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Research Paper

ROCCA observational study: Early results on safety of Sputnik V vaccine (Gam-COVID-Vac) in the Republic of San Marino using active surveillance

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ABSTRACT

Background: In August 2020, Sputnik V was registered as Gam-COVID-Vac by the Russian Ministry of Health, and since December 2020 it has been distributed in 61 countries worldwide. On 25 February 2021, the Republic of San Marino started its vaccination campaign, which includes Sputnik V. Our aim was to describe the adverse events following immunization (AEFIs) with this vaccine through participant-based active surveillance in the country.

Methods: Beginning from 4 March to 8 April 2021, a nationwide study was conducted on San Marino's population aged 18–89 years who received one or two doses of Sputnik V. E-questionnaire dissemination occurred through e-mails, QR-codes or live/phone interviews ~7 days after the first and second vaccine dose. A descriptive analysis was conducted to quantify AEFI incidence on both occasions, stratifying results by type and severity of symptoms.

Findings: Mean age of the 2558 vaccine recipients was 66 ± 14 years. First-dose AEFI incidence was 53.3% (systemic reactions at 42.2%), while second-dose AEFI incidence was 66.8% (systemic reactions at 50.4%) ($n = 1288$). In general, 76.0% of two-dose recipients reported some AEFIs after either vaccine dose, and 2.1% suffered severe reactions; in 60- to 89-year-olds ($n = 1021$), AEFI incidence was 70.0%, with 53.0% of subjects describing systemic reactions and 0.8% reporting severe symptoms. The most frequent symptoms were local pain, asthenia, headache and joint pain.

Interpretation: Our results, albeit preliminary, suggest that Sputnik V has a high tolerability profile in the population aged ≥ 60 years in terms of short-term AEFIs.

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1. Introduction

One year after the onset of the COVID-19 pandemic, deaths approach 3 million worldwide [1]. The Republic of San Marino was among the first countries to be struck by the still ongoing COVID-19 pandemic, and also one of the countries with the highest death toll if compared with its population [2]. Faced with the dire consequences of the pandemic, this country decided to employ all the available resources in order to reach the population coverage needed to grant herd immunity. The Sputnik V vaccine was included in its vaccination campaign [3].

Research in context

Evidence before this study

In December 2020 mass distribution of the recently developed Gam-COVID-Vac vaccine started, with the vaccine currently being distributed in 61 countries.

Phase 1, 2 and 3 trials showed a high efficacy and safety profile, though these data need post-marketing confirmation through dedicated studies.

Added value of this study

The majority of AEFIs reported in our study were mild and moderate. The results of our study, carried out in a real-world context, in terms of overall safety align with the findings of phase 3 of the Gam-COVID-Vac trial.

The preliminary analysis of the Gam-COVID-Vac vaccine safety suggests a higher or equal tolerability profile - especially in the 60+ age group - as compared with other widely adopted COVID-19 vaccines.

Implications of all the available evidence

These real-world results might contribute to the full acceptance of COVID-19 vaccines in the San Marino Republic, helping reaching herd immunity; besides they provide data that can be used by other countries to consider this vaccine amongst the other options for their immunization campaigns.

relating to the detection, assessment, understanding and communication of AEFIs and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation [10].

The aim of the ROCCA¹ study is to conduct an active vaccine surveillance programme (i.e., solicited reporting) and to present the preliminary data on prevalence and characteristics of AEFIs to the Sputnik V vaccine among the population of the Republic of San Marino. We intend to compare our results with already existing data for phase 3 trial and other currently used anti-COVID vaccines. Besides, we intend to address and analyse specifically the differences between the first and the second dose.

2. Methods

2.1. Study design and participants

This is a nationwide active pharmacovigilance study to assess safety of Sputnik V COVID-19 vaccine in the Republic of San Marino. The vaccination process includes one dose of rAd26-S (0.5 ml) administered intramuscularly on day 0 and one dose of rAd5-S (0.5 ml) administered intramuscularly on day 21. Both vaccination hubs set up for the campaign by the Social Security Institute (SSI) are involved in participants recruitment. All the people vaccinated with Sputnik V are actively recruited by physicians immediately after the administration of the vaccine. Eligibility criteria have been defined as: age ≥ 18 years, having had at least one dose of COVID-19 vaccine administered, being covered by the SSI health insurance. Exclusion criteria have been defined as: not being able to understand or answer the questionnaires properly. No randomisation or special selection was carried out. All participants provided informed consent to being included in the database for study participation.

The study protocol has been reviewed and approved by the Ethics Committee for Research and Experimentation of the Republic of San Marino with the approval number 30/CERS/2021 of 17th of March 2021. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.

2.2. Outcomes

The primary outcome measure has been defined as safety of the Sputnik V (Gam-COVID-Vac) COVID-19 vaccine, measured as the number of participants reporting AEFIs, in the first week after the first dose, in the first week after the second dose, and - in the long term - within 3 months after the first dose. This enables the collection of patient-reported safety data in near real time and long term, and generates incident rate of AEFIs. Additionally, we aim at evaluating any quantitative or qualitative differences in occurrence of AEFIs between the first and second dose.

2.3. Procedure and questionnaire

The standardized e-questionnaires are administered actively to the participants to collect information about potential AEFIs following vaccine injection. The questionnaires have been generated using Google Forms, and can be filled in autonomously or with the help of a member of the research team.

Vaccine recipients are asked to fill in the questionnaires at fixed time intervals, namely: 1 week (Q1), 1 month (Q2), 3 months after the first vaccine dose (Q3) (Figure S1). Q1 investigates demographic information (*patient code; age; weight; height; gender; profession*), anamnestic data (*pregnancy; diseases; therapy; recent vaccinations; allergies; previous COVID-19*), date of the first injection, vaccine brand,

¹ ROCCA: RSM Observatory for COVID vaccination Campaign monitoring Adverse events

The Sputnik V vaccine, one of the first to be registered among COVID-19 vaccines, is a heterologous recombinant adenovirus vaccine with two different types of adenovirus vectors, rAd26 and rAd5, for the first and second dose respectively, developed by the Gamaleya National Centre of Epidemiology and Microbiology in Moscow [4]. It was registered in August 2020 by the Russian Ministry of Health as Gam-COVID-Vac [5], and starting from December 2020 mass distribution in several countries took place including Argentina, Belarus, Hungary, Serbia and the United Arab Emirates. The list of countries where Sputnik V has been registered has since then expanded, reaching the current number of 61, including Russia [6].

On 23 February 2021, the Republic of San Marino received its first supply of Sputnik V, launching the national vaccination campaign on the 25th of the same month [7], starting from health professionals and the most vulnerable citizens. At 55 days from the beginning, 46.1% ($n = 15,621$) of the population has been vaccinated with the first dose [8] with the goal of a rapid vaccination campaign for the entire population.

In the process of planning a national vaccination campaign, the acquisition of solid evidence on vaccine efficacy and safety is of the utmost importance. The only available phase 3 trial on Sputnik V showed a 91.6% (95% CI 85.6–95.2) efficacy with no significant differences assessed in the age strata, and 100% (95% CI 94.4–100.0) efficacy against moderate or severe COVID-19. The most common adverse events following immunisation (AEFIs) reported were flu-like illness, injection-site reactions, headache, and asthenia; most of these (94%) were grade 1, 5.7% were grade 2, and 0.4% were grade 3. None of the serious AEFIs were considered to be associated with vaccination [9].

Evidence deriving from clinical trials preceding approval of vaccines is essential but not sufficient. In fact, it needs to be complemented in a real-world setting by an immediate and continuous stream of information gathered alongside the campaign progression. Vaccine pharmacovigilance (i.e., post-marketing safety monitoring of vaccines) fills this gap, being defined as the science and activities

the potential AEFIs occurring in the week after the first dose, and the severity/impact of the symptoms (including need for medical assistance and hospitalization). Q1 includes 7 sections for a total of 25 questions with closed mandatory answers, while Q2 and Q3 contain 2 sections for a total of 6 questions. In order to link the questionnaires one to another, the patient code is asked also in Q2 and in Q3. Q2 investigates the potential AEFIs occurring in the week after the second dose. Q3 investigates further potential AEFIs occurring in the long-term period after the vaccination and it will be administered starting from June 2021. Answers to questions concerning relevant variables were made mandatory in order to complete the questionnaire to minimize missing data.

The list of AEFIs and most of the questions were adapted from vaccine surveillance studies conducted by the European Medicines Agency. The events indicated are in line with the typical vaccine AEFIs already identified by the relevant Regulatory Agencies, as well as for the latency of possible occurrence. The clinical features of any AEFIs, their frequency and intensity were specified on the questionnaires using the CTCAE scale (Common Terminology Criteria for Adverse Events) version 5.0. Specifically, grade 1 includes asymptomatic or mild symptoms and without indication for intervention; grade 2 covers moderate symptoms; grade 3 indicates severe or medically significant symptoms and grade 4 includes symptoms with indication of urgent intervention. Grade 5 (death) was not directly investigated in the questionnaire. However, a cross-check with the State Hospital's access records was performed.

An informed consent form was attached to the e-questionnaire, and each participant consented to participate in the survey after reading the information sheet. Sensitive information collected is hence stored anonymously in order to guarantee participants privacy.

2.4. Data collection

Time frame for data collection lasts from 4 March 2021 to the end of the national vaccination campaign. The collection timeframe for data included in this analysis was from 4 March to 8 April 2021. Data collection is carried out through the administration of a questionnaire with three different approaches: face-to-face interviews at vaccination sites, telephone interviews, and online access to the questionnaire which can be accessed either by QR-code scanning or through a link sent via e-mail.

2.5. Medical history assessment

The modest population size of the Republic of San Marino allows for all study participants to be connected via their SSI personal code to their clinical records, which enables consultation of anamnestic data and drug use, as well as the verification of the accesses to the national health service following the vaccination.

2.6. Statistical analysis

Numerical variables were summarised as mean \pm standard deviation and/or as median [interquartile range (IQR)], where appropriate; categorical variables were summarised as frequencies and percentages. Frequency distributions were depicted with the aid of bar charts and frequency polygons.

In this early analysis, having recruited a total of 1946 individuals aged 60–89 years from a population of 8799 (source: <https://www.statistica.sm>), our sample size was sufficient to estimate a proportion of adverse events equal to $1\% \pm 0.4\%$ up to $50\% \pm 2\%$ with a confidence level of 95%. Although this precision and sample-size analysis was based on the Wald method for the binomial distribution, in practice we estimated our confidence intervals (CIs) using the Wilson score

method, which has been shown to be more accurate and robust in most situations [11].

In a secondary, exploratory analysis, McNemar's test was used to evaluate differences in the occurrence of adverse reactions after the first and the second dose of the vaccine; this analysis was restricted to those who filled both the Q1 and Q2. Moreover, we calculated the conditional distributions of second-dose AEFIs according to the presence/absence of first-dose AEFIs; differences between groups were assessed using the two-sample test of proportions for large samples (i.e., asymptotically normal).

All analyses were carried out using Stata software, version 15 (StataCorp, 2017, *Stata Statistical Software: Release 15*, College Station, Texas, USA: StataCorp LP). The significance level was set at 5%.

2.7. Role of funding sources

The authors did not receive any external financial support or funding while carrying out this research.

3. Results

3.1. Population characteristics

We recruited 2558 participants who received Sputnik V (Gam-COVID-Vac) between 25 February and 8 April 2021: 55.7% ($n = 1424$) were female. In the same period of time about half of the study participants (50.4%, $n = 1288$) received both vaccine doses. Mean age was 66 ± 14 years, median age was 68 years [IQR: 60–76], and the most represented age group was 60–69 years (45.4%, $n = 576$) (Table 1, Fig. 1).

Of the 2558 participants, 75.1% ($n = 1920$) had at least one underlying medical condition. Hypertension was the most frequent coexisting condition (46.4%, $n = 1188$), followed by cardiovascular diseases (32.1%, $n = 822$) and obesity (body mass index ≥ 30) (19.4%, $n = 496$). A previous infection with SARS-CoV-2 was reported in 3.6% ($n = 93$) of the participants. Participants suffering from at least one allergy were 24.5% ($n = 627$), most frequently to drugs (12.0%, $n = 307$) (Table 2).

3.2. First-dose AEFIs

Overall, the incidence of AEFIs after the first dose was 53.3%. Vaccine recipients described both local and systemic reactions in 16.4% of cases; besides, 25.8% reported systemic reactions and 10.2% reported local symptoms only. The most frequent local reactions were pain (24.8%), nodules (3.7%), warmth (2.2%) and swelling (1.9%). The most frequent systemic reported symptoms were asthenia (23.8%), headache (18.5%), joint pain (16.5%), chills (16.5%), muscle pain (16%), fever (11.9%) and malaise (11.8%) (Figs. 2 and 3). See Table S1 for other AEFIs that were not included in the list provided but were spontaneously reported by recipients.

Most symptoms appeared within 24–48 h after the injection (85.7%), and less frequently after a few minutes (4.5%), 3–5 days (4.2%) and 6–7 days (1.4%); 4.3% of the patients who suffered from AEFIs did not provide information about the timing of onset of symptoms.

The incidence of AEFIs in the 60–89 age group was 43.7% (95% CI 41.5–45.9); 10.1% of individuals reported local symptoms (95% CI 8.9–11.5), 24.7% reported systemic symptoms (95% CI 22.8–26.6), and 8.0% reported both local and systemic symptoms (95% CI 6.9–9.3). Overall, we found that the incidence of participants reporting no AEFIs progressively increased from 10.4% in the 18–39 age group to 63.2% in the 80–89 age group (Fig. 2).

AEFIs were treated with drugs by 29.2% of the patients (4.1% of missing values). Eighty-eight (3.4%) reported that they had taken

Table 1

Sociodemographic characteristics of the study sample, overall and by age group - Republic of San Marino (2021). Values are counts (percentages) or mean \pm standard deviation.

Characteristic	All (n = 2558)	Age group					
		18–39 y (n = 183)	40–49 y (n = 177)	50–59 y (n = 252)	60–69 y (n = 786)	70–79 y (n = 799)	80–89 y (n = 361)
Female	1424 (55.7)	103 (56.3)	111 (62.7)	176 (69.8)	427 (54.3)	427 (53.4)	180 (49.9)
Age, y	65.6 \pm 14.3	30.4 \pm 5.4	44.5 \pm 2.9	54.7 \pm 2.8	65.2 \pm 2.7	74.8 \pm 2.9	82.1 \pm 1.6
BMI, kg/m ²	26.5 \pm 4.8	23.8 \pm 4.6	25.4 \pm 5.5	25.9 \pm 5.8	27.1 \pm 4.6	26.9 \pm 4.5	26.8 \pm 3.8
BMI category, kg/m ²							
<18.5	41 (1.6)	12 (6.6)	3 (1.7)	3 (1.2)	2 (0.3)	15 (1.9)	6 (1.7)
18.5–<25	997 (39.0)	112 (61.2)	96 (54.2)	133 (52.8)	272 (34.6)	276 (34.5)	108 (29.9)
25–<30	1017 (39.8)	43 (23.5)	55 (31.1)	73 (29.0)	334 (42.5)	335 (41.9)	177 (49.0)
30–<35	374 (14.6)	11 (6.0)	10 (5.6)	28 (11.1)	133 (16.9)	134 (16.8)	58 (16.1)
35–<40	89 (3.5)	3 (1.6)	7 (4.0)	6 (2.4)	37 (4.7)	28 (3.5)	8 (2.2)
\geq 40	33 (1.3)	2 (1.1)	5 (2.8)	8 (3.2)	8 (1.0)	9 (1.1)	1 (0.3)
Unspecified	7 (0.3)	0 (0.0)	1 (0.6)	1 (0.4)	0 (0.0)	2 (0.3)	3 (0.8)
Healthcare worker	289 (11.3)	79 (43.2)	72 (40.7)	98 (38.9)	39 (5.0)	1 (0.1)	0 (0.0)
Non-physician profession*	157 (6.1)	51 (27.9)	39 (22.0)	53 (21.0)	14 (1.8)	0 (0.0)	0 (0.0)
Clerk	98 (3.8)	22 (12.0)	28 (15.8)	34 (13.5)	14 (1.8)	0 (0.0)	0 (0.0)
Physician	23 (0.9)	3 (1.6)	3 (1.7)	6 (2.4)	10 (1.3)	1 (0.1)	0 (0.0)
Pharmacist	7 (0.3)	2 (1.1)	2 (1.1)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Volunteer	4 (0.2)	1 (0.5)	0 (0.0)	2 (0.8)	1 (0.1)	0 (0.0)	0 (0.0)

* Nurse, midwife, physical therapist, podiatrist, speech-language pathologist, orthoptist, audiologist, dental hygienist, dietician, etc.
BMI, body mass index.

painkillers and/or anti-inflammatory drugs the day of the vaccination, before receiving it (Table 2).

3.3. Second-dose AEFIs

About half (50.4%, $n = 1288$) of the study participants who answered the Q1 questionnaire filled in the Q2 after the second dose of the vaccine (Table 3). Overall, the incidence of AEFIs was 66.8%; both local and systemic reactions were reported in 31.9% of cases; besides, 18.5% reported systemic reactions, and 16.1% reported local symptoms only. Amongst local reactions, the most reported ones were pain (43.8%), nodules (9.9%), swelling (6.4%) and warmth (5.6%) in the injection site. Frequently reported systemic symptoms were asthenia (31.9%), joint pain (21.9%), muscle pain (21.4%), headache (21.0%), chills (18.1%), malaise (17.8%) and fever (15.5%) (Figs. 3 and 4). See Table S2 for other AEFIs that were not included in the list provided but were spontaneously reported by recipients.

Most symptoms appeared within 24–48 h after the injection (87.2%), and less frequently after a few minutes (4.3%), 3–5 days (3.4%) and 6–7 days (0.6%); 4.5% of the patients who suffered from

AEFIs did not provide information about the timing of onset of symptoms.

The incidence of AEFIs in the 60–89 age group was 60.0% (95% CI 57.0–63.0); 16.9% of individuals reported local symptoms (95% CI 14.8–19.4), 19.4% reported systemic symptoms (95% CI 17.1–21.9), and 23.4% reported both local and systemic symptoms (95% CI 20.9–26.1). The incidence of participants reporting no AEFIs progressively increased from 3.9% in the 18–39 age group to 46.3% in the 80–89 age group (Fig. 4).

AEFIs were treated with drugs by 27.3% of the patients. Forty-four (3.4%) reported that they had taken painkillers and/or anti-inflammatory drugs before receiving the second dose of the vaccine.

In Fig. 5, differences between the two doses of Sputnik V in the post-injection incidence of AEFIs are shown. In particular, data for subjects ≥ 60 years of age were statistically significant ($p < 0.001$). The highest incidence (81.8%) of AEFIs after the second dose having reported AEFIs after the first dose occurred in the age group 60–69, while for those not having reported any AEFIs after the first dose we found a 58.0% incidence after the second dose in the same age group.

3.4. AEFI grading

After the first dose of the vaccine, participants reporting at most grade 1 symptoms were 43.5% ($n = 1112$), at most grade 2 were 8.7% ($n = 223$), at most grade 3 were 0.8% ($n = 20$), and at most grade 4 were 0.3% ($n = 8$). Grade 4 was self-reported in 0.1% of the recipients respectively for chills, headache, and local symptoms. After the second dose of the vaccine, participants reporting at most grade 1 symptoms were 53.8% ($n = 693$), at most grade 2 were 11.3% ($n = 146$), at most grade 3 were 1.3% ($n = 17$), and at most grade 4 0.3% were ($n = 4$). Symptoms self-reported as grade 4 were asthenia (0.2%), headache (0.2%), joint pain (0.2%), chills (0.1%), muscle pain (0.1%), and local symptoms (0.1%) (Table S3, S4).

After cross-checking with the State Hospital's access records, no grade 5 (death) was reported. among the vaccine recipients who self-reported grade 4 symptoms, 10 were actually admitted to the Emergency Department. One of them, with a medical history of multiple allergies, experienced laryngospasm, chest rash, severe headache, and severe joint pain that required urgent drug treatment and medical observation. Another patient experienced syncope, having had similar episodes in the past. Finally, 8 patients were admitted to the emergency department complaining of various symptoms (e.g.,

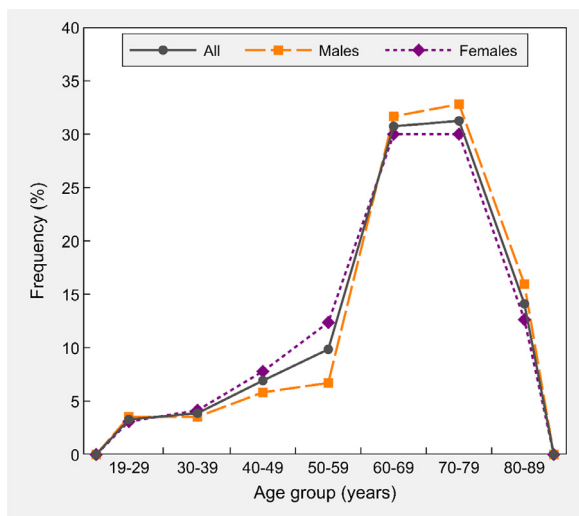


Fig. 1. Percentage age distribution of the study sample ($n = 2558$), overall and by sex - Republic of San Marino (2021).

Table 2
Baseline clinical characteristics of the study sample, overall and by age group - Republic of San Marino (2021). Values are counts (percentages).

Characteristic	All(n = 2558)	Age group					
		19–39 y (n = 183)	40–49 y (n = 177)	50–59 y (n = 252)	60–69 y (n = 786)	70–79 y (n = 799)	80–89 y (n = 361)
Underlying medical conditions	1920 (75.1)	44 (24.0)	50 (28.2)	147 (58.3)	591 (75.2)	736 (92.1)	352 (97.5)
Hypertension	1188 (46.4)	3 (1.6)	13 (7.3)	58 (23.0)	347 (44.1)	507 (63.5)	260 (72.0)
Cardiovascular diseases	822 (32.1)	2 (1.1)	5 (2.8)	34 (13.5)	221 (28.1)	345 (43.2)	215 (59.6)
Osteoarticular diseases	388 (15.2)	1 (0.5)	3 (1.7)	11 (4.4)	65 (8.3)	185 (23.2)	123 (34.1)
Diabetes mellitus	297 (11.6)	6 (3.3)	5 (2.8)	16 (6.3)	79 (10.1)	126 (15.8)	65 (18.0)
Mental disorders	181 (7.1)	2 (1.1)	5 (2.8)	14 (5.6)	34 (4.3)	79 (9.9)	47 (13.0)
Respiratory diseases	171 (6.7)	9 (4.9)	3 (1.7)	12 (4.8)	30 (3.8)	73 (9.1)	44 (12.2)
Neurological diseases	159 (6.2)	8 (4.4)	7 (4.0)	11 (4.4)	29 (3.7)	57 (7.1)	47 (13.0)
Malignant tumours	132 (5.2)	0 (0.0)	1 (0.6)	11 (4.4)	24 (3.1)	57 (7.1)	39 (10.8)
Nephropathy	77 (3.0)	0 (0.0)	0 (0.0)	5 (2.0)	8 (1.0)	27 (3.4)	37 (10.2)
Immunosuppression	65 (2.5)	3 (1.6)	2 (1.1)	4 (1.6)	26 (3.3)	22 (2.8)	8 (2.2)
Liver diseases	52 (2.0)	1 (0.5)	1 (0.6)	3 (1.2)	9 (1.1)	25 (3.1)	13 (3.6)
Other*	779 (30.5)	23 (12.6)	20 (11.3)	63 (25.0)	203 (25.8)	315 (39.4)	155 (42.9)
Allergies	627 (24.5)	64 (35.0)	59 (33.3)	90 (35.7)	167 (21.2)	180 (22.5)	67 (18.6)
Drugs	307 (12.0)	15 (8.2)	19 (10.7)	34 (13.5)	95 (12.1)	106 (13.3)	38 (10.5)
Rhinitis	209 (8.2)	47 (25.7)	30 (16.9)	39 (15.5)	40 (5.1)	39 (4.9)	14 (3.9)
Contact dermatitis	85 (3.3)	7 (3.8)	12 (6.8)	12 (4.8)	28 (3.6)	18 (2.3)	8 (2.2)
Food	59 (2.3)	6 (3.3)	8 (4.5)	7 (2.8)	16 (2.0)	14 (1.8)	8 (2.2)
Asthma	52 (2.0)	13 (7.1)	7 (4.0)	8 (3.2)	12 (1.5)	9 (1.1)	3 (0.8)
Insect sting	27 (1.1)	1 (0.5)	4 (2.3)	4 (1.6)	9 (1.1)	5 (0.6)	4 (1.1)
Other	16 (0.6)	2 (1.1)	3 (1.7)	4 (1.6)	2 (0.3)	4 (0.5)	1 (0.3)
Ongoing drug therapies	1847 (72.2)	50 (27.3)	46 (26.0)	134 (53.2)	569 (72.4)	710 (88.9)	338 (93.6)
Other vaccines in the two weeks before	5 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	4 (1.1)
Painkillers/anti-inflammatory drugs before vaccination	88 (3.4)	8 (4.4)	4 (2.3)	6 (2.4)	17 (2.2)	25 (3.1)	28 (7.8)
Previous infection with SARS-CoV-2							
No	2465 (96.4)	166 (90.7)	165 (93.2)	231 (91.7)	761 (96.8)	785 (98.2)	357 (98.9)
Asymptomatic	14 (0.5)	3 (1.6)	2 (1.1)	2 (0.8)	5 (0.6)	2 (0.3)	0 (0.0)
Mild symptoms	46 (1.8)	11 (6.0)	7 (4.0)	7 (2.8)	10 (1.3)	7 (0.9)	4 (1.1)
Moderate/severe symptoms	22 (0.9)	2 (1.1)	2 (1.1)	12 (4.8)	4 (0.5)	2 (0.3)	0 (0.0)
Severe symptoms with hospitalisation	11 (0.4)	1 (0.5)	1 (0.6)	0 (0.0)	6 (0.8)	3 (0.4)	0 (0.0)

* Thyroid disorders, prostate disorders, gastroesophageal reflux disease, glaucoma. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

upper extremity paraesthesia, dry mouth, intercostal pain) but with stable vitals. They were treated with anxiolytics and referred home. No patients were hospitalized.

Amongst ≥60-year-old recipients, after the first dose 1.3% (n = 17) reported at most grade 3 AEFIs and 0.3% (n = 4) at most grade 4 AEFIs; for what concerns the second dose, the severity of AEFIs was reported by 0.4% (n = 4) and by 0.3% (n = 3) for at most grade 3 and 4 respectively (Table S3, S4).

3.5. First-and-second-dose AEFIs

In general, 979 out of 1288 participants (76.0%) reported some AEFIs after either vaccine dose; 14.7% reported only local

symptoms, 19.8% only systemic symptoms, and 40.8% both local and systemic symptoms (the remaining 0.7% did not specify whether systemic or local). Twenty-seven out of 1288 subjects (2.1%) declared that they had suffered from symptoms of grade 3–4.

In the 60–89 age group (n = 1021), the overall incidence of AEFIs was 70.0% (95% CI 67.1–72.8); 16.3% (95% CI 14.1–18.6) reported only local symptoms, 21.6% (95% CI 19.2–24.3) only systemic symptoms, and 31.4% (95% CI 28.7–34.4) both local and systemic symptoms (unspecified symptoms were 0.7%). Eight out of 1021 subjects (0.8%, 95% CI 0.4–1.5) declared that they had suffered from symptoms of grade 3–4.

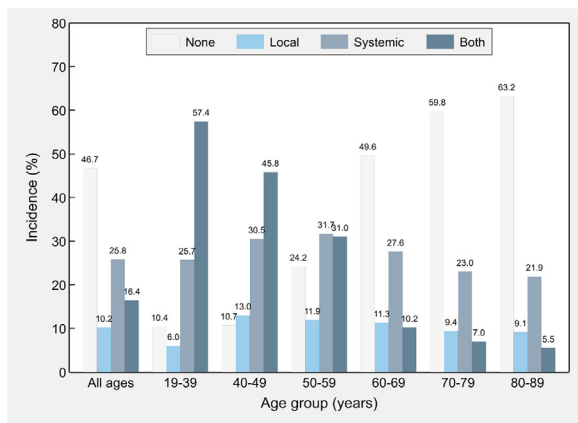


Fig. 2. Incidence of local and systemic adverse events following immunisation with the first shot of Sputnik V (n = 2558), overall and by age group - Republic of San Marino (2021).

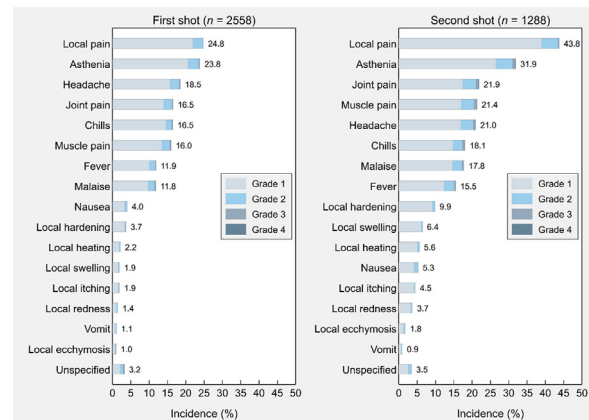


Fig. 3. Incidence of specific adverse events, both local and systemic, following immunisation with the first shot and second shot of Sputnik V - Republic of San Marino (2021).

Table 3

Sociodemographic and clinical characteristics of the individuals who received one dose versus two doses of Sputnik V - Republic of San Marino (2021). Values are counts (percentages) or mean \pm standard deviation.

Characteristic	Only first vaccine dose (n = 1270)	First and second vaccine dose (n = 1288)
Female	720 (56.7)	704 (54.7)
Age, y	62.5 \pm 13.4	68.7 \pm 14.5
Age group, y		
19–39	106 (8.3)	77 (6.0)
40–49	100 (7.9)	77 (6.0)
50–59	139 (10.9)	113 (8.8)
60–69	576 (45.4)	210 (16.3)
70–79	260 (20.5)	539 (41.8)
80–89	89 (7.0)	272 (21.1)
Underlying medical conditions	876 (69.0)	1044 (81.1)
Allergies	318 (25.0)	309 (24.0)
Ongoing drug therapies	853 (67.2)	994 (77.2)
Infection with SARS-CoV-2 before first vaccination	52 (4.1)	41 (3.2)

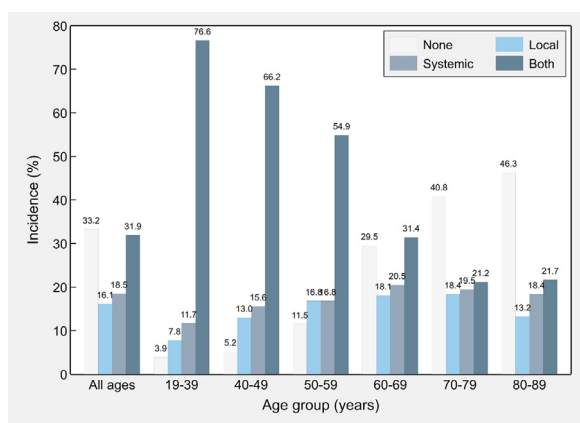


Fig. 4. Incidence of local and systemic adverse events following immunisation with the second shot of Sputnik V ($n = 1288$), overall and by age group - Republic of San Marino (2021).

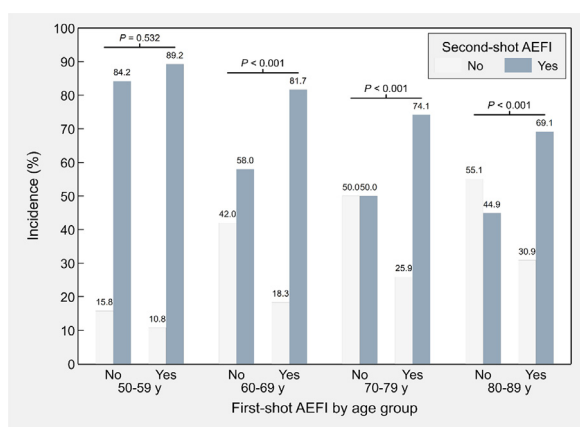


Fig. 5. Incidence of specific adverse events, either local or systemic, following immunisation (AEFI) with the second shot of Sputnik V according to the presence or absence of (AEFI) after the first shot, by age group - Republic of San Marino (2021).

4. Discussion

The ongoing ROCCA study on Sputnik V (Gam-COVID-Vac) is the first observational study conducted to assess the safety of this vaccine, and represents an opportunity to highlight potential AEFIs in a

real-world context of active surveillance, thus mirroring actual incidence.

This preliminary analysis suggests a higher or equal tolerability profile of the Sputnik V vaccine in the 60+ age group, after both doses, as compared with other widely adopted COVID-19 vaccines [12–14]. Our results also align with the findings of phase 1 and 2 previously conducted studies [15], then confirmed by phase 3 of the vaccine trial [9], in terms of overall safety and tolerability. No hospitalizations or deaths were reported. Nearly all reported AEFIs were mild or moderate and/or lasted less than 2 days, and in more than two thirds of cases no need for any medication was reported. The incidence of participants who reported no AEFIs grew consistently along with the progression of age groups, after both doses. The vast majority of AEFIs appeared within 2 days of the inoculation. This applies both to the first and second dose of the vaccine. Local pain was the most recurrent AEFIs both after the first and second dose, followed by asthenia, and headache for the first dose, vs. joint pain for the second dose. In particular, the rate of local symptoms is substantially lower than the ones observed in other approved COVID-19 vaccine trials in age groups similar to our sample (≥ 60 years) [16,17]. The majority of AEFIs was described as mild and moderate (grade 1 and 2), whereas only a few participants reported severe (grade 3 and 4) AEFIs. For participants aged 60 or more we can confidently affirm that Sputnik V (Gam-COVID-Vac) showed no safety concerns, particularly having displayed a very limited number of grade 3 and 4 AEFIs both after the first and the second dose; amongst the severe self-reported symptoms (grade 4) the majority matched with the cross-check run with the State Hospital but only few were admitted to the Emergency Department for observation.

Overall, systemic events had a similar incidence if compared with available data regarding other vaccines used worldwide [16–19]. Amongst these, asthenia was reported less frequently than for available mRNA vaccines, for both first and second dose, whereas fever and chills showed a higher frequency, especially after the first dose [16,17].

Participants experiencing both local and systemic AEFIs increased in the second dose when compared to the first one; when referring to those experiencing only local AEFIs, the same increase was especially prominent in older age groups.

Our findings allowed us to point out how, in the population aged 60+, having reported AEFIs after the first dose could be a predictor of AEFIs recurrence after the second dose. Amongst those who had an AEFI after the first dose, the probability of AEFIs after the second dose decreased with the increasing age. About half of the participants experienced AEFIs after the second dose, not having had one after the first dose.

The ROCCA study presents several limitations. Being the one we are presenting an unfunded, preliminary analysis and considering that the vaccination campaign is still ongoing, the sample of the study is limited. In particular, this compromises the possibility of fully detecting rare AEFIs, such as potential thrombosis as a complication of adenovirus vector vaccines [20], which was described instead in one case in the supplemental materials of the phase 3 trial [9]. Collection of more data is needed especially for different demographics, and of subgroups presenting specific comorbidities (e.g. diabetes, neurological diseases) that are limited in this study to the oldest age groups. Indeed, the youngest age groups are inadequately represented in our sample, as the vaccination campaign is still in the early phases that prioritize the elderly, among others. Thus, these findings will be subject to change when the final analysis will be presented; being the collection of data planned to be complete by the end of August 2021, we expect to share the final results by the end of 2021. We plan on resolving these issues as the campaign progresses towards the younger population as scheduled, and sharing further analysis at the end of the 3-month follow-up including those performed for subgroups with comorbidities. Finally, our follow-ups still

cover a short timeframe and might not be sufficiently distanced from the administration of the vaccine to reveal any delayed AEFIs.

The ROCCA vaccine-vigilance study represents the first attempt at investigating AEFIs of the Sputnik V vaccine, in real-life conditions with an unselected population with comorbidities unlike its phase 1, 2, and 3 trials. As stated earlier, follow-ups to at least 3 months after the administration of the first dose and the inclusion in the vaccination campaign of other age groups will allow having a representative sample of the whole population of San Marino and to describe any other atypical or rare AEFIs. Further studies on the efficacy and effectiveness are clearly needed to complete the overall picture of this vaccine.

The vaccination campaign in the Republic of San Marino began later than in other countries, but is quickly closing the gaps thanks to the adoption of the Sputnik V vaccine on a mass scale. The demonstration of its safety is another step on the long journey to finally overcome the pandemic, and the ROCCA study will keep monitoring it until the end of the campaign. We hope that these real-word results will contribute to the full acceptance of COVID-19 vaccines in order to reach vaccine coverage levels (herd immunity) necessary to contain the spreading of the infection.

Contributors

All the authors have contributed equally to the conceptualization and design of the manuscript. MM, GS, ZDV, AS, GLF, DG were responsible for drafting the manuscript. JL and MF conducted all data analyses. MM, GS, ZDV, AS, GLF were integral to the design and development of the vaccine safety surveillance questionnaire. MM, GS, ZDV, AS, EB, RM, GLF were involved in the data collection process. All authors made substantial contributions to the interpretation of data for the work and revised the manuscript critically for important intellectual content. All authors had final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing statement

The dataset generated and analysed during the current study can be made available by the corresponding author, AS, on reasonable request. MM, GS, ZDV, AS, JL, MF, GLF and DG are responsible and accessed the raw data involved with the study.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication. The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies

from the study as planned (and, if relevant, registered) have been explained.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclinm.2021.101027](https://doi.org/10.1016/j.eclinm.2021.101027).

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