptomatic sequenced cases of COVID-19 in England to estimate the proportion of cases with Delta and Alpha variants according to the patients' vaccination status, found that Comirnaty was 88.0% effective against symptomatic disease from the Delta variant two weeks after a second dose, compared to 93.7% effective against the Alpha strain, while Vaxzevria was 67.0% effective against the Delta variant, compared to 74.5% effective against the Alpha variant over the same period [53]. As already mentioned, the virus-neutralizing activity of sera obtained from people vaccinated with Sputnik V showed 2.5-fold reduction for Delta variant [40]. Although reductions in virus-neutralizing activity are not directly correlated to a vaccine's overall effectiveness at preventing infection, antibody evasion of Delta variant may contribute to the rapid spread of this variant.

These data are interesting, but do not allow a real differentiation between the various vaccines available, although they do suggest a greater efficacy against SARS-CoV-2 variants for the mRNA-based vaccines. Nonetheless, apart from the observation that the antibody response after vaccination differs enormously between individuals [54] irrespective of the vaccine used, which indicates that the exact functioning of the immunisation process of anti-SARS-CoV-2 sera is still unknown, the current opinion is that using a less effective vaccine now may be better than waiting for a more effective one to arrive later [55].

Vaccines offer a hope toward ending the global pandemic caused by SARS-CoV2. Consequently, the vaccination should be done at mass scale to eradicate the severe COVID-19 symptoms and to minimize the chances of infection. However, low- and medium-income nations face monumental challenges in procurement, allocation, distribution, and uptake of vaccines [56].

Due to the described characteristics, Sputnik V could be another useful means of satisfying the need for mass vaccination, mainly in developing countries not only because it costs less than competitor vaccines, a part Vaxzevria, but also, and mainly, because it fits well with the needs of nations in which lack of adequate transport, storage and distribution facilities is a challenge compromising delivery of vaccine (table).

By now, Sputnik V has been approved in 70 different countries, mainly lower-middle-income nations with a high unmet need when it comes to access to vaccines but also two EU members, and has also come to the aid of several low and middle-income countries through the COVID-19 Vaccines Global Access (COVAX) agreement [57]. COVAX is a global multilateral initiative to develop, manufacture and deploy COVID-19 vaccines on a fair and equitable basis.

However, as already mentioned, EMA, FDA, and WHO have not yet approved it. Gamaleya has not yet submitted the raw data after numerous requests to allay concerns of data manipulation, which makes it somewhat problematic to verify the strength of the evidence [58]. On August 4th, EMA indicates that the Russian vaccine is still in the process of "continuous review" [59].

What happened in Brazil regarding the approval of Sputnik V is

Table
Comparing Sputnik V with top COVID-19 vaccines (from [56], modified).

	Sputnik V	AZD1222 or Vaxzevria	Ad26.COV2.S or Janssen COVID-19 Vaccine	BNT162b2 or tozinameran or Comirnaty	mRNA-1273 or Moderna COVID-19 vaccine or Spikevax
Type of vaccine	Adenovirus vector (Ad26 priming and Ad5 boost)	Adenovirus vector (nonreplicating chimpanzee adenovirus)	Adenovirus vector (Ad26)	mRNA in lipid nanoparticles	mRNA (part of virus genetic code) in lipid nanoparticles
Efficacy	91.6%	62–90%	66.3%	95%	94.5%
Storage requirement	−18.5 °C (liquid form) 2–8 °C (dry form)	2–8 °C	2–8 °C	−70 °C ± 10 °C	−20 °C ± 5 °C
Number of shots	X2 (3 weeks apart)	X2 (8–12 weeks apart)	X1	X2 (3 weeks apart)	X2 (4 weeks apart)
Cost per dose	$10	$2.15 in the EU; $3–4 in the UK and U.S.; $5.25 in South Africa	$10	$19.50	$25-$37
Efficacy on variants	Unknown. Clinical trials were largely conducted in Russia prior to the emergence of major variants. Some data suggest reduced effect against the Beta and Gamma variants	Little effect against the Beta variant, but appears effective against Alpha and Gamma variants	Effective against the variants, although less so against Beta and Gamma variants	Lab data suggest "quite effective" against Alpha variant as well as Beta and Gamma variants	Lab data suggest "quite effective" against Alpha variant as well as Beta and Gamma variants

interesting. Initially, Brazil drug regulator rejected import and use of Sputnik V because a Brazilian study reported that the Ad5 vector is not inactivated and is capable of replication [60]. Sputnik V formed plaques on cultured lung epithelial cells (A549 cells) likely due to Ad5 infection. The presence of replicating viruses in Ad5 suggests that E1 has not been eliminated or it recombined during manufacturing with a full-length Ad genome in that allows Ad5 to be able to replicate, as suggested by Angela Rasmussen, a noted virologist who is associated with Georgetown Global Health Science & Security in Washington DC [61]. Later, the Brazilian authorities granted the authorisation with conditions [62]. The main conditions for the use of Sputnik include: 1) import only vaccines from factories inspected by Brazil drug regulator in Russia; 2) obligation of batch-to-batch analysis that proves the absence of replicating viruses and other quality characteristics; and 3) notification of serious adverse events within 24 h.

However, irrespective of the different views on the granting of approval, important information is still missing. Thus, we still do not know what the efficacy of this vaccine is in individuals with high (>200) pre-existing anti-Ad26 and Ad5-neutralizing antibody titers and what its actual efficacy and safety are in subjects younger than 18 or older than 60 years of age [20], although in the study conducted in the Republic of San Marino, Sputnik showed a high short-term tolerability profile in the population aged ≥60 years [8].

In addition, we ignore whether vaccination with Sputnik V may cause the rare development of immune thrombocytopenia that has been observed with other so-called vector vaccines such as Vaxzevria, and Janssen COVID-19 Vaccine [63,64]. These events might resemble heparin-induced thrombocytopenia, but antibodies from patients with vaccine-induced thrombocytopenia and thrombosis do not cross-react with the S protein [65]. An interim analysis of the Phase 3 trial on patients who received the Sputnik V vaccine showed 1 patient who developed deep vein thrombosis, 1 incidence of cerebral circulatory failure, 1 patient with transient ischemic attack, and 1 patient with vascular encephalopathy [5]. Furthermore, a study that explored the safety of this vaccine in a cohort of health professionals did not report thromboembolism or thrombocytopenia vasculitis [66]. Argentina has not reported any clotting events, despite receiving more than four million doses of the vaccine, and Serbia, which has also been using Sputnik V widely, has so far reported no cases of the blood-clotting condition described with other Ad vaccines [57]. These observations are quite reassuring, but as with all other vaccines, continued surveillance of the neutralizing activity induced by the Sputnik V vaccine sera will be necessary.

6. Sputnik Light

Interestingly, it has been reported that a one-shot Sputnik Light version that consists of only the first component (Ad26) of Sputnik V and has been designed as a temporary solution for those countries with high levels of infection that need to rapidly vaccinate their population, could be soon approved [67]. Sputnik Light had a good safety profile and induced strong humoral and cellular immune responses both in sero-negative and seropositive participants in an open, non-randomized, 1/2 Phase study [68]. It has been reported that it demonstrated 79.4% efficacy 28 days after its administration based on the analysis of data that referred to citizens of the Russian Federation who participated in the mass vaccination program during the period December 5, 2020–April 15, 2021 [69]. However, this figure is unreliable because the Sputnik Light study was observational and people who received the single dose were not compared to a control group [70]. Additionally, a standard peer review process has not yet confirmed this information. In any case, a recent study in a cohort of 288 volunteers has shown that a single Sputnik V dose elicits higher antibody levels and virus neutralizing capacity in previously infected individuals than in naïve ones receiving the full two-dose schedule [71]. This finding suggests the use of Sputnik Light in those subjects who have already been infected with SARS-CoV-2, although it should be noted that an efficacy study has not been carried out yet.

It is possible, however, that Sputnik Light version was designed to overcome the problems of the second dose of Sputnik, which is more volatile and difficult to produce than the first dose. This suspicion is supported by the recent report from the Russian Direct Investment Fund of positive preliminary safety data from a study assessing Vaxzevria in combination with Sputnik Light in the Republic of Azerbaijan [72]. Sputnik Light will also be used as a third (booster) dose for those who received Sputnik V at least 6 months earlier [73].

7. Conclusion

There has been substantial controversy surrounding the Sputnik V vaccine. It is hoped that the now widespread use of this vaccine will generate a large pragmatic real-world study with data accessible to anyone interested in verifying them. Furthermore, several other studies are currently under way in countries that have approved Sputnik, including in Argentina, Venezuela, Russia, and Turkey, which should help to build a more accurate picture of the vaccine's safety and efficacy [57]. Only then any remaining doubts about its effectiveness will be erased.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence what is reported in this paper.

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