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A Multi-Center Retrospective Cohort Analysis of COVID-19 Vaccine Effectiveness in Patients with Mild or Asymptomatic Infection During the Omicron Outbreak in Guangzhou

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Abstract

Although COVID-19 vaccination has been widely implemented, its effectiveness in individuals with asymptomatic or mild infections remains unclear. This study aimed to evaluate the influence of different vaccine types and dosing regimens on isolation duration, discharge rates, viral shedding periods, and the rate of negative test conversion in patients with asymptomatic or mild COVID-19. We analyzed adult patients admitted to Fangcang isolation facilities in Pazhou and Yongning from November to December 2022. Data collected included demographic characteristics, admission records, laboratory results, and vaccination history. A total of 6,560 COVID-19 patients were analyzed (3,584 from Pazhou and 2,976 from Yongning). Among them, 90.6% had received inactivated vaccines, 3.66% recombinant SARS-CoV-2 spike protein subunit vaccines, and 0.91% adenovirus-based vaccines. Of the 6,173 vaccinated individuals, 71.9% had received a booster dose. By day 9, half of the vaccinated patients had completed their isolation, and by day 7.5, 50% of the patients had tested negative. Complete vaccination proved effective in reducing viral persistence and promoting recovery, with heterologous vaccine regimens outperforming inactivated vaccines alone. Nonetheless, no notable differences in protective effects were observed 12 months post-vaccination.

Keywords: Omicron, Recombinant protein vaccine, Inactivated vaccine, Adenovirus type-5 (Ad5) vectored COVID-19 vaccine, Heterologous, Booster vaccine

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Introduction

Since SARS-CoV-2 emerged in December 2019, causing COVID-19, the virus has spread worldwide, infecting over 700 million people and resulting in more than 6 million deaths by February 2023 [1]. In response, vaccines have been rapidly developed and deployed, with nearly 70% of the global population receiving at least one dose and over 13 billion doses administered overall [2]. Evidence consistently shows that vaccination significantly reduces the risk of severe illness and mortality [3–6]. Despite this,

vaccines are less effective at preventing mild or asymptomatic infections and do not entirely halt virus transmission [7]. Consequently, unvaccinated populations remain key drivers of viral spread, particularly in regions with high vaccination coverage, highlighting the need for strategies that protect vulnerable groups and reduce overall infection rates [8].

The continuing evolution of SARS-CoV-2, including variants with higher transmissibility and partial immune evasion [9–12], has complicated pandemic control efforts. Variants such as B.1.351 and P.1 have raised concerns about the reduced effectiveness of vaccines and other interventions. Studies suggest that BNT162b2 may offer weaker protection against these strains [12]. Additionally, immunity tends to wane over time, emphasizing the potential benefits of heterologous booster strategies, as recommended by the World Health Organization (WHO) [13]. Vaccine effectiveness is further influenced by co-infections, concurrent medications [14], and demographic factors like age, sex, and socioeconomic status [14]. Vaccination may also affect isolation dynamics [15, 16]. Therefore, population-based studies are critical for accurately assessing vaccine effectiveness and informing strategies to overcome vaccine hesitancy and guide public health decisions [17].

Asymptomatic infections, which contribute substantially to SARS-CoV-2 transmission [17], have become an essential focus of study. Vaccines have demonstrated efficacy in reducing asymptomatic cases [18], suggesting that vaccination could shorten both isolation periods and viral shedding in these patients, thereby limiting the onward transmission of the virus. To examine this hypothesis, we conducted a multi-center study evaluating the effect of COVID-19 vaccination on isolation duration and viral shedding, aiming to inform optimal vaccine strategies to curb community spread.

Materials and Methods

Patient selection

Adults aged 18 years or older with first-time COVID-19 infection were enrolled from Fangcang isolation centers in Pazhou and Yongning between November and December 2022. Only patients with asymptomatic or mild disease were included; those with severe or critical illness were excluded. Individuals with underlying health conditions or other specific circumstances were also omitted from the study (Table E1). This investigation followed the strengthening of the reporting of observational studies in epidemiology (STROBE) guidelines (Online Supplement 2) [19] and received approval from the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (approval number ES-2023-116-01).

Study design

We collected comprehensive demographic data, including age, sex, marital status, ethnicity, occupation, and province of residence. Admission information (such as hospital stay duration, date when the health code changed to yellow, dates of nucleic acid tests (NATs), and laboratory indicators including NAT outcomes and cycle threshold (Ct) values) was also recorded. Vaccination details, including the type of vaccine and the administration date, were documented.

Patient discharge from the Fangcang isolation centers followed these criteria: (1) body temperature remained normal for at least three consecutive days; (2) notable improvement in respiratory symptoms; (3) clear resolution of acute infiltrative lesions on pulmonary imaging; and (4) completion of seven days of centralized medical observation, with nasal and pharyngeal swabs collected for NAT on days 6 and 7 (minimum 24-hour interval between samples). Patients were eligible for discharge if the Ct values for both the nucleocapsid (N) gene and ORF1ab gene in both NATs were $\geq$ 35 (via fluorescence quantitative PCR with a detection threshold of 40) or if tests returned negative (Ct < 35). Patients who did not meet these criteria remained in isolation until all requirements were satisfied.

The discharge rate was defined as the proportion of patients meeting the criteria for release from isolation, while the isolation rate was calculated as 1 minus the discharge rate. Viral shedding duration was defined as the interval from the first positive NAT to the first day of continuous negative results. Full vaccination referred to completion of the primary vaccine series, whereas a booster indicated any additional doses received after achieving full vaccination [16]. The negative rate was defined as the proportion of patients achieving continuous negative test results, with the positive rate calculated as 1 minus the negative rate.

Statistical analysis

Continuous variables following a normal distribution were reported as mean ± standard deviation (SD), and those not normally distributed were expressed as median with interquartile range (IQR). Categorical variables were presented as counts and percentages. Group differences were assessed using analysis of variance, Kruskal–Wallis test, Chi-square test, or Fisher's exact test, depending on data characteristics.

The effects of vaccination on isolation and viral shedding duration were examined using multivariable Cox regression models. Differences in negative and discharge rates among vaccine types and dosage groups were evaluated through Kaplan–Meier curves and multivariable Cox regression analyses. For missing Ct values, imputation was performed using the median Ct value of the respective positive or negative group from the same day. To address sample size disparities across vaccine

regimens, propensity score matching was applied in sensitivity analyses using nearest-neighbor matching with a 1:1 ratio and a caliper of 0.2 SD of the propensity score probit. A P-value < 0.05 was considered statistically significant. All analyses were conducted using R software (version 4.1.2, R Project for Statistical Computing, Vienna, Austria).

Results

Patient recruitment and baseline characteristics

A total of 6,560 COVID-19 patients were included, comprising 3,584 from Pazhou and 2,976 from Yongning. Patient baseline characteristics are summarized in **Table 1**. Among these, 69 individuals received heterologous vaccination combining inactivated and recombinant protein vaccines. Overall, 47.9% of participants were female, and the median age was 39 years. The majority (80.5%) were married. At admission, the median Ct values for the nucleocapsid (N) gene and ORF1ab gene were 31.6 and 29.0, respectively.

Table 1. Demographic and clinical characteristics of patients in two fangcang isolation centers

Characteristic	Total (n = 6560)	Not vaccinated (n = 387)	Only inactivated (n = 5873)	Heterologous (n = 69)	Other (n = 231)	P-value
Sex						
Female	3141 (47.9%)	168 (43.4%)	2843 (48.4%)	24 (34.8%)	106 (45.9%)	.031
Male	3419 (52.1%)	219 (56.6%)	3030 (51.6%)	45 (65.2%)	125 (54.1%)	
Age, median [Q1; Q3]	39.0 [32.0; 49.0]	39.0 [32.0; 51.0]	39.0 [33.0; 49.0]	34.0 [30.0; 41.0]	40.0 [32.0; 51.0]	.005
Center						
Pazhou	3584 (54.6%)	240 (62.0%)	3187 (54.3%)	25 (36.2%)	132 (57.1%)	< .001
Yongning	2976 (45.4%)	147 (38.0%)	2686 (45.7%)	44 (63.8%)	99 (42.9%)	
Marital status						
Married	5280 (80.5%)	276 (71.3%)	4770 (81.2%)	48 (69.6%)	186 (80.5%)	< .001
Other	1280 (19.5%)	111 (28.7%)	1103 (18.8%)	21 (30.4%)	45 (19.5%)	
Occupation						
Other	3489 (53.2%)	202 (52.2%)	3126 (53.2%)	38 (55.1%)	123 (53.2%)	.968
Worker	3071 (46.8%)	185 (47.8%)	2747 (46.8%)	31 (44.9%)	108 (46.8%)	
Province						
Guangdong	1261 (19.2%)	96 (24.8%)	1113 (19.0%)	8 (11.6%)	44 (19.0%)	
Hubei	3150 (48.0%)	186 (48.1%)	2849 (48.5%)	21 (30.4%)	94 (40.7%)	< .001
Other	2149 (32.8%)	105 (27.1%)	1911 (32.5%)	40 (58.0%)	93 (40.3%)	
Ct of N gene, median [Q1; Q3]	31.6 [31.6; 31.6]	31.6 [31.6; 31.6]	31.6 [31.6; 31.6]	31.6 [31.6; 31.6]	31.6 [31.6; 31.6]	.300
Ct of ORF gene, median [Q1; Q3]	29.0 [29.0; 29.0]	29.0 [29.0; 29.0]	29.0 [29.0; 29.0]	29.0 [29.0; 29.0]	29.0 [29.0; 29.0]	.401
Isolation center stay (days), median [Q1; Q3]	9.12 [6.86; 11.0]	9.78 [7.59; 11.4]	9.08 [6.85; 10.9]	8.38 [6.52; 10.4]	9.16 [6.79; 11.3]	< .001
Duration from yellow code to 1st NAT (days)						
Mean (SD)	10.5 (6.03)	11.3 (6.33)	10.5 (6.05)	10.8 (4.36)	9.84 (5.46)	.143
Missing	2540 (38.7%)	161 (41.6%)	2254 (38.4%)	35 (50.7%)	90 (39.0%)	
Duration from yellow code to 2nd NAT (days)						
Mean (SD)	12.7 (6.04)	13.4 (6.37)	12.7 (6.05)	12.6 (3.98)	12.3 (5.79)	.316
Missing	2935 (44.7%)	174 (45.0%)	2617 (44.6%)	38 (55.1%)	106 (45.9%)	
Duration to 1st NAT (days)						

Median [Q1;Q3]	7.42 [5.29; 9.51]	7.74 [5.40; 10.5]	7.41 [5.30; 9.47]	6.65 [4.63; 7.88]	7.51 [4.72; 9.78]	.003
Missing	74 (1.1%)	0 (0%)	72 (1.2%)	1 (1.4%)	1 (0.4%)	
Duration to 2nd NAT (days)						
Mean (SD)	11.9 (25.8)	11.8 (5.62)	11.7 (23.7)	9.37 (3.72)	20.3 (69.2)	.005
Missing	3032 (46.2%)	178 (46.0%)	2701 (46.0%)	36 (52.2%)	117 (50.6%)	
Inactivated vaccine						
No	618 (9.42%)	387 (100%)	0 (0.00%)	0 (0.00%)	231 (100%)	< .001
Yes	5942 (90.6%)	0 (0.00%)	5873 (100%)	69 (100%)	0 (0.00%)	
Recombinant protein vaccine						
No	6320 (96.3%)	387 (100%)	5873 (100%)	6 (8.70%)	54 (23.4%)	< .001
Yes	240 (3.66%)	0 (0.00%)	0 (0.00%)	63 (91.3%)	177 (76.6%)	
Adenovirus type-5 (Ad5) vectored COVID-19 vaccine						
No	6500 (99.1%)	387 (100%)	5873 (100%)	63 (91.3%)	177 (76.6%)	< .001
Yes	60 (0.91%)	0 (0.00%)	0 (0.00%)	6 (8.70%)	54 (23.4%)	
Booster status						
Not vaccinated	387 (5.90%)	387 (100%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
One or two doses	1736 (26.5%)	0 (0.00%)	1606 (27.3%)	22 (31.9%)	108 (46.8%)	N/A
Booster	4437 (67.6%)	0 (0.00%)	4267 (72.7%)	47 (68.1%)	123 (53.2%)	
****Duration from last vaccine to onset (months)**[1]**						
Median (SD)	11.4 (3.10)	N/A	11.4 (3.04)	9.66 (4.77)	12.2 (3.70)	< .001
Missing	242 (3.9%)	N/A	221 (3.8%)	4 (5.8%)	17 (7.4%)	
****Category of duration from last vaccine to onset (months)**[1]**						
< 12	4128 (62.9%)	0 (0.00%)	3998 (68.1%)	41 (59.4%)	89 (38.5%)	
≥ 12	1803 (27.5%)	0 (0.00%)	1654 (28.2%)	24 (34.8%)	125 (54.1%)	< .001
Missing	629 (9.59%)	387 (100%)	221 (3.76%)	4 (5.80%)	17 (7.36%)	

[1]Includes only vaccinated cases (n = 6173).

In this study population, most participants (90.6%) had received inactivated COVID-19 vaccines, whereas 3.06% were administered recombinant SARS-CoV-2 spike protein subunit vaccines, and 0.85% received adenovirus-based vaccines. Among the 6,173 vaccinated individuals, nearly three-quarters (71.9%) had obtained a booster dose, with 67.3% having received their most recent vaccine within the year preceding infection.

Isolation Duration and Discharge Outcomes in Vaccinated Versus Unvaccinated Patients

Analysis of isolation trends revealed that 50% of vaccinated patients remained in isolation until day 9, while an equivalent proportion of unvaccinated patients were discharged by day 10 ($P < .001$; **Figure 1(A)). Table 2**) summarizes the baseline characteristics for both groups. After adjusting for potential confounders including sex, age, marital status, and geographic location, vaccination was associated with a significantly faster discharge, with vaccinated individuals having a 21.1% higher likelihood of being released from isolation within 14 days compared to unvaccinated individuals (hazard ratio [HR] = 1.211; 95% confidence interval [CI]: 1.084–1.351; $P < .001$) **(Figure 1(B))**.

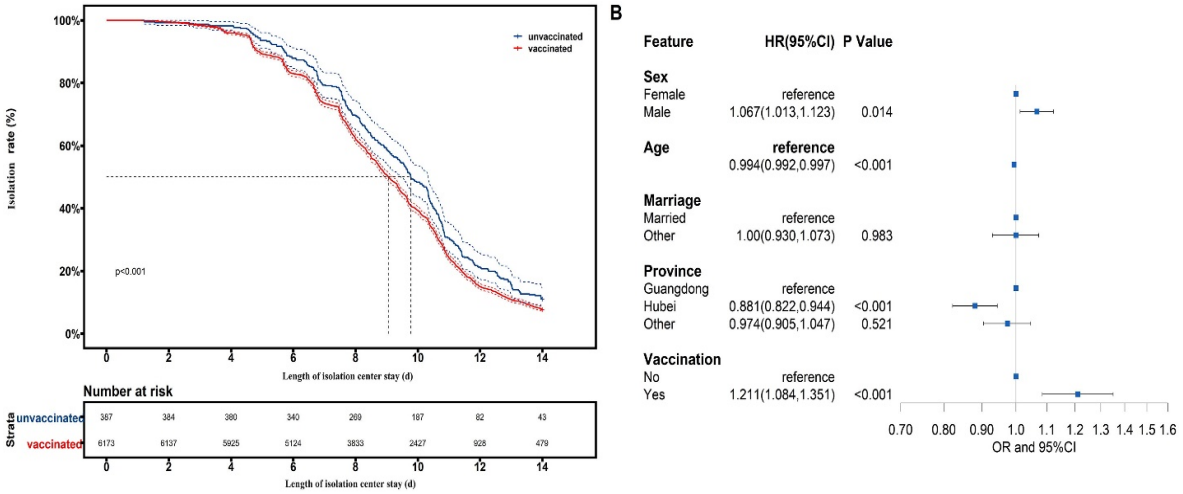

Figure 1. Impact of vaccination on 14-day isolation outcomes: (A) Isolation trends among vaccinated versus unvaccinated patients. The red line indicates the proportion of vaccinated individuals remaining in isolation, while the blue line shows the corresponding rate for unvaccinated individuals. (B) The likelihood of discharge from the isolation center within 14 days for vaccinated and unvaccinated groups is also shown.

Table 2. Baseline characteristics of vaccinated vs. unvaccinated populations

Characteristic	Total (n = 6560)	Unvaccinated (n = 387)	Vaccinated (n = 6173)	P-value
Sex				
Female	3141 (47.9%)	168 (43.4%)	2973 (48.2%)	.078
Male	3419 (52.1%)	219 (56.6%)	3200 (51.8%)	
Age, median [Q1; Q3]	39.0 [32.0; 49.0]	39.0 [32.0; 51.0]	39.0 [32.0; 49.0]	.264
Center				
Pazhou	3584 (54.6%)	240 (62.0%)	3344 (54.2%)	.003
Yongning	2976 (45.4%)	147 (38.0%)	2829 (45.8%)	
Marital status				
Married	5280 (80.5%)	276 (71.3%)	5004 (81.1%)	<.001
Other	1280 (19.5%)	111 (28.7%)	1169 (18.9%)	
Occupation				
Other	3489 (53.2%)	202 (52.2%)	3287 (53.2%)	.727
Worker	3071 (46.8%)	185 (47.8%)	2886 (46.8%)	
Province				
Guangdong	1261 (19.2%)	96 (24.8%)	1165 (18.9%)	
Hubei	3150 (48.0%)	186 (48.1%)	2964 (48.0%)	.005
Other	2149 (32.8%)	105 (27.1%)	2044 (33.1%)	
Ct of N gene, median (SD)	31.6 (0.83)	31.7 (0.85)	31.6 (0.83)	.381
Ct of ORF gene, median (SD)	29.0 (0.87)	29.1 (0.84)	29.0 (0.87)	.255
Isolation center stay (days), median [Q1; Q3]	9.12 [6.86; 11.0]	9.78 [7.59; 11.4]	9.07 [6.84; 11.0]	<.001
Duration from yellow code to 1st NAT (days)				
Mean (SD)	10.5 (6.03)	11.3 (6.33)	10.5 (6.01)	.063
Missing	2540 (38.7%)	161 (41.6%)	2379 (38.5%)	
Duration from yellow code to 2nd NAT (days)				
Mean (SD)	12.7 (6.04)	13.4 (6.37)	12.6 (6.02)	.096
Missing	2935 (44.7%)	174 (45.0%)	2761 (44.7%)	
Duration to 1st NAT (days)				
Median [Q1;Q3]	7.42 [5.29; 9.51]	7.74 [5.40; 10.5]	7.41 [5.28; 9.47]	.002
Missing	74 (1.1%)	0 (0%)	74 (1.2%)	
Duration to 2nd NAT (days)				
Mean (SD)	11.9 (25.8)	11.8 (5.62)	11.9 (26.5)	.777
Missing	3032 (46.2%)	178 (46.0%)	2854 (46.2%)	

Viral Clearance and Negative Test Trends in Vaccinated Versus Unvaccinated Patients

Analysis of viral shedding revealed that half of the vaccinated participants had converted to negative COVID-19 test results by approximately day 7.5. In contrast, unvaccinated individuals reached the same milestone slightly later, around day 8 (P < .001; **Figure 2(A)**). When adjusting for confounding factors such as age, sex, marital status, and geographic region, vaccination was associated with a faster rate of viral clearance, with vaccinated patients exhibiting a 23.9% higher probability of achieving negative tests within 14 days compared to those

unvaccinated (hazard ratio [HR] = 1.239; 95% confidence interval [CI]: 1.113–1.378; P < .001) (Figure 2(B)).

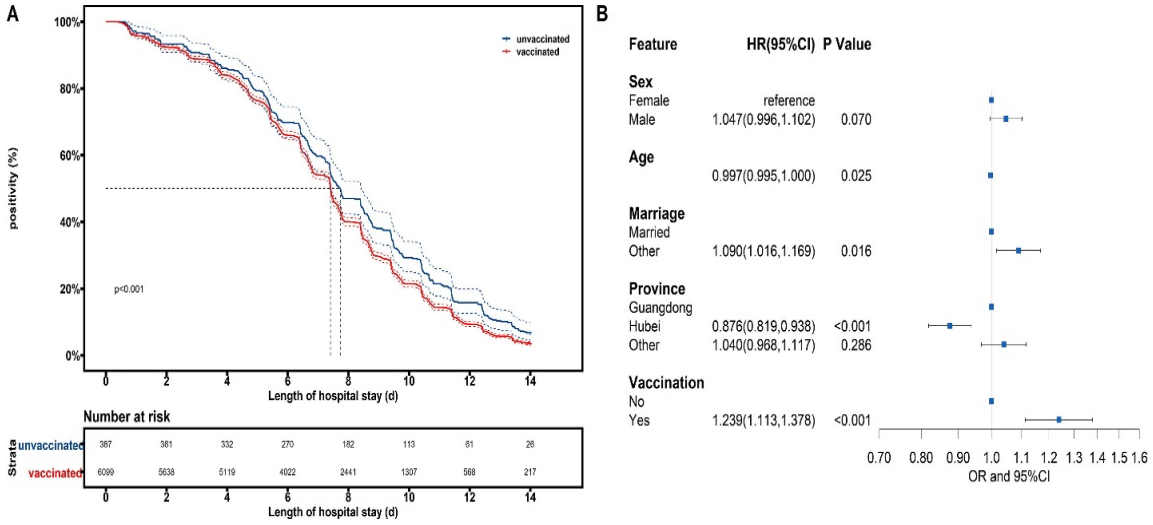

Figure 2. Effect of vaccination on 14-Day positivity outcomes: (A) Trends in positivity rates during isolation among patients receiving different vaccine types and doses. The red line depicts the proportion of vaccinated individuals remaining positive. In contrast, the blue line shows the corresponding trend for unvaccinated patients. (B) Likelihood of achieving negative test results within 14 days across vaccine types and dosage groups.

Comparison of Isolation Duration and Discharge Between Heterologous and Inactivated Vaccine Recipients

Among all vaccinated participants, half were discharged by approximately day 8, whereas unvaccinated individuals reached the same milestone around day 9. Importantly, patients who received heterologous vaccination displayed a higher probability of discharge within 14 days compared with those receiving only inactivated vaccines or other regimens (P = 0.029; **Figure 3(A)**). Baseline characteristics for patients across different vaccination strategies are summarized in **Table 3**.

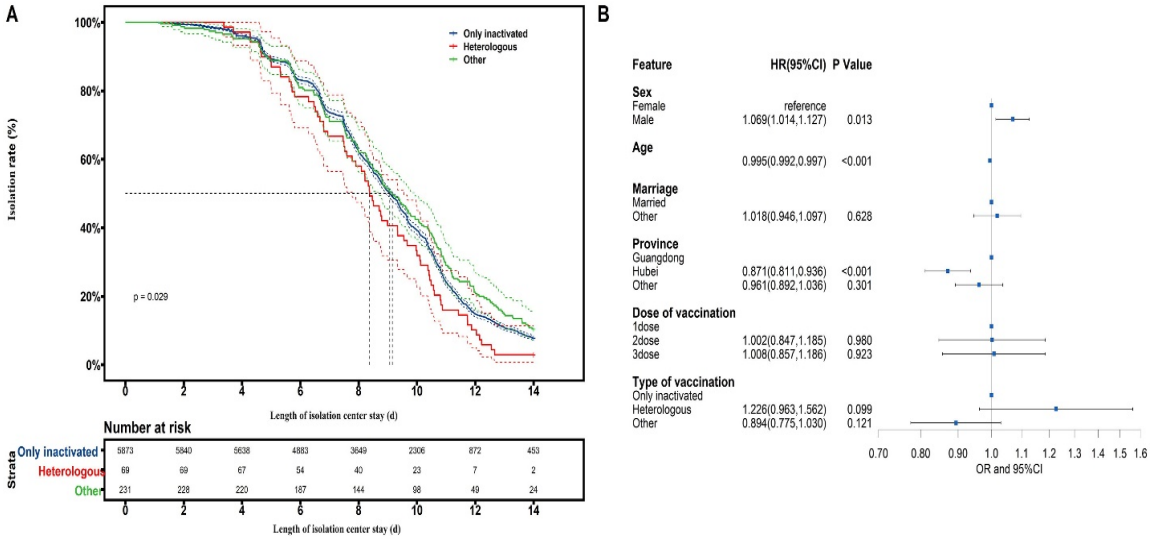

Figure 3. Influence of vaccine type and dosage on 14-day isolation outcomes: (A) Isolation trends during the observation period according to vaccine regimen. The blue line represents patients who received only inactivated vaccines, the red line indicates those with heterologous vaccination, and the green line shows patients on other vaccination schedules. (B) Probability of discharge within 14 days across different vaccine types and dosing regimens

Table 3. Comparison of baseline characteristics across different vaccination regimens

Characteristic	Total (n = 6173)	Only Inactivated (n = 5873)	Heterologous (n = 69)	Other (n = 231)	P-value
Sex					
Female	2973 (48.2%)	2843 (48.4%)	24 (34.8%)	106 (45.9%)	.062
Male	3200 (51.8%)	3030 (51.6%)	45 (65.2%)	125 (54.1%)	
Age, median [Q1; Q3]	39.0 [32.0; 49.0]	39.0 [33.0; 49.0]	34.0 [30.0; 41.0]	40.0 [32.0; 51.0]	.003
Center					
Pazhou	3344 (54.2%)	3187 (54.3%)	25 (36.2%)	132 (57.1%)	.007
Yongning	2829 (45.8%)	2686 (45.7%)	44 (63.8%)	99 (42.9%)	
Marital status					
Married	5004 (81.1%)	4770 (81.2%)	48 (69.6%)	186 (80.5%)	.048
Other	1169 (18.9%)	1103 (18.8%)	21 (30.4%)	45 (19.5%)	
Occupation					
Other	3287 (53.2%)	3126 (53.2%)	38 (55.1%)	123 (53.2%)	.954
Worker	2886 (46.8%)	2747 (46.8%)	31 (44.9%)	108 (46.8%)	
Province					
Guangdong	1165 (18.9%)	1113 (19.0%)	8 (11.6%)	44 (19.0%)	
Hubei	2964 (48.0%)	2849 (48.5%)	21 (30.4%)	94 (40.7%)	<.001
Other	2044 (33.1%)	1911 (32.5%)	40 (58.0%)	93 (40.3%)	
Ct of N gene, median [Q1; Q3]	31.6 [31.6; 31.6]	31.6 [31.6; 31.6]	31.6 [31.6; 31.6]	31.6 [31.6; 31.6]	.420
Ct of ORF gene, median [Q1; Q3]	29.0 [29.0; 29.0]	29.0 [29.0; 29.0]	29.0 [29.0; 29.0]	29.0 [29.0; 29.0]	.344
Isolation center stay (days), median [Q1; Q3]	9.05 [6.83; 10.9]	9.07 [6.84; 10.9]	8.38 [6.52; 10.4]	9.16 [6.79; 11.3]	.169
Duration from yellow code to 1st NAT (days)					
Mean (SD)	10.5 [5.61; 13.8]	10.6 [5.59; 13.8]	11.8 [8.61; 13.8]	9.75 [5.83; 12.9]	.312
Missing	2380 (38.6%)	2255 (38.4%)	35 (50.7%)	90 (39.0%)	
Duration from yellow code to 2nd NAT (days)					
Mean (SD)	12.6 [8.09; 15.9]	12.6 [8.00; 16.0]	12.6 [10.6; 15.4]	12.3 [8.61; 14.7]	.685
Missing	2762 (44.7%)	2618 (44.6%)	38 (55.1%)	106 (45.9%)	
Duration to 1st NAT (days), median [Q1; Q3]	7.41 [5.29; 9.48]	7.41 [5.31; 9.48]	6.66 [4.69; 8.42]	7.51 [4.72; 10.0]	.117
Duration to 2nd NAT (days)					
Mean (SD)	10.4 [8.43; 12.5]	10.4 [8.44; 12.5]	8.44 [7.61; 10.7]	10.8 [9.38; 12.7]	.007
Missing	2855 (46.2%)	2702 (46.0%)	36 (52.2%)	117 (50.6%)	
Doses of vaccination					
1 dose	174 (2.82%)	128 (2.18%)	0 (0.00%)	46 (19.9%)	
2 doses	1562 (25.3%)	1478 (25.2%)	22 (31.9%)	62 (26.8%)	N/A
3 doses	4437 (71.9%)	4267 (72.7%)	47 (68.1%)	123 (53.2%)	
****Duration from last vaccine to onset (months)**[1]**					
Median (SD) [1]	11.4 (3.10)	11.4 (3.04)	9.66 (4.77)	12.2 (3.70)	< .001
Missing	242 (3.9%)	221 (3.8%)	4 (5.8%)	17 (7.4%)	
****Category of duration from last vaccine to onset (months)**[1]**					
< 12	4128 (66.9%)	3998 (68.1%)	41 (59.4%)	89 (38.5%)	
≥ 12	1803 (29.2%)	1654 (28.2%)	24 (34.8%)	125 (54.1%)	N/A
Missing	242 (3.92%)	221 (3.76%)	4 (5.80%)	17 (7.36%)	

[1]Includes only vaccinated cases (n = 6173).

To explore whether the type of vaccine influenced isolation outcomes—specifically the likelihood of discharge from the isolation center within 14 days—a detailed analysis was performed, adjusting for potential confounders including sex, age, marital status, province of residence, and number of vaccine doses. The findings indicated no statistically significant difference in 14-day isolation rates between patients receiving heterologous vaccination and those who had only inactivated vaccines (hazard ratio [HR] = 1.226; 95% confidence interval [CI]: 0.963–1.562; P = 0.099) **(Figure 3(B))**. These results suggest that, within the 14-day observation window, both vaccination strategies yielded comparable outcomes in terms of isolation.

Comparison of Viral Shedding Duration and Positive Test Rates Between Heterologous and Inactivated Vaccine Recipients

Between days 6 and 8, approximately 50% of patients tested positive for COVID-19. When comparing viral shedding durations, patients who received either inactivated vaccines alone or heterologous vaccination exhibited shorter viral shedding periods compared with other vaccination groups (P = 0.015). Notably, individuals who received heterologous vaccination cleared the virus

more quickly than those vaccinated solely with inactivated vaccines (P = 0.011) **(Figure 4(A))**.

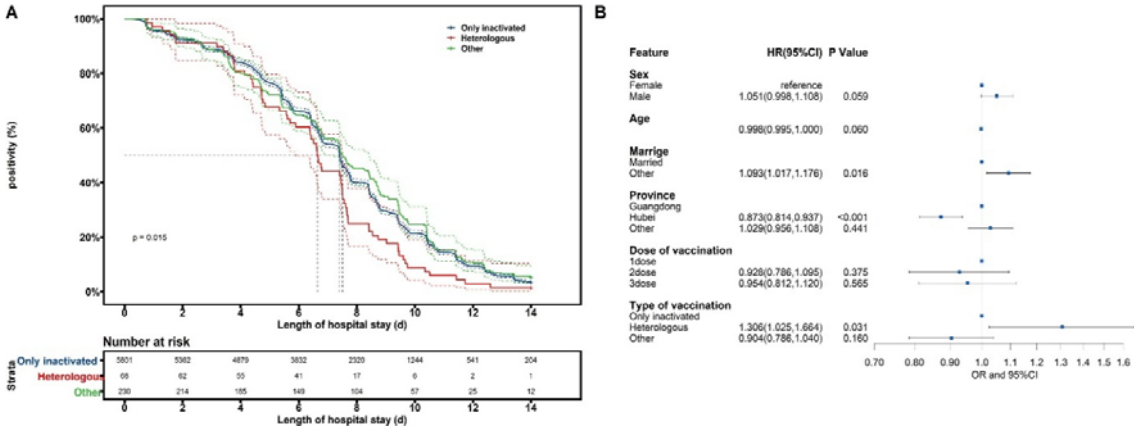

Figure 4. Effect of vaccine type and dosage on 14-day positivity: (A) Positivity trends during isolation according to different vaccine regimens. The blue line represents patients who received only inactivated vaccines, the red line indicates those with heterologous vaccination, and the green line reflects patients on other vaccine schedules. (B) Probability of achieving negative test results within 14 days across various vaccine types and dosing strategies

After adjusting for potential confounding factors, patients who had received heterologous vaccination demonstrated a higher likelihood of achieving viral clearance within 14 days compared with individuals vaccinated solely with inactivated vaccines (hazard ratio [HR] = 1.306; 95% confidence interval [CI]: 1.025–1.664; P = 0.031) (Figure 4(B)). The relationship between the timing of vaccination and outcomes such as discharge rate and positivity of Ct values is illustrated in Figures E1 and E2.

Sensitivity analysis

Propensity score–matched sensitivity analyses revealed that heterologous vaccination was associated with a significantly shorter isolation period compared with inactivated vaccine alone (HR = 1.729; 95% CI: 1.197–2.497; P = 0.004). Similarly, the probability of viral clearance within 14 days was higher for the heterologous group versus the inactivated vaccine group (HR = 1.577; 95% CI: 1.115–2.232; P = 0.010). Detailed results of these analyses are provided in Tables E2–E4.

Discussion

This multi-center study enrolled patients with asymptomatic or mild COVID-19 to evaluate how vaccine type and dosage influenced hospital stay duration and time to viral clearance. The main findings include:

1. Patients who had received two vaccine doses exhibited a higher likelihood of discharge from isolation within 14 days compared with unvaccinated individuals. Moreover, heterologous vaccination was associated with faster conversion to negative test results than inactivated vaccines alone.
2. The interval from the last vaccine dose to infection—whether greater or less than 12 months—did not significantly alter discharge or negativity rates within 14 days, supporting the continued effectiveness of COVID-19 vaccination.
3. Heterologous vaccination regimens demonstrated superior efficacy relative to other vaccine approaches.

Our findings align with existing evidence that complete vaccination reduces the duration of COVID-19-related isolation and provides protection against infection [20]. Clinical trials report the WIVO4 inactivated vaccine to be 72.8% effective and the HB02 inactivated vaccine 78.1% effective [5]. Observational data from Shanghai further indicate that vaccinated individuals experienced milder symptoms compared with unvaccinated individuals (risk ratio = 0.92; P < 0.001) [21].

Analysis of booster effects revealed no significant differences in isolation duration or viral shedding among patients receiving additional doses. Although vaccine effectiveness against SARS-CoV-2 variants may decline, booster doses restore protection by enhancing neutralizing antibody responses, showing good efficacy against variants such as Omicron [22, 23]. Evidence suggests that three-dose regimens outperform two-dose regimens in neutralizing Omicron, with vaccine effectiveness (VE) observed at 55.9% for complete vaccination and 80.8% for booster vaccination [23]. In a Hong Kong cohort, BNT162b2 booster recipients experienced fewer symptoms (adjusted HR = 0.59; 95% CI: 0.45–0.77) [24], and a UK study demonstrated reduced disease severity across age groups following vaccination [25].

While the primary goal of vaccination remains prevention of severe disease, protection against mild cases is limited, especially as new variants emerge that may evade existing

immunity. Continuous adaptation of vaccine formulations to match circulating strains—similar to the annual influenza vaccines—is crucial for maintaining efficacy as the virus evolves [8].

Numerous studies have highlighted the strong efficacy of the adenovirus type-5 (Ad5) vectored COVID-19 vaccine [26], while additional research indicates that mRNA vaccines provide even higher protection [27]. Evidence also supports the effectiveness of a single-dose recombinant protein vaccine [28]. In the current study, we specifically aimed to investigate whether heterologous vaccination confers greater benefits compared with using only inactivated vaccines. It has been suggested that implementing mass vaccination campaigns with multiple vaccine types can improve overall vaccination coverage [29]. Our results demonstrate that by day 8.5 of isolation, half of the patients who received heterologous vaccination had been discharged, and 50% had achieved a negative COVID-19 test by day 6.5. These patients also showed higher rates of discharge and faster viral clearance within 14 days compared with individuals receiving other vaccine regimens. In addition, the single-dose adenovirus-vectored vaccine, which has completed phase III trials, was reported to be 66% effective within 14 days of vaccination, 67% effective within 28 days, and 77% effective against moderate to severe COVID-19 [28]. Taken together, these findings underscore the potential advantages of heterologous vaccination and support strategies involving the use of multiple vaccine types in mass vaccination programs.

Another key focus of this study was to determine whether vaccine effectiveness depends on the timing of infection. Our analysis showed no significant differences in discharge rates or time to achieve negative test results between patients infected more than 12 months after their last vaccination and those infected within 12 months. Nevertheless, prior evidence indicates that vaccine-induced protection gradually wanes after approximately six months [30]. Although neutralizing antibody levels decline over time, vaccines continue to provide over 70% effectiveness in preventing severe disease and death. This suggests that protection against severe outcomes is not solely dependent on antibodies but also involves long-lasting memory and cell-mediated immune responses, which contribute to sustained immunity [7, 8, 30].

Cycle threshold (Ct) values serve as a relevant measure of viral infectivity, with Ct values above 33 from surface samples considered to have limited epidemiological significance [31]. Several studies indicate that vaccination reduces SARS-CoV-2 viral load. For instance, an Irish survey found that unvaccinated individuals had 2–4 times higher viral loads in nasal mucosa samples compared with vaccinated participants [32]. Similarly, another study reported that partially or fully vaccinated individuals exhibited a 40% lower mean viral RNA load compared with unvaccinated individuals (95% CI = 16–57) [33]. Additionally, research has shown that vaccination reduced the viral load of Delta breakthrough infections within two months of vaccination [34]. It is important to note, however, that these findings are not directly comparable to our study, which relied on observational data and only recorded Ct values at admission. Since Ct values tend to rise as symptoms progress, assessments of viral load may be affected by timing.

This study has several limitations. First, it was restricted to patients with asymptomatic or mild COVID-19 in isolation centers, limiting the ability to evaluate vaccine effects on severe disease. Although comorbidities can influence hospital stay and time to viral clearance, our cohort mainly included individuals with no or mild symptoms, as patients with severe illness were not admitted to these centers. Consequently, this study does not address the impact of comorbidities on vaccine effectiveness. Moreover, the high vaccination coverage in China, exceeding 90% in our sample, resulted in small numbers of individuals receiving heterologous vaccination or remaining unvaccinated. This imbalance in vaccine regimens may introduce bias. To mitigate this, we applied multivariate and sensitivity analyses. Nevertheless, as an observational study, our findings should be interpreted cautiously. Continuous data updates and rigorous evaluation are crucial to ensure that public health policies are grounded in robust scientific evidence [8].

Conclusions

Within 14 days, vaccinated individuals exhibited faster viral clearance and shorter isolation times compared with those who were unvaccinated, highlighting the protective effect of COVID-19 vaccination. Heterologous vaccination strategies proved more effective than using inactivated vaccines alone. Importantly, no significant decline in protection was observed within 12 months following vaccination, demonstrating sustained vaccine efficacy over time.

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