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COVID−19 vaccine effectiveness in adults aged 60 years and older: A case−control study in south India

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ABSTRACT

Objective: To evaluate the effectiveness of COVID-19 vaccines in preventing symptomatic and severe diseases among the adults aged 60 years and older, identify key risk factors that influence infection and severity, and explore strategies to enhance the protection for this high-risk group.

Methods: A test-negative case-control study was conducted among individuals aged 60 years and older, comprising 300 COVID-19-positive cases and 300 COVID-19-negative controls. Data on vaccination status and other variables were collected via telephone interviews using a pre-tested questionnaire. Vaccine effectiveness was calculated as 1 minus the crude odds ratio (*OR*), with 95% confidence interval (*CI*). Additionally, univariate logistic regression and multivariable logistic regression were employed to identify factors associated with SARS-CoV-2 infection and disease severity.

Results: Among 600 participants, 13.7% (82/600) were identified as unvaccinated individuals. Multivariable analysis revealed that vaccinated status was the only factor determining both the infection of SARS-CoV-2 (adjusted *OR* 2.63; 95% *CI*: 1.57-4.41) and severity of COVID-19 (adjusted *OR* 1.85; 95% *CI*: 1.00-3.62). The estimated vaccine effectiveness was 68.0% (95% *CI*: 0.45-0.82) for fully vaccinated individuals and 59.0% (95% *CI*: 0.30-0.76) for partially vaccinated individuals. Of the cases, 22.0% (66/300) were identified as severe. The vaccine demonstrated an effectiveness of 73.0% (95% *CI*: 0.47-0.86) against severe COVID-19 among fully vaccinated individuals and 68.0% (95% *CI*: 0.44-0.83) for partially vaccinated individuals.

Conclusions: The effectiveness of COVID-19 vaccines among the adults aged 60 years and older is lower than anticipated. In addition to the administration of booster doses, other interventions such as using higher doses, adjuvants, and intradermal routes should be evaluated to protect this highly vulnerable group that is at the greatest risk of adverse outcomes.

KEYWORDS: COVID-19 vaccine; Vaccine effectiveness; Severity

1. Introduction

Since its emergence in December 2019, SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), has taken a tremendous toll globally. It has also caused widespread morbidity and necessitated control measures that have devastated economies worldwide. In response to the pandemic, the global efforts to develop multiple vaccines to protect against COVID-19 disease have been unrivaled in the history of public health[1]. Kerala State successfully rolled out COVID-19 vaccination on 16th January 2021 to healthcare workers and front-line workers. COVID-19 vaccination was started in the adults above 60 years in Kerala on March 1st, 2021[2].

Significance

Previous evidence shows that vaccines significantly reduce the risk of COVID-19 and severe disease. This study quantifies vaccine effectiveness in the adults aged 60 years and older using a robust test-negative case-control methodology, demonstrating that full vaccination reduces the COVID-19 risk by 68.0% and the risk of severe disease by 73.0%. Partial vaccination also offers substantial protection, while being unvaccinated is a single independent risk factor for severe disease.

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Evaluating the performance of COVID-19 vaccines post-licensure is critical as several factors can impact real-world vaccine effectiveness, including variability in the cold chain during transportation and storage, the administration process, advanced age, underlying medical conditions, and previous SARS-CoV-2 infection. Post-licensure evaluations of COVID-19 vaccines provide critical insights for public health authorities, helping them understand the duration of protection of vaccines, the need and frequency for re-vaccination, estimate effectiveness against severe disease and death, and assess the relative effectiveness of different vaccine types, different doses, and efficacy against virus variants[3].

Although COVID-19 impacts every age group, morbidity and mortality among older adults are higher than in other age groups. According to World Health Organization (WHO), vaccines should demonstrate an estimated risk reduction of at least 50%, with sufficient precision to conclude that the true vaccine efficacy is above 30%[4].

The elderly are at an increased risk of developing COVID-19 due to immune senescence combined with other medical, mental, and psychosocial issues, that accelerate the risk. There is also a reduction in vaccine effectiveness in the elderly due to a reduced adaptive immune response, chronic elevation of inflammatory cytokine levels, and the regulation of cytokine production[5]. In vaccine efficacy studies adequate representation of the elderly is not ensured[6]. So, the vaccine efficacy reported from studies may not reflect the protection it confers to the elderly. Therefore, it is important to study the COVID-19 vaccine effectiveness in the elderly. With an annual growth rate of 3.9%, much higher than any other state in India, and a projected elderly population to reach 21.0% by 2031, this study from this small state will be relevant throughout the world since the growing elderly population is a global phenomenon.

This study was therefore planned to assess the COVID-19 vaccine effectiveness among the adults 60 years and above, determine vaccine type-specific effectiveness, and investigate whether being unvaccinated is an independent determinant of SARS-CoV-2 infection and its severity.

2. Methods

2.1. Study design and setting

A test-negative case-control study was conducted in Kerala, a small southwestern coastal state of India that constitutes only about one percent of the total area of the country. It is one of the states which reported the maximum number of COVID-19 cases in the country during the pandemic. Instead of the WHO's methodology for hospital surveillance of Severe Acute Respiratory Illness (SARI) patients, this study modified the surveillance to focus on influenza-like illness patients tested for COVID-19.

2.2. Data collection

The study focused on adults aged 60 years and above who were registered for COVID-19 testing in the Labsys (Lab Diagnosis Management System) portal of the Government of Kerala over a three-month period starting in August 2021. It is a web-based portal with software that enabled the integration of laboratory diagnosis at the state level. The government could obtain data for taking action, and people could download the reports effortlessly with one click.

The sample size was calculated using the WHO sample size calculator for vaccine effectiveness. A minimum required sample size of 300 per group was obtained. Using the Labsys portal, 50 COVID-positive cases (confirmed by antigen/RTPCR testing) and 50 COVID-negative individuals were randomly selected daily throughout August 2021, resulting in a list of 1 550 positive and 1 550 negative partcipants. From this list, the first 10 respondents from each group was interviewed daily by telephomic interviews using a pre-tested researcher administered questionnaire. Data was collected on vaccination status, severity of COVID-19 disease, infection control practices, and other variables.

2.3. Data storage and analysis

Data were entered in Microsoft Excel sheets and analyzed using the SPSS 24 trial version. Vaccine effectiveness was calculated using the formula as 1 minus crude odds ratio (*OR*) and described as a percentage with the 95% confidence interval (*CI*). To evaluate whether vaccination status served as an independent determinant for contracting COVID-19, and to identify factors influencing disease severity, univariate analysis was conducted initially for qualitative and quantitative variables. Subsequently, multivariable analysis was performed using logistic regression for potential confounders, and the adjusted *OR* with 95% *CI* was caculated to quantify the association.

2.4. Ethical approval

Approval was obtained from the National Health Mission, Kerala (NHM/3554/SNO(ME&E)/2021/SPMSU, Dated, 07.09.2021). In addition, informed verbal consent was obtained from participants before collecting data with recording. Privacy and confidentiality were maintained throughout the study.

3. Results

3.1. Baseline description

In this study, 300 cases and 300 controls were recruited, of which 294 (49.0%) were females and 306 (51.0%) were males. Representation from all the districts were included among the study subjects (Figure 1). The number of COVID-19 cases in Thiruvananthapuram and Ernakulam was relatively higher, indicating a greater burden compared to other districts. Table 1 presents a comparison of demographic, behavioural, clinical, and vaccination status between cases and controls.

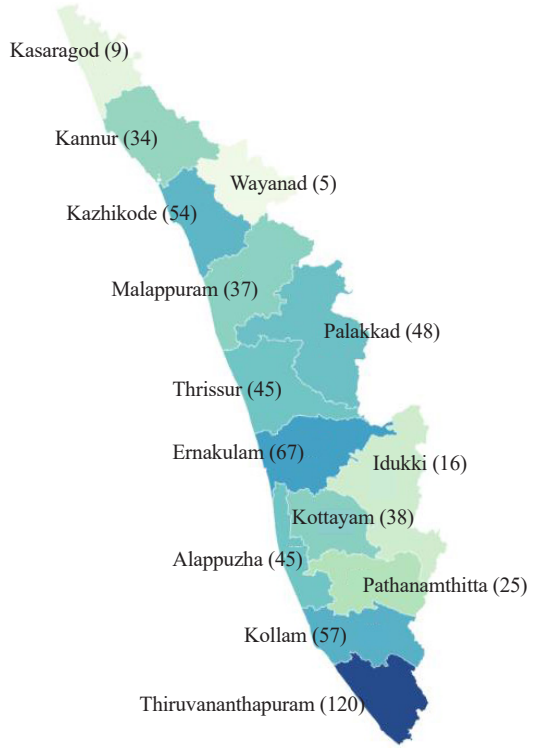


Figure 1. Distribution of study participants across districts in Kerala, India.

3.2. COVID–19 vaccine effectiveness

Among the study participants, 43.3% (260/600) were fully vaccinated, 43.0% (258/600) were partially vaccinated with one dose, and 13.7% (82/600) were unvaccinated. The vaccine effectiveness for fully vaccinated individuals is 68.0% (*OR* 0.32; 95% *CI*: 0.18-0.55; *P*<0.001) while it is 59.0% (*OR* 0.41; 95% *CI*: 0.24-0.70; *P*<0.001) for partially vaccinated individuals (Supplementary Table 1).

The most common reason for not being vaccinated was allergy, accounting for 29.3%, followed by difficulty in getting slots at 23.2%, comorbidities at 12.0%, being bedridden or palliative at 9.0%, recent SARS-CoV-2 infection at 7.0%, lack of interest at 7.0%, and limited access to vaccination centers as well as older age, both at 2.0%.

The comparison of vaccination status among cases and controls was conducted. A higher number of unvaccinated individuals were observed in the case group compared to the control group, with 58 and 24, respectively, while fully vaccinated individuals were more prevalent in the control group. Simultaneously, the result shows that all types of vaccines offered significant protection against COVID-19. The effectiveness of the two vaccines in the participants was 64.0% (*OR* 0.36; 95% *CI*: 0.21-0.59; *P*<0.001) for covishield and 58.0% (*OR* 0.42; 95% *CI*:0.21-0.85; *P*=0.01) for covaxin (Supplementary Table 2). There were only three who received other vaccines. No significant difference in COVID-19 cases were observed depending on the vaccine taken. Statistical analysis showed the following results: covishield *vs*. covaxin (*P*=0.52), covishield *vs*. other vaccines (*P*=0.10), covaxin *vs*. other vaccines (*P*=0.08) .

Table 1. Comparison of demographic, behavioural, clinical, and vaccination status between cases and controls [*n*(%)].

Variables	Case (*n*=300)	Control (*n*=300)	*P*
Age (years) Mean±SD	66.84 ±6.94	66.41± 5.92	0.42
Sex			
Female	148(49.3)	146(48.7)	0.87
Male	152(50.7)	154(51.3)	
Occupation			
Not working	222(74.0)	226(75.3)	0.70
Working	78(26.0)	74(24.7)	
Smoking†			
Yes	15(5.0)	21(7.0)	0.30
No	285(95.0)	279 (93.0)	
Alcoholism			
Yes	17(5.7)	21(7.0)	0.50
No	283(94.3)	279(93.0)	
Residence			
Rural	237(79.0)	214(71.3)	0.03
Urban	63(21.0)	86(28.7)	
Comorbidity			
Yes	179(59.7)	197(65.7)	0.13
No	121(40.3)	103(34.3)	
Household contact			
Yes	126(42.0)	0	<0.001
No	174(58.0)	0	
Number of family members Mean±SD	4.34±2.24	3.95±1.87	0.02
Wearing mask			
Single mask‡	151(50.3)	125(41.7)	0.03
Double mask§	149(49.7)	175(58.3)	
Public transport			
Yes	75(50.0)	75(50.0)	1.00
No	225(50.0)	225(50.0)	
Going outside			
Yes	173(57.7)	194(64.7)	0.08
No	127(42.3)	106(35.3)	
Frequency of the family members going outside three times or more per week			
Yes	216(72.0)	195(31.7)	0.07
No	84(28.0)	105(35.0)	
Shopping online or home delivery			
Yes	103(34.3)	100(33.3)	0.80
No	197(65.7)	200(66.7)	
Vaccinated status			
Vaccinated¶	242(80.7)	276(92.0)	<0.001
Unvaccinated	58(19.3)	24(8.0)	

Note: †Smoking is defined as having smoked more than 100 cigarettes in a lifetime; ‡Cloth or surgical mask; §Cloth and surgical or N95; ¶Fully vaccinated and partially vaccinated; *P*<0.05 significant.

3.3. Determinants of COVID–19 risks and severity

In the univariate analysis, people in rural areas had a higher risk of developing COVID-19 compared to urban (*P*=0.03). Those who wore single masks (cloth or surgical) were at higher risk

of COVID-19 compared to those with double masks and N95 (P=0.03). No significant differences were observed between cases and controls in terms of demographic variables (age, sex, occupation), behavior variables (smoking, alcoholism), comorbidity, family size, frequency of family members going outside, use of public transport, modes of going outside or shopping mode. In the multivariate analysis, vaccination status was identified as the sole significant factor associated with contracting COVID-19 (Table 2).

The severity was determined based on the levels of care required by the patients. Patients required hospitalization, Intensive Care Unit (ICU) treatment, or oxygen were taken as severe cases, while those who only required home isolation or admission in domiciliary care centers like COVID-19 first-line Treatment Centres or COVID-19 second-line treatment centers were considered as non severe. Accordingly, 234 cases (78.0%) were non severe and 66 cases (22.0%) were severe. None of the fully vaccinated required ICU treatment, oxygen or ventilator (Supplementary Table 3).

The results of the multivariable analysis (Table 3) indicated that vaccination status was the only significant factor influencing the severity of COVID-19. Among severe cases, the number of vaccinated and unvaccinated individuals was 19 and 47, respectively. Unvaccinated individuals have 1.85 times higher odds of experiencing severe COVID-19 compared to vaccinated individuals (Adjusted *OR* 1.85; 95% *CI*: 1.00-3.62; P=0.03). The effectiveness of being fully vaccinated against severe COVID-19, compared to unvaccinated, was 73.0% (*OR* 0.27; 95% *CI*: 0.14-0.53; P<0.01), highlighting the significant protection of full vaccination. The effectiveness of being partially vaccinated against severe COVID-19 was 68.0% (*OR* 0.32; 95% *CI*: 0.17-0.56; P<0.01) (Supplementary Table 4).

Table 2. Key determinants of SARS-CoV-2 infection.

Variables	Univariate regression		Multivariate regression	
	OR (95% *CI*)	*P*	Adjusted *OR* (95% *CI*)	*P*
Age (years)	0.99(0.96-1.02)	0.42	-	
Female *vs.* male	0.97(0.71-1.34)	0.87	-	
Working (yes *vs.* no)	0.93(0.65-1.35)	0.71	-	
Smoking (yes *vs.* no)	0.73(0.34-1.55)	0.41	-	
Alcoholism (yes *vs.* no)	0.91(0.44-1.88)	0.79		
Rural *vs.* urban	1.50(1.04-2.19)	0.03	1.36 (0.92-2.01)	0.10
Comorbidity (yes *vs.* no)	0.77(0.55-1.07)	0.13	0.76(0.54-1.06)	0.11
Wearing mask (single[‡] *vs.* double[§])	1.42(1.03-1.96)	0.03	1.30(0.93-1.82)	1.15
Public transport (yes *vs.* no)	1.00(0.69 -1.54)	1.00	-	
Going outside (yes *vs.* no)	0.79(0.54-1.04)	0.08	-	
Family members going outside three times or more per week (yes *vs.* no)	1.39(0.98-1.96)	0.07	-	
In-store shopping (yes *vs.* no)	0.96(0.68-1.34)	0.80	-	
Higher number of family members	1.09(1.01-1.18)	0.02	0.95(0.86-1.03)	0.94
Vaccinated[¶] *vs.* unvaccinated	2.57(1.67-4.57)	<0.001	2.63(1.57-4.41)	<0.001

Note: [‡]Cloth or surgical mask; [§]Cloth and surgical mask or N95; [¶]Fully vaccinated and partially vaccinated; P<0.05 significant.

Table 3. Key determinants of COVID-19 severity.

Variables	Severe (n=66)	Non severe (n=234)	Adjusted *OR* (95% *CI*)	*P*
Age (years)				
>80	5(7.6)	10(4.3)	0.99(0.94-1.01)	0.27
≤80	61(92.4)	224(95.7)		
Sex				
Male	38(57.6)	114(48.7)	1.51(0.84-2.72)	0.20
Female	28(42.4)	120 (51.3)		
Comorbidity				
Yes	45(68.2)	134(57.3)	1.50 (0.80-2.66)	0.11
No	21(31.8)	100(42.7)		
Wearing double mask				
Yes	33(50.0)	116(49.6)	0.90(0.50-1.69)	0.95
No	33(50.0)	118(50.4)		
Vaccination status				
Vaccinated[¶]	19(28.8)	195(83.3)	1.85(1.00-3.62)	0.03
Unvaccinated	47(71.2)	39(16.7)		

Note: [¶]Fully vaccinated and partially vaccinated; P<0.05 significant.

4. Discussion

Many of the Phase III trials have made a conscious effort to recruit older people, however, older people with co-morbidities and frailty have been largely excluded[7] and there are no published data on safety and efficacy in this group with adequate representation[8]. So, a measure of vaccine effectiveness is the need of the hour in this specific population.

In our study, the vaccine effectiveness for preventing symptomatic COVID-19 among the adults aged 60 years and older who are either fully vaccinated or partially vaccinated exceeds the WHO recommended levels. The vaccine effectiveness obtained in our study is comparable to that obtained for elderly above 80 years of age, in a study from Germany[9]. The vaccine effectiveness in this study is lower compared to other age groups in studies that have involved all age groups[10].

In this study, the vaccine effectiveness of being fully vaccinated against severe COVID-19 was 73.0% compared to being unvaccinated, which was not significantly higher than the vaccine effectiveness of vaccination for infection. The result is similar to previous studies[10], indicating that the vaccine effectiveness of vaccines against severe cases in the elderly is generally lower than the vaccine effectiveness for all-age vaccination. Additionally, taking two doses compared to a single dose did not give a significant advantage in terms of protection. In the study from Germany, the vaccine effectiveness also did not differ significantly by the number of cumulative doses[9].

Experience with the influenza vaccine showed that vaccine effectiveness can be enhanced by giving higher doses, the use of adjuvants, and intradermal administration[11]. The effectiveness increased by 82%, 52%, and 32%, respectively. There is evidence that the use of adjuvants may produce adverse effects but these are generally considered as mild[12]. There are studies on mRNA vaccines done using different dose escalations in different age

groups including the elderly. It showed similar antibody responses in all age groups. Hence it has been concluded that mRNA vaccines are likely to be effective in the elderly[13, 14].

In this study, the only factor that determined the occurrence of COVID-19 was vaccination status. Unvaccinated individuals were 2.63 times more likely to develop the disease compared to those who were fully vaccinated. There were no significant differences across sex, residence, comorbidity and protective behaviors. Although SARS-CoV-2 infections are more severe among smokers, there is no evidence of smoking and increased risk of infection[15]. In our study, no significant differences across smokers and nonsmokers. Wearing a double mask (a surgical mask with a cloth mask) offer the best protection after N95[16]. Consistently, our study found that individuals wearing cloth masks were at higher risk of contracting COVID-19 compared to those wearing double masks or N95 masks. However, we did not find any such independent associations with factors such as older age, comorbidities, and overcrowding. Both in univariable and multivariable analysis, only being unvaccinated emerged as a significant determinant of severity with an adjusted *OR* of 1.85 (95% *CI*: 1.00-3.63; *P*=0.03). In our study, among vaccinated individuals, a significantly higher proportion managed the illness with home isolation compared to the unvaccinated. None of the fully vaccinated required ICU, oxygen, or ventilator. There was a significant association between disease severity and vaccination status. Reviews of several studies showed that all vaccine types of vaccines effectively reduce the risk of severe illness compared to no vaccination[17].

Old age was a risk factor for adverse outcomes for COVID-19 before vaccination was introduced and it is still so after vaccination[18]. Reduced vaccine effectiveness in the elderly, the emergency of new variants like BA.2.86 and persistent vaccine hesitancy underscore an urgent need for focused research and proactive strategies to protect this high-risk group from this illness which not only affects physical health but also mental health adversely[19–21]. Ensuring their protection demands innovation, adaptive, and targeted approaches to address these evolving challenges.

5. Conclusions and recommendations

This study highlights the importance of laboratory surveillance in assessing vaccine effectiveness. While COVID-19 vaccine effectiveness in the adults aged 60 years and older exceeds the thresholds recommended by WHO, it falls below expected levels. Notably, being unvaccinated is the single most significant independent risk factor for symptomatic COVID-19, and vaccination significantly reduce disease severity.

To protect this vulnerable population, it is crucial to ensure that all adults aged 60 years and older receive COVID-19 vaccination. Priority should be given to administering the first dose to unvaccinated adults aged 60 years and older before focusing on subsequent doses, emphasizing the need for vaccine equity.

Since the vaccine effectiveness in the adults aged 60 years and older is below 80%, additional preventive strategies, including reinforcing COVID-appropriate behavior, must remain a priority. The study further demonstrated the superior protective benefits of wearing double masks or N95 masks compared to cloth masks, advocating their use among the adults aged 60 years and older.

Recognizing the unique immune responses of the adults aged 60 years and older, it is essential to conduct dedicated clinical trials to evaluate vaccine efficacy in this age group, with appropriately calculated sample sizes. Innovative approaches, such as higher vaccine doses, the use of adjuvants, or alternative routes of administration like intradermal vaccination, should be explored to enhance vaccine effectiveness in the adults aged 60 years and older.

These findings highlight the need for a comprehensive approach to protect the adults aged 60 years and older, combining vaccination, behavioral measures, and innovative strategies to address their specific vulnerabilities.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Thomas SB, Nujum ZT and Ramakrishnan D conceptualized and designed the study protocol. Paul L and Divya SN were instrumental in getting the data and resources, Nujum ZT did the analysis, Thomas SB was responsible for overall supervision, Nujum ZT and Thomas SB drafted the manuscript; Ramakrishnan D, Paul L and Divya SN critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. Thomas SB and Nujum ZT are guarantors of the paper.

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Supplementary materials

Table 1. Comparison of vaccine effectiveness between cases and controls.

Vaccination status	Case	Control	*P*	*OR* (95% *CI*)	Vaccine effectiveness (95% *CI*)
Fully vaccinated *vs*. unvaccinated					
Fully vaccinated	114	146	＜0.001	0.32(0.18-0.55)	68(0.45-0.82)
Unvaccinated	58	24			
Partially vaccinated *vs*. unvaccinated					
Partially vaccinated	128	130	＜0.001	0.32(0.17-0.56)	59(0.30-0.76)
Unvaccinated	58	24			

P＜0.05 significant.

Table 2. Vaccine effectiveness of covishield and covaxin.

Vaccine	Case (*n*=300)	Control (*n*=300)	*OR* (95% *CI*)	Vaccine effectiveness (95% *CI*)	*P*
Covishield vaccinated†	210	242	0.36(0.21-0.59)	64(0.41-0.79)	＜0.001
Covaxin vaccinated	32	31	0.42(0.21-0.85)	58(0.15-0.79)	0.01

†Vaccinated: Taken one or two doses; *P*＜0.05 significant.

Table 3. Severity of COVID-19 categorized by levels of care.

Care required	Unvaccinated *n*=58	Partially vaccinated *n*=128	Fully vaccinated *n*=114	Total (*n*=300)
Home isolation	31(53.4)	93(72.7)	100(77.4)	214(70.8)
CFLTC	7(12.1)	7(5.5)	5(4.4)	19(6.3)
CSLTC	0(0.0)	1(0.8)	0(0.0)	1(0.3)
Hospital admission in wards†	16(27.6)	25(19.5)	19(18.2)	60(20.2)
ICU admission†	3(5.2)	1(0.8)	0(0.0)	4(1.3)
Oxygen†	0(0.0)	1(0.8)	0(0.0)	1(0.3)
Ventilator†	1(1.7)	0(0.0)	0(0.0)	1(0.3)

†Severe COVID-19.

Table 4. Vaccine effectiveness against severe COVID-19.

Vaccination status	Severe cases	No COVID-19 and not severe	*P*	*OR* (95% *CI*)	Vaccine effectiveness (95% *CI*)
Fully vaccinated *vs.* Unvaccinated					
Fully vaccinated	21	247	＜0.01	0.27(0.14-0.53)	73(0.47-0.86)
Unvaccinated	20	62			
Any dose taken *vs.* Unvaccinated					
Any dose taken	46	472	＜0.01	0.32(0.17-0.56)	68(0.44-0.83)
Unvaccinated	20	62			

P＜0.05 significant.