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A retrospective survey on the effectiveness of vaccines administered to individuals in China with regard to inactivated COVID-19 vaccines, Ad5-nCoV and/or aerosolized Ad5-nCoV

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ABSTRACT

We administered a questionnaire to participants who received different vaccination regimens to evaluate the effectiveness of Ad5-vectored COVID-19 vaccines. The results showed that administration of intramuscular Ad5-nCoV provided 21.32% more protection against SARS-CoV-2 infection than that of the inactivated COVID-19 vaccine in people who had received only one type of COVID-19 vaccine. Furthermore, aerosolized Ad5-nCoV exhibited good protection, whether it was administered as a homologous booster to people vaccinated with the intramuscular Ad5-nCoV or as a heterologous booster to people vaccinated with inactivated COVID-19 vaccines. Our research indicates that Ad5-nCoV is an effective booster. This finding supports the future selection of COVID-19 immunization strategies.

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KEYWORDS COVID-19; aerosolized Ad5-nCoV; mucosal; booster; relative effectiveness

Background

At the end of 2022, after China changed its COVID-zero policy, there was a sudden outbreak of the Omicron subvariants BF.7 and BA.5.2 [1]. People who had received different COVID-19 vaccines as their primary or booster vaccinations reported breakthrough infections. The effectiveness for COVID-19 vaccines in preventing Omicron variant-associated infection varies from 23% to 65% due to differences in vaccine type and dose [2]. In the pursuit of more effective vaccines, the World Health Organization (WHO) speculates that developing multiple COVID-19 vaccines, including mucosal delivery vaccines, is a promising direction [3]. The Ad5-nCoV vaccine, which is delivered through inhalation, has shown good immunogenicity and effectiveness as a heterologous booster immunization [4–6]. However, the effectiveness of Ad5-nCoV in providing protection against COVID-19 using different immunization strategies is still unknown. To gather data to support future vaccination strategies, a questionnaire survey was conducted to analyze the protective effects of Ad5-nCoV and/or inactivated vaccines in individuals against the 2022 wave of infections.

Methods

In May 2023, we released a questionnaire to assess the effectiveness of inactivated and Ad5-vectored vaccines against the COVID-19 Omicron subvariant outbreak that occurred in December 2022 in Shanghai and Xi'an, China. Sample size was calculated using PASS 15.0.5 software, based on an incidence rate of 64.6% in the general population [6]. In the questionnaire, we asked the participants for their basic information, vaccination histories, and SARS-CoV-2 infection statuses. The SARS-CoV-2-positive participants were asked about their symptoms and their dates of infection. To be considered a COVID-19 patient, participants had to have tested positive for SARS-CoV-2 using an antigen rapid test or a nucleic acid amplification test, or have had exposure to someone with COVID-19 and at least two symptoms associated with the disease (e.g. fever, dry throat, sore throat, cough, or shortness of breath) [7]. The breakthrough

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cases were graded by the investigators according to the WHO guidelines [8]. We included participants who were vaccinated before June 2022 and excluded participants who were infected before November 2022, and those who could not determine their own infection status. Ultimately, a total of 3773 samples were included in the subsequent analysis. The chi-square test was used to calculate the significance of the differences in frequency between the groups, and p values $\leq$ 0.05 were considered to indicate statistical significance. All participants voluntarily participated in the survey and provided their informed consent. This study was approved by the Ethics Committee of Beijing Institute of Biotechnology (No.: AF/SC-08/02.299).

Results

A total of 3773 individuals who met the inclusion criteria were included in the analysis. These individuals had received single or multiple doses of various COVID-19 vaccines, such as the inactivated COVID-19 vaccine, intramuscular Ad5-nCoV, and/or aerosolized Ad5-nCoV. All participants were male and had similar baseline characteristics. Supplementary Table 1 provides information on the ages and diverse vaccination experiences of the participants, including the number of doses and types of vaccines administered. Of the total participants, 2619 received a single type of COVID-19 vaccine, whereas 1155 received mixed types of COVID-19 vaccines. Among these participants, 1781 received only the inactivated COVID-19 vaccine, 832 received only intramuscular Ad5-nCoV, 515 received the inactivated COVID-19 vaccine as well as aerosolized Ad5-nCoV, and 640 received intramuscular Ad5-nCoV as well as aerosolized Ad5-nCoV. All participants had received their last vaccination more than 7 months before the outbreak in Dec 2022. The time interval between the last vaccination and infection was similar among participants who had completed the same vaccination programme.

The protective effects of vaccination were then analyzed (Table 1). In participants who had received a single type of COVID-19 vaccine, the overall protection of intramuscular Ad5-nCoV against infection versus that of the inactivated COVID-19 vaccine was 21.32% (95% CI, 16.62%-25.75%) (p<0.0001), including both the prime and booster vaccination. Compared with the inactivated COVID-19 vaccine recipients, Ad5-nCoV recipients had a greater relative protection of 20.66% (95% CI, 14.76%-26.16%) (p<0.0001) against mild infection and 57.75% (95% CI, 47.26%-66.15%) (p<0.0001) against severe infection. Moreover, the participants previously vaccinated with intramuscular Ad5-nCoV or the inactivated COVID-19 vaccine showed considerable protection when administered aerosolized Ad5-nCoV as a booster. Slightly greater vaccine protection estimates were reported for patients confirmed by SARS-CoV-2 detection than for clinically diagnosed patients. According to the analysis of the impact of the vaccination programme, an increase in the number of doses did not lead to a decrease in the infection rate or symptom severity, as shown in Supplementary Figure 1. However, the use of aerosolized Ad5-nCoV as a booster, whether as the first or second dose, significantly reduced the infection rate and was shown to be a novel and effective approach.

Discussion

Here, we aimed to describe the effectiveness of the Ad5-nCoV vaccine in protecting against COVID-19 infection. We analyzed the protective effects of the vaccine in terms of single-type vaccine immunization, a heterologous booster, and a homologous booster via a heterologous route. Individuals immunized with the intramuscular Ad5-nCoV vaccine had a lower risk of infection than those who only received the inactivated COVID-19 vaccines. Seven months after booster immunization with aerosolized Ad5-nCoV, individuals who were previously vaccinated with 1–2 doses of intramuscular Ad5-nCoV and those who were previously vaccinated with 2–3 doses of inactivated COVID-19 vaccines showed similar levels of anti-infection effects. Hence, an aerosolized Ad5-nCoV booster may be a priority for preventing COVID-19 infection.

Our findings indicate that individuals who have received only a single type of COVID-19 vaccine may experience better protection against COVID-19 with intramuscular Ad5-nCoV compared to inactivated vaccines. This finding is consistent with those of other clinical studies. The adenovirus-vectored COVID-19 vaccines seem to be more effective against multiple variants than the inactivated vaccines are [9]. The inactivated vaccine may only provide 17% to 22% protection against Omicron BA.1 infection, although it still offers over 90% protection against severe infections [10]. Immunogenic results support this observation. Administering 2 or 3 doses of the ChAdOx1 nCoV-19 vaccine has been found to result in higher levels of anti-spike IgG, which are longer lasting than those resulting from inactivated COVID-19 vaccines [11].

Compared to the inactivated COVID-19 vaccine, the intramuscular Ad5-nCoV can offer better protection against SARS-CoV-2 infection in unvaccinated people. However, after receiving the same heterologous booster vaccination, individuals who were primed with the inactivated vaccine showed less susceptibility to infection than those who were primed with the adenovirus-vectored vaccine. The effectiveness of the CoronaVac-CoronaVac-BNT162b2 and ChAdOx1-ChAdOx1-BNT162b2 vaccines was

Table 1. Protection against COVID-19 by Ad5-nCoV in participants with different vaccination regimens. The data are expressed as n (%), unless otherwise specified. *Clinical cases involve participants that confirmed to have SARS-CoV-2 via etiological testing. Ad5-IM = intramuscular Ad5-nCoV, Ad5-IH = aerosolized Ad5-nCoV, ICV = inactivated COVID-19 vaccine, CI = confidence interval, NA = not applicable. The hazard ratio was estimated by Cox regression analysis. Protection was calculated as one minus the hazard ratio.

Schedule type	Matched pairs		Hazard ratio (%)	Relative effectiveness (95% CI)	*p* value
A single type of COVID-19 vaccines	Ad5-IM	ICV			
Number of participants	n = 832	n = 1784			
Number of cases (%)	518 (62.26%)	1409 (78.98%)	78.6	21.32 (16.62 to 25.75)	<0.0001
Case type					
Antigen rapid test or nucleic acid test confirmed cases	199 (23.92%)	782 (43.83%)	54.45	45.55 (37.87 to 52.29)	<0.0001
Clinical cases*	479 (57.57%)	1138 (63.79%)	90.09	9.91 (3.58 to 15.83)	<0.0001
Severity					
Mild	414 (49.76%)	941 (52.74%)	79.34	20.66 (14.76 to 26.16)	<0.0001
Moderate	82 (9.86%)	414 (23.21%)	42.25	57.75 (47.26 to 66.15)	<0.0001
Severe or critical	1 (0.12%)	8 (0.45%)	26.82	73.18 (−114.07 to 96.64)	1.00
Multiple types of COVID-19 vaccines	Ad5-IM + Ad5-IH	ICV + Ad5-IH			
Number of participants	n = 640	n = 514			
Number of cases (%)	289 (45.16%)	254 (49.42%)	91.38	8.62 (−3.26 to 19.13)	1.00
Case type					
Antigen rapid test or nucleic acid test confirmed cases	178 (27.81%)	177 (34.44%)	80.77	19.23 (4.01 to 32.04)	<0.0001
Clinical cases*	235 (36.72%)	196 (38.13%)	96.29	3.71 (−11.87 to 17.11)	1.00
Severity					
Mild	204 (31.88%)	174 (33.85%)	91.40	8.60 (−7.12 to 22.02)	1.00
Moderate	54 (8.44%)	59 (11.48%)	74.21	25.79 (−5.26 to 47.68)	1.00
Severe or critical	0 (0.00%)	0 (0.00%)	N/A	N/A	N/A

estimated at 56% and 39%, respectively [2]. Interestingly, administering aerosolized Ad5-nCoV as a homologous booster via a heterologous route to recipients of intramuscular Ad5-nCoV vaccine has been shown to offer comparable or even superior protection to heterologous boosting in recipients of the inactivated COVID-19 vaccine. This can be attributed to the robust antibody and cellular immune response stimulated by this vaccination approach [12].

Timely vaccination with the booster dose can offer effective protection against SARS-CoV-2 Omicron infections. Studies have shown that the effectiveness of CoronaVac in preventing infection was 26%; this effectiveness increased to 53% and 56% after receiving the ChAdOx1 and BNT162b2 booster vaccination, respectively [2]. However, a booster dose with inactivated COVID-19 vaccines only provides a low level of protection against infection, with an effectiveness of 28.6% compared to full vaccination [13]. Due to limitations in sample size, we were unable to conduct a subgroup analysis of vaccine effectiveness between individuals with full vaccination and those who received a booster dose. However, several clinical studies have confirmed that heterologous boosting with aerosolized Ad5-nCoV provokes a significant immune response and provides protection against SARS-CoV-2 [4,14], which strongly supports our observations. Overall, these findings suggest that aerosolized Ad5-nCoV is an important option for heterologous booster vaccination.

The prevalence of Omicron variants has promoted studies on the effectiveness of various COVID-19 vaccines, including virus-vectored vaccines, protein subunit vaccines and mRNA vaccines. dNS1-RBD, a live-attenuated influenza virus vector-based intranasal SARS-CoV-2 vaccine, has shown an overall efficacy of 28.2% compared to placebo [15]. The relative efficacy of an mRNA vaccine, designated as SYS6006, was 51.6% compared to that of ZF2001, a recombinant subunit protein vaccine [16]. In another clinical trial of an Omicron BA.5-adapted mRNA vaccine, the vaccine achieved an efficacy of 51.9% compared to the placebo [17]. A booster dose of aerosolized Ad5-nCoV provided 56.4% additional protection for individuals who had received three doses of inactivated COVID-19 vaccines [4], showing a comparable protective effect to the mRNA vaccines. Given the complexity of COVID-19 infection, additional clinical trials are required to compare the protection provided by these vaccines against different Omicron variants.

Notably, our study has certain limitations. First, we did not analyze the effects of age and sex on vaccine effectiveness because the participant demographics were similar. The survey subjects in this study did

not include elderly individuals, who are more vulnerable to SARS-CoV-2 infection and have an increased risk of developing severe symptoms. Second, we did not explore the effectiveness of mRNA vaccines and recombinant protein subunit vaccines in this study, despite evidence of their ability to generate strong immune responses in clinical trials. Third, the data we analyzed only pertained to wild-type SARS-CoV-2 vaccines, and we did not have any data on the effectiveness of vaccines against the SARS-CoV-2 Omicron subvariants or the protection offered by vaccines in the context of new Omicron subvariants infection. Finally, the reliability of the information in the questionnaire depends on participants' self-perception, leading to an inevitable recall bias that could impact assessment outcomes. Further research is required in these regards.

Overall, aerosolized Ad5-nCoV provides effective protection against SARS-CoV-2 infection for more than seven months after booster administration, in both inactivated COVID-19 vaccine recipients and Ad5-nCoV vaccine recipients. This study provides valuable information for selecting future mucosal vaccine immunization strategies against SARS-CoV-2.

Author contributions

W. C., L. H.-H., Z. Z. and X. Y-C conceptualized the study, conceived the questionnaire questions and developed the statistical methods. Z. Z. wrote the first draft. W. C., L. H.-H. and X. Y-C revised the manuscript. G. Y-Z., Zhang. Z., S. H.-L., M. J.-L., and L. J.-L. helped distribute the questionnaire. J. L.-Z., F. Z.-S. and Y. Z. obtained and analyzed the data.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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