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Original article

The impact of COVID-19 vaccination programme in the Republic of San Marino: Focus on effectiveness of Gam-Covid-Vac

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A B S T R A C T

Objective: The adenovirus-based vaccine Gam-COVID-Vac (Sputnik V) showed promising effectiveness in a phase 3 clinical trial; however, data concerning its impact at a population level are scarce. The Republic of San Marino (RSM) conducted a SARS-CoV-2 vaccination programme mainly based (>80%) on Gam-COVID-Vac. Our aims were to investigate the impact of Gam-COVID-Vac vaccination programme and its effectiveness in a retrospective observational study based on the entire RSM population aged ≥12 years.

Methods: We calculated the incidence rate and the vaccine effectiveness (VE) in the entire RSM population not previously infected, against SARS-CoV-2 infection and COVID-19-related hospitalization, from 25 February to 1 October 2021, considering any vaccine and separately according to the vaccine used. Vaccine effectiveness was calculated using a multivariable negative binomial regression model as 1-Incidence Rate Ratio.

Results: During the study period, 21,568/28,791 (74.9%) not previously infected subjects received at least one dose of the Gam-COVID-Vac (84%) or BNT162b2, vaccines with 98% completing the vaccination schedule. Overall, 1,634 SARS-CoV-2 infections and 166 COVID-19-related hospitalizations were observed with 17 COVID-19-related deaths reported. Incidence rates of SARS-CoV-2 infection and COVID-19-related hospitalization were 7.11 and 0.49/100,000 person-days in the fully vaccinated population, respectively. The adjusted overall VE was 67.6% (95% CI: 61.8–72.5) against SARS-CoV-2 infection and 87.9% (95% CI: 77.4–93.5) against COVID-19-related hospitalizations. Gam-COVID-Vac against SARS-CoV-2 infection VE peaked 91.8% (95% CI: 86.3–95.1) in the first bimester from the second dose, declining to 57.8% (95% CI: 42.2–69.2) at 6 months. Protection against hospitalization with COVID-19 was overall 91.6% (95% CI: 81.5–96.2), with no relevant waning trend over time.

Discussion: Our study demonstrated the effectiveness of overall vaccination (Gam-COVID-Vac [84%] and BNT162b2 [16%]) in the prevention SARS-CoV-2 infection (pre-Omicron variant), waning over time but still with sustainable effectiveness against COVID-19-related hospitalization in the Republic of San Marino.

Introduction

Vaccine development against SARS-CoV-2 received unprecedented efforts since the early stages of the COVID-19 pandemic [1]. As of May 2022, >11 billion vaccine doses were administered worldwide [2], and several observational studies have analysed real world effectiveness of vaccines against SARS-CoV-2 [3].

Gam-COVID-Vac (also referred to as Sputnik V, Gamaleya Research Institute) is a vaccine based on two recombinant adenovirus (rAd26-S and rAd5-S) vectors, both carrying the gene for full-length SARS-CoV-2 spike protein, administered intramuscularly 21 days apart [4], which showed 91.6% efficacy with a reassuring
safety profile in phase 3 trial [5]. Gam-COVID-Vac is still under review by WHO and EMA; nonetheless, it has been used in >70 countries [6]. However, data concerning the impact of vaccination programs in which Gam-COVID-Vac has been used are still scarce [7].

The Republic of San Marino (RSM) is a small landlocked state located in the north-central Italian peninsula, with a population of 33 909 inhabitants [8]. Its public and universalistic Health System assists all RSM residents. On 25 February 2021, RSM started the COVID-19 vaccination campaign. BNT162b2 (Comirnaty; Pfizer-BioNTech, Mainz, Germany) vaccine was administered to selected population groups, whereas Gam-COVID-Vac was offered to the general population and was administered to >80% of vaccinated persons.

The present study was conducted to assess the impact of this vaccination campaign until the initiation of booster campaign in late October 2021 and its effectiveness, in terms of protection from SARS-CoV-2 infection and COVID-19-related hospitalization.

Methods

A retrospective observational study was conducted using data on the entire RSM Health System assisted population aged ≥12 years. The study period spanned from 25 February 2021 to 1 October 2021. The data on all enrolled individuals included information on demographics, vaccinations, documented SARS-CoV-2 infections, hospitalizations, and death. Data were fully deidentified to the researchers.

The details on vaccine rollout and public health measures adopted in RSM to contain the pandemics are provided in the Supplementary material.

The study was approved by the RSM Ethical Committee (decision n. 58/2021).

Vaccination exposure status definition

At baseline, all RSM Health System—assisted individuals aged ≥12 years were included in the unvaccinated cohort; we excluded those with a previous SARS-CoV-2-diagnosed infection, ascertained by PCR or validated antigen test on nasopharyngeal swabs, and those receiving any COVID vaccine before the start of RSM vaccination campaign.

The exposure status changed over time; according to vaccination received, subjects were dynamically categorized as unvaccinated (no doses received), within 13 days from first dose, partially vaccinated (>14 days from first dose and up to 6 days from second dose), or fully vaccinated (>7 days after second dose). Time at risk in each status was accrued according to the above defined classification.

Study endpoints (infection, hospitalization)

Each study subject was considered to be at risk of the outcome of interest (i.e. documented laboratory-confirmed SARS-CoV-2 infection, as well as any COVID-19–related hospitalizations) from the beginning of the study until the first occurrence of any of the following events: outcome of interest, death, 180 days from second dose, or end of study.

Among SARS-CoV-2–infected subjects, those who needed acute-care hospitalization within 30 days because SARS-CoV-2 infection were considered COVID-19–related hospitalizations. The COVID-19 hospitalizations were further classified as critical cases if admitted to an intensive care unit (ICU). The COVID-19–related deaths were defined as those occurring in a confirmed COVID-19 case unless there is a clear alternative cause of death (e.g. trauma). All of these classifications followed the World Health Organization guidelines [9,10], and assessments were made by trained medical personnel using individual chart reviews.

Statistical analysis

The continuous variables were expressed as medians and interquartile ranges. The categorical variables were summarized as counts and percentages. The comparisons between groups were performed using the Mann-Whitney U test for continuous variables or the χ² test for categorical variables.

The COVID-19 trends in incidence and hospitalization rate as well as mortality were analysed globally and by sex, age group, vaccine used, and vaccination status.

A negative binomial regression model (nbreg command in STATA), better suited for over-dispersion of variance than the traditional Poisson regression method, was used to derive incidence rate ratios (IRRs) with 95% CIs for each outcome, comparing incidence in those fully vaccinated (overall or with Gam-COVID-Vac only) with that observed in unvaccinated, using exposure command to account for varying patient days across strata. Vaccine effectiveness (VE) was calculated as (1 – IRR) and expressed as relative percentages [11].

In the multivariable model, IRRs were adjusted for sex, age group, and for calendar period (February–March, April–June, and July–September) to account for differences over time in COVID-19 incidence and public health restriction applied in Italy [12] and RSM, as detailed in the Supplementary material.

To assess the effectiveness of full vaccination, contributions of subjects in the partial vaccination status were excluded. Vaccine product–specific estimates excluded the contribution of those who received a different COVID-19 vaccine after the first dose of a given vaccine. Because Gam-COVID-Vac was not offered to persons aged 12 to 17, these subjects were excluded from Gam-COVID-Vac VE estimates.

The VE was calculated overall, according to age group and time from full vaccination (within 59 days, ≤119 days, and ≤180 days from second dose).

To compare our findings with data collected in other studies when the Alpha variant of concern (VoC), was prevalent (i.e. 25 February–4 July 2021), we performed a subanalysis of VE limited to this period.

All statistical analyses were performed using STATA release 17 (StataCorp LLC, College Station, TX).

Results

Study population and cohorts

A total of 32 126 persons aged ≥12 years assisted by the RSM Health System as of 1 January 2021 were considered for inclusion in the study population. A total of 3335 (10.4%) individuals were excluded for the following reasons occurred before the study start: 3140 (9.8%) infected with SARS-CoV-2; 158 (0.5%) received a vaccine dose abroad; and 37 (0.1%) deceased (see flowchart in Fig. S1).

The final study population consisted of 28 791 individuals (51.2% females) with a median age of 50 years (IQR: 34–63). During the study period, 21 568 individuals (74.9%) received at least one vaccine dose: 18 109 (84.0%) received Gam-COVID-Vac and 3457
(16.0%) BNT162b2; 21 134 individuals (98.0%) completed the two-dose regimen. The median time from first to second dose was 21 days (IQR: 21–22 days), with 98.8% of individuals receiving their second dose ≤30 days after the first dose (Table S1).

Fig. 1 shows the time course of vaccine rollout, SARS-CoV-2 infection cases and corresponding incidence rates, as well as COVID-19-related hospitalization during the study period, showing a decreasing incidence of infections and hospitalizations along with increased vaccine coverage.

Overall, we registered 1634 laboratory-confirmed COVID-19 cases, 166 (10.1%) COVID-19–related hospitalizations, of which 37 (2.2%) needed access to ICU, and, overall, 17 (1.0%) COVID-19–related deaths.

Incidence of SARS-CoV-2 infection and related vaccine effectiveness

At the beginning of vaccination campaign, the weekly incidence of COVID-19 in the RSM general population was 800 per 100 000
The incidence of COVID-19-related hospitalizations and related vaccine effectiveness

We recorded 69,46 COVID-19 hospitalizations per 100,000 persons weekly at the beginning of the study, peaking at 114.61 per 100,000 people during the third week of March 2021, then declining throughout April, reaching zero cases during the second week of May and no further COVID-19-related hospitalizations until August.

Overall, we observed 166 (10.1%) COVID-19 cases in the study population needing hospitalization, of which 37 (2.2%) defined as critical.

The median age of inpatients was significantly higher than outpatients (71 vs 44, p < 0.001) with prevalence of male sex (60.2% vs 49.2%, p = 0.007), whereas the median age of the 37 critical inpatients was slightly lower (68 vs 72, p = 0.09).

Among 159 deaths observed during the study period, 22 were reported in SARS-CoV-2 cases (13.8%), of which 17/22 (77.3%) classified as COVID-19-related deaths; 9 observed in females (52.9%), and all reported in inpatients. Fatal COVID-19 cases were significantly older than hospitalized who recovered (median age 88 vs 69 years, p < 0.001). Fourteen out of 17 COVID-19 related deaths (82.4%) occurred in subjects not previously vaccinated (5 admitted also in ICU), 2 in partially vaccinated individuals and 1 in a fully vaccinated subject (all of them with BNT162b2, none admitted to ICU) (see Figure S3).

Table 1 and Table S3 shows incidence of COVID-19 hospitalizations according to vaccination status.

The VE against hospitalization was overall 87.9% (95% CI: 77.4–93.5) with a limited change over time (Table 2 and Figs. 2 and 3).

During the Alpha-VoC prevalent period, VE against COVID-19-related hospitalizations was 94.2% overall and 96.9% for those vaccinated with Gam-COVID-Vac (Table S4). Overall, VE against hospitalization was <85% only for those in the 50- to 59-year-old age group (Fig. 3[B]).

Discussion

Our study provided additional data on effectiveness of Gam-COVID-Vac, which was the most administered vaccine (84%) in RSM, with an overall 68.5% VE against SARS-CoV-2 infections and 91.6% against COVID-19-related hospitalizations.

Table 1
Incidence of SARS-CoV-2 confirmed cases according to final vaccination status during the study period (25 Feb – 1 Oct 2021)

| Total cases | Unvaccinated | Fully vaccinated | Fully vaccinated |
|-------------|--------------|------------------|------------------|
|              | Cases | PDs x10^3 | IR/10^5 PDs | Cases | PDs x10^3 | IR/10^5 PDs | Cases | PDs x10^3 | IR/10^5 PDs |
| SARS-CoV-2 infections |
| Sex | F  | 812 | 630 | 1147.28 | 54.91 | 102 | 1587.31 | 6.43 | 88 | 1341.74 | 6.56 |
| M  | 822 | 628 | 1143.37 | 54.93 | 5 | 815.15 | 6.14 | 98 | 1301.03 | 7.53 |
| Age 12–17 | 122 | 116 | 335.97 | 34.53 | 115 | 1463.78 | 7.66 | 114 | 1063.22 | 10.72 |
| 18–49 | 817 | 650 | 1135.88 | 57.23 | 122 | 1151.26 | 10.6 | 48 | 571.29 | 8.4 |
| 50–59 | 350 | 280 | 443.41 | 63.15 | 50 | 606.05 | 8.25 | 15 | 484.54 | 3.1 |
| 60–69 | 161 | 112 | 213.51 | 52.46 | 17 | 513.54 | 3.31 | 6 | 398.15 | 1.51 |
| 70–79 | 110 | 63 | 97.25 | 64.80 | 10 | 420.66 | 2.38 | 3 | 125.56 | 2.39 |
| 80+ | 74 | 37 | 64.63 | 57.26 | 11 | 278.09 | 4.67 | 186 | 2642.77 | 7.04 |
| Total | 1634 | 1258 | 2290.65 | 54.92 | 217 | 3051.09 | 7.11 | 186 | 2642.77 | 7.04 |
| COVID-19-related hospitalizations |
| Sex | F  | 66 | 48 | 1147.28 | 4.18 | 5 | 1587.31 | 0.32 | 1 | 1341.74 | 0.07 |
| M  | 100 | 64 | 1143.37 | 5.60 | 10 | 1463.78 | 0.68 | 7 | 1301.03 | 0.54 |
| Age 12–17 | 0 | 0 | 335.97 | — | 0 | 815.15 | — | — | — | — |
| 18–49 | 20 | 17 | 1135.88 | 1.50 | 1 | 1151.26 | 0.09 | 1 | 1063.22 | 0.09 |
| 50–59 | 31 | 25 | 443.41 | 5.64 | 4 | 606.05 | 0.66 | 4 | 571.29 | 0.70 |
| 60–69 | 27 | 18 | 213.51 | 8.43 | 3 | 513.54 | 0.58 | 2 | 484.54 | 0.41 |
| 70–79 | 44 | 28 | 97.25 | 28.79 | 2 | 420.66 | 0.48 | 0 | 398.15 | 0.80 |
| 80+ | 44 | 24 | 64.63 | 37.13 | 5 | 278.09 | 1.80 | 1 | 125.56 | 0.80 |
| Total | 166 | 112 | 2290.65 | 4.89 | 15 | 3051.09 | 0.49 | 8 | 2462.77 | 0.30 |

PDs x10^3 – person-days per 1000; IR/10^5 PDs – incidence rate per 100,000 person-days.
Table 2
Crude and adjusted VE% against SARS-CoV-2 infection and COVID-19 hospitalization of fully vaccinated versus unvaccinated status, according to type of vaccine and age over time from vaccination

| Period   | Any vaccine | Gam-COVID-vac |
|----------|-------------|---------------|
|          | Cases*      | Crude         | Adjusted*   | Cases*      | Crude         | Adjusted*   |
|          | VE          | 95% CI        | VE          | 95% CI      | VE          | 95% CI      | VE          | 95% CI      |
| SARS-CoV-2 infections |             |               |             |             |             |             |             |             |
| <60 d    | 25          | 96.6          | 94.9–97.8   | 88.7        | 82.8–92.6   | 16          | 97.1        | 95.3–98.2   | 91.8        | 86.3–95.1   |
| 60-119 d | 122         | 84.7          | 81.0–87.7   | 51.6        | 40.3–60.7   | 117         | 81.1        | 77.1–84.4   | 47.0        | 34.3–57.2   |
| 120+ d   | 70          | 85.5          | 81.1–88.9   | 52.1        | 36.7–63.8   | 53          | 85.8        | 81.3–89.2   | 57.8        | 42.2–69.2   |
| Total    | 217         | 89.3          | 87.2–91.0   | 67.6        | 61.8–72.5   | 186         | 89.9        | 87.7–91.6   | 68.5        | 62.5–73.6   |
| COVID-19-related hospitalizations |             |               |             |             |             |             |             |             |
| <60 d    | 5           | 94.5          | 84.9–98.0   | 90.6        | 74.9–96.5   | 2           | 97.5        | 88.9–99.4   | 95.2        | 79.1–98.9   |
| 60-119 d | 4           | 96.2          | 88.4–98.7   | 90.5        | 73.4–96.6   | 4           | 95.5        | 86.5–98.5   | 87.8        | 66.0–95.6   |
| 120+ d   | 6           | 89.3          | 71.5–95.9   | 76.1        | 35.1–91.2   | 2           | 96.2        | 82.5–99.2   | 89.7        | 52.7–97.7   |
| Total    | 15          | 94.0          | 88.1–97.0   | 87.9        | 77.4–93.5   | 8           | 96.4        | 91.6–98.4   | 91.6        | 81.5–96.2   |

VE, vaccine effectiveness.
*Cases reported are those observed in fully vaccinated people.
*aAdjusted for age group, sex, calendar period (see Methods for further details).

Fig. 2. Vaccine efficacy (VE; expressed as percentage VE%) in fully vaccinated persons versus unvaccinated individuals against SARS-CoV-2 infections (A) and COVID-19-related hospitalizations (B) in Republic of San Marino according to days from second dose (vaccine schedule completed). Left panels refer to the use of any vaccine, whereas right panels to the use of Gam-COVID-Vac. Dotted line reports the overall VE% for the specific group. The shaded areas show 95% CIs of VE.
A. Vaccine Efficacy (VE) against SARS-CoV-2 infections

![Graph showing vaccine efficacy against SARS-CoV-2 infections](image1)

B. Vaccine Efficacy (VE) against COVID-19-related Hospitalizations

![Graph showing vaccine efficacy against COVID-19-related hospitalizations](image2)

**Fig. 3.** Vaccine efficacy (expressed as percentage - VE% - and 95% confidence intervals) in fully vaccinated persons versus unvaccinated individuals against SARS-CoV-2 infections (A) and COVID-19-related hospitalizations (B) in Republic of San Marino according to age group. Left panels refer to the use of any vaccine, whereas right panels to the use of Gam-COVID-Vac (note that Gam-COVID-Vac was not offered for persons aged 12–17). *p < 0.05.

Our study covered a first period (February to June 2021) of Alpha-VoC predominant circulation, and a second period (July to September 2021) characterized by the spread of the Delta-VoC [13].

There are, up to now, only two population-based studies where VE of Gam-COVID-Vac was investigated. In a first study conducted in Argentina in the first trimester of 2021 [14], Gam-COVID-Vac effectiveness in preventing laboratory-confirmed infection was 78.6% and 87.6% in reducing COVID-19-related hospitalization, but the study was limited to persons aged 60 to 79.

A second nationwide study performed in Hungary [15] covering the period characterized by a high prevalence of Alpha-VoC (up to June 2021) estimated a Gam-COVID-Vac VE of 85.7% against SARS-CoV-2-confirmed infection and of 97.5% against fatal COVID-19.

To compare our findings with these studies, in a subanalysis limited to the period of Alpha-VoC circulation, VE was 97.3% against SARS-CoV-2 infection and >95% against hospitalization for those fully vaccinated with Gam-COVID-Vac consistently with the Hungarian study.

Our estimates of long-term effectiveness and waning of protection against SARS-CoV-2 infections were consistent with results from similar studies [16–21], but no other population-based studies where Gam-COVID-Vac vaccine was used covering all populations for a longer period were conducted. A recent study from Argentina analysed risk of SARS-CoV-2 infection and of death in persons vaccinated with several vaccines including Gam-COVID-Vac with a similar trend, but the analysis, conducted with a different methodology, was limited to persons aged >60 years [22].

A study from Argentina observed that Gam-COVID-Vac elicited high titers of anti-receptor-binding domain antibodies beginning to decrease at 60 days, persisting in only 31% at 180 days [23].

The COVID vaccination could have induced changes in vaccinated people’s behaviour, likely increasing social contacts and reducing adherence to prevention measures [27,28], and public health restrictions have been eased differently for vaccinated and unvaccinated individuals [29].
unvaccinated persons in RSM. It is likely that this phenomenon had a greater impact on young adults, explaining the reduced VE against SARS-CoV-2 infection observed in this age group.

The increased SARS-CoV-2 testing activity performed in RSM during the summer season has likely contributed to an increased identification of otherwise missed asymptomatic infections.

Despite the waning of protection against SARS-CoV-2 infection, the protection against severe forms of COVID-19 in Gam-COVID-Vac fully vaccinated peoples was >90% even 6 months from second dose, consistent with data reported for other vaccines [3].

Our study presented some limitations, such as the small size of the RSM population. Although this allowed excellent traceability of epidemiological and clinical data for all study subjects [29], we could not exclude some underreporting of SARS-CoV-2 infections diagnosed in Italy not notified to RSM.

In our analysis we excluded subjects with a confirmed SARS-CoV-2 infection diagnosed before the study period (roughly 10% of the original population). However, one can speculate that, given the high incidence of SARS-CoV-2 infection in the RSM and Italy mainly in the early phases of the pandemic, the number of persons with naturally acquired immunity due to undiagnosed SARS-CoV-2 occurred before study start, and possibly vaccinated, was not negligible [30]. This could have affected the final VE estimates. Moreover, the lower incidence observed as in many European countries in May to June 2021 could be explained not solely by the effect of vaccination but also by other factors such as warmer climate or more outdoor activity, though adjusting for calendar period was meant to deal with this possible limitation.

The available data did not include motivation of testing or the category of people being vaccinated (health care workers, other prioritized professional categories, or those with comorbidities). Accordingly, the adjustment performed based on available data cannot rule out residual confounding.

Another important limitation is that our study period does not cover the spread of the now ubiquitous Omicron-VoC.

Finally, the study was not designed to compare effectiveness between Gam-COVID-Vac and BNT162b2 vaccines, which was administered only in specific population groups (see Supplementary Appendix).

Regardles of these limitations, this study addressed a data gap on Gam-COVID-Vac effectiveness in real life. Vaccination with Gam-COVID-Vac generates similar results to that obtained with other vaccines and, despite an expected waning immunity against SARS-CoV-2 infections, generates a substantial protection against severe COVID-19 cases 6 months from full vaccination.

Transparency declaration

Authors report no competing interest. This study did not receive any specific funding. PP, CC, AA, FV, EN, and EG were supported by funds from the Italian Ministry of Health, “Ricerca Corrente” INMI L. Spallanzani, Linea 1.

Author contributions

GT, PP, and CC contributed to conceptualization, methodology, formal analysis, validation, data curation, and writing the original draft, review, and editing. MA, EN, AA, FV, and EG contributed to conceptualization, methodology, investigation, and writing review and editing. GT performed the chart review of all hospitalizations and deaths that arose in SARS-CoV-2 infected subjects. ES, AL, SM, FM, and AZ contributed to data collection and final revision of the paper. MA and SR were involved in the decision-making process of the vaccination campaign in RSM, project administration, and paper validation. GT and PP contributed equally to this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.06.026.

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