

## Willingness of college students to receive COVID-19 heterologous vaccination in Taizhou, China

Hui Shao<sup>a\*</sup>, Xiao-Qing Lin<sup>a\*</sup>, Yan Chen<sup>a</sup>, Li Lv<sup>b</sup>, Chen-Qian Ying<sup>a</sup>, Tao-Hsin Tung<sup>c</sup>, and Jian-Sheng Zhu<sup>a</sup>

<sup>a</sup>Department of Infectious Diseases, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Linhai, Zhejiang, China; <sup>b</sup>Department of Infectious Diseases, Taizhou Hospital, Zhejiang University, Linhai, Zhejiang, China; <sup>c</sup>Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province, Wenzhou, Medical University, Wenzhou, Linhai, Zhejiang, China

### ABSTRACT

This study aimed to determine the willingness of college students to choose COVID-19 heterologous vaccination and its associated influencing factors in Taizhou, China. A population-based, self-administered online questionnaire was conducted from March 15 to 17, 2022. Of the 2,463 participants who had received the invitation, 1,821 responded to the survey (response rate = 73.9%). Only 14% (86/614) of those willing to receive a booster would choose a heterologous vaccination; the perception of better effectiveness of a COVID-19 heterologous vaccination booster was the significant factor ( $\chi^2 = 22.671$ ,  $p < .001$ ). Additionally, female college students' older age ( $\chi^2 = 7.523$ ,  $P = .023$ ), major of medical ( $\chi^2 = 6.294$ ,  $P = .012$ ), and better perceived effectiveness of COVID-19 heterologous vaccination booster ( $\chi^2 = 22.659$ ,  $P < .001$ ), were more willing to receive heterologous booster doses. Chinese college students have a strong willingness to receive booster shots, but the percentage of those willing to receive a heterologous vaccine is only 14.0%, and the lack of understanding of its effectiveness is an important factor in the low proportion of heterologous vaccine selection. Health education, public health awareness, and the disclosure of heterologous vaccine information can help improve the public's understanding of heterologous vaccines and provide them with more choices.

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Heterologous vaccination; willingness; college students; COVID-19; booster

### Introduction

Since the end of 2019, COVID-19 has continued to sweep the world with its impact. Globally, as of 20 May 2022; 521,920,560 cases of COVID-19 have been confirmed, including 6,274,323 deaths, as reported by WHO.<sup>1</sup> As of 16 May 2022, a total of 12,186,798,032 vaccine doses have been administered.<sup>1</sup> Vaccination has become a pivotal means to prevent the spread of COVID-19 and ultimately quell the pandemic, while reducing the fatality rate,<sup>2-4</sup> and booster shots are considered an effective way to increase the effectiveness of vaccinations.<sup>5,6</sup> Borobia A et al. found that a heterologous vaccine can induce a robust immune response with an acceptable and manageable reactogenicity profile.<sup>7</sup> Heterologous vaccination can significantly improve the immunization effect<sup>2-8-10</sup> and has a stronger protective effect as well.<sup>10,11</sup>





The willingness to get vaccinated with either homologous or heterologous vaccines of COVID-19 is affected by factors such as gender, occupation, and age.<sup>12,13</sup> College students, as a special group, may be at higher risk of exposure to COVID-19 due to occupational and behavioral factors and are more likely to transmit the virus to others, including those at higher risk of becoming seriously ill.<sup>14,15</sup> It is particularly important to improve the willingness and effectiveness of vaccination for college students for the prevention and control of the COVID-19 epidemic.<sup>15,16</sup> At

present, few studies have focused on the willingness to receive a heterologous COVID-19 vaccine, and research on the willingness of college students to choose the heterologous COVID-19 vaccine as a booster shot and related factors is even rarer. The purpose of this study was to describe the willingness of college students to choose a heterologous booster shot and the related influencing factors.

### Methods

#### Study design and data collection

An anonymous, cross-sectional, population-based online survey was conducted using the WeChat-Inc Wen-Juan-Xing, China's largest online survey platform. The subjects were college students in Taizhou, China. Interviewees volunteered to answer self-administered questionnaires by scanning the QR code on their phones between March 15 and 17 March 2022. The study was reviewed by the Ethics Committee of Taizhou Hospital in Zhejiang Province (approval number: K20210705), as the questionnaire was conducted using data anonymization to ensure the confidentiality of enrollees. All proceedings were conducted in accordance with the guidelines of the authors' institutional ethics committee and in accordance with the tenets of the Helsinki Declaration.

**CONTACT** Jian-Sheng Zhu  [zhujs@enzemed.com](mailto:zhujs@enzemed.com)  Department of Infectious Diseases, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, 150 Ximen Street, Linhai, Zhejiang 317000, China; Tao-Hsin Tung  [ch2876@yeah.net](mailto:ch2876@yeah.net)  Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, 150 Ximen Street, Linhai, Zhejiang 317000, China.

\*These authors contributed equally to this work and share first authorships.

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## Structured questionnaires and measurements

An online self-filled questionnaire consisting of four parts was constructed. First, the introduction to the questionnaire described the background and purpose of the survey and indicated that participation in the survey was voluntary and that the responses would remain anonymous. The meaning and significance of receiving homologous or heterologous booster doses were explained. In China, the primary doses of COVID-19 vaccine were mainly inactivated vaccines. Therefore, homologous vaccination refers to inactivated vaccine in all three doses, while heterologous vaccination refers to other types of COVID-19 vaccine such as mRNA vaccine in the third dose. The second part included basic demographic information, such as age, gender, residence, chronic diseases, major, flu vaccination history, and risk perception of COVID-19 infection. The third part investigated college students' knowledge and attitudes about the COVID-19 vaccine booster dose. Confidence in the effectiveness of COVID-19 heterologous vaccination booster was measured as follows: better, no better, unclear. In the fourth part, the main topics included: "Have you received the COVID-19 vaccine?" (options: no, one dose, two doses, three doses [booster]); then, respondents who answered "two doses" were asked, "Are you willing to have a booster of the COVID-19 vaccine?" (yes or no); respondents who were willing to receive a booster were asked, "Which vaccination method will you choose?" (options: homologous or heterologous); finally, respondents who had received a booster were asked, "Which vaccination method did you choose?" (options: homologous or heterologous).

## Statistical analysis

Class variables related to essential features were expressed as counts and percentages. Data of respondents who were willing to receive the COVID-19 booster were included in the next phase of the chi-square test, which was used to initially assess

differences in demographic and personal background variables between participants willing to receive a dose of homologous or heterologous booster doses. All data were analyzed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). A difference with  $P < .05$  was considered statistically significant.

## Results

A total of 2463 students received the questionnaire, and 1821 responses were valid. The overall response rate was 73.9%. Further, 62.7% (1,141/1,821) of respondents had received three doses; 35.7% (651/1,821) of them had only received two doses; and 94.3% (614/651) of those who had received only two doses were willing to receive the booster dose (Figure 1). Therefore, totally, 614 college students who were willing to receive booster doses were selected for the following analysis. The respondents' mean ( $\pm$  SD) age was  $18.93 \pm 1.14$  years (range from 18 years to 23 years), and 60.3% of them were female (Table 1).

Moreover, only 14% (86/614) of those willing to receive a booster chose a heterologous vaccination. Table 2 also shows that college students' willingness to receive heterologous booster doses of COVID-19 vaccine were related to older age ( $\chi^2 = 11.765$ ,  $P = 0.003$ ) and better perceived effectiveness of COVID-19 heterologous vaccination booster ( $X^2 = 22.671$ ,  $P < .001$ ). Additionally, female college students' older age ( $\chi^2 = 7.523$ ,  $P = .023$ ), major of medical ( $\chi^2 = 6.294$ ,  $P = .012$ ), and better perceived effectiveness of COVID-19 heterologous vaccination booster ( $\chi^2 = 22.659$ ,  $P < .001$ ), were more willing to receive heterologous booster doses.

## Discussion

### Clinical implications

Vaccination is an effective public health measure to control the COVID-19 pandemic, and the protective effect of the vaccine is affected by time and virus mutations.<sup>5,17</sup> The emergence of

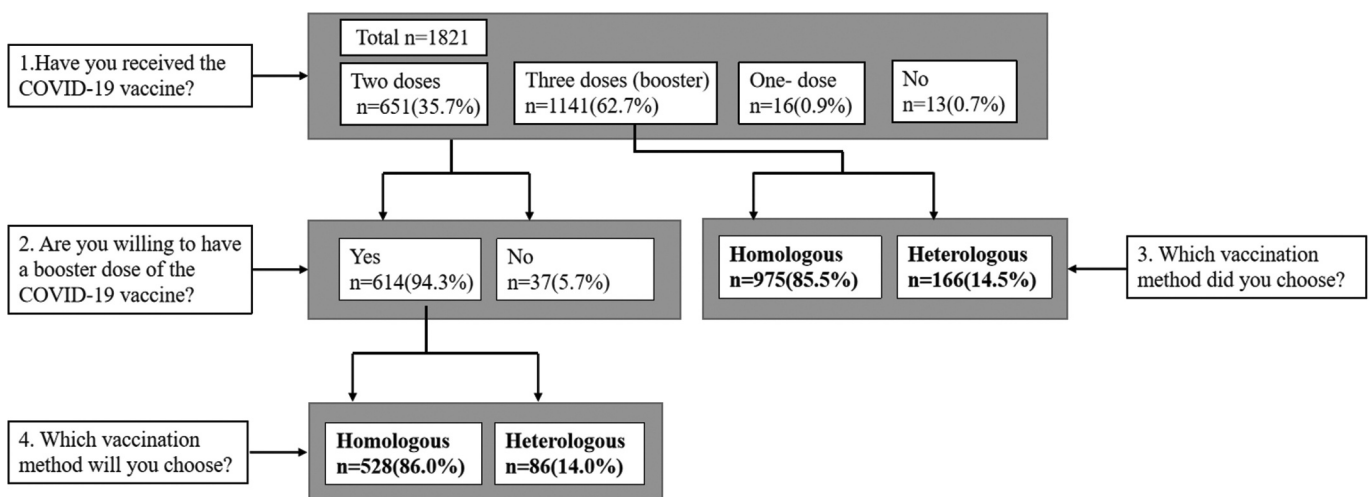


Figure 1. COVID-19 vaccination rate and willingness to receive booster doses among college students.

**Table 1.** Baseline characteristics of the college students who willing to receive booster doses of COVID-19 vaccine (n = 614).

Characteristics	Category	n (%) / $\bar{x}$ ( $\pm$ s)
Total		1821(100)
Age	18 years	267(43.5)
	19 years	224(36.5)
	20–23 years	123(20.0)
Gender	Male	244 (39.7)
	Female	370 (60.3)
Residence	Rural/Town	323 (53.6)
	Urban	291 (47.4)
Major	Medical	84 (13.7)
	Non-medical	530 (86.3)
Have you ever received the influenza vaccine?	No	264 (43.0)
	Yes	350 (57.0)
History of allergic	No	522(85.0)
	Yes	92(15.0)
Risk perception of COVID-19 infection	High	1 84 (10.1)
	Low	1637 (89.9)

variants of concern (VOC)<sup>18–23</sup> poses a great challenge to the efficacy of existing vaccines. The main virus strain currently circulating, Omicron, has high infectivity and a powerful ability to escape immunity.<sup>22,23</sup> The heterologous COVID-19 vaccine has shown higher immunogenicity<sup>5–6,10–24–27</sup> and neutralization efficiency,<sup>11,28</sup> supporting the sequential vaccination with heterologous vaccines.

This study found that 94.3% of the research subjects were willing to choose booster injections, while only 14.0% chose heterologous vaccines. A small number of studies have shown a large difference in the proportion of heterologous vaccines selected. Rababa'h et al. found that 26.5% of Jordanians chose heterologous vaccines,<sup>29</sup> and Marco Clari et al. found that 76.1% of Italians chose a heterologous COVID-19 vaccination regimen.<sup>13</sup>

Heterologous vaccines have been widely valued as a way to alleviate intermittent supply shortages and improve the immunogenicity and safety of COVID-19 vaccine. Many countries, including China, are conducting large-scale COVID-19 vaccinations using CoronaVac, an inactivated vaccine. Academic studies have indicated that both homologous CoronaVac and heterologous BNT162b2 vaccines boosted antibody responses in CoronaVac-immunized individuals, but heterologous BNT162B2 was markedly superior in immunogenicity.<sup>25,26</sup> Similarly, heterologous dosing with the adenovirus-based ChAdOx1 (AstraZeneca) vaccine followed by an mRNA vaccine induced stronger immune responses than did the homologous ChAdOx1 vaccine series.<sup>24</sup> Pozzetto et al. report that the sera from heterologous vaccinated individuals displayed a stronger neutralizing activity regardless of the COVID-19 variant.<sup>10</sup> In addition, COVID-19 S1 T-cell reactivity after boost immunization was highest in recipients of heterologous ChAdOx1 nCov-19–BNT162b2 compared with that in recipients of homologous ChAdOx1 nCov-19 and homologous BNT162b2 vaccination.<sup>5</sup> This implies improved immunogenicity outcomes with heterologous dosing and suggests possible superiority of this strategy to homologous substrate enhancement schemes, facilitating cellular responses and neutralization of variants.

In our study, the factors related to the selection of heterologous vaccination showed significant differences in the cognition of the effectiveness of heterologous vaccines between the two groups of college students willing to chose heterologous or homologous vaccines. Our research suggests that a lack of knowledge about the effectiveness of heterologous vaccines may reduce the proportion of college students choosing heterologous vaccines, while college students not aware of the differences in the effectiveness of heterologous and homologous vaccines will tend to choose the latter.

The effectiveness of vaccines has always been a public concern,<sup>30,31</sup> and it is also an important factor affecting the public's choice of vaccines.<sup>32–34</sup> Although heterologous vaccines have shown advantages in immunogenicity and antibody levels, the implementation of heterologous vaccination methods has been short-lived, and the public's understanding is not yet widespread.<sup>13,29</sup> This situation may affect the public's willingness to choose heterologous vaccines.<sup>35,36</sup>

Previous studies have shown that vaccination history can influence the public's choice of vaccine.<sup>30,31</sup> According to WHO data released on 10 May 2022, 155 vaccines have been approved for clinical trials, and 197 vaccines are in preclinical trials. These vaccines mainly include inactivated vaccines, live attenuated vaccines, viral vector vaccines, RNA vaccines, DNA vaccines, protein subunit vaccines, and VLP vaccines.<sup>37</sup> In China, inactivated vaccines are mainly inactivated COVID-19 vaccines,<sup>38,39</sup> which also show good efficacy and safety.<sup>40–42</sup> Our study found that 83.1% of college students recognized the effectiveness of the vaccine, and 82.6% recognized its safety. The previous experience of receiving the COVID-19 vaccine has made Chinese college students confident in receiving the booster shot. In this context, people who are unaware of the effectiveness of heterologous vaccines are likely to show hesitancy toward them.<sup>35,43,44</sup> For their confidence in the homologous vaccine and personal inertial thinking, people will be more inclined to choose the homologous vaccine.<sup>45,46</sup>

Table 2. Cardinal analysis of potential factors influencing willingness to receive homologous or heterologous booster doses (N = 614).

Independent Variables	Categories	Total			Male			Female					
		Homologous, n(%)	Heterologous, n(%)	$\chi^2$	p	Homologous, n(%)	Heterologous, n(%)	$\chi^2$	p	Homologous, n(%)	Heterologous, n(%)	$\chi^2$	p
Total		528(86.0)	86(14.0)			204(83.6)	40(16.4)			324(87.6)	46(12.4)		
Gender	Male	204(83.6)	40(16.4)	1.915	.166	/	/			/	/		
	Female	324(87.6)	46(12.4)			/	/			/	/		
Age (years)	18	237(11.2)	30(11.2)	11.765	.003	89(86.4)	14(13.6)	3.937	.140	148(90.2)	16(9.8)	7.523	.023
	19	197(87.9)	27(12.1)			73(85.9)	12(14.1)			124(89.2)	15(10.8)		
	20-23	94(76.4)	29(23.6)			42(75.0)	14(25.0)			52(77.6)	15(22.4)		
Residence	Rural	282(87.3)	41(12.7)	0.975	.323	101(83.5)	20(16.5)	0.003	.955	181(89.6)	21(10.4)	1.695	.193
	Urban	246(84.5)	45(15.5)			103(83.7)	20(16.3)			143(85.1)	25(14.9)		
Major	Medical	67(79.8)	17(20.2)	3.137	.077	22(84.6)	4(15.4)	0.022	.883	45(77.6)	13(22.4)	6.294	.012
	Non-medical	461(87.0)	69(13.0)			182(83.5)	36(16.5)			279(89.4)	33(10.6)		
Have you ever received the influenza vaccine?	No	224(84.8)	40(15.2)	0.504	.478	82(80.4)	20(19.6)	1.321	.250	142(87.7)	20(12.3)	0.002	.964
	Yes	304(86.9)	46(13.1)			122(85.9)	20(14.1)			182(87.5)	26(12.5)		
History of allergic	No	449(86.0)	73(14.0)			174(82.1)	38(17.9)	1.979	.160	275(88.7)	35(11.3)	2.290	.130
	Yes	79(85.9)	13(14.1)			30(93.8)	2(6.3)			49(81.7)	11(18.3)		
Perceived effectiveness of COVID-19 heterologous vaccination booster	Better	152(76.4)	47(23.6)	22.671	<.001	72(78.3)	20(21.7)	3.421	.181	80(74.8)	27(25.2)	22.659	<.001
	No better	115(89.8)	13(10.2)			37(84.1)	7(15.9)			78(92.9)	6(7.1)		
	Unclear	261(90.9)	26(9.1)			95(88.0)	13(12.0)			166(92.7)	13(7.3)		
Risk perception of COVID-19 infection	High	55(80.9)	13(19.1)	1.659	.198	16(69.6)	7(30.4)	3.653	.056	39(86.7)	6(13.3)	0.038	.845
	Low	473(86.6)	73(13.4)			188(85.1)	33(14.9)			285(87.7)	40(12.3)		
Knowledge of COVID-19 heterologous vaccination booster	High	290(87.6)	41(12.4)	1.564	.211	112(85.5)	19(14.5)	0.737	.391	178(89.2)	22(11.0)	0.820	.365
	Low	238(84.1)	45(15.9)			92(81.4)	21(18.6)			146(85.9)	24(14.1)		
Perceived safety of COVID-19 vaccine booster dose	High	432(85.2)	75(14.8)	1.494	.222	174(83.7)	34(16.3)	0.002	.962	258(86.3)	41(13.7)	2.345	.126
	Low	96(89.7%)	11(10.3)			30(83.3)	6(16.7)			66(93.0)	5(7.0)		

Therefore, it is recommended that improvement in the population's understanding of heterologous vaccines must begin. Measures such as health education, public health awareness, and the disclosure of heterologous vaccine information for health care personnel can improve the public's understanding of heterologous vaccines,<sup>32–34</sup> and this can allow the public to make better choices.

## Methodological considerations

Our research also has some limitations: (1) our sample was not generated by random sampling, but the questionnaire was filled out voluntarily by students, which implies a certain self-selection bias. (2) Due to the time limit for filling in the questionnaire, students' willingness to receive the heterologous vaccination was not assessed with a scale. (3) Multivariate regression analysis was not conducted in this study, probably because of the consideration of insufficient variables. There may be other uninvestigated factors that affect the willingness of college students to receive the heterologous vaccination and, therefore, other influencing factors should be considered for further research in the future. (4) Our survey was conducted in the early stage of the implementation of heterologous vaccination thus, the public's willingness to receive the heterologous vaccination may be underestimated, and it may change over time. (5) This study included only 614 respondents in the main analysis out of 1821 respondents. In addition, 1141 of the participants had already received their third dose of vaccination. Therefore, it is likely that the 614 participants in this study were those who had delayed their vaccinations. There may be a selection bias here. (6) The data may be a result of the heterogeneity of the sample rather than a generalizable population effect. (7) The study was a cross-sectional study, but the study group comprised only college students with a median age of approximately 19. Therefore, we will conduct a further investigation and comparative analysis in the next stage.

## Conclusion

Our research found that Chinese college students have a strong willingness to receive a COVID-19 vaccine booster shot, but only 14.0% are willing to receive the heterologous vaccine, while most college students prefer the homologous vaccination. The lack of knowledge about the effectiveness of heterologous vaccines is an important factor in the low proportion of heterologous vaccine selection, and our results provide valuable evidence for future public health policy and vaccination campaigns. Health education, public health awareness, and the disclosure of heterologous vaccine information can help improve the public's understanding of heterologous vaccines and help them make better choices.

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## Author contributions

J.S.Z. and T.H.T. were involved in the conception and design. X.Q.L., Y.C., L.L. and C.Q.Y. were involved in the analysis and interpretation of the data. H.S. and X.Q.L. were involved in the drafting of the paper, revising it critically for intellectual content, and the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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## ORCID

Xiao-Qing Lin  <http://orcid.org/0000-0003-4986-2835>  
 Yan Chen  <http://orcid.org/0000-0002-4975-989X>  
 Li Lv  <http://orcid.org/0000-0002-2132-6558>  
 Tao-Hsin Tung  <http://orcid.org/0000-0003-2097-8375>  
 Jian-Sheng Zhu  <http://orcid.org/0000-0002-4961-7437>

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province (Approval number: K20210705) in China.

## Data availability statement

The data that support the findings of this study are available from the corresponding author, T.H.T, upon reasonable request.

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