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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effectiveness of the first and the second dose of COVID-19 vaccines in Serbia during the first three months of rollout

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SUMMARY

Introduction/Objective The main aim of this study was to assess COVID-19 vaccination effectiveness (VE) of BBIBP-CorV, Gam-COVID-Vac, BNT162b2, and ChAdOx1-nCoV-19 in Serbia during the first three months of rollout.

Methods The data from the Serbian National Immunization Registry, the Primary Health Centre Report, and the University Clinical Centre Report for Kragujevac, Serbia, for the period from January 1 to March 31, 2021 were used to compare COVID-19 vaccinated population to unvaccinated individuals in terms of laboratory confirmed SARS-CoV-2 infection, COVID-19-related hospitalization and intensive care unit (ICU) admission due to COVID-19. VE was estimated based on the incidence rate ratio, adjusted for age and sex.

Results Overall VE after the first dose reached 20.6%, 28.2%, and 56.1%, and 55.7%, 63.9%, and 79.8%, after the second dose for SARS-CoV-2 infection, COVID-19-related hospitalization, and ICU admission, respectively. BNT162b2 exhibited 96.7% VE against infection and no hospitalization after the second dose. Complete vaccination with BBIBP-CorV and Gam-COVID-Vac demonstrated VE of 43.2% and 78.6% against infection, 56.9% and 85.3% against hospitalization, and 82.3% and 52.7% against ICU admission, respectively. ChAdOx1-nCoV-19 after the first received dose showed VE of 10.3% and 74.7% against infection and hospitalization, with no ICU admission.

Conclusion COVID-19 vaccination in general, as well as each of the four studied vaccines, reduces the risk of SARS-CoV-2 infection, hospitalization due to COVID-19, and COVID-19-related ICU admission. Vaccine effectiveness significantly increases with the second received dose for all study outcomes.

Keywords: vaccine effectiveness; BBIBP-CorV; Gam-COVID-Vac; BNT162b2; ChAdOx1-nCoV-19

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INTRODUCTION

Since the outbreak of coronavirus disease 2019 (COVID-19), many scientific research groups and pharmaceutical companies worldwide joined their knowledge and efforts, giving rise to over 300 vaccines and vaccine candidates [1]. In Serbia, vaccination campaign started at the end of December 2020, with four different vaccines readily available [2]. Yet, initially rapid vaccine rollout, ranking Serbia first worldwide in terms of share of people vaccinated against COVID-19, has been reduced to worryngly low vaccination rate of only about 47% in January of 2022 (https://ourworldindata.org/covid-vaccinations). Public distrust of vaccines was deemed to be among the major reasons for this decline [3], warranting additional country-based investigations.

Phase 3 clinical trials have already shown that the efficacy in preventing COVID-19 of the vaccines in question clearly exceeds the threshold of 50% [4–7], set by the WHO [8]. However, due to constrained study populations, rigid criteria, and narrow range of possible outcomes, these conclusions may not reflect the real-world setting. On the other hand, vaccine effectiveness (VE), defined as an ability

to reduce the risk of infection, development of disease, or any other unwanted disease outcome in real-world conditions [8], has been recognized as very useful in assessing the actual COVID-19 vaccine performance. Yet, the reports on effectiveness of COVID-19 vaccines, although numerous, are usually limited to only certain vaccines, countries, and populations, considered only some of the relevant endpoints, or reported only a few of the important measures of effect [9, 10, 11].

Although recent meta-analyses indicate that VE generally decreases over time [12, 13], in the present study we aimed to assess the initial VE, as well as other indicators of short-term vaccine performance [including vaccine-preventable disease incidence (VPDI), and the number of subjects to be vaccinated to prevent one episode of COVID-19-related adverse outcome (NNV)], of four different COVID-19 vaccines during first three months of vaccine rollout in Serbia.

METHODS

Study design

This retrospective comparative cohort study was based on the data from the Serbian National Immunization Registry for the City of Kragujevac, and the Kragujevac Primary Health Centre and the Kragujevac University Clinical Centre Reports.

Registry data were used to assess COVID-19 vaccination coverage of population older than 16 years of age in Kragujevac, Serbia, between January 1 and March 31, 2021. Vaccinated subjects were considered those who received at least one dose of any of the four different COVID-19 vaccines available in Serbia at the time of the study, i.e. RNA-based BNT162b2 (Comirnaty®, Pfizer–BioNTech; New York, NY, USA; Mainz, Germany), inactivated BBIBP-CorV (Vero Cell®, Sinopharm Group Co. Ltd., Hong Kong, China), and vector-based Gam-COVID-Vac (Sputnik V®, Gamaleya National Center of Epidemiology and Microbiology, Moscow, Russia), and ChAdOx1-nCoV-19 (Vaxzevria®, University of Oxford/AstraZeneca; Oxford, UK; Cambridge, UK). Completely vaccinated (i.e. revaccinated) were considered those who received two doses of the same vaccine administered as recommended by the guidelines.

Reports data were explored for retrieving the information on unvaccinated subjects, assessing reverse transcription polymerase chain reaction (RT-PCR) or antigen test-confirmed cases of SARS-CoV-2 infection, and detecting the number of COVID-19 patients requiring hospitalization or intensive care unit (ICU) admission, registered within the same population between January 1 and May 3, 2021 (i.e. six weeks after the vaccination or revaccination of the last included vaccinated subject). RT-PCR or antigen test confirming SARS-CoV-2 infection was considered the primary outcome of the study, while the secondary outcomes included hospitalization due to COVID-19 and ICU admission. During the study period, 20I/Alpha was the predominant SARS-CoV-2 strain in Serbia [14].

The crude COVID-19 attack rate in Serbia, calculated for the period of three months preceding the study based on a cumulative number of confirmed COVID-19 cases in Serbia (https://ourworldindata.org/), was used for estimation of the minimum sample size for the study, according to the recommendations by the WHO [1].

Key eligibility criteria and follow-up schedule

Vaccinated subjects were included in the cohort if the data on sex, age, vaccination status, time and type of vaccine, and COVID-19 test result (if tested) were available, and if they had not been infected with SARS-CoV-2 prior to, or six weeks after vaccination (Supplementary Figure S1). COVID-19 cases tested positive within one week after receiving the first dose were excluded from the analysis [8].

The minimum sample size for the study, based on the crude COVID-19 attack rate in Serbia of 3.5% at the time of calculation, and assuming VE of 50%, precision of ± 10%, and type 1 error rate (α) of 0.05, was estimated to 8148 subjects. To achieve greater precision (since follow-up of vaccinated population longer than six weeks was not feasible), sample size has been increased to all available eligible subjects at the time of the study. Namely, there were 38,454 subjects found in the Registry data that fulfilled all the inclusion criteria for the vaccinated cohort. Unvaccinated subjects were selected at random from the eligible population with no prior SARS-CoV-2 infection. Out of 126,049 subjects that composed eligible study base for the unvaccinated cohort, 76,908 were randomly selected (controlling for sex and age, with the size ratio of 2:1) to be included in the study.

In terms of SARS-CoV-2 infection, vaccinated and unvaccinated subjects were followed up individually to a maximum of 63 (42 if only one dose was administered) and 122 days, respectively, or until they had been diagnosed with COVID-19. In terms of hospitalization and ICU admission, all SARS-CoV-2 infected subjects were followed up during the clinical course of COVID-19.

The process of selection of study cohorts is presented in Supplementary Figure S1. The study was approved by the Ethics Committee of the University Clinical Centre and the Primary Health Centre, Kragujevac, Serbia (approvals No 01/20-405, No 01/20-497, and No 01-1148/1, obtained on April 3, 2020, May 5, 2020, and February 24, 2021, respectively), and conducted in accordance with the Declaration of Helsinki and its subsequent revisions.

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA), and Stata Statistical Software, release 16 (StataCorp LLC, Texas, USA). The frequencies of SARS-CoV-2 infection and COVID-19-related hospitalization and ICU admission over time were presented as incidence rate (IR). To estimate overall VE against all outcomes, vaccinated subjects were compared to unvaccinated by calculating incidence

Table 1. SARS-CoV-2 infection in the study cohorts, and the measures of vaccine effectiveness adjusted for age and sex

Variable	SARS-CoV-2 infection		IRR (95% CI)	VE (95% CI)	VPDI (95% CI)
	n	IR			
Unvaccinated	**5070**	**204**	NA		
Vaccinated (at least 1 dose)	**932**	**158.8**	**0.794 (0.740–0.852)**	**20.6% (14.8–26%)**	**40.4 (28.7–52.1)**
BBIBP-CorV	738	168.8	0.891 (0.824–0.964)	10.9% (3.6–17.6%)	891.2 (964.2–823.8)
Gam-COVID-Vac	116	152.3	0.671 (0.558–0.807)	32.9% (19.3–44.2%)	74.7 (46.2–103.1)
BNT162b2	34	63.3	0.273 (0.195–0.382)	72.7% (61.8–80.5%)	168.6 (146.2–191)
ChAdOx1-nCoV-19	44	222.7	0.897 (0.666–1.209)	10.3% (-20.9–33.4%)	25.2 (-41.2–91.6)
Revaccinated (2 doses)	**389**	**87**	**0.443 (0.399–0.491)**	**55.7% (50.9–60.1%)**	**107.8 (97.4–118.2)**
BBIBP-CorV	350	104.8	0.568 (0.509–0.634)	43.2% (36.6–49.1%)	78.7 (66.2–91.1)
Gam-COVID-Vac	36	48.5	0.214 (0.154–0.297)	78.6% (70.3–84.6%)	178.3 (161.2–195.4)
BNT162b2	3	7.7	0.033 (0.011–0.103)	96.7% (89.7–98.9%)	223.7 (212.6–234.8)

IR – incidence rate (per 1000 person-years); IRR – incidence rate ratio; VE – vaccine effectiveness; VPDI – vaccine-preventable disease incidence (per 1000 person-years); NA – not applicable

Table 2. SARS-CoV-2 infection in the vaccinated cohort per three weeks period, and the measures of vaccine effectiveness adjusted for age and sex

Variable	SARS-CoV-2 infection		IRR (95% CI)	VE (95% CI)	VPDI (95% CI)
	n	IR			
Unvaccinated	**5070**	**204**	NA		
First three weeks after 1st dose	**410**	**70.5**	**0.354 (0.320–0.391)**	**64.6% (60.9–68%)**	**128.7 (120–137.6)**
BBIBP-CorV	287	66.4	0.351 (0.311–0.395)	64.9% (60.5–68.9%)	121.7 (112.1–131.3)
Gam-COVID-Vac	67	88.6	0.391 (0.307–0.497)	60.9% (50.3–69.3%)	138.4 (116.2–160.5)
BNT162b2	26	48.4	0.209 (0.142–0.307)	79.1% (69.3–85.8%)	183.4 (163.5–203.4)
ChAdOx1-nCoV-19	30	152.7	0.616 (0.430–0.882)	38.4% (11.8–57%)	95.1 (39.8–150.4)
First three weeks after 2nd dose	**211**	**36.3**	**0.180 (0.156–0.206)**	**82% (79.4–84.4%)**	**162.9 (155.3–170.4)**
BBIBP-CorV	186	43	0.225 (0.194–0.361)	77.5% (63.9–80.6%)	145.1 (136.6–153.6)
Gam-COVID-Vac	22	29.1	0.128 (0.084–0.195)	87.2% (80.5–91.6%)	197.8 (184.1–211.6)
BNT162b2	3	5.6	0.024 (0.008–0.075)	97.6% (92.5–99.2%)	226.3 (216.7–235.8)
Second three weeks after 2nd dose	**169**	**29**	**0.145 (0.124–0.169)**	**85.5% (83.1–87.6%)**	**170.0 (162.9–177.4)**
BBIBP-CorV	156	36	0.190 (0.163–0.224)	81% (77.6–83.7%)	152.2 (144–160.2)
Gam-COVID-Vac	13	17.2	0.076 (0.044–0.131)	92.4% (86.9–95.6%)	209.7 (198.3–221)
BNT162b2	0	0	ND	ND	231.8 (224.7–238.9)

IR – incidence rate (per 1000 person-years); IRR – incidence rate ratio; VE – vaccine effectiveness; VPDI – vaccine-preventable disease incidence (per 1000 person-years); NA – not applicable; ND – not determined [due to zero event count (no COVID-19-positive cases) in vaccinated subjects]

rate ratio (IRR), using Mantel–Haenszel method to adjust for age and sex. VE was estimated by subtracting IRR between vaccinated and unvaccinated subjects (expressed as percentage) from 100% [1]. VPDI was calculated as a difference between incidences of an outcome in vaccinated and unvaccinated subjects, and reported per 1000 person-years [15]. NNV, as a number of subjects to be vaccinated to prevent one episode of COVID-19, one COVID-19-related hospitalization, or admission to ICU, was calculated as 1000 divided by VPDI [16].

RESULTS

Study participants

Demographic characteristics and the total length of the follow-up for SARS-CoV-2 infection of all 115,362 subjects involved in the study are presented in Supplemental Table S1.

Measures of VE against SARS-CoV-2 infection

IR (per 1000 person-years) of COVID-19 cases was 195.4 in the whole cohort, 158.8 in those who received at least one dose of any vaccine, and 204 in unvaccinated subjects. The risk of SARS-CoV-2 infection was significantly lower among vaccinated subjects as compared to unvaccinated population. Overall, VE increased with the second dose, as well as with time during the follow-up. Comparison among vaccines revealed the highest VE in BNT162b2, followed by Gam-COVID-Vac. The distribution of vaccinated and unvaccinated subjects among confirmed cases of SARS-CoV-2 infection, and the measures of VE during the total length of the follow-up and per three-week periods are presented in Tables 1 and 2.

Measures of VE against COVID-19 hospitalization

Hospitalization due to COVID-19 was registered among all study subjects with IR of 27.6 per 1000 person-years, and with IRs of 22.5 and 28.8 per 1000 person-years among vaccinated and unvaccinated, respectively. COVID-19 vaccination significantly reduced the risk, with VE increasing

Table 3. COVID-19-related hospitalization in the study cohorts, and the measures of vaccine effectiveness adjusted for age and sex

Variable	COVID-19-related hospitalization		IRR (95% CI)	VE (95% CI)	VPDI (95% CI)
	n	IR			
Unvaccinated	**715**	**28.8**	NA		
Vaccinated (at least 1 dose)	**132**	**22.5**	**0.718 (0.597–0.864)**	**28.2% (13.6–40.3%)**	**9.2 (4.7–13.8)**
BBIBP-CorV	125	28.6	0.856 (0.709–1.035)	14.4% (-3.5–29.1%)	5.4 (0.3–11.1)
Gam-COVID-Vac	5	6.6	0.240 (0.100–0.578)	76.0% (42.2–90%)	20.1 (14.7–27)
BNT162b2	1	1.9	0.079 (0.011–0.557)	92.1% (44.3–98.9%)	21.9 (17.7–26)
ChAdOx1-nCoV-19	1	5.1	0.253 (0.036–1.792)	74.7% (-79.2–96.4%)	15.0 (04.9–25.2)
Revaccinated (2 doses)	**52**	**11.6**	**0.361 (0.272–0.478)**	**63.9% (52.2–72.8%)**	**20.9 (16.8–24.9)**
BBIBP-CorV	49	14.7	0.431 (0.323–0.575)	56.9% (42.5–67.7%)	19.9 (14.9–24.9)
Gam-COVID-Vac	3	4	0.147 (0.047–0.457)	85.3% (54.3–95.3%)	23.5 (18.4–28.5)
BNT162b2	0	0	ND	ND	24.2 (22.2–26.1)

IR – incidence rate (per 1000 person-years); IRR – incidence rate ratio; VE – vaccine effectiveness; VPDI – vaccine-preventable disease incidence (per 1000 person-years); NA – not applicable; ND – not determined [due to zero event count (no hospitalization) in vaccinated subjects]

Table 4. COVID-19-related hospitalization in the vaccinated cohort per three-week periods, and the measures of vaccine effectiveness adjusted for age and sex

Variable	COVID-19-related hospitalization		IRR (95% CI)	VE (95% CI)	VPDI (95% CI)
	n	IR			
Unvaccinated	**715**	**28.8**	**NA**		
First three weeks after 1st dose	**63**	**10.8**	**0.345 (0.267–0.446)**	**65.5% (55.4–73.3%)**	**20.9 (17.3–24.5)**
BBIBP-CorV	61	14.1	0.422 (0.325–0.547)	57.8% (45.3–67.5%)	19.9 (15.4–24.3)
Gam-COVID-Vac	1	1.3	0.048 (0.007–0.342)	95.2% (65.8–99.3%)	26.1 (22.8–29.5)
BNT162b2	0	0	ND	ND	23.7 (21.8–25.7)
ChAdOx1-nCoV-19	1	5.1	0.254 (0.036–1.800)	74.6% (-80.0–96.4%)	15 (4.8–25.2)
First three weeks after 2nd dose	**32**	**7.2**	**0.225 (0.158–0.320)**	**77.5% (68–84.2%)**	**25.3 (21.7–28.9)**
BBIBP-CorV	30	6.9	0.210 (0.146–0.300)	79% (70–85.4%)	27 (23.4–30.7)
Gam-COVID-Vac	2	2.6	0.097 (0.024–0.386)	90.3% (61.4–97.6%)	24.8 (20.6–29)
BNT162b2	0	0	ND	ND	23.7 (21.8–25.7)
Second three weeks after 2nd dose	**17**	**2.9**	**0.091 (0.056–0.148)**	**90.9% (85.2–94.4%)**	**28.8 (26.0–31.6)**
BBIBP-CorV	16	3.7	0.108 (0.066–0.178)	89.2% (82.2–93.4%)	30.3 (27.0–33.6)
Gam-COVID-Vac	1	1.3	0.048 (0.007–0.342)	90.3% (65.8–99.3%)	26.2 (22.8–29.5)
BNT162b2	0	0	ND	ND	23.7 (21.8–25.7)

IR – incidence rate (per 1000 person-years); IRR – incidence rate ratio; IRD – incidence rate difference (per year); VE – vaccine effectiveness; VPDI – vaccine-preventable disease incidence (per 1000 person-years); NA – not applicable; ND – not determined [due to zero event count (no hospitalization) in vaccinated subjects]

with both doses received and with time during the follow-up. BNT162b2 and Gam-COVID-Vac exhibited the highest VE against hospitalization. The distribution of vaccinated and unvaccinated subjects among hospitalized cases of SARS-CoV-2 infection, and the measures of VE during the total length of the follow-up and per three week-periods are presented in Tables 3 and 4.

Measures of VE against COVID-19-related ICU admission

COVID-19-related ICU admission was registered among all study subjects with IR of 8.3 per 1000 person-years. COVID-19 vaccination significantly reduced the risk of COVID-19-related ICU admission: among unvaccinated, IR was 9.2 per 1000 person-years, as compared to the vaccinated cohort, with IR of 4.6 per 1000 person-years. VE increased with the second received dose and with time during the follow-up, and the higher VE was associated with BNT162b2, ChAdOx1-nCoV-19, and BBIBP-CorV. The distribution of vaccinated and unvaccinated subjects among SARS-CoV-2-infected admitted to ICU, and the measures of VE during the total length of the follow-up and per three-week periods are presented in Tables 5 and 6. Figure 1 presents NNV values for all three investigated COVID-19 outcomes among all vaccinated subjects, as well as per vaccine type in vaccinated with at least one, or with two doses of vaccine.

DISCUSSION

In the present study, we assessed the effectiveness of four different COVID-19 vaccines in terms of SARS-CoV-2 infection, hospitalization due to COVID-19, and COVID-19-related ICU admission. As to our best knowledge, this is the first time COVID-19 VE was investigated using the real-world data from Serbia. Our findings indicate that COVID-19 vaccination in general, as well as each of the investigated vaccines, significantly reduces the risk of all studied outcomes when compared to unvaccinated population. VE invariably increased with the second

Table 5. COVID-19-related intensive care unit (ICU) admission in the study cohorts, and the measures of vaccine effectiveness adjusted for age and sex

Variable	COVID-19-related ICU admission		IRR (95% CI)	VE (95% CI)	VPDI (95% CI)
	n	IR			
Unvaccinated	**229**	**9.2**	NA		
Vaccinated (at least 1 dose)	**27**	**4.6**	**0.439 (0.294–0.654)**	**56.1% (34.6–70.6%)**	**6 (3.7–8.2)**
BBIBP-CorV	22	5	0.441 (0.285–0.682)	55.9% (31.8–71.5%)	6.5 (3.9–9.2)
Gam-COVID-Vac	4	5.3	0.618 (0.230–1.658)	38.2% (-65.8–77%)	3.3 (2–8.6)
BNT162b2	1	1.9	0.264 (0.038–1.859)	73.6% (-85.9–96.2%)	5.3 (1.5–9.1)
ChAdOx1-nCoV-19	0	0	ND	ND	5.7 (4.7–6.7)
Revaccinated (2 doses)	**10**	**2.2**	**0.202 (0.106–0.382)**	**79.8% (61.8–89.4%)**	**8.7 (6.7–10.8)**
BBIBP-CorV	7	2.1	0.177 (0.083–0.376)	82.3% (62.4–91.7%)	9.8 (7.5–12.1)
Gam-COVID-Vac	3	4	0.473 (0.151–1.478)	52.7% (-47.8–84.9%)	4.5 (0.2–9.2)
BNT162b2	0	0	ND	ND	7.3 (6.3–8.3)

IR – incidence rate (per 1000 person-years); IRR – incidence rate ratio; VE – vaccine effectiveness; VPDI – vaccine-preventable disease incidence (per 1000 person-years); NA – not applicable; ND – not determined [due to zero event count (no admission to ICU) in vaccinated subjects]

Table 6. COVID-19-related intensive care unit (ICU) admission in the vaccinated cohort per three-week periods, and the measures of vaccine effectiveness adjusted for age and sex

	COVID-19-related ICU admission		IRR (95% CI)	VE (95% CI)	VPDI (95% CI)
	n	IR			
Unvaccinated	**229**	**9.2**	**NA**		
First three weeks after 1st dose	**12**	**2.1**	**0.197 (0.111–0.352)**	**80.3% (64.8–88.9%)**	**8.5 (6.7–10.4)**
BBIBP-CorV	12	2.8	0.244 (0.137–0.434)	75.6% (56.6–86.3%)	8.8 (6.6–11)
Gam-COVID-Vac	0	0	ND	ND	8.5 (7.4–9.7)
BNT162b2	0	0	ND	ND	7.1 (6.1–8.1)
ChAdOx1-nCoV-19	0	0	ND	ND	5.7 (4.7–6.7)
First three weeks after 2nd dose	**6**	**1.3**	**0.122 (0.054–0.276)**	**87.8% (72.4–94.6%)**	**9.6 (7.7–11.4)**
BBIBP-CorV	4	0.9	0.081 (0.030–0.216)	91.9% (78.4–97%)	10.7 (8.8–12.5)
Gam-COVID-Vac	2	2.7	0.316 (0.079–1.273)	68.4% (-27.3–92.1%)	5.8 (1.9–9.8)
BNT162b2	0	0	ND	ND	7.3 (6.3–8.3)
Second three weeks after 2nd dose	**3**	**0.7**	**0.059 (0.018–0.189)**	**94.1% (81.1–98.2%)**	**10.3 (8.6–12)**
BBIBP-CorV	2	0.6	0.048 (0.012–0.202)	95.2% (79.8–98.8%)	11.3 (9.4–12.2)
Gam-COVID-Vac	1	1.4	0.157 (0.022–1.128)	84.3% (-12.8–97.8%)	7.9 (4.3–10.1)
BNT162b2	0	0	ND	ND	7.3 (6.3–8.3)

IR – incidence rate (per 1000 person-years); IRR – incidence rate ratio; VE – vaccine effectiveness; VPDI – vaccine-preventable disease incidence (per 1000 person-years); ND – not determined [due to zero event count (no admission to ICU) in vaccinated subjects]

received dose, and the similar trend has been observed over the six-week-long follow up after complete vaccination. BNT162b2, followed by Gam-COVID-Vac demonstrated the highest VE against all outcomes of interest in terms of SARS-CoV-2 infection and hospitalization due to COVID-19, which was the case with ChAdOx1-nCoV-19 and BBIBP-CorV in terms of COVID-19-related ICU admission.

Since the 18th century, vaccination has been recognized as one of the most effective measures for reducing morbidity and mortality of infectious diseases [17]. Thus, it came as no surprise that "once in a century" pandemic such as COVID-19, after failing to succumb to intensive public health interventions, would raise high expectations for the vaccine. Once available, vaccination triggered both efficacy and effectiveness studies, where SARS-CoV-2 strong transmission ability and extremely unpredictable course of the disease placed infection rate, hospitalization, and ICU admission among the most important COVID-19-related outcomes. Numerous real-world-setting investigations have been conducted so far, and VE has been assessed in different countries on hundreds of thousands of subjects [10, 18, 19]. To the best of our knowledge, this study is the first to simultaneously investigate and report VE of BNT162b2, ChAdOx1-nCoV-19, Gam-COVID-Vac, and BBIBP-CorV for three different COVID-19-related outcomes in Serbia.

Previous studies were unified in conclusion that COVID-19 vaccination with BNT162b2 provides significant protection, which increases with time, and achieves its full potential after the second dose [20, 21, 22]. In terms of SARS-CoV-2 infection, hospitalization due to COVID-19 and COVID-19-related ICU, reported BNT162b2 VE in completely vaccinated subjects ranged from 65% [21] to 97% [9], from 80% to 98% [23], and from 90% [21] to 98% [9], respectively. In our study, BNT62b2 proved to have the highest VE in terms of all investigated outcomes, corresponding well to previously published data. Our study

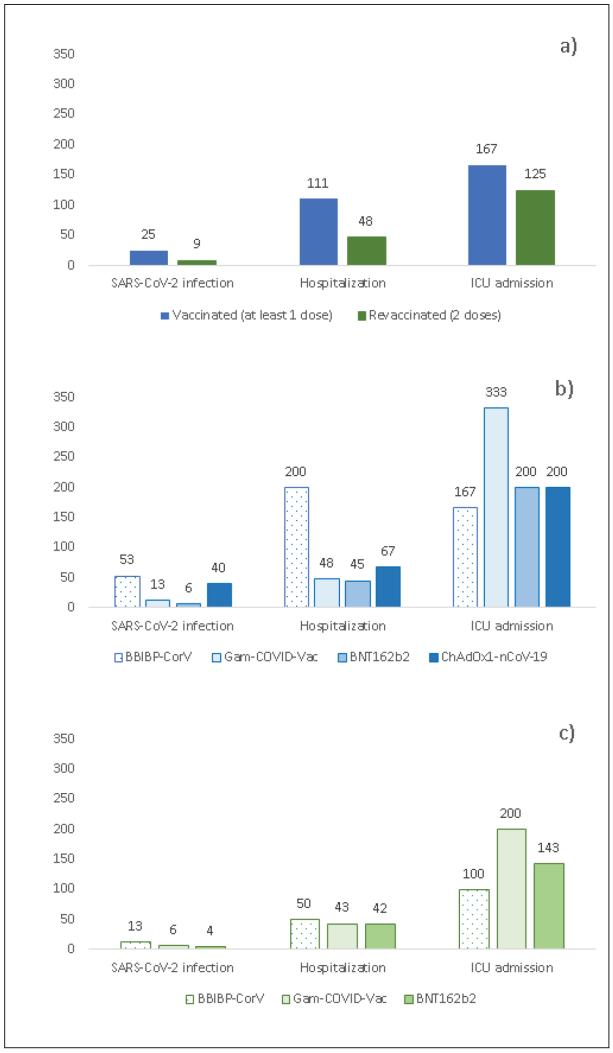

Figure 1. NNV (number of subjects to be vaccinated to prevent one episode of COVID-19, one COVID-19-related hospitalization, or admission to ICU) for three investigated COVID-19-related outcomes in a) all vaccinated subjects, b) vaccinated with at least one dose, and c) vaccinated with two doses

contributes to the existing evidence on BNT162b2 VE in two different ways: a) by providing the data from a population that has not been previously explored in this regard, and b) by simultaneously reporting VPDI and NNV values, which are recognized as important clinical indicators of the vaccination-driven COVID-19 risks reduction [24].

On the other hand, the effectiveness studies on ChAdOx1-nCoV-19 are scarce and mainly associated with VE after the first dose [11, 19, 20, 21]. In terms of SARS-CoV-2 infection and hospitalization due to COVID-19, ChAdOx1-nCoV-19 VE after one dose ranged from 36% [11] to 78% [21], and from 50% to 88% [19], respectively. Yet, none of the previous studies reported its VE for COVID-19-related ICU admission. Our data indicate that ChAdOx1-nCoV-19 in one dose modestly decreases the risk of infection, but significantly reduces the risk of hospitalization or ICU admission due to COVID-19. Limited by relatively short follow-up, we were not able to assess VE of ChAdOx1-nCoV-19 after revaccination, which remains to be elucidated in the future.

In spite of the worldwide deployment of Gam-COVID-Vac and BBIBP-CorV, we were able to find only a few published reports on their effectiveness against COVID-19-related outcomes [25]. In a Hungarian study by Voko et al. [26], Gam-COVID-Vac and BBIBP-CorV demonstrated VE against SARS-CoV-2 infection, assessed at least seven days after the second dose, of 85.7% and 68.7%, respectively. In Argentina, administration of one dose of Gam-COVID-Vac displayed VE of 78.6%, 87.6%, and 84.8% in preventing laboratory-confirmed infection, reducing hospitalizations, and deaths, respectively [27]. On the other hand, Zhang et al. [28] reported BBIBP-CorV VE against hospitalization for serious or critical illness in Morocco of 88.5%, while the data from the United Arab Emirates indicate effectiveness of the same vaccine against hospitalization, critical care admission, and death due to COVID-19 of 79.6%, 86%, and 84.1%, respectively [29]. In our study, in terms of SARS-CoV-2 infection these two vaccines proved to be slightly more effective when assessed three weeks after complete vaccination, and their effectiveness during the study follow-up increased with time. In addition, we have shown that both Gam-COVID-Vac and BBIBP-CorV are effective against two other investigated outcomes, namely hospitalization and ICU admission. They differed in terms of outcomes for which they were more effective, with Gam-COVID-Vac demonstrating higher VE in reducing the risk of hospitalization and the risk of infection, and BBIBP-CorV, the most frequently administered vaccine in Serbia, being more protective against COVID-19-related ICU admission.

It should be noted that this report has several limitations. Firstly, we were unable to assess the level of exposure to SARS-CoV-2 among vaccinated and unvaccinated subjects. The exposure risk can vary considerably, as it depends on the environment, health status, human behavior, and many other factors [30]. Since it enables viral transmission and significantly affects the initial infectious dose, the level of exposure to SARS-CoV-2 can be crucial for the development and the fate of COVID-19 [31]. Furthermore, certain factors associated with the risk of exposure could also limit the accuracy of our findings, leading to either under- or overestimation of VE. On one hand, there is the healthy adherer effect, which suggests that the vaccinated subjects should be more likely to practice preventive measures that decrease the risk of infection [32], hence attributing at least part of the observed effect to precautions rather than to vaccination. On the other hand, COVID-19 vaccination could trigger the so-called Peltzman effect, which implies that vaccinated individuals might feel more protected and thus get involved in riskier behavior [33], blurring the real VE. Also, we did not assess the symptoms of the infected subjects, so there is a possibility that asymptomatic people, who are generally less likely to be tested for SARS-CoV-2 infection were omitted from our study. Having in mind that the "silent" infections can comprise more than one third of all COVID-19 cases [34], and that their viral loads, as well as the risk of further disease transmission, can be comparable to symptomatic infections, it would be prudent to include them

too in the assessment of VE. Furthermore, our data were collected before the appearance of new Delta and Omicron variants of SARS-CoV-2 in Serbia [35], during only a six-week-long period, and before the third dose of vaccines was available, rendering our results less relevant to new strains of the virus, and missing out the information on the VE later during the period after complete vaccination, or after receiving more than two doses. Also, most of the vaccinated subjects received BBIBP-CorV, and that might potentially affect the results of comparison among different types of vaccines. Finally, our study included population of only one region in Serbia, which is mainly of Serbian origin. Since the susceptibility to SARS-CoV-2 infection and the severe form of the disease has been linked to polymorphism of certain genes [36], there is a possibility that the effect of vaccination in Serbs is under the influence of their ethnicity-related genetic signature, depreciating the applicability of our results to other populations.

CONCLUSION

In conclusion, our study, based on the real-world data from Serbia, demonstrates that COVID-19 vaccination in general, as well as each of the four studied vaccines, reduces the risk of SARS-CoV-2 infection, hospitalization due to COVID-19, and COVID-19-related ICU admission. VE significantly increases with the second received dose for all study outcomes.

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Ефективност прве и друге дозе вакцина против ковида 19 у Србији током прва три месеца од почетка вакцинације

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САЖЕТАК

Увод/Циљ Циљ студије је био да се процени ефективност вакцинације (ЕВ) против ковида 19 вакцинама *BBIBP-CorV*, *Gam-COVID-Vac*, *BNT162b2* и *ChAdOx1-nCoV-19* у Србији током прва три месеца од почетка вакцинације.

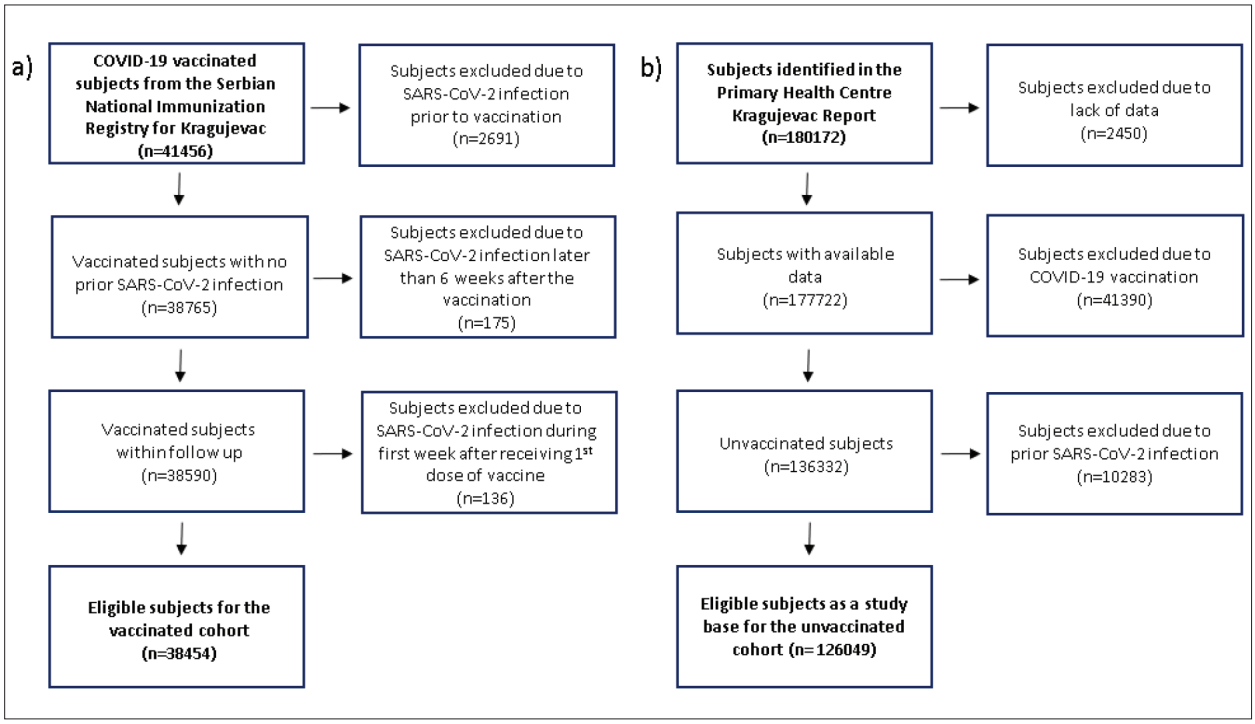
Методе Подаци за период од 1. јануара до 31. марта 2021. прикупљени из Националног регистра за имунизацију Србије, Извештаја Дома здравља и Извештаја Универзитетског клиничког центра „Крагујевац", Србија, коришћени су за поређење вакцинисане са невакцинисаном популацијом у погледу лабораторијски потврђене инфекције *SARS-CoV*-2, хоспитализације због ковида 19 и пријема у јединицу интензивне неге (ЈИН) због ковида 19. ЕВ је процењена на основу односа стопе инциденције, прилагођене за старост и пол.

Резултати Укупна ЕВ за све вакцине после прве дозе достигла је 20,6%, 28,2% и 56,1% у погледу инфекције *SARS-CoV*-2, хоспитализације због ковида 19 и пријема у ЈИН, а 55,7%, 63,9% и 79,8% после друге дозе за исте исходе. *BNT162b2* је достигла ЕВ од 96,7% против инфекције, и није било хоспитализације после друге дозе. Потпуна вакцинација вакцинама *BBIBP-CorV* и *ChAdOx1-nCoV-19* показала је ЕВ од 43,2% и 78,6% против инфекције, 56,9% и 85,3% против хоспитализације и 82,3% и 52,7% против пријема у ЈИН. *ChAdOx1-nCoV-19* је после прве дозе показала ЕВ од 10,3% и 74,7% против инфекције и хоспитализације, без пријема у ЈИН.

Закључак Вакцинација против ковида 19 уопште, као и свака појединачна вакцина, смањила је ризик од инфекције *SARS-CoV*-2, хоспитализације због ковида 19 и пријема у ЈИН због ковида 19. Ефикасност вакцине значајно се повећава са другом примљеном дозом за сва три исхода праћена у студији.

Кључне речи: ефективност вакцине; *BBIBP-CorV*; *Gam-COVID-Vac*; *BNT162b2*; *ChAdOx1-nCoV-19*

SUPPLEMENTARY MATERIAL



Supplementary Figure S1. The process of selection: a) the cohort of vaccinated subjects, and b) the study base for the cohort of unvaccinated subjects

Supplementary Table S1. Demographic characteristics, vaccination status, and the total length of the follow-up of subjects involved in the study

Characteristics	Vaccinated subjects		Unvaccinated subjects		Total	
	n	%	n	%	n	%
Total	38,454	33.33	76,908	66.67	115,362	100
Age groups (years)						
Up to 24	268	0.7	536	0.7	804	0.7
25–34	1309	3.4	2618	3.4	3927	3.4
35–44	4238	11.02	8476	11.02	12,714	11.02
45–54	5318	13.83	16,519	21.48	21,837	18.93
55–64	7994	20.79	15,897	20.67	23,891	20.71
65–74	13,030	33.88	16,823	21.87	29,853	25.88
75 and over	6297	16.38	16,039	20.85	22,336	19.36
Sex						
Male	20,534	53.4	41,044	53.37	61,578	53.38
Female	17,920	46.6	35,864	46.63	53,784	46.62
Vaccinated (at least 1 dose)	38,454	33.33	0	0	38,454	33.33
BBIBP-CorV	28,630	24.82	0	0	28,630	24.82
Gam-COVID-Vac	4522	3.92	0	0	4522	3.92
BNT162b2	3559	3.09	0	0	3559	3.09
ChAdOx1-nCoV-19	1743	1.51	0	0	1743	1.51
Vaccinated (only 1 dose)	12,477	10.82	0	0	12,477	10.82
BBIBP-CorV	9206	7.98	0	0	9206	7.98
Gam-COVID-Vac	223	0.19	0	0	223	0.19
BNT162b2	1305	1.13	0	0	1305	1.13
ChAdOx1-nCoV-19	1743	1.51	0	0	1743	1.51
Revaccinated (2 doses)	25,977	22.52	0	0	25,977	22.52
BBIBP-CorV	19,424	16.84	0	0	19,424	16.84
Gam-COVID-Vac	4299	3.73	0	0	4299	3.73
BNT162b2	2254	1.95	0	0	2254	1.95
Total person time						
In days	2,138,842		9,075,850		11,214,692	
In years	5,859.84		24,865.34		30,725.18	