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Comparing the protection of heterologous booster of inhaled Ad5-nCoV vaccine and hybrid immunity against Omicron BA.5 infection: a cohort study of hospital staff in China

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Abstract

Background After the exit "zero-COVID" strategy in mainland China by the end of 2022, a large-scale COVID-19 outbreak seeded by Omicron variants occurred. An inhaled adenovirus type-5 vector-based (i.e., inhaled Ad5-nCoV) COVID-19 vaccine was licensed earlier in 2021. In this study, we aimed to assess the real-world effectiveness of a heterologous booster of inhaled Ad5-nCoV vaccine against Omicron infection and compared with the protection from hybrid immunity (i.e., prior breakthrough infection).

Methods In this retrospective cohort study, we identified 1087 out of a total of 1146 hospital staff from a tertiary hospital in Urumqi city, China from November 22 to December 29, 2022. Demographic characteristics, baseline health status, occupation, behavioral factors, laboratory test of serological IgG antibody, and timeline from immunization to laboratory-testing outcome were obtained. We analysed the individual-level vaccination status of inhaled Ad5-nCoV vaccine, prior SARS-CoV-2 infection status and baseline vaccination status, and other risk factors before follow-up. The protective effects of the heterologous inhaled Ad5-nCoV vaccine and hybrid immunity against Omicron BA.5 infection and hospitalization were calculated as relative rate reduction (RRR), which was estimated using multivariate Poisson regression models.

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Results A total of 1087 hospital staff (median age of 34 years, and 343 males [31.6%]), including 931 accepted for serological antibody tests, were recruited to assess the vaccine effectiveness (VE) of the inhaled Ad5-nCoV booster and hybrid immunity. Among the 1087 participants, 413 had a history of prior SARS-CoV-2 infection (before follow-up) but did not receive an inhaled Ad5-nCoV booster, and 674 reported no prior infection, including 390 who received an inhaled Ad5-nCoV booster. The highest serological IgG antibody level was detected among the inhaled Ad5-nCoV group, with a median of 294.59 S/CO, followed by the hybrid immunity group, with a median of 93.65 S/CO compared to the reference level of the inactivated vaccine group (most of whom received the Sinopharm/BBIBP-CorV vaccine). The inhaled Ad5-nCoV booster and hybrid immunity yielded RRRs of 41.9% (95% CI: 24.8, 55.0) and 97.9% (95% CI: 94.2, 99.2), respectively, against Omicron BA.5 infection, regardless of symptom status.

Conclusion We found that hybrid immunity could provide a high level of protection against Omicron infection, while a heterologous inhaled Ad5-nCoV booster conferred a moderate level of protection. Our findings supported the rollout of a heterologous vaccination strategy regardless of preexisting vaccine coverage.

Keywords SARS-CoV-2, Inhaled Ad5-nCoV vaccine, Vaccine effectiveness, Serological IgG antibody

Research in context

Evidence before this study

With the rapid evolution of SARS-CoV-2, previous understanding of the protective performance of various types of COVID-19 vaccines against Omicron variants becomes increasingly important. We examined the evidence in the literature for the protective performance of inhaled adenovirus type-5 vector-based (Ad5-nCoV) COVID-19 vaccine against SARS-CoV-2. As the inhaled Ad5-nCoV vaccine was licenced since early 2021, we searched PubMed using the terms ((“eff*”) AND (“SARS-CoV-2” OR “COVID*” OR “Omicron” OR “B.1.1.529”) AND (“Ad5-nCoV”)) for articles published from January 1, 2021 to December 31, 2022. We found two peer-reviewed studies that reported the safety, immunogenicity, and protective effects of inhaled Ad5-nCoV vaccine against SARS-CoV-2 infections for genetic strains that occurred before Delta variants, under the setting of randomized clinical trials. We did not identify any peer-reviewed observational study that assessed the inhaled Ad5-nCoV vaccine effectiveness (VE) against Omicron BA.5 variants using real-world individual-level data. Owning to the previous “zero-COVID” policy in mainland China, COVID-19 was at a relatively low level before December 2022, and thus no VE estimate of inhaled Ad5-nCoV against Omicron infection in mainland China was reported.

Added value of this study

After the exit “zero-COVID” strategy in mainland China in December 2022, a historical large-scale COVID-19 outbreak seeded by Omicron variants occurred. We aimed to assess the effectiveness of the heterologous booster of inhaled Ad5-nCoV vaccine against Omicron infection, and compared it with the protective performance of hybrid immunity (i.e., prior breakthrough infection). We identified 1087 out of a total of 1146 hospital staff from a tertiary hospital in Urumqi city, the capital and largest city in Xinjiang Uygur Autonomous Region of China, from November 22 to December 29, 2022. The highest serological IgG antibody level was detected among the inhaled Ad5-nCoV group, followed by the hybrid immunity group compared to the inactivated vaccine group (most of whom received the Sinopharm/BBIBP-CorV vaccine). The inhaled Ad5-nCoV booster and hybrid immunity yielded RRRs of 41.9% (95% CI: 24.8, 55.0) and 97.9% (95% CI: 94.2, 99.2), respectively, against Omicron BA.5 infection. These findings were the first estimates of inhaled Ad5-nCoV VE against Omicron BA.5 variants.

Implications of all the available evidence

Moderate but significant protective effects against Omicron BA.5 infection were found for the booster doses of inhaled Ad5-nCoV vaccine, whereas hybrid immunity could provide a high level of protection. The VE estimates were important contributions to inform the vaccination policy in places where inhaled Ad5-nCoV vaccine were in use. Our findings supported the rollout of a heterologous vaccination strategy regardless of pre-existing vaccine coverage.

Introduction

The persistent spread of SARS-CoV-2 Omicron variants, which is characterized by enhanced transmissibility and immune escape from both natural and vaccine-induced immunity, has led to unprecedented challenges to restrict the spread of the infection [1, 2]. The global COVID-19 pandemic has been persistently fueled by the SARS-CoV-2 Omicron variant, declared the fifth variant of concern (VOC) by the World Health Organization (WHO) in November 2021 [3]. The current pandemic is dominated by the Omicron BA.5 variant and its descendant lineages, first detected in South Africa in February 2022, which accounted for more than 78.9% of all viral sequences sampled globally during epidemiological week 39 (i.e.,

from September 26 to October 2, 2022) [4]. Additionally, the Omicron BA.5 variant and its descendant lineages accounted for 68.1% of globally sequenced lineages as of January 8, 2023[5]. In vitro studies have shown evidence of reduced neutralizing antibody titers induced by prior SARS-CoV-2 Omicron infection [5] or by vaccination [6] among individuals infected by the Omicron BA.5 variant compared to earlier circulating Omicron subvariants. Since the beginning of the COVID-19 pandemic, healthcare workers have been at higher risk of infection than the general population due to their prolonged duration of exposure and interaction with infected individuals, fomites, and aerosols in healthcare-related facilities [7]. Isolation of frontline healthcare workers could pose an additional burden to healthcare services that are already overwhelmed during the ongoing epidemic.

Encouragingly, with the rapid development and rollout of the COVID-19 vaccine, vaccination among healthcare workers has been prioritized in many regions, including China [8, 9]. Real-world observational studies conducted among healthcare workers indicated that one or two doses of adenovirus vector or mRNA vaccine in relation to the wild-type strain or the Delta variant conferred considerable vaccine effectiveness (VE) against infection [10, 11], death, and hospitalizations [10, 12]. However, the VE may be significantly compromised for the Omicron variant; thus, booster doses of COVID-19 vaccination are needed, especially to protect high-risk groups such as healthcare personnel. Although homologous prime boosting is considered normal practice, studies have demonstrated that a heterologous booster could provide enhanced immunogenicity, enhanced antibody responses, and decreased reactogenicity, thereby increasing the VE [13–16]. In addition, the protective effect might even be more potent when someone has a hybrid form of immunity, that is, a combination of prior infection and vaccination, compared to vaccination alone or natural immunity alone [17, 18]. Due to the high risk of breakthrough infection and reinfection during the Omicron predominant phase [19, 20], it is necessary to evaluate the protective effects of hybrid immunity and additional vaccinations against Omicron variants [21].

Although most of the available vaccines are injected intramuscularly, aerosolized vaccines are found to provide additional protection by provoking the IgA immune response that defends the upper respiratory tract, which could reduce virus replication and shedding and thus limit the risks of infection and transmission [22–25]. Randomized clinical trials have reported that an inhaled adenovirus type-5 vector-based COVID-19 vaccine (i.e., inhaled Ad5-nCoV) was safe and well-tolerated [26, 27], with a high immunogenicity profile in people with a heterologous vaccination regimen [27–29]. Given that the regular intramuscular vaccine requires strict conditions for storage and trained healthcare personnel to deliver, the inhaled vaccine is promising due to its ease of administration and could particularly be helpful for lower-income and/or developing countries. In China, the inhaled Ad5-nCoV vaccine developed by the CanSinoBIO company has been granted emergency use authorization since October 2022 30]. The real-world effectiveness of a booster dose of inhaled Ad5-nCoV against the circulating Omicron subvariant has yet to be investigated among healthcare workers, and such data would be critical in guiding the vaccination policy.

In this study, we recruited a cohort involving all hospital staff members in a tertiary hospital in Xinjiang, China, and we compared the protective effects of previous SARS-CoV-2 infection and a heterologous booster-dose regimen of inhaled Ad5-nCoV vaccine against the Omicron BA.5 variant.

Methods

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Setting, study design and population

The "zero COVID" was in effect before December 2022; accordingly, Urumqi, the capital and largest city of Xinjiang Uygur Autonomous Region, China, had a relatively low incidence of COVID-19, such that over 99% of the population was infection-naive before August 2022. The "Zero COVID" strategy refers to a control approach aimed at achieving "Zero COVID" in the prevention and control of the COVID-19 pandemic. This strategy includes several key components, including rapid response, mass testing, localized lockdowns, and the dynamic adjustment of control measures based on the evolving situation of the epidemic, all aiming to achieve "zero COVID" in the pandemic [31]. Since then, COVID-19 outbreaks induced by Omicron BA.5 variants (confirmed by whole genome sequencing and classified using PANGO lineage assignment; the results were reported by the CDC of Urumqi city, data not shown) emerged at the community level [32, 33]. The city-level number of cases increased slowly between August 2022 and December 2022. Then, when the "zero COVID" strategy was suspended in mainland China in December 2022, the number of cases rapidly increased. As of December 2022, the majority of the general population in Urumqi was vaccinated, with vaccination coverage of over 90% for 2-dose inactivated COVID-19 vaccines (most individuals received the Sinopharm/BBIBP-CorV vaccine; a few individuals received the CoronoVac/Sinovac vaccine) and over 60% for the booster dose [34]. These vaccination coverages were even higher among hospital staff.

This retrospective cohort study aimed to assess the effectiveness of the inhaled Ad5-nCoV vaccine booster and compare it to the protective effect provided by previous SARS-CoV-2 infections among vaccinated healthcare workers. The study population included all hospital staff from the Sixth Affiliated Hospital of Xinjiang Medical University, a tertiary hospital in Urumqi. Participants were recruited from December 26 to 29. We excluded individuals who had received their vaccine within 14 days before enrollment. Enrolled subjects were asked to complete a questionnaire to report demographic information, baseline health status, occupation, vaccination status, history of SARS-CoV-2 infection, and behavioral factors.

Variable of interest

The Ad5-nCoV vaccine was administered intranasally to hospital staff who were not previously infected with SARS-CoV-2 from the Sixth Affiliated Hospital of Xinjiang Medical University from November 22 to 23, 2022. The vaccine status of inhaled Ad5-nCoV vaccine was the primary variable of interest. As we also aimed to evaluate the protective effect of immunity from previous breakthrough infection (among populations with prior vaccination) against Omicron BA.5, history of breakthrough infections before follow-up was the secondary variable of interest and was also used to assess the protective effect of the inhaled Ad5-nCoV vaccine. As such, eligible subjects were divided into three groups: individuals without prior infection and without inhaled vaccine (reference group), individuals without prior SARS-CoV-2 infection but with inhaled vaccine (I-Ad5 group), and individuals with prior infection but without inhaled vaccine (hybrid immunity group, defined as the hospital staff with a prior infection who were previously vaccinated intramuscularly).

Outcomes

The primary outcome of this study is Omicron BA.5-related infection, regardless of symptom status and hospital admission. SARS-CoV-2 infection was determined by reverse transcription polymerase chain reaction (RT−PCR). The follow-up of the enrolled hospital staff started on November 24, 2022, and ended upon the date of the occurrence of the outcome or the end date of the study period (December 29), whichever occurred first. For the I-Ad5 group, there were no Omicron infections reported from November 24 to 29 (i.e., 7 days after the uptake of inhaled Ad5-nCoV); thus, lagging the follow-up period by one week would not change our main findings. Sensitivity analyses were performed, but the results are not shown herein. The infection status (RT−PCR test results) was updated every 2 days during the follow-up period. We collected the following data from each participant: age, sex, ethnicity (Han, Uyghur, Hui, Kazakh, Mongol, other ethnic minorities), occupation (doctor, nurse, medical technician, nonmedical supporting staff, and others), number of existing comorbidities, body mass index (BMI), vaccination status before follow-up, number of household members, self-reported anticipated exposure to SARS-CoV-2 in the workplace since follow-up, anticipated exposure to SARS-CoV-2 in the community or household since follow-up, smoking exposure levels, and drinking status (lifetime abstainer, former drinker for >6 months, and current drinker).

The secondary outcome was serological IgG antibody titer, which was measured to assess the immunogenicity of enrolled participants who provided blood samples. Three microliters of venous blood were collected from the arm between December 27 and 28 at the laboratory test center in the hospital, and an IgG diagnostic test was performed immediately after sample collection, approximately 40 days after the vaccination on November 22–23, 2022. This timeframe allows for an adequate assessment of the antibody response, which typically begins to develop around two weeks after vaccination [35–37]. The magnetic particle chemiluminescence method was adopted to detect IgG-specific antibodies against the RBD of the SARS-CoV-2 spike protein in human serum samples. The IgG test kit used in this study was the Diagnostic Kit for Novel Coronavirus (2019-nCoV) IgG Antibody (Magnetic particle CLIA) developed by Autobio Diagnostics Co., Ltd. The relative light unit (RLU) could be read from the IgG test kit after a series of automatically performed testing tasks, and the obtained RLU was converted to titer units of S/CO.

Statistical analyses

The characteristics of the study cohorts and clinical symptoms among test-positive individuals were presented by using descriptive statistics. Fisher's exact tests were performed to examine the crude association between baseline characteristics and vaccination or previous infection status.

Poisson regression models were adopted to calculate the relative rate (RR) of BA.5-related infection and hospitalization between the inhaled Ad5-nCoV vaccinees with/without prior SARS-CoV-2 infection and the reference group. The protective effectiveness was quantified as the relative rate reduction (RRR), which can be calculated based on the RR and reported as a "percentage reduction" in RR, that is, $RRR = (1-RR) \times 100\%$. We controlled for potential confounding variables in the multivariate models, including sex, age, ethnicity, occupation strata, possible exposure in the workplace or household, smoking exposure, and inactivated vaccine dosage received within one year. To assess the differences in cumulative incidence among RT-PCR test-negative individuals stratified based on inhaled vaccination status (individuals with

inhaled Ad5-nCoV and those without), we utilized the Kaplan-Meier estimator. Furthermore, we employed the log-rank test to compare the survival curves derived from the Kaplan-Meier analysis, providing statistical rigor to our comparisons. We assessed the statistical uncertainty by calculating the 95% confidence intervals (CIs) using the Delta method, which is a standard and widely adopted likelihood-based statistical approach.

Subgroup analyses were performed by estimating the RRR based on age group (<45 years and ≥45 years), ethnicity group, occupation, time interval between vaccination and enrollment for individuals who had received three doses of inactivated vaccine (<12 months and ≥12 months before enrollment), smoking exposure status, and existing comorbidities (individuals without comorbidities and individuals with at least 1 comorbidity).

The serological IgG antibody titers were presented for the three study cohorts, with further stratifications within each cohort defined as follows: the inhaled vaccine cohort was stratified by the time lag from the last inactivated vaccine dose to the start of follow-up (<12 months and ≥12 months); the cohort with prior infection but without inhaled vaccine was stratified by the time lag from the prior infection time to the start of follow-up (<2 months, 2–3 months, and >3 months); and the cohort without prior infection and without inhaled vaccine was stratified by the time interval from the last inactivated vaccine dose to the start of follow-up (<12 months, and ≥12 months).

All statistical analyses were performed by using R statistical software (version 4.3.3).

Results

There were 1087 hospital staff out of a total of 1146 included in the analysis of VE. Of the 1087 recruited participants, 413 individuals had a history of prior SARS-CoV-2 infection but did not receive inhaled Ad5-nCoV vaccine, and 674 had no history of SARS-CoV-2 infection (390 individuals received inhaled Ad5-nCoV and 284 did not) (Fig. 1). The baseline characteristics of study cohorts were detailed in Table 1. The majority of the participants were female, with a lower proportion of females in the I-Ad5 group (60.3%) than in the other two groups (hybrid immunity group: 72.6%; reference group: 73.6%). There was a higher proportion of individuals aged above 50 years in the hybrid immunity group (19.7%) than in the reference group (7.5%) and the I-Ad5 group (12.1%). The distribution of ethnicity among the three cohorts was similar, with most of the individuals reporting Han ethnicity. The enrolled study population comprised primarily doctors and nurses (>50%) and hospital staff without any comorbidities (>90%). In addition, the majority of the participants were nonsmokers, lifetime abstainers from alcohol, and vaccinated with three doses of inactivated vaccines.

During the follow-up period, the reference group, I-Ad5 group, and hybrid immunity group contributed a total of 8832, 12,998, and 14,807 person-days, respectively, and 142 (55.7%, 142 out of 255 RT−PCR test-positive), 109 (42.7%), and 4 (1.6%) hospital staff members developed SARS-CoV-2 Omicron BA.5 infections the reference group, I-Ad5 group and hybrid immunity group, respectively (Fig. 1). Among the test-positive subjects who received the inhaled Ad5-nCoV vaccine, 13.76% were cured at least 10 days after the onset of the first clinical symptom, while this rate was40.77% among test-positive individuals who did not receive the inhaled Ad5-nCoV vaccine. The clinical symptoms for test-positive individuals were shown in Table S1. Notably, the proportions of test-positive individuals manifesting fever, diarrhea, loss of appetite, nausea, and vomiting were significantly lower for individuals who received the inhaled Ad5-nCoV vaccine than for those who without inhaled Ad5-nCoV.

When categorizing all participants by inhaled vaccination status in the univariate model, we observed a significantly lower cumulative incidence of infection among individuals who received the inhaled Ad5-nCoV vaccine than for those who did not receive the inhaled vaccine during the follow-up period (p-value<0.001 from the log-rank test; Fig. 2). When using individuals who had no prior infection and did not receive the inhaled Ad5-nCoV vaccine as the reference group in the multivariate model, the booster dose of inhaled Ad5-nCoV and the combination of prior SARS-CoV-2 infection with inactivated vaccinations (hybrid immunity) yielded RRRs of 41.9% (95% CI: 24.8, 55.0) and 97.9% (94.2, 99.2), respectively, against Omicron BA.5 infection (Table 2). A similar pattern of the RRR estimates was observed in the subgroup analyses except for the subgroup of individuals with at least one comorbidity, where the RRR was nonsignificant for the hybrid immunity group and was not available for the I-Ad5 group due to missing data. Notably, the number of hospitalizations within the follow-up period was 1, 4, and 1 for the reference group, I-Ad5 group, and hybrid immunity group, respectively, and the RRRs for the booster dose of inhaled Ad5-nCoV and hybrid immunity were nonsignificant (Table S2).

We assessed the immunogenicity of the study population by examining the serum IgG antibody titer. A total of 156 out of the 1087 enrolled hospital staff were excluded from blood test sample collection due to being unwilling to provide a blood sample. The highest serological IgG antibody titers were observed in the I-Ad5 group, with a median of 294.59 S/CO (IQR: 170.05, 438.16), followed by the hybrid immunity group (median of 93.65 S/CO; IQR: 45.50, 162.53) and the reference group

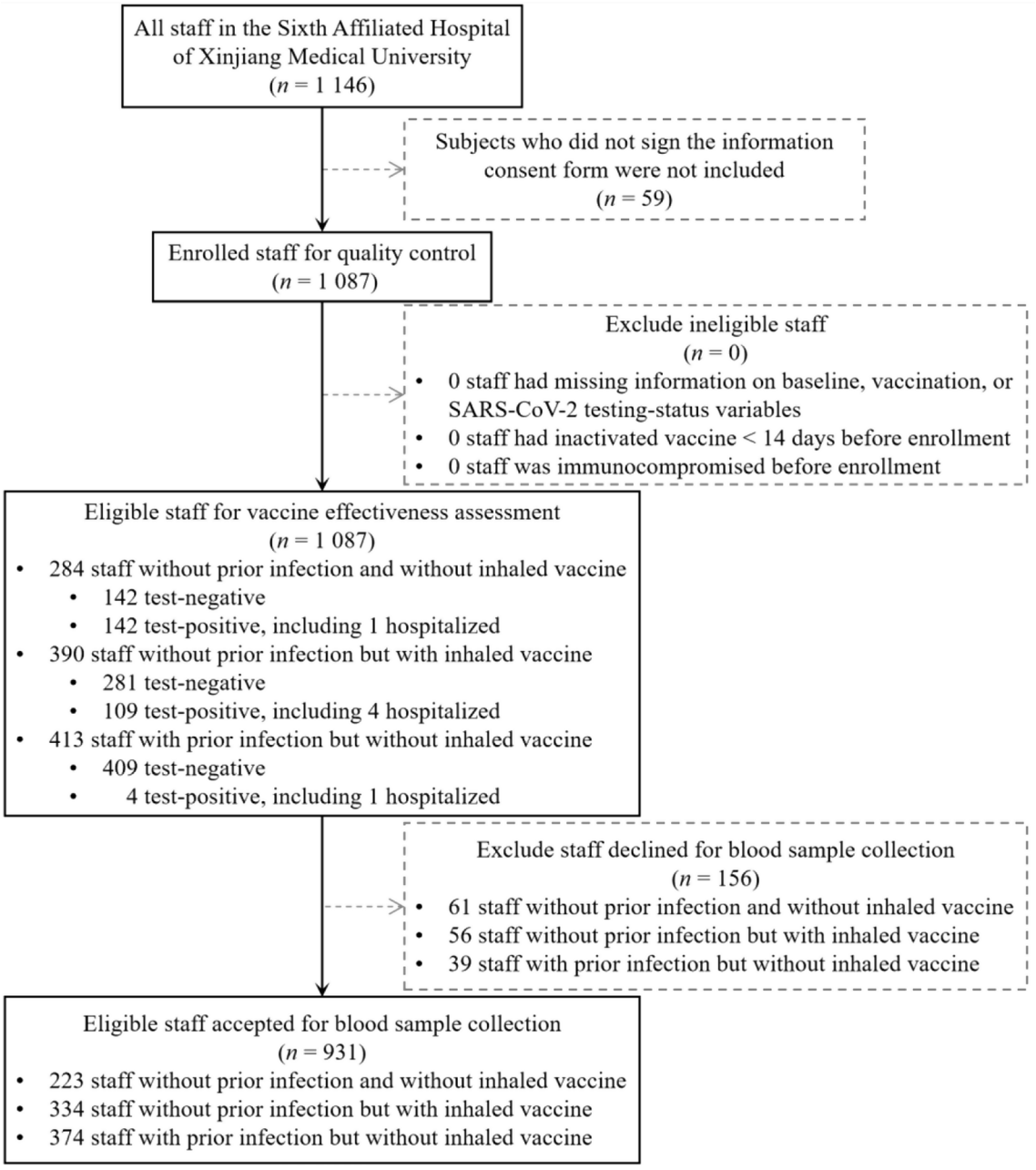

Fig. 1 Flowchart of the selection process of study participants

(median of 71 S/CO; IQR: 8.54, 161.24) (Fig. 3). In both the reference group and the I-Ad5 group, individuals who received the third dose of inactivated vaccine < 12 months before the start of follow-up had a higher serum IgG level than those with a lag > 12 months (reference group: 87.73 vs. 70.13, respectively; I-Ad5 group: 306.71 vs. 292.31, respectively). Similarly, the IgG antibody titers decreased over time in the hybrid immunity group, with the highest level observed for individuals who had a prior infection < 2 months before enrollment, followed by individuals with a lag of 2–3 months and individuals with a lag > 3 months (Fig. 3). Notably, after being infected by the Omicron BA.5 variant, the IgG antibody level attenuated in the I-Ad5 group but increased in the reference group, and this pattern was maintained over time (Fig. 3).

Discussion

In this study, we recruited a cohort of hospital staff to compare the protective effects of hybrid immunity (i.e., breakthrough infection after an inactivated vaccination regimen) and the immunity induced by a heterologous booster dose of inhaled Ad5-nCoV against the emerging

Table 1 Baseline characteristics of subject without and with inhaled Ad5-nCoV vaccine or prior SARS-CoV-2 infection

Characteristics	Subjects without inhaled vaccine		Subjects with inhaled vaccine, *n* (column %)	*p*-value*
	Without prior infection, *n* (column %)	With prior infection, *n* (column %)		
Total	284 (100%)	413 (100%)	390 (100%)	NA
Sex				
Male	75 (26.4%)	113 (27.4%)	155 (39.7%)	< 0.001
Female	209 (73.6%)	400 (72.6%)	235 (60.3%)	
Age group				
18–34 yr	128 (45.1%)	222 (53.8%)	206 (52.8%)	< 0.001
35–49 yr	100 (35.2%)	160 (38.7%)	137 (35.1%)	
50–60 yr	52 (18.3%)	31 (7.5%)	47 (12.1%)	
60 + yr	4 (1.4%)	0 (0)	0 (0)	
Median age, yr [IQR]	35.00 [30.00, 46.25]	33.00 [29.00, 40.00]	33.00 [29.00, 43.00]	0.001
Ethnicity				
Han	209 (73.6%)	277 (67.1%)	292 (74.9%)	0.084
Uyghurs	47 (16.5%)	99 (24.0%)	66 (16.9%)	
Hui	17 (6.0%)	19 (4.6%)	16 (4.1%)	
Kazakhs	5 (1.8%)	10 (2.4%)	6 (1.5%)	
Mongols	1 (0.4%)	6 (1.5%)	3 (0.8%)	
Other ethnicities	5 (1.8%)	2 (0.5%)	7 (1.8%)	
Occupation				
Doctor	76 (26.8%)	118 (28.6%)	97 (24.9%)	< 0.001
Nurse	88 (31.0%)	161 (39.0%)	155 (39.7%)	
Medical technician	42 (14.8%)	24 (5.8%)	26 (6.7%)	
Non-medical supporting staff	42 (14.8%)	55 (13.3%)	86 (22.1%)	
Others	36 (12.7%)	55 (13.3%)	26 (6.7%)	
Number of existing comorbidities				
0	259 (91.2%)	400 (96.9%)	372 (95.4%)	0.017
1	20 (7.0%)	11 (2.7%)	17 (4.4%)	
2	3 (1.1%)	2 (0.5%)	1 (0.3%)	
> 2	2 (0.7%)	0 (0)	0 (0)	
BMI				
Underweight: < 18.5	11 (3.9%)	25 (6.1%)	42 (10.8%)	0.024
Normal: 18.5–23.0	133 (46.8%)	191 (46.2%)	160 (41.0%)	
Overweight: 23.0–27.5	101 (35.6%)	150 (36.3%)	141 (36.2%)	
Obese: > 27.5	39 (13.7%)	47 (11.4%)	47 (12.1%)	
Baseline vaccination status of injected COVID-19 vaccine before follow-up				
0–1 dose	13 (4.6%)	10 (2.4%)	1 (0.3%)	< 0.001
2 doses	23 (8.1%)	16 (3.9%)	6 (1.5%)	
3 doses with a lag < 6 months	7 (2.5%)	8 (1.9%)	2 (0.5%)	
3 doses with a lag 6–9 months	9 (3.2%)	18 (4.4%)	27 (6.9%)	
3 doses with a lag 9–12 months	86 (30.3%)	327 (79.2%)	93 (23.8%)	
3 doses with a lag of 12 + months	146 (51.4%)	34 (8.2%)	261 (66.9%)	
Number of household members				
0	75 (26.4%)	123 (29.8%)	122 (31.3%)	0.038
1	64 (22.5%)	64 (15.5%)	92 (23.6%)	
2	52 (18.3%)	91 (22.0%)	75 (19.2%)	
3	51 (18.0%)	68 (16.5%)	61 (15.6%)	
> 3	42 (14.8%)	67 (16.2%)	40 (10.3%)	
Anticipated exposure to SARS-CoV-2 in workplace since follow-up				
Yes	167 (58.8%)	296 (71.7%)	261 (66.9%)	0.002
No	117 (41.2%)	117 (28.3%)	129 (33.1%)	
Anticipated exposure to SARS-CoV-2 in community or household since follow-up				

Table 1 (continued)

Characteristics	Subjects without inhaled vaccine		Subjects with inhaled vaccine, *n* (column %)	*p*-value*
	Without prior infection, *n* (column %)	With prior infection, *n* (column %)		
Yes	176 (62.0%)	237 (57.4%)	228 (58.5%)	0.466
No	108 (38.0%)	176 (42.6%)	162 (41.5%)	
First-hand smoking status				
Never smoked	244 (85.9%)	349 (84.5%)	285 (73.1%)	< 0.001
Ex-smoking for > 6 months	14 (4.9%)	22 (5.3%)	23 (5.9%)	
Currently smoking	26 (9.2%)	42 (10.2%)	82 (21.0%)	
Second-hand smoking exposure from household members or co-workers				
Yes	153 (53.9%)	227 (55.0%)	238 (61.0%)	0.111
No	131 (46.1%)	186 (45.0%)	152 (39.0%)	
Drinking status				
Lifetime abstainer	205 (72.2%)	281 (68.0%)	236 (60.5%)	< 0.001
Former drinker for > 6 months	59 (20.8%)	86 (20.8%)	72 (18.5%)	
Current drinker	20 (7.0%)	46 (11.1%)	82 (21.0%)	

* The statistical significance was measured by using two-sided *p*-value from Fisher's exact test

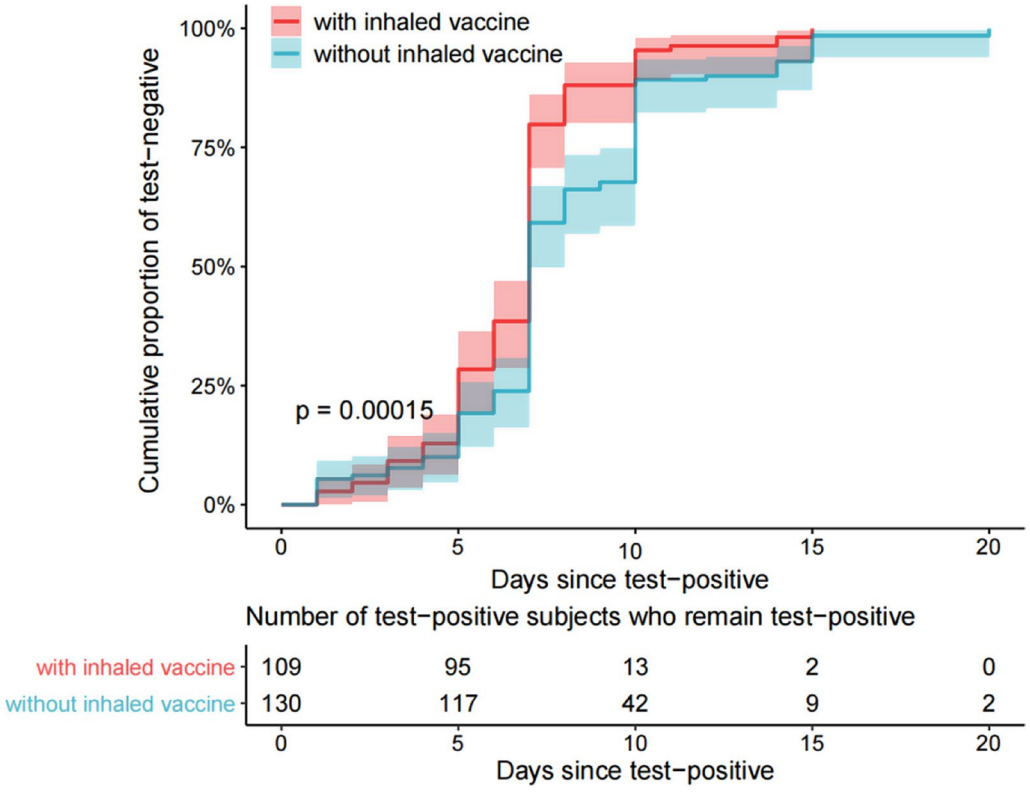

Fig. 2 The cumulative incidence of recovery from Omicron infection among groups of subjects without precious SARS-CoV-2 infection, stratified by the vaccination status of inhaled Ad5-nCoV vaccine (i.e., I-Ad5 group versus reference group). *Note*: The subjects in the groups with prior infection but without inhaled vaccine (i.e., hybrid immunity group) were not included because of insufficient sample ($n = 4$)

SARS-CoV-2 Omicron BA.5 variants. We found that the booster dose of inhaled Ad5-nCoV conferred a substantial protective effect against BA.5 infection, but hybrid immunity conferred an even stronger protective effect. The strong protective effects were observed across different subpopulations classified by age, ethnicity, occupation, lifestyle, number of comorbidities, and lag between the third-dose inactivated vaccination and follow-up. Moreover, we found that a heterologous booster dose of inhaled Ad5-nCoV might induce a higher serum IgG antibody level than hybrid immunity and a homologous inactivated vaccination regimen (reference group). These findings support the rollout of inhaled Ad5-nCoV among hospital staff for protection against the Omicron BA.5

Table 2 Summary of the relative rate reduction (RRR) estimates of inhaled Ad5-nCoV vaccine (I-Ad5) and hybrid immunity, versus without inhaled Ad5-nCoV vaccine (reference level), against SARS-CoV-2 Omicron BA.5 infection

Stratification	Sample size (column %)		Durationof follow-up, person-day	Incidence rate, per 100 000 person-day	Relative rate reduction, (95% CI)	
	Test-positive	Total			Crude	Adjusted[$]
Overall						
without prior infection and without inhaled vaccine (ref.)	142 (55.7%)	284 (26.1%)	8832	1607.79	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	109 (42.7%)	390 (35.9%)	12,998	838.59	44.1% (28.3, 56.4)	41.9% (24.8, 55.0)
with prior infection but without inhaled vaccine	4 (1.6%)	413 (38.0%)	14,807	27.01	98.1% (94.8, 99.3)	97.9% (94.2, 99.2)
with prior infection or with inhaled vaccine (combined)	113 (44.3%)	803 (73.9%)	27,805	406.40	71.9% (64.0, 78.0)	66.9% (57.0, 74.5)
Subjects with age < 45 yr						
without prior infection and without inhaled vaccine (ref.)	112 (54.9%)	206 (24.0%)	6353	1762.95	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	90 (44.1%)	305 (35.5%)	10,102	890.91	45.7% (28.4, 58.9)	42.7% (23.5, 57.0)
with prior infection but without inhaled vaccine	2 (1.0%)	349 (40.5%)	12,544	15.94	98.9% (95.7, 99.7)	98.8% (95.0, 99.7)
Subjects with age of 45 + yr						
without prior infection and without inhaled vaccine (ref.)	30 (58.8%)	78 (34.4%)	2479	1210.17	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	19 (37.3%)	85 (37.4%)	2896	656.08	41.9% (-3.1, 67.3)	46.1% (3.4, 69.9)
with prior infection but without inhaled vaccine	2 (3.9%)	64 (28.2%)	2263	88.38	91.9% (66.0, 98.1)	93.1% (68.3, 98.5)
Subjects of Han ethnicity						
without prior infection and without inhaled vaccine (ref.)	98 (55.7%)	209 (26.9%)	6585	1488.23	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	76 (43.2%)	292 (37.5%)	9808	774.88	44.5% (25.1, 58.9)	43.8% (23.8, 58.6)
with prior infection but without inhaled vaccine	2 (1.1%)	277 (35.6%)	9951	20.1	98.5% (93.8, 99.6)	98.2% (92.4, 99.6)
Subjects of ethnicities other than Han						
without prior infection and without inhaled vaccine (ref.)	44 (55.7%)	75 (24.3%)	2247	1958.17	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	33 (41.8%)	98 (31.7%)	3190	1034.48	42.6% (9.9, 63.5)	40.6% (4.7, 63.0)
with prior infection but without inhaled vaccine	2 (2.5%)	136 (44.0%)	4856	41.19	97.5% (89.7, 99.4)	97.5% (89.1, 99.4)
Doctors and nurses						
without prior infection and without inhaled vaccine (ref.)	87 (51.5%)	164 (23.6%)	5055	1721.07	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	79 (46.7%)	252 (36.3%)	8320	949.52	40.9% (19.9, 56.4)	39.7% (17.2, 56.1)
with prior infection but without inhaled vaccine	3 (1.8%)	279 (40.1%)	9993	30.02	98.0% (93.6, 99.4)	97.9% (93.1, 99.3)
Subjects who were not doctor or nurse						
without prior infection and without inhaled vaccine (ref.)	55 (64.0%)	120 (30.6%)	3777	1456.18	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	30 (34.8%)	138 (35.2%)	4678	641.30	52.6% (26.0, 69.6)	42.1% (7.6, 63.7)
with prior infection but without inhaled vaccine	1 (1.2%)	134 (34.2%)	4814	20.78	98.4% (88.2, 99.8)	98.0% (85.1, 99.7)
Subjects who have injected 3-dose inactivated COVID-19 vaccines with lag ≤ 12 months before follow-up						

Table 2 (continued)

Stratification	Sample size (column %)		Durationof follow-up, person-day	Incidence rate, per 100 000 person-day	Relative rate reduction, (95% CI)	
	Test-positive	Total			Crude	Adjusted[$]
without prior infection and without inhaled vaccine (ref.)	45 (52.3%)	102 (17.6%)	3231	1392.76	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	38 (44.2%)	124 (21.3%)	4031	942.69	30.5% (-6.5, 54.9)	34.1% (-3.8, 58.2)
with prior infection but without inhaled vaccine	3 (3.5%)	355 (61.1%)	12,750	23.53	98.1% (93.8, 99.4)	98.2% (94.0, 99.4)
Subjects who have injected 3-dose inactivated COVID-19 vaccines with lag of 12 + months before follow-up						
without prior infection and without inhaled vaccine (ref.)	97 (57.4%)	182 (36.0%)	5601	1731.83	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	71 (42.0%)	266 (52.5%)	8967	791.79	49.9% (32.0, 63.1)	46.0% (25.9, 60.6)
with prior infection but without inhaled vaccine	1 (0.6%)	58 (11.5%)	2057	48.61	96.8% (76.8, 99.5)	96.4% (74.4, 99.5)
Subjects without first-hand nor second-hand smoking exposure						
without prior infection and without inhaled vaccine (ref.)	70 (63.1%)	126 (28.8%)	3821	183.20	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	39 (35.1%)	135 (30.9%)	4506	86.55	48.0% (23.1, 64.9)	47.1% (21.1, 64.5)
with prior infection but without inhaled vaccine	2 (1.8%)	176 (40.3%)	6296	3.18	98.0% (91.7, 99.5)	97.6% (90.0, 99.4)
Subjects with first-hand or second-hand smoking exposure						
without prior infection and without inhaled vaccine (ref.)	72 (50.0%)	158 (24.3%)	5011	1436.84	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	70 (48.6%)	255 (39.2%)	8492	824.31	39.8% (16.3, 56.6)	39.6% (15.0, 57.1)
with prior infection but without inhaled vaccine	2 (1.4%)	237 (36.5%)	8511	23.5	98.1% (92.5, 99.5)	98.1% (92.0, 99.5)
Subjects without any comorbidity						
without prior infection and without inhaled vaccine (ref.)	133 (54.3%)	259 (25.1%)	8051	1651.97	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	109 (44.5%)	372 (36.1%)	12,350	882.59	42.9% (26.5, 55.7)	39.9% (22.0, 53.6)
with prior infection but without inhaled vaccine	3 (1.2%)	400 (38.8%)	14,349	20.91	98.5% (95.4, 99.5)	98.4% (94.9,99.5)
Subjects with at least 1 comorbidity						
without prior infection and without inhaled vaccine (ref.)	9 (90.0%)	25 (44.7%)	781	1152.37	0% (ref.)	0% (ref.)
without prior infection but with inhaled vaccine	0 (0.0%)	18 (32.1%)	648	0.00	100% (not estimated)	not estimated
with prior infection but without inhaled vaccine	1 (10.0%)	13 (23.2%)	458	218.34	78.6% (-40.7, 97.3)	67.4% (-69.3, 96.7)

$ The adjusted VE was estimated by using multivariate regression model with the adjustment for covariables including sex, age, ethnicity, occupation, smoking exposure, vaccination status before follow-up, calendar date of SARS-CoV-2 test, and anticipated SARS-CoV-2 exposure in workplace or household.

variant. We found that the protective effect of the inhaled Ad5-nCoV booster showed the same level of VE (approximately 41.9%) across various subgroups (Table 2).

To the best of our knowledge, this is the first study to examine the real-world vaccine effectiveness conferred by a booster dose of inhaled Ad5-nCoV. Although inhaled Ad5-nCoV is a replication-defective vaccine encoding the full-length spike gene of the wild-type strain of SARS-CoV-2, our findings demonstrated the high VE of a booster dose of inhaled Ad5-nCoV against BA.5 variant infection, which is higher than the VE of a single-dose intramuscularly delivered Ad5-nCoV against infection by the wild-type strain and the Delta variants (18% for individuals infected at least 2 weeks after the last vaccination) [38], and the VE of a prime-booster dose of intramuscularly delivered Ad5-nCoV against infection by BA.2 subvariants (<20% for individuals infected at least 3 weeks after the last vaccination) [39]. The difference in

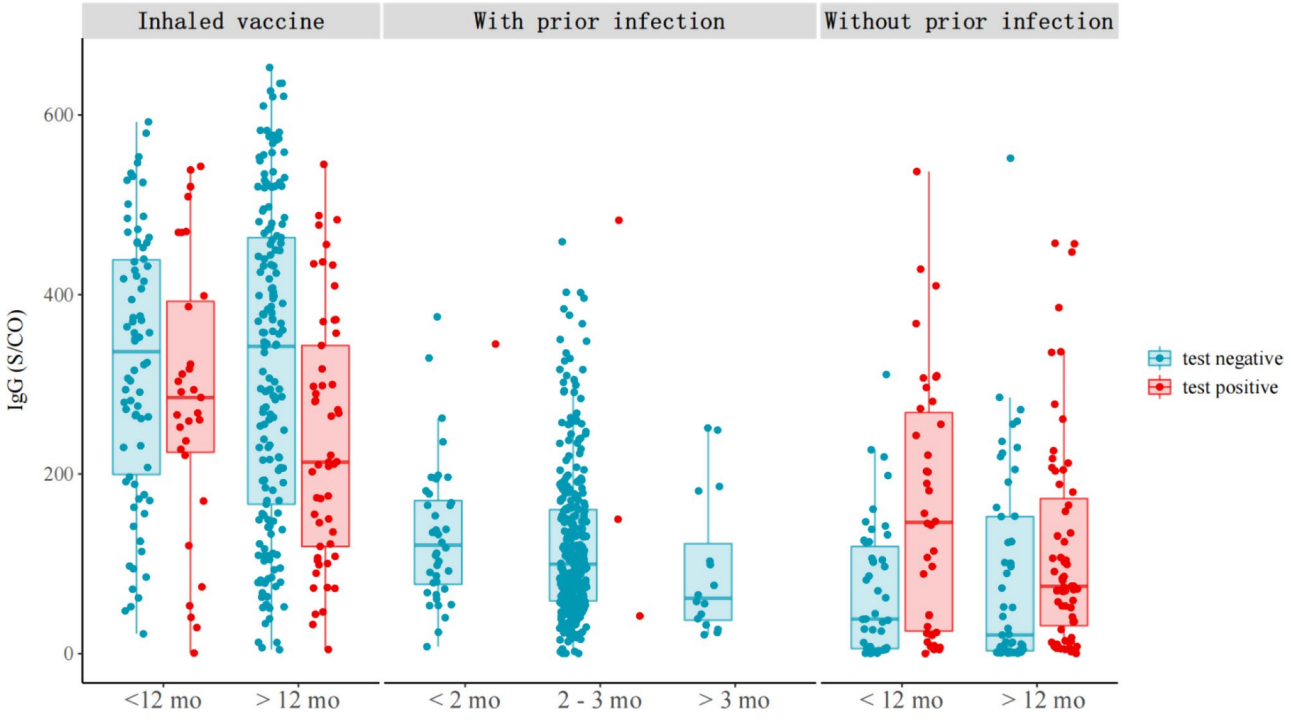

Fig. 3 The serological IgG antibody level among groups of subjects with inhaled Ad5-nCoV vaccine (i.e., I-Ad5 group, labeled as "inhaled vaccine" in the top row of figure), with prior infection but without inhaled vaccine (i.e., hybrid immunity group, labeled as "with prior infection" in the top row of figure), and without prior infection and without inhaled vaccine (i.e., reference group, labeled as "without prior infection" in the top row of figure), further stratified by the testing status for Omicron infection. The text label at the bottom axis indicated the time lag between the date of latest immunization (i.e., vaccination or previous infection) and the date of blood sample collection

VE may be attributable to various types of SARS-CoV-2 variants with different degrees of immune escape, study designs, vaccine dosages (the majority of participants in the I-Ad5 group were previously vaccinated with 3-dose inactivated vaccines), and routes of delivery. In our study, we observed a higher level of serological IgG antibody for individuals who received a heterologous booster regimen than for individuals with hybrid immunity and those who only received a homologous inactivated vaccine regimen. This finding was consistent with studies showing that a heterologous booster of inhaled Ad5-nCoV after the prime series of inactivated vaccination elicited higher serum IgG antibody titers than a homologous inactivated prime-boost regimen [27, 28]. We found that due to a relatively short observational period (approximately 40 days after the administration of the inhaled Ad5-nCoV booster), the durability of antibody reactions needed to be further investigated. The intramuscular-injection vaccine could effectively induce serum IgG antibody responses to protect the lower respiratory tract but could not provoke the epithelial IgA antibody that safeguards the upper respiratory tract [23]. In contrast, aerosolized inhaled vaccines not only induce a robust local immune response in mucosal sites, including secretory IgA antibodies, mucosal IgG antibodies, and the expression of cytokines in T cells, which serve as the frontline of defense by blocking infection entrance [40] but also robustly induce robust systemic humoral immunity that eradicates any virus particle escaping from the immune response generated at the mucosal site, as suggested by animal models and clinical trials [24, 41–43]. The long-term profile for the magnitude of the immune response provoked by inhaled Ad5-nCoV is warranted for further investigation.

Notably, we found that the protection provided by a previous SARS-CoV-2 infection far exceeded that provided by inhaled Ad5-nCoV, which was consistent with previous real-world studies suggesting that the protective effect conferred by hybrid immunity was stronger than that of vaccine [21] or infection alone [18], although the magnitude of the effectiveness differs. Several studies have indicated that the immune responses elicited by hybrid immunity are stronger than those elicited by vaccination or naturally acquired immunity alone [44–47]. One of the reasons might be that most of the marketed vaccines target the spike protein belonging to the previous circulating subvariants or strains, and the currently predominant variants have accumulated spike changes that enable them to escape antibody recognition [17]. An infection from the emerging variants might improve the cellular responses by generating more cross-reactive B cells that could recognize the newer antigens [48].

Additionally, the relevance of our findings lends support to the findings from a systematic review and meta-analysis conducted by Song et al., showing a favorable protective efficacy, immunogenicity, and safety profile of inhaled COVID-19 vaccines. This further highlights the importance of our research in the context of developing effective vaccination strategies [49].

Notwithstanding that hybrid immunity appeared to be more immunologically favorable, we stressed that protection from prior infection should not diminish the necessity of vaccination, considering the appreciable acute and long-term clinical risk after infection, such as cardiovascular diseases or long-term COVID. Vaccination is therefore the safer choice for preventing severe clinical complications.

Limitations

Our study had some limitations. First, since the follow-up period was relatively short (largely within 40 days), the duration and waning process of the protective effect cannot be evaluated. Considering that the VE against Omicron infection would wane quickly within months and that the majority of the test-positive participants were infected 5 weeks after receiving the inhaled vaccine, the inferred VE of the booster dose of inhaled Ad5-nCoV may approach the upper bound level. Second, our study cohorts were generally working-age individuals with no underlying late-stage comorbidities and were therefore less likely to develop severe clinical outcomes and be hospitalized. Therefore, our results may not be generalizable to the general population. Third, there might be unobservable confounders missed in the multivariate analysis, such as precarious behavioral factors in relation to COVID-19. Lastly, while our study is a single-center investigation, our findings on the favorable immunogenicity profile of aerosolized Ad5-nCoV are consistent with those of the multi-center study conducted by Li et al., suggesting that individuals received a booster dose of aerosolized Ad5-nCoV after two-dose of inactivated vaccine had higher neutralized antibody than did those who received the inactivated vaccines [50].

Conclusions

In conclusion, our real-world analysis showed that hybrid immunity could confer a stronger protective effect against SARS-CoV-2 Omicron BA.5 infection than a booster dose of inhaled Ad5-nCoV among healthcare personnel. Nevertheless, a heterologous booster dose of inhaled Ad5-nCoV could elicit a more robust serum IgG immune response in the long term than hybrid immunity and a homologous inactivated vaccination regimen. Our findings support the use of an inhaled Ad5-nCoV vaccine or other heterologous boosters during the Omicron-predominant phase.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

Conceptualization: SZ and KW. Methodology: SZ and KW. Software: KW and TZ. Validation: ZG and SZ. Formal analysis: KW and TZ. Investigation: KW, TZ and SZ. Resources: JL and ZL. Data Curation: JL, CY, LY, LW and ZL. Writing - Original Draft: KW, TZ and ZG. Writing - Review and Editing: All authors. Visualization: KW and SZ. Supervision: KW and SZ. Project Administration: KW and TZ. Funding acquisition: TZ and KW. All authors critically read the manuscript and gave final approval for publication.

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Data availability

The original data containing confidential patient information cannot be made publicly available. The anonymized data used in this study were available based on reasonable request to the corresponding authors.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics committee of Xinjiang Medical University. Medical records were kept confidential in full at the Sixth Affiliated Hospital of Xinjiang Medical University, and the personal identity of the subjects was not and will not be disclosed in any report on the results of this study. Informed consent is obtained from all the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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