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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effectiveness of a third dose of COVID-19 vaccines against delta variant of SARS-CoV-2 – a Serbian cohort study

Nataša Đorđević[1], Sanja Matić[2], Dragan Milovanović[1,3], Srđan Stefanović[2], Suzana Popović[4], Danijela Todorović[5], Predrag Đurđević[6,7], Predrag Sazdanović[8,9], Vasilije Antić[10], Slavica Lončar[10], Slavica Bukumira[11], Marko Radenković[11], Tijana Šušteršič[12,13], Nenad Filipović[12,13], Dejan Baskić[4,14]

[1]University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacology and Toxicology, Kragujevac, Serbia;
[2]University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy, Kragujevac, Serbia;
[3]Kragujevac University Clinical Centre, Department of Clinical Pharmacology, Kragujevac, Serbia;
[4]University of Kragujevac, Faculty of Medical Sciences, Centre for Molecular Medicine and Stem Cell Research, Kragujevac, Serbia;
[5]University of Kragujevac, Faculty of Medical Sciences, Department of Genetics, Kragujevac, Serbia;
[6]University of Kragujevac, Faculty of Medical Sciences, Department of Internal medicine, Kragujevac, Serbia;
[7]Kragujevac University Clinical Centre, Clinic for Hematology, Kragujevac, Serbia;
[8]University of Kragujevac, Faculty of Medical Sciences, Department of Anatomy, Kragujevac, Serbia;
[9]Kragujevac University Clinical Centre, Clinic for Gynecology and Obstetrics, Kragujevac, Serbia;
[10]Kragujevac Primary Health Centre, Kragujevac, Serbia;
[11]Kragujevac Primary Health Centre, Department of Social Medicine, Kragujevac, Serbia;
[12]University of Kragujevac, Faculty of Engineering, Kragujevac, Serbia;
[13]Bioengineering Research and Development Center (BioIRC), Kragujevac, Serbia;
[14]Kragujevac Institute of Public Health, Serbia

SUMMARY
Introduction/Objective The duration of vaccine-induced protection against SARS-CoV-2 is shown to be limited.
The aim of this study was to assess vaccine effectiveness (VE) of a third dose of four different COVID-19 vaccines during Delta variant predominance in Serbia.
Methods The data for the period from August 18, to October 1, 2021 were used to estimate the incidence rates (IR) of the SARS-CoV-2 infection, COVID-19-related hospitalization, and intensive care unit (ICU) admission. The study included 41,186 fully vaccinated subjects, of which 13,589 had received the third dose. VE was estimated based on the IR ratio following vaccination with three *vs*. two doses.
Results We found that a third dose of all investigated vaccines reduces the incidence of both SARS-CoV-2 infection and severe illness that requires hospitalization or ICU admission. The highest VE against infection demonstrated BNT162b2, followed by Gam-COVID-Vac and BBIBP-CorV. Third dose vaccination reduced the risk of hospitalization (IR = 0 for Gam-COVID-Vac and BBIBP-CorV), and ICU admission (IR = 0 for all vaccines). The hazard distributions for SARS-CoV-2 infection and hospitalization following vaccination with three versus two doses were significantly different.
Conclusion These findings indicate that an additional, third dose of studied vaccine boosters protection against all investigated outcomes.
Keywords: COVID-19; vaccine effectiveness; BBIBP-CorV; Gam-COVID-Vac; BNT162b2; ChA-dOx1-nCoV-19

INTRODUCTION

In March 2020, the World Health Organization declared the pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During the last two years, the multiple waves of COVID-19 pushed healthcare systems to the breaking point; lockdowns and mobility restrictions left severe consequences on the economy; and social distancing and isolation heavily disrupted human physical and mental wellbeing. The world has been witnessing the magnitude, the extent and the continuance of the perturbations COVID-19 brought on to all spheres of human life, yet, only less than 10% of humanity has been infected with the SARS-CoV-2 so far (https://covid19.who.int/), and the virus continues to spread globally.

The virus spreading can be stopped only by achieving herd immunity – either by infection or by vaccination. SARS-CoV-2 infection, unlike vaccination, enables virus transmission to non-immune people, and in those who are infected could take severe form, lead to hospitalization or intensive care unit (ICU) admission, and end fatally. Hence, the safest and the most effective way to achieve protection against COVID-19 is vaccination. Up to now, about 11.3 billion doses of a COVID-19 vaccine have been administered globally, and 64.6% of the world population has received at least one dose [1]. Although vaccination

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Correspondence to:
Suzana POPOVIĆ
Svetozara Markovica 69
34000 Kragujevac
Serbia
suzana.popovic@medf.kg.ac.rs

reduces the possibility of infection and lessens the risk of developing severe form of the disease, it has been reported that the SARS-CoV-2 specific response, even after receiving the second dose of vaccine, diminishes over time [2, 3].

Since the waning immunity, especially in the presence of new viral strains, warrants booster immunization, data on a third dose vaccine effectiveness (VE) are of great importance. The main aim of this study was to assess VE of the third dose of four different COVID-19 vaccines, namely BNT162b2 (Comirnaty®, Pfizer-BioNTech, Tokyo, Japan), BBIBP-CorV (Vero Cell®, Sinopharm Group Co. Ltd., Shanghai, China), Gam-COVID-Vac (Sputnik V®, Gamaleya Institute, Moscow, Russia) and ChAdOx1-nCoV-19 (Vaxzevria®, University of Oxford/AstraZeneca, Cambridge, United Kingdom), during Delta variant predominance in Serbia.

METHODS

Study design

This retrospective comparative cohort study was conducted among the resident population of the city of Kragujevac, Serbia, between August 18, 2021 (start of the third dose of COVID-19 vaccines rollout in Serbia) and October 1, 2021. To be included in the study, subjects needed to be older than 16 years of age and completely vaccinated against SARS-CoV-2 (i.e., to have received at least two doses of either BBIBP-CorV, Gam-COVID-Vac, BNT162b2, or ChAdOx1-nCoV-19 vaccine) by the end of the study follow up. However, as the neutralizing antibody levels, which are highly predictive of vaccine efficacy against SARS-CoV-2 infection [4], decrease substantially until three months after vaccination [5], recipients of only two doses were included only if the second dose was received at least three months before the beginning of the study. Subjects were excluded from the analyses if the data on sex, age, vaccination status, and COVID-19 test results were not available, but also if infection with SARS-CoV-2 took place prior to vaccination, or within the first seven days after receiving the vaccine (Figure 1).

The data on vaccination coverage was extracted from the Serbian National Immunization Registry. The Reports of the Primary Health Centre and the University Clinical Centre in Kragujevac provided information on the study outcomes, namely RT-PCR or antigen test confirmed SARS-CoV-2 infection, hospitalization due to COVID-19 and COVID-19-related ICU admission. Subjects were followed up either from the beginning of the study (if they had been vaccinated earlier), or from the day of receiving the last dose of the vaccine; until the end of the study, or until they had been diagnosed with COVID-19. According to available data [6], the Delta variant was the most predominant (if not the sole) circulating strain of SARS-CoV-2 in Serbia during the study period.

The study was approved by the Ethics committee at 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 analysis

SPSS Statistics, version 20 (IBM Corp., Armonk, NY, USA) and Stata Statistical Software, release 16 (StataCorp LLC,

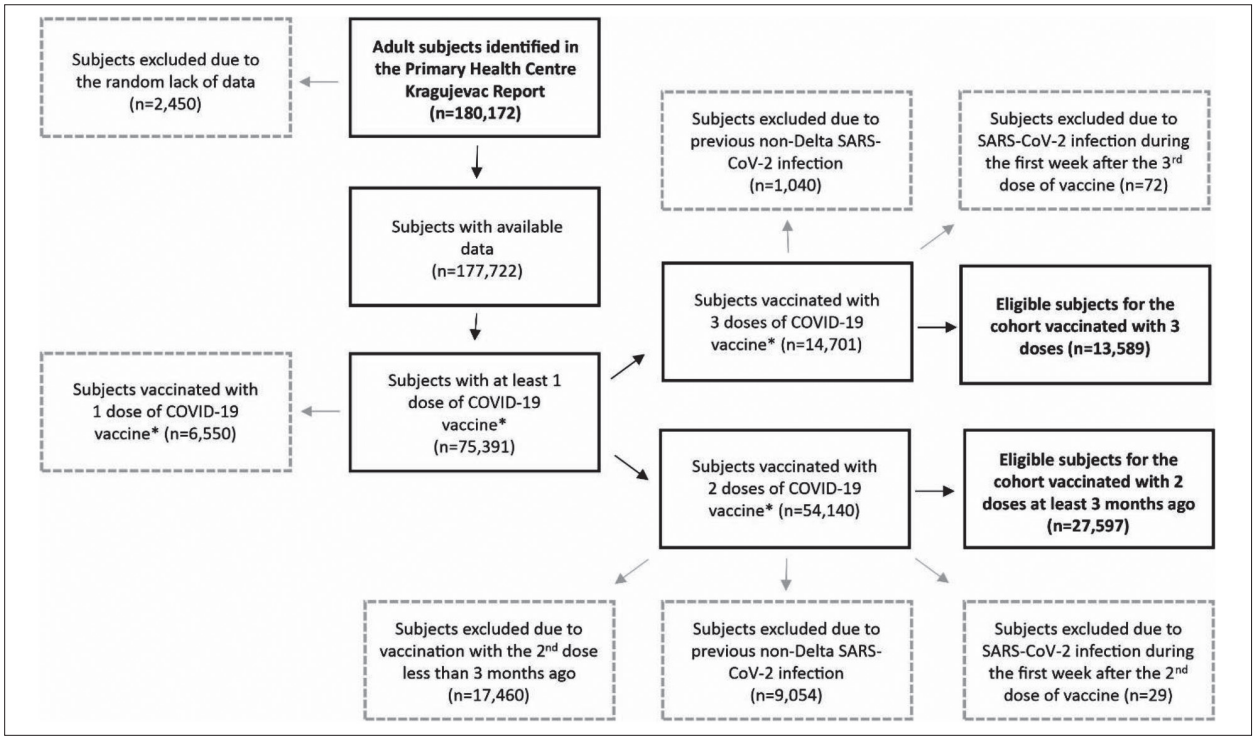

Figure 1. The cohorts' selection process;

*since the launch of the COVID-19 vaccines roll out in Serbia, until October 31, 2021

Table 1. Demographic characteristics, vaccination status, and the total length of the follow-up of subjects involved in the study

Parameters	Vaccinated with three doses		Vaccinated with two doses[a]		Total	
	n	%	n	%	n	%
Total	13,589	33	27,597	67	41,186	100
Age groups (years)						
Up to 24	36	0.26	464	1.68	500	1.21
25–34	180	1.32	1769	6.41	1949	4.73
35–44	807	5.94	4527	16.4	5334	12.95
45–54	1327	9.77	4692	17	6019	14.61
55–64	2502	18.41	5807	21.04	8309	20.17
65–74	5888	43.33	6882	24.94	12,770	31.01
75 and over	2849	20.97	3456	12.52	6305	15.31
Sex						
Male	6538	48.11	12,639	45.8	19,177	46.56
Female	7051	51.89	14,958	54.2	22,009	53.44
Type of vaccine						
BBIBP-CorV	8477	62.38	17,270	62.58	25,747	62.51
Gam-COVID-Vac	1139	8.38	5022	18.2	6161	14.96
BNT162b2	944	6.95	4536	16.44	5480	13.31
ChAdOx1-nCoV-19	0	0	768	2.78	768	1.86
Mix-and-match	3,029	22.29	1	0	3030	7.36
Total person time						
In days	315,033		1,179,279		1,494,312	
In years	863.1		3,230.9		4094	

[a]Second vaccine dose received at least three months before the beginning of the study follow-up

College Station, Texas, USA) were used for statistical analyses. The frequencies of the COVID-19-related events were expressed as incidence rates (IR). VE against all study outcomes was determined based on the sex- and age-adjusted IR ratio (IRR) among those vaccinated with either two or three COVID-19 vaccine doses. Vaccine-preventable disease incidence, the parameter that more directly presents an impact of the vaccines on reducing infection, hospitalization, and ICU admission, is a measure of the difference in the incidence of any particular outcome between vaccinated and unvaccinated populations, and was calculated according to Gessner and Feikin [7]. The number needed to vaccinate, i.e., the number of people or vaccine doses needed to prevent the investigated outcomes, was calculated according to Tripepi et al. [8]. To compare hazard distributions for the study outcomes following vaccination with three versus only two doses, the Kaplan–Meier method and a Logrank (Mantel–Cox) test were used. P values of less than 0.05 were considered significant.

RESULTS

Demographic characteristics, type of vaccine received, and the total length of follow up of all subjects involved in the study, stratified according to the vaccination status, are presented in Table 1. As subjects participating in the study were followed for different lengths of time, a cumulative amount of time (Total person time) was calculated as the sum of the total time contributed by all subjects.

Table 2. The effectiveness of the third dose of COVID-19 vaccinea as compared to two vaccine dosesb in terms of SARS-CoV-2 infection, hospitalization due to COVID-19, and COVID-19-related ICU admission

Infection, hospitalization, ICU admission	Number of events (IR) three doses[a] / two doses[b]	IRR (95% CI)	VE (95% CI), %	NNV	VPDI (95% CI)
SARS-CoV-2 infection					
Any type of vaccine	164 (190) / 1684 (521.2)	0.394 (0.334;0.464)	60.6 (53.6; 66.6)	3	289.9 (248.7; 329)
BBIBP-CorV	139 (256) / 1164 (577.7)	0.494 (0.413; 0.591)	50.6 (40.9; 58.7)	4	265.7 (210.1; 321.4)
Gam-COVID-Vac	7 (154.5) / 299 (507.4)	0.335 (0.159; 0.707)	66.5 (29.3; 84.1)	3	310.2 (182.7; 437.7)
BNT162b2	1 (22.7) / 180 (335.7)	0.074 (0.011; 0.510)	92.6 (49.0; 98.9)	3	295.2 (227.9; 362.7)
ChAdOx1-nCoV-19	0 (ND) / 41 (454.3)	ND			
Mix and match	17 (73.6) / 0 (0)	ND			
Hospitalization due to COVID-19					
Any type of vaccine	8 (9.3) / 126 (39)	0.154 (0.073; 0.235)	84.6 (67.5; 92.7)	21	42.2 (34.8; 59.7)
BBIBP-CorV	8 (14.7) / 113 (56.1)	0.190 (0.090; 0.398)	81.0 (60.2; 91.0)	21	47.6 (35.6; 59.5)
Gam-COVID-Vac	0 (0) / 8 (13.6)	ND		74	13.6 (4.2; 23)
BNT162b2	0 (0) / 5 (9.3)	ND		108	9.3 (1.2; 17.5)
ChAdOx1-nCoV-19	0 (ND) / 0 (0)	ND			
Mix and match	0 (0) / 0 (0)	ND			
COVID-19-related ICU admission					
Any type of vaccine	0 (0) / 7 (2.2)	ND		455	2.2 (0.6; 3.8)
BBIBP-CorV	0 (0) / 6 (3)	ND		333	3.0 (0.6; 5.4)
Gam-COVID-Vac	0 (0) / 0 (0)	ND			
BNT162b2	0 (0) / 1 (1.9)	ND		526	1.9 (1.8; 5.5)
ChAdOx1-nCoV-19	0 (ND) / 0 (0)	ND			
Mix and match	0 (0) / 0 (0)	ND			

IR – crude incidence rate (per 1000 person-years); IRR – incidence rate ratio adjusted for age and sex; VE – vaccine effectiveness; NNV – number needed to vaccinate; VPDI – vaccine-preventable disease incidence (per 1000 person-years);
[a]3rd vaccine dose received at any time during the study follow-up;
[b]2nd vaccine dose received at least three months before the beginning of the study follow-up;
[c] heterologous prime-boost strategy applied;
NA – not applicable; ND – not determined (due to zero vaccinated or zero event count)

The third dose of any vaccine, as compared to only two doses, decreased the overall IRs of SARS-CoV-2 infection, hospitalization due to COVID-19, and COVID-19-related ICU admission. The frequencies of COVID-19-related study outcomes in both cohorts (overall and per vaccine type), and the measures of VE against SARS-CoV-2 infection and hospitalization in subjects vaccinated with three doses, are presented in Table 2.

The complete absence of ICU admission among subjects vaccinated with three doses of any vaccine, as well as hospitalization among those who have received three doses of Gam-COVID-Vac or BNT162b2, precluded VE estimation against these outcomes. The VE of ChAdOx1-nCoV-19 could not be assessed due to the lack of subjects receiving this type of vaccine in three doses. Similarly, only one recipient of only two doses received two different vaccine types, preventing assessment of heterologous prime-boost strategy effectiveness.

Cumulative hazard functions comparing the incidence of the study outcomes following vaccination with three versus only two doses of any of the four available COVID-19 vaccines are presented in Figure 2. The hazard distributions for SARS-CoV-2 infection and hospitalization due to COVID-19 were significantly different ($\chi^2(1) = 150.468$, $p < 0.0001$ and $\chi^2(1) = 21.404$, $p < 0.0001$, respectively). The comparison could not be made for ICU admission, due to the lack of this event among subjects vaccinated with the third dose.

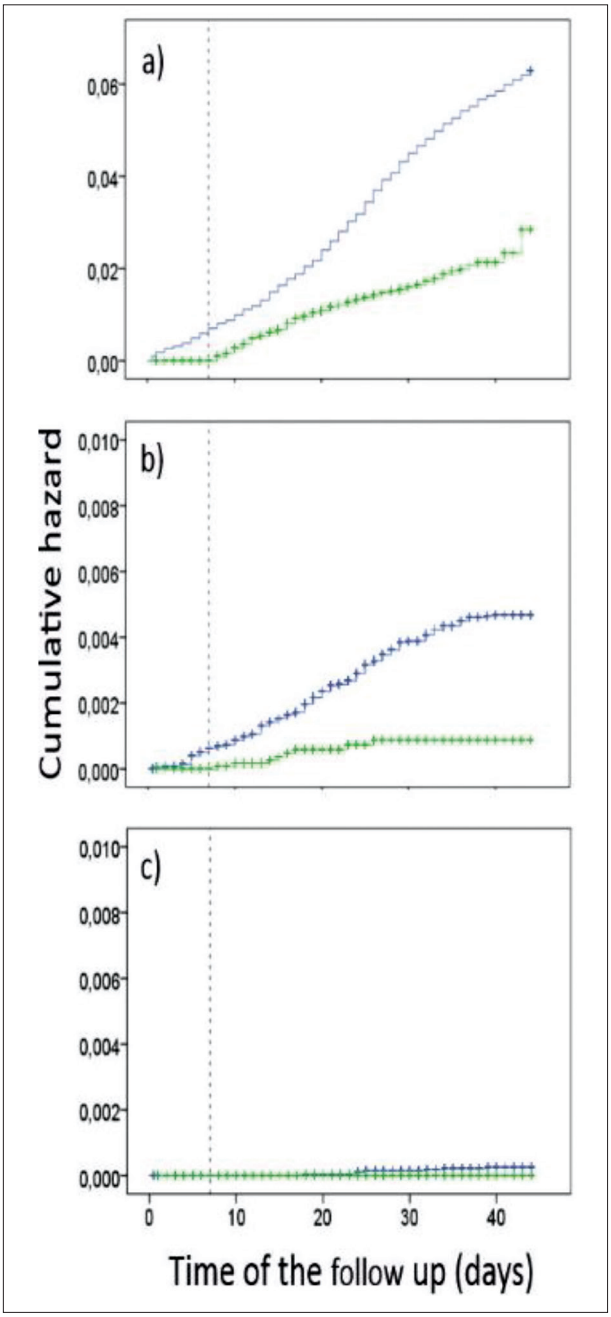

Figure 2. Cumulative hazard function comparing the incidence of a) SARS-CoV-2 infection, b) hospitalization due to COVID-19, and c) COVID-19-related Intensive Care Unit admission, following vaccination with three (green) versus only two (blue) doses of any of the four available COVID-19 vaccines; the dashed vertical line indicates day seven, when the analyses began

DISCUSSION

Our main finding is that the third dose of any of the four investigated COVID-19 vaccines, as compared to the second dose received at least three months prior, significantly reduces the incidence of Delta variant SARS-CoV-2 infection, but also the incidence of hospitalization due to COVID-19, and COVID-19-related ICU admission. Our results support the recommendation of administration of a booster dose in general adult population to restore protection against COVID-19 and its complications.

In terms of infection, the highest VE of a third versus two doses in our study reached almost 93% in those vaccinated with BNT162b2, with as little as three subjects that needed to be vaccinated with a booster dose of BNT162b2 or Gam-COVID-Vac to prevent one case of COVID-19. To prevent one hospitalization, a third dose of any of the COVID-19 vaccines investigated in our study had to be given to 21 subjects fully vaccinated at least three months prior, and VE of the booster reached almost 85%. On the other hand, rare admissions to ICU after receiving two doses, and none in a third dose group, precluded assessment of third dose VE and NNT. In line with our findings, a retrospective cohort study from Israel, comparing infection rates among nearly a million subjects vaccinated with either two or three doses of BNT162b2 vaccine, reported third dose VE of 89.1% [9]. Another Israeli study on almost 1 and a half million participants estimated VE of three versus two BNT162b2 doses to be 93% for hospital admission [10]. Similarly, a large study from United States, conducted on almost half a million veterans, reported 84% and 77% VE of three as compared to two doses of BNT162b2 vaccine against symptomatic SARS-CoV-2 Delta strain infection and COVID-19-related hospitalization, respectively [11]. Among more than a million subjects from California, who were vaccinated with either two or three doses of BNT162b2, VE of a third dose reached 75% against infection and 70% against hospital admission [12]. Again, study from United States, conducted during Delta predominance across 10 states and more than 250 hospitals, estimated BNT162b2 vaccine third-dose effectiveness against hospitalization and ICU admission due to COVID-19, when compared to unvaccinated

population, to reach 94% [13]. In the limited number of studies concerning the effectiveness of three versus two doses of SARS-CoV-2 vaccines, the BNT162b2 vaccine, as the first one approved by WHO, was clearly by far the most investigated [9, 10, 13, 14, 15]. Yet, there are several other vaccines against COVID-19 deployed worldwide [16], calling for the future research to widen the scope, and include not only other internationally available vaccines, but also both available concepts of vaccination – homologous and heterologous [17].

As for the BBIBP-CorV vaccine, while the large-scale effectiveness studies are lacking, strong SARS-CoV-2 specific immunity after the third dose has been reported [18, 19, 20]. Similarly, it has been observed that a third dose of ChAdOx1-nCov-19 boosts T-cell response and increases antibody titers [21]. On the other hand, there were no available reports on Gam-COVID-Vac vaccine boosting. In our study, considerable effectiveness of a booster dose of the same vaccine type against of SARS-COV-2 infection was confirmed for three out of four investigated vaccines. Namely, due to the specific dosing regimen and the relatively short follow-up, our study did not include subjects who had received three doses of ChAdOx1-nCov-19. Also, we were unable to calculate third dose VE of a mix-and-match prime-boost strategy, as the only subject in the two-dose group who was vaccinated with different vaccine types did not get infected with SARS-CoV-2. Nevertheless, it is worth noting that among over 3000 subjects, whose third dose of the vaccine differed from the previous two (mix and match approach), only about 0.5% got COVID-19 during the follow-up, and none were hospitalized or admitted to the ICU. Our results correspond well to the previous reports showing that the immunogenicity of a heterologous third dose boost was as good as, or better than homologous [22–25], especially in fighting against newer SARS-CoV-2 variants of concern [26]. However, after the third vaccine dose, the same level of protection was achieved in both the homologous and heterologous COVID-19 vaccination regimens [27, 28].

The Omicron variant, first identified in South Africa in November 2021 as highly transmissible, has become a globally dominant strain. The Omicron has raised significant global concern due to its large number of mutations, which may impact the effectiveness of vaccines and therapeutics. According to emerging real-world data, the VE of COVID-19 vaccines against symptomatic infection due to Omicron is lower than for the Delta variant, although all vaccines provide high levels of protection against hospitalization and death [29]. However, several studies have shown that the decline in two-dose vaccine VE against Omicron could be increased or restored by a third vaccine dose, emphasizing the importance of booster vaccination [30].

The limitations of the present study include the short follow-up time after the third dose, single-strain- and a single-center study design, as well as the lack of data on many potential confounders, such as the level of exposure to SARS-CoV-2; potential behavioral changes after vaccination; possible under-reporting of COVID-19-like symptoms; asymptomatic (thus undiagnosed) COVID-19 cases; coexisting illnesses and immunocompromising conditions; as well as other medical and demographic risk factors that might affect the susceptibility to COVID-19, and the severity and the outcome of the disease.

CONCLUSION

Despite the limitations of the present study, our results speak in favor of booster vaccination as a necessity in controlling the COVID-19 pandemic. In a view of a waning immunity against SARS-CoV-2 and the emergence of new virus variants, periodic vaccine boosting will most probably become indispensable in future years.

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Ефективност треће дозе вакцине против делта варијанте вируса *SARS-CoV*-2 – кохортна студија заснована на подацима из Србије

Наташа Ђорђевић[1], Сања Матић[2], Драган Миловановић[1,3], Срђан Стефановић[2], Сузана Поповић[4], Данијела Тодоровић[5], Предраг Ђурђевић[6,7], Предраг Саздановић[8,9], Василије Антић[10], Славица Лончар[10], Славица Букумира[11], Марко Раденковић[11], Тијана Шуштершич[13,14], Ненад Филиповић[12,13], Дејан Баскић[4,14]

[1]Универзитет у Крагујевцу, Факултет медицинских наука, Катедра за фармакологију и токсикологију, Крагујевац, Србија;
[2]Универзитет у Крагујевцу, Факултет медицинских наука, Одсек за фармацију, Крагујевац, Србија;
[3]Универзитетски клинички центар Крагујевац, Служба за клиничку фармакологију, Крагујевац, Србија;
[4]Универзитет у Крагујевцу, Факултет медицинских наука, Центар за молекуларну медицину и истраживање матичних ћелија, Крагујевац, Србија;
[5]Универзитет у Крагујевцу, Факултет медицинских наука, Катедра за генетику, Крагујевац, Србија;
[6]Универзитет у Крагујевцу, Факултет медицинских наука, Катедра за интерну медицину, Крагујевац, Србија;
[7]Универзитетски клинички центар Крагујевац, Клиника за хематологију, Крагујевац, Србија;
[8]Универзитет у Крагујевцу, Факултет медицинских наука, Катедра за анатомију, Крагујевац, Србија;
[9]Универзитетски клинички центар Крагујевац, Клиника за гинекологију и акушерство, Крагујевац, Србија;
[10]Дом здравља Крагујевац, Крагујевац, Србија;
[11]Дом здравља Крагујевац, Одељење социјалне медицине, Крагујевац, Србија;
[12]Универзитет у Крагујевцу, Факултет инжењерских наука, Крагујевац, Србија;
[13]Центар за истраживање и развој биоинжењеринга (БиоИРЦ), Крагујевац, Србија;
[14]Институт за јавно здравље Крагујевац, Крагујевац, Србија

САЖЕТАК

Увод/Циљ Показало се да је заштита коју пружа вакцина против *SARS-CoV*-2 временски ограничена.

Циљ ове студије био је да се процени ефективност четири различите вакцине против ковида 19 после примања треће дозе. Истраживање је спроведено у Србији током доминације делта варијанте *SARS-CoV*-2.

Методе Подаци за период од 18. августа до 1. октобра 2021. коришћени су за процену стопе инциденције инфекције *SARS-CoV*-2, хоспитализације због ковида 19 и пријема у јединицу интензивне неге. Студија је обухватила 41.186 субјеката вакцинисаних са најмање две дозе, од којих је 13.589 примило и трећу дозу. Ефективност вакцине је процењена на основу односа стопе инциденције после вакцинације са три у односу на две дозе.

Резултати Трећа доза свих испитиваних вакцина смањила је учесталост и инфекције *SARS-CoV*-2 и тешког облика болести који захтева хоспитализацију или пријем у интензивну негу. Највећу ефективност против инфекције показала је вакцина *BNT*1*62b*2, а затим *Gam-COVID-Vac* и *BBIBP-CorV*. Трећа доза вакцине смањила је ризик од хоспитализације (стопа инциденције *IR* = 0 за *Gam-COVID-Vac* и *BBIBP-CorV*) и пријема у интензивну негу (*IR* = 0 за све вакцине). Расподела ризика за инфекцију *SARS-CoV*-2 и хоспитализацију после вакцинације са три у односу на две дозе значајно су се разликовале.

Закључак Добијени резултати указују на то да додатна, трећа доза испитиваних вакцина појачава заштиту од свих испитиваних исхода.

Кључне речи: ковид 19; ефективност вакцине; *BBIBP-CorV*; *Gam-COVID-Vac*; *BNT*162*b*2; *ChAdOx*1-*nCoV*-19