BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063919
Article Type:	Original research
Date Submitted by the Author:	19-Apr-2022

Complete List of Authors:	Tang, Lin; Chinese Center for Disease Control and Prevention, National Immunization Program Zhang, Yanyang; Henan Provincial Center for Disease Control and Prevention Wang, Fuzhen; Chinese Center for Disease Control and Prevention Wu, Dan; Chinese Center for Disease Control and Prevention Qian, Zhao-Hui; NHC Key laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China Zhang, Rui; National Center for Clinical Laboratories, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences Wang, Ai-Bin; Beijing Ditan Hospital Capital Medical University Huang, Chang; Chinese Center for Disease Control and Prevention; China Field Epidemiology Training Program Wang, Haifeng; Henan Provincial Center for Disease Control and Prevention Ye, Ying; Henan Provincial Center for Disease Control and Prevention Lu, Mingxia; Henan Provincial Center for Disease Control and Prevention Wang, Changshuang; Henan Provincial Center for Disease Control and Prevention Ma, Ya-ting; Henan Province Center for Disease Control and Prevention Pan, Jingjing; Henan Province Center for Disease Control and Prevention Li, Ya-fei; Henan Province Center for Disease Control and Prevention Lv, Xiao-Ya; Development Center for Medicine and Science &Technology, National Health Commission An, Zhijie; Chinese Center for Disease Control and Prevention, National Immunization Program Rodewald, Lance; Chinese Center for Disease Control and Prevention, National Immunization Program Wang, Xuan-Yi; Fudan University Shao, Yi-Ming; State Key Laboratory of Infectious Disease Prevention and Control, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention Wu, Zhi-Yin; Development Center for Medicine and Science &Technology, National Health Commission Yin, Zundong; Chinese Center for Disease Control and Prevention, National Immunization Program

Keywords:	COVID-19, Infectious diseases & infestations < DERMATOLOGY, Epidemiology < INFECTIOUS DISEASES, Immunology < NATURAL SCIENCE DISCIPLINES

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Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study

Lin Tang[1*], Yan-Yang Zhang[2*], Fu-Zhen Wang[1], Dan Wu[1], Zhao-Hui Qian[3], Rui Zhang[4], Ai-Bin Wang[5], Chang Huang[1,6], Hai-feng Wang[2], Ying Ye[2],Ming-Xia Lu[2],Chang-Shuang Wang[2], Ya-ting Ma[2],Jingjing Pan[2], Ya-fei Li[2], Xiao-Ya Lv[7], Zhi-Jie An[1], Lance E. Rodewald[1], Xuan-Yi Wang[8&], Yi-Ming Shao[9&],Zhi-Yin Wu[7&], Zun-Dong Yin[1&]

[*]Join first authors.
Lin Tang and Yan-yang Zhang contributed equally to this work.
[&]Joint corresponding authors
Correspondence to: yinzd@chinacdc.cn yshao@chinaaids.cn
zhiyinwu@126.com xywang@shmu.edu.cn

1.National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China
2. Henan Provincial Disease Control and Prevention, China
3. NHC Key laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
4.National Center for Clinical Laboratories, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, China
5. Beijing Ditan Hospital Capital Medical University
6.China Field Epidemiology Training Program
7.Development Center for Medicine and Science &Technology, National Health Commission, China
8.Shanghai Institute of Infectious Disease and Biosecurity, Key Laboratory of Medical Molecular Virology of MoE & MoH, and Institutes of Biomedical Sciences, Shanghai Medical College, Fudan University, China
9.State Key Laboratory of Infectious Disease Prevention and Control, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention Beijing, China

ABSTRACT

Objective

Two COVID-19 outbreaks occurred in Henan province in early 2022 – one was a Delta variant outbreak and the other was an Omicron outbreak. COVID-19 vaccines used at the time of the outbreak were inactivated, 91.8%; protein subunit, 7.5%; and adenovirus5-vectored, 0.7%. The outbreaks provided an opportunity to evaluate the performance of COVID-19 vaccines used in China, including homologous boosting of inactivated COVID-19 vaccines.

Design: A retrospective cohort study

Methods

We evaluated relative vaccine effectiveness (rVE) with a retrospective cohort study of close contacts of infected individuals using a time-dependent Cox regression model. Demographic and epidemiologic data were obtained from the local Center for Disease Control and Prevention; clinical and laboratory data were obtained from COVID-19-designated hospitals. Vaccination histories were obtained from the national COVID-19 vaccination dataset. All data were linked by national identification number.

Results

Among 784 SARS-CoV-2 infections, 379 (48.3%) were caused by Delta and 405 (51.7%) were caused by Omicron, representing breakthrough rates of 9.9% and 17.8%, respectively. Breakthrough rates among boosted individuals were 8.1% and 4.9%. Compared with subjects who received primary vaccination series ≥ 180 days before infection, Cox regression modeling showed that homologous inactivated booster vaccination was statistically significantly associated with protection from symptomatic infection caused by Omicron (rVE 59%; 95% CI: 14%-80%) and pneumonia caused by Delta (rVE 62%; 95%CI: 34%-77%) and Omicron (rVE 87%; 95%CI: 3%-98%).

Conclusions

Protection from Delta and Omicron COVID-19 declined over time, notably 6 months after primary vaccination. A homologous inactivated booster dose restored protection against both variants.

What is already known on this topic

Previous research reported that vaccine effectiveness of currently approved vaccines against Delta and Omicron COVID-19. Real-world evidence shows that all approved COVID-19 vaccines have various degrees of waning vaccine effectiveness (VE) over time and demonstrate different protection against Delta and Omicron variants, but with VE against serious illness maintained significantly better than protection against SARS-CoV-2 infection and symptomatic COVID-19, and receipt of booster doses can restore waning protection, including against Delta and Omicron. There are fewer studies of China-produced COVID-19 vaccines than of WHO-approved vaccines produced in other countries. Several studies conducted in Guangdong, Jiangsu, and Henan provinces of China found that among adults aged 18–59 years old, vaccine effectiveness (VE) against Delta COVID-19 was 50%-60%, and effectiveness against severe illness was 80%-100%. Some real-world study results showed the vaccine effectiveness by COVID-19 vaccine declined to lower to prevent Pneumonia after 6 months. A study in Hong Kong showed better 2-dose protection against serious illness with mRNA vaccine than an inactivated vaccine, but equivalent 98% protection with a homologous booster dose.

What this study adds

Our study used a Delta and Omicron outbreak in China's infection-naïve population to evaluate population-level protection from COVID-19 pneumonia that was built by a provincial immunization program with China-produced vaccines that were used as recommended by China's National Health Commission. In a retrospective cohort study, we found that homologous inactivated booster vaccination induced protection against Delta and Omicron pneumonia was 62% and 87% compared with vaccination ≥ 6 months prior to exposure to SARS-CoV-2. There were too few cases of Omicron pneumonia in boosted subjects to evaluate relative effectiveness against pneumonia.

How this study might affect research, practice, or policy

Population immunity built with China-produced vaccines in an infection-naïve population effectively prevented progression to pneumonia caused by Delta and Omicron variants. Booster doses 6 months after primary vaccination are essential for building the strongest population immunity. All age-eligible people should be vaccinated, and schedule-eligible people should receive timely booster doses.

INTRODUCTION

Most countries have experienced epidemic waves of COVID-19 caused by SARS-CoV-2 variants. As of December 11, 2021, five SARS-CoV-2 Variants of Concern (VOCs) have been identified, with Alpha (B.1.1.7) and Delta (B.1.617.2) predominant[1]. Omicron emerged November 2021 and rapidly replaced Delta to be the predominant global strain, accounting for 90% of GISAID SARS-CoV-2 sequences [2-4]. The World Health Organization (WHO) has listed nine COVID-19 vaccines for emergency use, including the two most commonly used vaccines in China - BBIBP-CorV and CoronaVac inactivated whole-virus vaccines. Over 3 billion doses of these vaccines have been used in China, and 1.5 billion doses have been procured overseas [5 6].

Good safety and short-term efficacy against the ancestral strain have been demonstrated for these vaccines [7], and real-world evidence on protection against VOCs and protection with booster doses is available, for example, from Guangdong, Jiangsu, and Henan[8-11] in China and Chile and Brazil overseas [12 13]. In China, the Zero-COVID policy severely limits outbreak size, and very high COVID-19 primary vaccination coverage makes unvaccinated comparison groups too small and too different for conducting absolute vaccine effectiveness (VE) studies. In January 2022, two outbreaks occurred in Henan – one caused by Delta (B.1.617.2) and the other by Omicron (B.1.1.529.1) – that provided an opportunity to assess relative VE (rVE) of China-produced vaccines against COVID-19 caused by these two variants. We report results of our evaluation.

METHODS

Outbreak setting

The setting was Henan province where there were two simultaneous outbreaks. Henan has a population of 100 million; the three involved cities were Zhengzhou (8.6 million, whole-population primary series coverage 87.2%), Yuzhou (1.2 million, 94.7%), and Anyang (1.5 million, 80.3%). The COVID-19 vaccines used were inactivated vaccines, 91.8%; ZF2001, 7.5%; and Ad5-nCoV vaccine, 0.7%. In all of China, SARS-CoV-2 infections are traced, and contacts quarantined for at least two weeks and tested periodically in quarantine. China's immunization program records all COVID-19 vaccinations in a national vaccination database indexed by national ID number. The national COVID-19 surveillance system is also indexed by ID.

On January 2, 2022, a Yuzhou factory worker tested RT-PCR-positive in a routine pre-surgery screening. Contact tracing identified a Delta-variant community transmission chain that spread to Zhengzhou. On January 8, a medical device company employee and a middle school student tested positive when seeking health care in Anyang. Investigation revealed an Omicron outbreak in a boarding school with 4,103 students and teachers along with community transmission (**Figure 1**).

Study design and subjects

We used a retrospective cohort design to estimate rVE. Subjects were confirmed SARS-CoV-2 infections and their close contacts, grouped by vaccination status. Outcomes were infection, pneumonia, and severe of illness.

A SARS-CoV-2 infection was a person with a positive RT-PCR, including all asymptomatic

and symptomatic infection regardless of severity; COVID-19 pneumonia was a SARS-CoV-2 infection with acute onset of fever AND cough OR acute onset with any three or more of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status; OR having chest CT imaging findings suggestive of pneumonia. Severe illness was characterized by respiratory failure with need for mechanical ventilation OR shock combined with other organ failure requiring ICU care [14].

Close contacts had exposure to confirmed SARS-CoV-2 infections up to four days before illness onset of symptomatic cases or the first RT-PCR-positive specimen for asymptomatic cases. Exposure included living in the same apartment, sharing a table for meals, studying, or working in the same room, or sharing a ward.

Subject data were obtained from the local Center for Disease Control and Prevention (CDC) and included the epidemiological investigation report, transmission chain, age, gender, date of first and last exposure, mode and location of exposure, and frequency and duration of exposure. For confirmed SARS-CoV-2 infections, we reviewed medical records from designated COVID-19 management hospitals in Zhengzhou and Anyang to determine clinical management, laboratory tests conducted, and chest imaging.

Vaccine status

Without knowledge of infection status, we obtained vaccination records from the national vaccination database using subjects' national IDs. Vaccination was defined as receipt of at least one dose of COVID-19 vaccine. Partial vaccination was receipt of either one dose of an inactivated COVID-19 vaccine or two doses of an inactivated vaccine with receipt of the second dose less than 14 days before exposure. Primary vaccination was completion of two doses of inactivated vaccine 14 days or more before exposure and/or a third dose of inactivated vaccine less than 7 days of exposure. Booster vaccination was a third more than 7 days before exposure. Primary vaccination was further classified as being either <180 days before exposure or ≥180 days before exposure.

Data analysis

A breakthrough infection was an RT-PCR-confirmed SARS-CoV-2 infection at least 14 days after completion of primary vaccination. We estimated unadjusted and adjusted (gender and age group) rVE against Delta and Omicron infections using a Cox regression models. The reference group was primary vaccination ≥180 days before exposure; rVE was 1-adjusted hazard ratio for COVID-19 symptomatic infection or pneumonia.

Ninety-five percent of co-morbidities were among subjects 50 years and older. Our age groupings were under 18 years, 18 to 50 years, and over 50 years. Subjects in the Omicron and Delta outbreaks differed since the Omicron outbreak involved a fully vaccinated middle school with 94.7% of cases under 20 years of age, with its higher force of infection. We therefore conducted rVE analyses with and without subjects under 20 years of age.

We used SAS (SAS Institute Inc., Cary, NC, USA) for statistical analysis and R (version 4.1.0) for Cox survival analysis of pneumonia. P-values < 0.05 (two-tailed) were considered statistically significant.

Patient and Public Involvement statement:

This real-world, observational study was designed without patient or public involvement. COVID-19 is managed as a Level-1 infectious disease, and as such, investigations of outbreaks and public health effort to prevent illness and stop transmission are required of public health agencies. Subjects were not recruited into the study, as they were cases or close contacts managed in accordance with the National Health Commission's Protocol for Prevention and Control. Neither patients nor the public were involved in the conduct of the study, as testing and data aggregation were conducted under the prevention and control policy. Results will be disseminated through publicly-available scientific publications.

RESULTS

Subjects

Table 1 shows the characteristics of the subjects. Between January 2 and 23, 2022, a total of 6,521 SARS-CoV-2 infections and close contacts were identified in the three-city setting, among which 784 were SARS-CoV-2 infections and 5,737 were close contacts. Because of the 4,103-person middle school outbreak, subjects in the Anyang (Omicron) transmission chain were younger on average that in the Zhengzhou/Yuzhou (Delta) transmission chain (43.5% vs 23.8% < 20 years, $p<0.05$). Most (72.7%) subjects completed primary vaccination; 14.9% received 0-1 dose; and 12.4% received booster doses. In the Delta chain, the median number of days between primary vaccination and exposure was 117 days (IQR:40-134) among subjects completed primary <180 days before exposure and 196 days (IQR:191-203) among subjects completed primary ≥180 days before exposure. Respective medians in the Omicron chain were 133 days (IQR:121-138) and 203 days (IQR:196-210). Boosters were completed 20 (IQR:12-68) and 19 days (IQR:11-64) before Delta and Omicron exposure.

Breakthrough infection

Breakthrough infection rates were 9.9% in the Delta chain and17.8% in the Omicron chain ($p<0.001$) among subjects completing primary vaccination. By vaccination group, breakthrough rates were 10.6% (Delta) and 11.0% (Omicron) among subjects who completed primary vaccination ≥180 days ($p>0.05$); 10.1% (Delta) and 22.2% (Omicron) among subjects who completed primary vaccination <180 days ($p<0.001$); and 8.1% (Delta) and 4.9% (Omicron) among boosted subjects ($p>0.05$).

When subjects under 20 years old were excluded, breakthrough rates were 10.8% (Delta) and 10.6% (Omicron) among subjects who completed primary vaccination ≥180 days ($p>0.05$); 12.3% (Delta) and 8.7% (Omicron) among subjects who completed primary vaccination <180 days ($p>0.05$); and 7.9% (Delta) and 4.5% (Omicron) among boosted subjects ($p>0.05$).

Table 1. Characteristics of SARS-CoV-2 infections and close contacts in Delta and Omicron transmission chain

Characteristics	Delta transmission chain					Omicron transmission chain				
	Non/Partial vaccination (n, %)	Primary vaccination		Booster vaccination (n, %)	p value	Non/Partial vaccination (n, %)	Primary vaccination		Booster vaccination (n, %)	p value
		≥180 days (n, %)	<180 days (n, %)				≥180 days (n, %)	<180 days (n, %)		
SARS-CoV-2 infections										
Subtotal	49	97	182	51		12	65	319	9	
Gender										
Female	33 (67.3)	53 (54.6)	104 (57.1)	34 (66.7)	<0.001	7 (58.3)	42 (64.6)	176 (55.2)	5 (41.7)	<0.001
Male	16 (32.7)	44 (45.4)	78 (42.9)	17 (33.3)		5 (41.7)	23 (35.4)	143 (44.8)	4 (58.3)	
Age group (yrs)										
< 18	8 (16.3)	0 (0)	53 (29.1)	0 (0)	<0.001	2 (16.7)	0 (0)	191 (59.9)	0 (0)	<0.001
18-49	19 (38.8)	54 (55.7)	50 (27.5)	31 (60.8)		7 (58.3)	45 (69.2)	107 (33.5)	7 (77.8)	
≥ 50	22 (44.9)	43 (44.3)	79 (43.4)	20 (39.2)		3 (25.0)	20 (30.8)	21 (6.6)	2 (22.2)	
Close contacts										
Subtotal	525	814	1619	575		386	524	1120	174	
Gender										
Female	270 (51.4)	430 (52.8)	792 (48.9)	307 (53.4)	<0.001	215 (55.7)	310 (59.2)	529 (47.2)	106 (60.9)	<0.001
Male	255 (48.6)	384 (47.2)	827 (51.1)	268 (46.6)		171 (44.3)	214 (40.8)	591(52.8)	68 (39.1)	
Age group (yrs)										
< 18	149 (28.4)	0 (0)	674 (41.6)	0 (0)	<0.001	100 (25.9)	0 (0)	616 (55.0)	0 (0)	<0.001
18-49	250 (47.6)	598 (73.5)	588 (36.3)	421 (73.2)		187 (48.5)	366 (69.9)	341(30.5)	123 (70.7)	
≥ 50	126 (24.0)	216 (26.5)	357 (22.1)	154 (26.8)		99 (25.6)	158 (330.1)	163 (14.5)	51 (29.3)	
Total	574	911	1801	626		398	589	1439	183	

Relative Vaccine effectiveness

Table 2 shows results of the Cox regression analyses for symptomatic infection and pneumonia by Delta and Omicron variants. For both variants, univariate analysis shows that being male and booster vaccination were associated with reduced risk of symptomatic infection. Age was associated with symptomatic infection, especially among subjects ≥50 years. Cox regression adjusting for age group, gender, and vaccination status were similar in magnitude for symptomatic infection risk from Delta vs Omicron. Hazard ratios among those ≥50 years differed in direction between Delta and Omicron (2.75 and 0.56), and relative protection increased from 24% to 59% in boosted subjects. After removing subjects < 20 years (primarily the school outbreak students) from the Cox regression analysis, primary vaccination <180 days and booster vaccination were both associated with protection from Delta and Omicron symptomatic infections.

For pneumonia, the relation with age was more pronounced than was the case for symptomatic infection, and more so with Delta than Omicron. Hazard ratios for pneumonia were consistent in direction, showing greater protection associated with primary vaccination <180 days and booster dose administration, regardless of variant. After excluding subjects < 20 years from the Cox regression analysis, hazard ratios against pneumonia change little, except for an increase in protection (from 17% to 35%) among subjects who received primary vaccination within 180 days. Survival curve analysis results for pneumonia for each variant by vaccination status group are shown in Figure 2. Although the three vaccination groups were statistically significantly different for Delta pneumonia, there was no statistically significant difference between the two primary vaccination groups for Omicron pneumonia, although both were different from the boosted group.

There were few severe infections in the two transmission chains. There were 12 severe cases in the Delta chain, with five included in Cox analysis (2 with primary vaccination ≥180 days group, 3 cases with primary vaccination< 180 days, and none in the booster vaccination group. There were no severe cases in the Omicron transmission chain.

Table 2. Cox regression analysis by vaccination status and by outcomes of SARS-CoV-2 infection

Covariates	Delta infection for all				Omicron infection for all				Omicron infection for ⩾20 yrs	
	Crude HR (95%CI)	p value	Adjusted HR (95%CI)	p value	Crude HR (95%CI)	p value	Adjusted HR (95%CI)	p value	Adjusted HR (95%CI)	p value
Symptomatic infection										
Gender										
Female	Ref		Ref		Ref		Ref		Ref	
Male	0.80 (0.64 - 1.00)	0.05	0.79 (0.63 - 0.98)	0.04	0.80 (0.65 – 0.99)	0.04	0.73 (0.59 - 0.90)	0.01	0.52(0.33 - 0.80)	0.003
Age group(age)										
< 18	Ref		Ref		Ref		Ref			
18-49	1.17 (0.84 - 1.63)	0.36	1.26 (0.87 - 1.81)	0.22	0.65 (0.52 – 0.81)	<0.01	0.92(0.72 - 1.18)	0.5	Ref (20-49 yrs)	
≥ 50	2.58 (1.86 - 3.60)	<0.01	2.75 (1.94 - 3.91)	<0.01	0.40 (0.28 – 0.56)	<0.01	0.56 (0.39 - 0.81)	0.01	1.33(0.89 - 2.00)	0.166
Vaccination status										
Primary vaccination≥180 days	Ref		Ref		Ref		Ref		Ref	
Primary vaccination<180 days	0.92 (0.72 - 1.18)	0.51	1.04 (0.79 - 1.36)	0.79	2.11 (1.60 – 2.78)	<0.01	1.95 (1.43 - 2.65)	<0.01	0.79(0.52 - 1.20)	0.261
Booster vaccination	0.75 (0.53 - 1.06)	0.11	0.76 (0.54 - 1.07)	0.11	0.41 (0.20 – 0.87)	0.02	0.41(0.20 - 0.86)	0.02	0.39(0.18 - 0.86)	0.019
Pneumonia										
Gender										
Female	Ref		Ref		Ref		Ref		Ref	
Male	0.65 (0.47 - 0.90)	0.01	0.65 (0.47 - 0.90)	0.01	0.96 (0.60 - 1.52)	0.85	0.93 (0.58 - 1.49)	0.77	0.77(0.39 - 1.54)	0.457
Age group (yrs)										
< 18	Ref		Ref		Ref		Ref			
18-49	8.61 (2.70 - 27.43)	<0.01	9.11 (2.81 - 29.5)	<0.01	0.88 (0.52 - 1.50)	0.63	0.89 (0.48 - 1.67)	0.73	Ref (20-49 yrs)	
≥ 50	28.00 (8.88 - 88.40)	<0.01	29.50 (9.26 - 94.0)	<0.01	1.11 (0.59 - 2.07)	0.75	1.13 (0.56 - 2.27)	0.74	1.70(0.87 - 3.32)	0.123
Vaccination status										
Primary vaccination≥180 days	Ref		Ref		Ref		Ref		Ref	
Primary vaccination<180 days	0.60 (0.43 - 0.83)	0.01	0.86 (0.61 - 1.20)	0.37	0.84 (0.51 - 1.37)	0.48	0.83 (0.46 - 1.50)	0.53	0.65(0.32 - 1.32)	0.231
Booster vaccination	0.38 (0.22 - 0.64)	<0.01	0.38 (0.23 - 0.66)	<0.01	0.13 (0.02 - 0.97)	0.047	0.13 (0.02 - 0.97)	0.047	0.15(0.02 - 1.08)	0.059

DISCUSSION

We used a 748-case, two-variant COVID-19 outbreak in Henan province to determine the relative vaccine effectiveness of the vaccines used in China to protect against symptomatic infection and pneumonia. Our study found an rVE of 62% against Delta pneumonia and 87% against Omicron pneumonia among homologous inactivated vaccine booster-dose recipients compared with individuals who received complete primary vaccination greater than 180 days prior to exposure to SARS-CoV-2. Relative VE was lower for individuals receiving primary vaccination less than 180 days prior to exposure than among boosted individuals, demonstrating an effectiveness advantage of the homologous booster dose. Results from our study support the current COVID-19 booster vaccination strategy in China in which everyone 18 years and older is recommended to receive a booster dose six months after their primary series.

Our study also found a higher breakthrough infection rate in the Omicron transmission chain than the Delta chain (22% vs 10%) and found no severe Omicron cases and only 12 severe Delta cases - 3% of the Delta outbreak. The low rate of severe infection provides information valuable for projection of health care resource needs in the future.

In licensure clinical trials for vaccines produced in China estimates of efficacy against symptomatic COVID-19 were 50% to 78% [15 16]. Our relative VE estimates are not directly comparable, since efficacy estimates are absolute rather than relative estimates. A relative VE estimate only indicates additional VE above and beyond an unmeasured absolute VE of the comparison group. There have been several real-world assessments of VE of the China-produced vaccines [8-11], but none that compare rVE against Delta and Omicron in simultaneous outbreaks, and few studies of relative VE from a booster dose of China-produced vaccine.

As of March 14, 2022, 457 million confirmed cases of COVID-19 and 6 million COVID-19 deaths were reported worldwide to the World Health Organization (WHO) [17]. To stop the virus from raging around the world, vaccines had high hopes. In less than a year after SARS-CoV-2 emergence, COVID-19 vaccines were developed via several technologies[18] and have been approved by regulators and WHO for emergency use. WHO approved the two inactivated vaccines that comprised the vast majority of COVID-19 vaccines used in China and included in our study.

In the real world, several studies reported high effectiveness of mRNA-based vaccines against SARS-CoV-2 infection, with a breakthrough infection of less than 1% of symptomatic SARS-CoV-2 infections, and a ~0.1% rate of hospitalization or death[19 20]. However, rapid decrease of neutralizing antibody levels in the first 3-month after the second dose was observed[21], accompanied by the significant decline of protection six month after completion of two-dose regimen[22 23]. However, a third dose could significantly restore protection, especially protection against severe COVID-19-related outcomes. In large observational studies conducted in Israel, compared with two doses regimen completed at least 5 months previously, adding a third dose was estimated to be > 90% effective in preventing severe outcomes of SARS-CoV-2 infections[24 25]. Also in Israel, among residents of long-term care facilities, a relative reduction of 71% and 80% on preventing SARS-CoV-2 infection and hospitalization were observed after receiving third doses [26]. In China, inactivated vaccines were implemented widely, and a similar decline of neutralizing titers was also observed. Homologous booster effectiveness of inactivated vaccines has been illustrated in clinical trials[7 27], however, due to the zero-COVID-19 policy in China, it is

challenging to measure real world protection in China - especially protection against Omicron infections.

The number of studies of COVID-19 VE against Omicron is growing. VEs of mRNA vaccines and adenovirus vector vaccines against Omicron were significantly lower than against Delta. At the end of 2021, a real world study on VE against Omicron pneumonia in South Africa showed that VE of Pfizer mRNA vaccine was 70% [2]. VE against infection was limited and VE against hospitalization decreased significantly with time since vaccination (82% within 14 days, 52% between 15 and 179 days, and 38% over 180 days). However, after a homologous booster dose, VE against hospitalization caused by Delta and Omicron increased to 94% and 90%. Although our study measured relative VE, the booster dose impact appears consistent, showing that booster vaccination improves protective effectiveness of the vaccines [3 28].

We found a higher breakthrough infection rate for Omicron than Delta exposure. A likely explanation is that most Omicron transmission was in a large boarding middle school. The crowded student dormitories, class rooms, and canteens may greatly increase pathogen exposure, leading to reduced protection[29]. After receiving boosters, we observed significantly lower breakthrough rates for Delta (22% vs 8%) and Omicron exposure (10% vs 5%). Immunity elicited by COVID-19 vaccines wanes over time[30], and giving booster doses is necessary for restoration[4 31 32].

Age was risk factor for pneumonia in our study. The hazard ratio among people over 50 years old was higher than in people under 18 years old for Delta pneumonia. Hypo-responsiveness among the elderly has been reported from clinical studies of COVID-19 vaccines[19 33 34]. Due to immunosenescence, elderly have a lower ability to fight respiratory infections and are hyporesponsive to vaccination[35 36].

There are several limitations in our study. First, the age distributions in the Delta and Omicron transmission chains were different. Delta transmission occurred in a community, while Omicron transmission was concentrated in a middle school. The imbalance in age did not appear to influence the relative VE of booster doses against Delta and Omicron in age-based sensitivity analysis. Second, we did not have data on comorbidities of most subjects. We therefore could not use comorbidities in the Cox regression model. Comorbidity data were available in a small subgroup, however, and these data indicated that more than 80% of comorbidity occurred in people ≥ 50 years. We therefore used 50 years of age as a cut-off for age group aggregation. Third, because coverage was very high at 90%, there were too few unvaccinated people to serve as control to measure absolute vaccine effectiveness. The small number of unvaccinated individuals are likely to be significantly different than vaccinated people, making them an unreliable control group. We therefore excluded subjects who did not complete primary vaccination, and instead used the numerous subjects who completed the primary vaccination ≥ 180 days as reference to measure the relative VE throughout the analysis. Finally, the outbreak was too small and the subjects too few to assess rVE for the different vaccines. Since almost all of the vaccine used in Henan (and China) are the two inactivated vaccines in our study, we believe it is reasonable to conclude that we assessed rVE for China's inactivated vaccines, especially the homologous booster dose, and that our results can generalize to the rest of mainland China. However, our study results cannot generalize to other countries.

Conclusion

Overall, protection against both Delta and Omicron variants declined over the time, especially after 6 months of primary vaccination. However, a booster dose of inactivated vaccines can restore and enhance protection against both variants.

Acknowledgements

We are very grateful for the data collection efforts by local CDC and infectious hospital staff of Zhengzhou, Yuzhou, and Anyang cities in Henan province. We are very grateful to Yaowen Zhang, Yang Liu (Beijing Institute of Biological Products CO., LTD, SINOPHARM), and Xiaobin Cao and Yupeng Liang (Sinovac Research & Development Co., Ltd) for help with data extraction and running SAS code for data analysis.

Contributors

ZDY, ZYW, XYW, XYL and YMS acquired funding and contributed to the study's conception and design. ABW, RZ, ZHQ, FZW, HZ, ZJ and YY conceptualized the study and prepared the original study protocol, which was subsequently reviewed by LER. DW, LT, and CH developed the statistical methods. DW, CH and XYW wrote and tested the SAS code for the data analysis and drafted the manuscript. YY, HFW, YYZ, JJP, YFL, MXL, CSW and YTM collected data from local CDCs and abstracted the data. DW, LT, LER ZJA, ZDY and YMS interpreted the results and revised the manuscript and critically reviewed the manuscript. All authors approved the final submitted version.

Funding

This work was supported by the Operation of Public Health Emergency Response Mechanism of Chinese Center for Disease Control and Prevention (131031001000150001).

Competing interests

All authors declare no competing interests.

Ethical approval

COVID-19 is a class A notifiable infectious disease according to the Law on the Prevention and Control of Infectious Diseases (SCSNPC, 1989) in China; case reporting and investigation are mandatory. This study was approved by the Institutional Review Board of Chinese Center for Disease Control and Prevention (Approval Notice:202101-01).

Data sharing

The data can be assessed from the China Information System for Disease Control and Prevention by researchers who meet the criteria for access to confidential data (for the criteria for access and details of how to request access see https://www.phsciencedata.cn/Share/en/index.jsp).

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LEGEND OF FIGURES

Figure 1. Epidemic curves of Delta and Omicron transmission between December 26, 2021 and January 23, 2022.

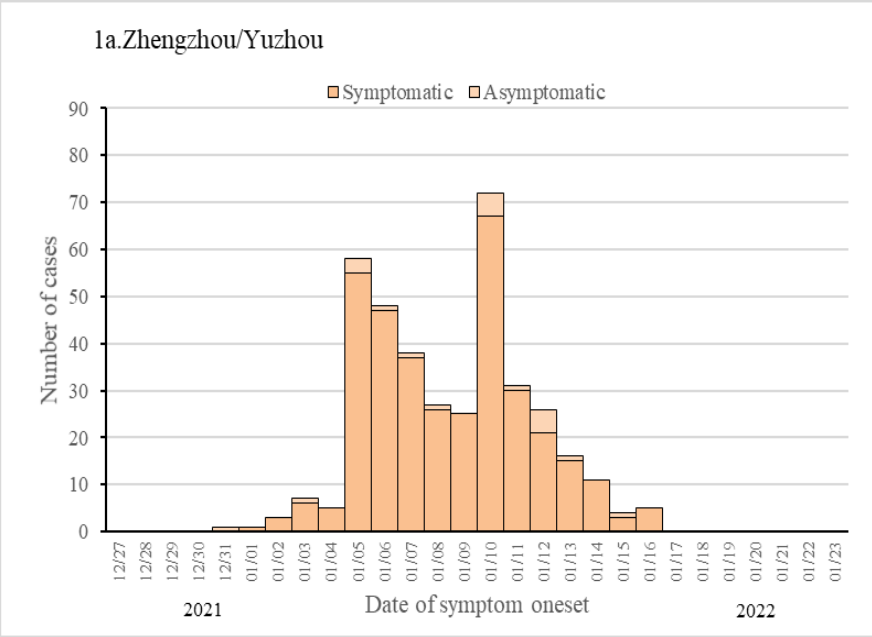
1a showed the COVID-19 epidemic curve with number of cases plotted by date of patient onset of symptoms from December 26, 2021 to January 16,2022 in Delta transmission chain. Confirmed, and asymptomatic cases are stacked to show total daily cases by date of symptom onset. The peak onset of symptoms for all cases overall occurred between January 5 and 10., 2022. Since then, onset of illness has declined.

1b showed the COVID-19 epidemic curve for confirmed cases only with number of cases plotted by date of patients' onset of symptoms from January 04, 2022 to January 23,2022 in Omicron transmission chain. The confirmed cases onset of illness peaked between January 9 and 16.

Figure 2. Survival curves of pneumonia caused by Delta and Omicron variants

2a and **2b** shown are Cox model estimates of the survival probability of pneumonia with the Delta and Omicron variant of SARS-CoV-2 according to vaccination status with adjusting gender and age, the start time of follow up since December 15,2021.

Figure 1. Epidemic curves of SARS-CoV-2 infections in Zhengzhou/Yuzhou and Anyang between December 26, 2021 and January 23, 2022.Summary of subjects



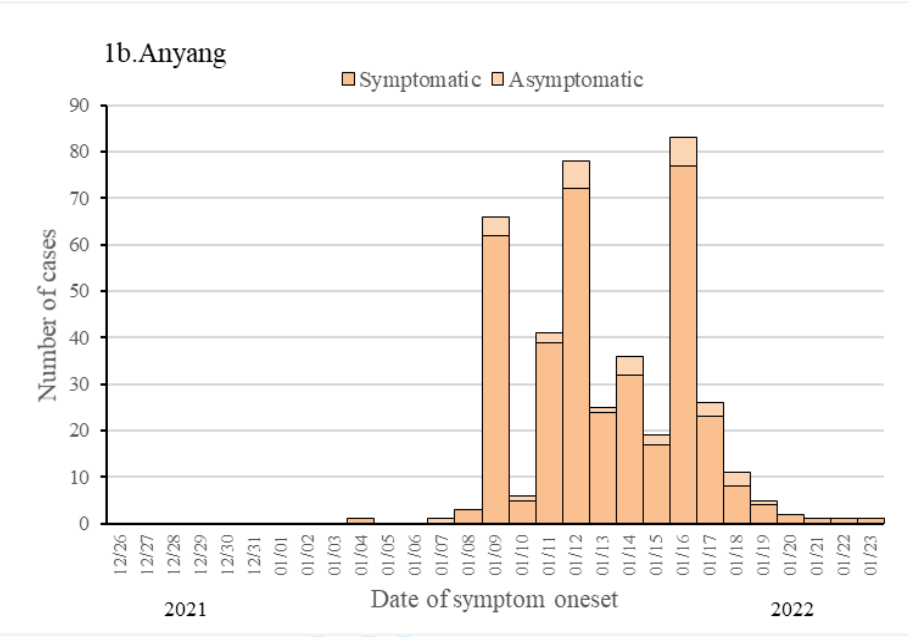
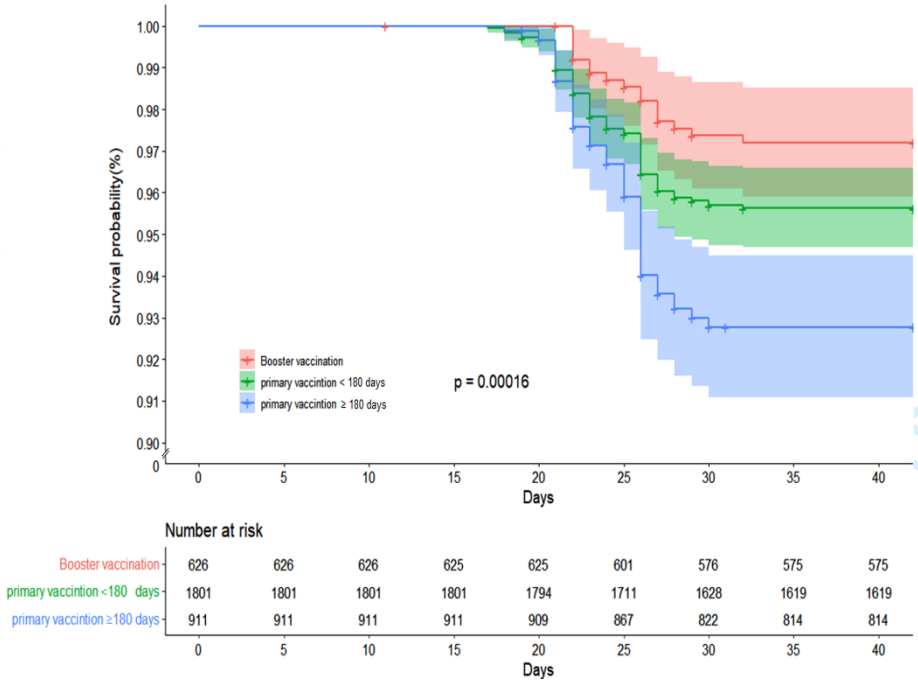
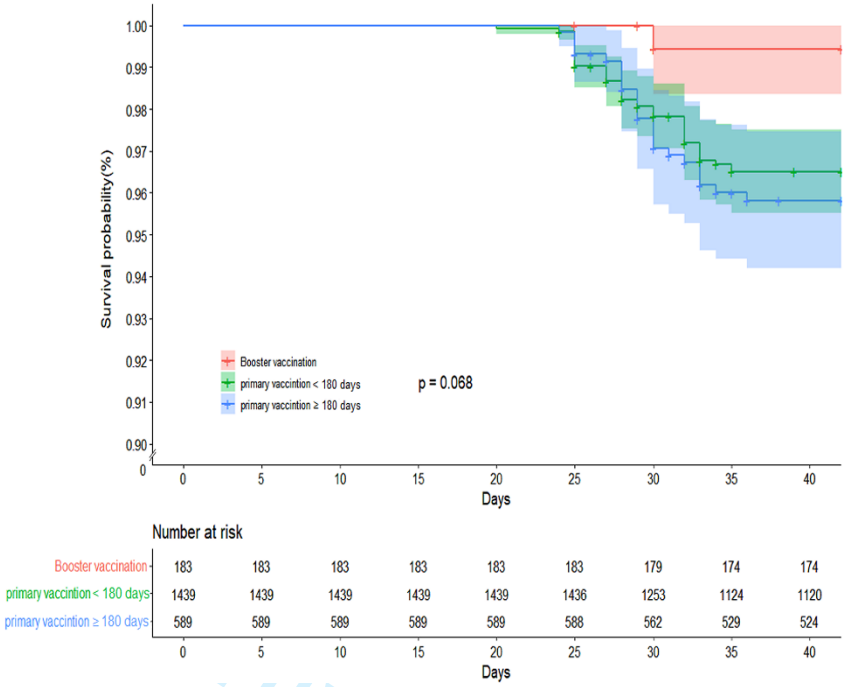


Figure 2. Survival curves of pneumonia caused by Delta and Omicron variants.



2a. Delta



2b. Omicron

BMJ Open

Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-063919.R1
Article Type:	Original research
Date Submitted by the Author:	13-Sep-2022
Complete List of Authors:	Tang, Lin; Chinese Center for Disease Control and Prevention, National Immunization Program Zhang, Yanyang; Henan Provincial Center for Disease Control and Prevention Wang, Fuzhen; Chinese Center for Disease Control and Prevention Wu, Dan; Chinese Center for Disease Control and Prevention Qian, Zhao-Hui; NHC Key laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China Zhang, Rui; National Center for Clinical Laboratories, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences Wang, Ai-Bin; Beijing Ditan Hospital Capital Medical University Huang, Chang; Chinese Center for Disease Control and Prevention; China Field Epidemiology Training Program Wang, Haifeng; Henan Provincial Center for Disease Control and Prevention Ye, Ying; Henan Provincial Center for Disease Control and Prevention Lu, Mingxia; Henan Provincial Center for Disease Control and Prevention Wang, Changshuang; Henan Provincial Center for Disease Control and Prevention Ma, Ya-ting; Henan Province Center for Disease Control and Prevention Pan, Jingjing; Henan Province Center for Disease Control and Prevention Li, Ya-fei; Henan Province Center for Disease Control and Prevention Lv, Xiao-Ya; Development Center for Medicine and Science &Technology, National Health Commission An, Zhijie; Chinese Center for Disease Control and Prevention, National Immunization Program Rodewald, Lance; Chinese Center for Disease Control and Prevention, National Immunization Program Wang, Xuan-Yi; Fudan University Shao, Yi-Ming; State Key Laboratory of Infectious Disease Prevention and Control, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention Wu, Zhi-Yin; Development Center for Medicine and Science &Technology, National Health Commission Yin, Zundong; Chinese Center for Disease Control and Prevention, National Immunization Program

Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health, Infectious diseases
Keywords:	COVID-19, Epidemiology < INFECTIOUS DISEASES, Immunology < NATURAL SCIENCE DISCIPLINES

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Relative vaccine effectiveness against Delta and Omicron COVID-19 after homologous inactivated vaccine boosting: a retrospective cohort study

Lin Tang[1*], Yan-Yang Zhang[2*], Fu-Zhen Wang[1], Dan Wu[1], Zhao-Hui Qian[3], Rui Zhang[4], Ai-Bin Wang[5], Chang Huang[1,6], Hai-feng Wang[2], Ying Ye[2],Ming-Xia Lu[2],Chang-Shuang Wang[2], Ya-ting Ma[2],Jingjing Pan[2], Ya-fei Li[2], Xiao-Ya Lv[7], Zhi-Jie An[1], Lance E. Rodewald[1], Xuan-Yi Wang[8&], Yi-Ming Shao[9&], Zhi-Yin Wu[7&], Zun-Dong Yin[1&]

[*]**Joint first authors**: Lin Tang and Yan-yang Zhang contributed equally to this work.

[&]**Joint corresponding authors**:
Zun-dong Yin:
27 Nanwei Road; Beijing; Xicheng District; China; 100050
Email: yinzd@chinacdc.cn; Phone: +86 630 27946; Fax: +86 631 71724
Yi-Ming Shao:
155 Changbai Road; Beijing; China; 102206
E-mail: yshao@chinaaids.cn Phone: 010-58900922
Zhi-Yin Wu:
Number 9 Chegongzhuang Street; Xicheng District; Beijing; 100037
E-mail: zhiyinwu@126.com; Phone: 010- 88387238
Xuan-Yi Wang:
138 Yi Xue Yuan Road; Shanghai; China 200032
E-mail: xywang@shmu.edu.cn; Phone: 021-54237865

1.National Immunization Program, Chinese Center for Disease Control and Prevention; Beijing, China
2. Immunization Program; Henan Provincial Disease Control and Prevention; Zhengzhou; China
3. Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology; National Health Commission; Chinese Academy of Medical Sciences; Peking Union Medical College; Beijing; China
4.National Center for Clinical Laboratories, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences; China
5. Infectious Diseases Department; Beijing Ditan Hospital Capital Medical University; Beijing; China
6.China Field Epidemiology Training Program; Chinese Center for Disease Control and Prevention; Beijing; China
7.Development Center for Medicine and Science &Technology; National Health Commission; Beijing; China
8.Shanghai Institute of Infectious Disease and Biosecurity, Key Laboratory of Medical Molecular Virology of Ministry of Education & Ministry of Health, and Institutes of Biomedical Sciences; Medical College; Fudan University; Shanghai; China
9.State Key Laboratory of Infectious Disease Prevention and Control, National Center for AIDS/STD Control and Prevention; Chinese Center for Disease Control and Prevention Beijing; China

Keywords: COVID-19; epidemiology; immunology
Word count: 2,985 **References**: 36

ABSTRACT

Objective

Two COVID-19 outbreaks occurred in Henan province in early 2022 – one was a Delta variant outbreak and the other was an Omicron variant outbreak. COVID-19 vaccines used at the time of the outbreak were inactivated, 91.8%; protein subunit, 7.5%; and adenovirus5-vectored, 0.7% vaccines. The outbreaks provided an opportunity to evaluate variant-specific breakthrough infection rates and relative protective effectiveness of homologous inactivated COVID-19 vaccine booster doses against symptomatic infection and pneumonia.

Design: Retrospective cohort study

Methods

We evaluated relative vaccine effectiveness (rVE) with a retrospective cohort study of close contacts of infected individuals using a time-dependent Cox regression model. Demographic and epidemiologic data were obtained from the local Center for Disease Control and Prevention; clinical and laboratory data were obtained from COVID-19-designated hospitals. Vaccination histories were obtained from the national COVID-19 vaccination dataset. All data were linked by national identification number.

Results

Among 784 SARS-CoV-2 infections, 379 (48.3%) were caused by Delta and 405 (51.7%) were caused by Omicron, with breakthrough rates of 9.9% and 17.8%, respectively. Breakthrough rates among boosted individuals were 8.1% and 4.9%. Compared with subjects who received primary vaccination series ≥ 180 days before infection, Cox regression modeling showed that homologous inactivated booster vaccination was statistically significantly associated with protection from symptomatic infection caused by Omicron (rVE 59%; 95% CI: 14%-80%) and pneumonia caused by Delta (rVE 62%; 95%CI: 34%-77%) and Omicron (rVE 87%; 95%CI: 3%-98%).

Conclusions

COVID-19 vaccination in China provided good protection against symptomatic COVID-19 and COVID-19 pneumonia caused by Delta and Omicron variants. Protection declined 6 months after primary series vaccination but was restored by homologous inactivated booster doses given 6 months after the primary series.

Strengths and limitations of this study

- The study was conducted in a simultaneous 2-variant outbreak in a single province in China and provided estimates of vaccine-built population immunity in an infection naïve population.
- The study was conducted among close contacts of people with known SARS-CoV-2 infection who were in quarantine and tested frequently for infection, ensuring accurate outcomes assessment of the exposed population.
- The study was limited by the small size of the outbreak, precluding analysis of vaccine brand-specific relative VE.
- Vaccine coverage in the outbreak setting was too high to have a comparable unvaccinated group, making absolute VE not possible to estimate accurately.
- Clinical data on comorbidities was not available, precluding analysis of rVE by comorbidity.

INTRODUCTION

Most countries have experienced epidemic waves of COVID-19 caused by SARS-CoV-2 variants. As of December 11, 2021, five SARS-CoV-2 Variants of Concern (VOCs) have been identified, with Alpha (B.1.1.7) and Delta (B.1.617.2) predominant [1]. Omicron emerged November 2021 and rapidly replaced Delta to be the predominant global strain, accounting for 90% of GISAID SARS-CoV-2 sequences [2],[3],[4]. The World Health Organization (WHO) has listed nine COVID-19 vaccines for emergency use, including the two most commonly used vaccines in China - BBIBP-CorV and CoronaVac inactivated whole-virus vaccines. As the end of July 2022, over 3.4 billion doses of these vaccines have been used in China, and over 2 billion dosses have been procured for overseas use [5],[6].

Good safety and short-term efficacy against the ancestral strain have been demonstrated for these vaccines [7], and real-world evidence on protection against VOCs and protection with booster doses is available, for example, from Guangdong, Jiangsu, and Henan [8],[9],[10],[11] in China and Chile and Brazil overseas [12],[13]. In China, the dynamic COVID-zero policy severely limits outbreak size, and very high COVID-19 primary vaccination coverage makes unvaccinated comparison groups too small and too different for conducting absolute vaccine effectiveness (VE) studies. In January 2022, two outbreaks occurred in Henan – one caused by Delta (B.1.617.2) and the other by Omicron (B.1.1.529.1) – that provided an opportunity to assess relative VE (rVE) of China-produced vaccines against COVID-19 caused by these two variants. We report results of our evaluation.

METHODS

Outbreak setting

The setting was Henan province where there were two simultaneous outbreaks. Henan has a population of 99.36 million people; the three involved cities were Zhengzhou (8.6 million, whole-population primary series coverage 87.2%), Yuzhou (1.2 million, 94.7%), and Anyang (1.5 million, 80.3%). The COVID-19 vaccines used were inactivated vaccines, 91.8%; ZF2001, 7.5%; and Ad5-nCoV vaccine, 0.7%. The COVID-19 prevention and control policy in the mainland of China requires that all SARS-CoV-2 infections are traced, and contacts quarantined for at least two weeks and tested periodically in quarantine. The COVID-19 vaccines used in the outbreak setting were two inactivated COVID-19 vaccines - BBIBP-CorV (Sinopharm, Beijing CNBG) and CoronaVac (Sinovac,Co., Ltd), accounting for 91.8% of vaccines used; a protein subunit vaccine, Zifivax (Zhifei Longcom, 7.5%); and an adenovirus5-vectored vaccine, Convidecia (Cansino, 0.7%). China's immunization program records all COVID-19 vaccinations in a national vaccination database indexed by national ID number. The national COVID-19 surveillance system is also indexed by national ID.

On January 2, 2022, a Yuzhou factory worker tested RT-PCR-positive in a routine pre-surgery screening. Contact tracing identified a Delta-variant community transmission chain that spread to Zhengzhou. On January 8, a medical device company employee and a middle school student both tested positive for SARS-CoV-2 infection when seeking health care in Anyang. Investigation revealed an Omicron outbreak in a boarding school with 4,103 students and teachers along with

community transmission (**Figure 1**).

Study design and subjects

We used a retrospective cohort design to estimate rVE. Subjects were confirmed SARS-CoV-2 infections and their close contacts, grouped by vaccination status. Outcomes were infection, pneumonia, and severe illness.

A SARS-CoV-2 infection was a person with a positive RT-PCR, including asymptomatic and symptomatic infections regardless of severity; COVID-19 pneumonia was a SARS-CoV-2 infection with acute onset of fever and cough or acute onset with any three or more of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status; or having chest CT imaging findings diagnostic of pneumonia. Severe illness was characterized by respiratory failure with need for mechanical ventilation or shock combined with other organ failure requiring ICU care[14]. Thus, the outcome definitions included subjective symptoms (e.g., sore throat and headache), elicited signs (e.g., fever, altered mental status, pneumonia on imaging), and objective health care actions (e.g., ICU admission and mechanical ventilation), with the more objective elements for the more severe outcomes.

Close contacts had exposure to confirmed SARS-CoV-2 infections up to four days before illness onset of symptomatic cases or the first RT-PCR-positive specimen for asymptomatic cases. Exposure included living in the same apartment, sharing a table for meals, studying, or working in the same room, or sharing a ward.

Subject data were obtained from the local Center for Disease Control and Prevention (CDC) and included the epidemiological investigation report, transmission chain, age, gender, date of first and last exposure, mode and location of exposure, and frequency and duration of exposure. For the confirmed SARS-CoV-2 infections, we reviewed medical records from designated COVID-19 management hospitals in Zhengzhou and Anyang to abstract clinical management data, laboratory testing and results, and chest imaging and results.

Vaccine status

Without knowledge of whether subjects had SARS-CoV-2 infection or not, we obtained vaccination records from the national vaccination database using subjects' national IDs. Vaccination was defined as receipt of at least one dose of COVID-19 vaccine. Partial vaccination was receipt of either one dose of an inactivated COVID-19 vaccine or two doses of an inactivated vaccine with receipt of the second dose less than 14 days before exposure. Primary vaccination was completion of two doses of inactivated vaccine 14 days or more before exposure and/or a third dose of inactivated vaccine less than 7 days of exposure. Booster vaccination was a third more than 7 days before exposure. Primary vaccination was further classified as being either <180 days before exposure or ≥180 days before exposure.

Data analysis

A breakthrough infection was an RT-PCR-confirmed SARS-CoV-2 infection at least 14 days after completion of primary vaccination. We estimated unadjusted and adjusted (gender and age group) rVE against Delta and Omicron infections using a Cox regression models. The reference group was primary vaccination ≥180 days before exposure; rVE was 1-adjusted hazard ratio (ratio

of incidences of the outcome of interest) for COVID-19 symptomatic infection or pneumonia.

Ninety-five percent of co-morbidities were among subjects 50 years and older. Our age groupings were under 18 years, 18 to 50 years, and over 50 years. Subjects in the Omicron and Delta outbreaks differed since the Omicron outbreak involved a fully vaccinated middle school with 94.7% of cases under 20 years old, with its higher force of infection. We therefore conducted rVE analyses with and without subjects under 20 years old.

We used SAS (SAS Institute Inc., Cary, NC, USA) for statistical analysis and R (version 4.1.0) for Cox survival analysis of pneumonia. P-values < 0.05 (two-tailed) were considered statistically significant.

Patient and Public Involvement statement:

This real-world, observational study was designed without patient or public involvement. COVID-19 is managed as a Level-1 infectious disease, and as such, investigations of outbreaks and public health effort to prevent illness and stop transmission are required of public health agencies. Subjects were not recruited into the study, as they were cases or close contacts managed in accordance with the National Health Commission's Protocol for Prevention and Control. Neither patients nor the public were involved in the conduct of the study, as testing and data aggregation were conducted under the prevention and control policy. Results will be disseminated through publicly-available scientific publications.

RESULTS

Subjects

Table 1 shows the characteristics of the subjects. Between January 2 and 23, 2022, a total of 6,521 SARS-CoV-2 infections and close contacts were identified in the three-city setting, among which 784 were SARS-CoV-2 infections and 5,737 were close contacts. Because of the 4,103-person middle school outbreak, subjects in the Anyang (Omicron) transmission chain were younger on average that in the Zhengzhou/Yuzhou (Delta) transmission chain (43.5% vs 23.8% < 20 years, $p<0.05$). Most (72.7%) subjects completed primary vaccination; 14.9% received 0-1 dose; and 12.4% received booster doses. In the Delta chain, the median number of days between primary vaccination and exposure was 117 days (IQR:40-134) among subjects completed primary <180 days before exposure and 196 days (IQR:191-203) among subjects completed primary ≥180 days before exposure. Respective medians in the Omicron chain were 133 days (IQR:121-138) and 203 days (IQR:196-210). Boosters were completed 20 (IQR:12-68) and 19 days (IQR:11-64) before Delta and Omicron exposure.

Breakthrough infection

Breakthrough infection rates were 9.9% in the Delta chain and 17.8% in the Omicron chain ($p<0.001$) among subjects completing primary vaccination. By vaccination group, breakthrough rates were 10.6% (Delta) and 11.0% (Omicron) among subjects who completed primary vaccination ≥180 days ($p>0.05$); 10.1% (Delta) and 22.2% (Omicron) among subjects who completed primary vaccination <180 days ($p<0.001$); and 8.1% (Delta) and 4.9% (Omicron)

among boosted subjects (p>0.05).

When subjects under 20 years old were excluded, breakthrough rates were 10.8% (Delta) and 10.6% (Omicron) among subjects who completed primary vaccination ≥180 days (p>0.05); 12.3% (Delta) and 8.7% (Omicron) among subjects who completed primary vaccination <180 days (p>0.05); and 7.9% (Delta) and 4.5% (Omicron) among boosted subjects (p>0.05).

Table 1. Characteristics of SARS-CoV-2 infections and close contacts in Delta and Omicron transmission chain

Characteristics	Delta transmission chain					Omicron transmission chain				
	Non/Partial vaccination (n, %)	Primary vaccination		Booster vaccination (n, %)	p value	Non/Partial vaccination (n, %)	Primary vaccination		Booster vaccination (n, %)	p value
		≥180 days (n, %)	<180 days (n, %)				≥180 days (n, %)	<180 days (n, %)		
SARS-CoV-2 infections										
Subtotal	49	97	182	51		12	65	319	9	
Gender										
Female	33 (67.3)	53 (54.6)	104 (57.1)	34 (66.7)	0.2989	7 (58.3)	42 (64.6)	176 (55.2)	5 (55.6)	0.5767
Male	16 (32.7)	44 (45.4)	78 (42.9)	17 (33.3)		5 (41.7)	23 (35.4)	143 (44.8)	4 (44.4)	
Age group (yrs)										
< 18	8 (16.3)	0 (0)	53 (29.1)	0 (0)	<0.001	2 (16.7)	0 (0)	191 (59.9)	0 (0)	<0.001
18-49	19 (38.8)	54 (55.7)	50 (27.5)	31 (60.8)		7 (58.3)	45 (69.2)	107 (33.5)	7 (77.8)	
≥ 50	22 (44.9)	43 (44.3)	79 (43.4)	20 (39.2)		3 (25.0)	20 (30.8)	21 (6.6)	2 (22.2)	
Close contacts										
Subtotal	525	814	1619	575		386	524	1120	174	
Gender										
Female	270 (51.4)	430 (52.8)	792 (48.9)	307 (53.4)	0.1513	215 (55.7)	310 (59.2)	529 (47.2)	106 (60.9)	<0.001
Male	255 (48.6)	384 (47.2)	827 (51.1)	268 (46.6)		171 (44.3)	214 (40.8)	591(52.8)	68 (39.1)	
Age group (yrs)										
< 18	149 (28.4)	0 (0)	674 (41.6)	0 (0)	<0.001	100 (25.9)	0 (0)	616 (55.0)	0 (0)	<0.001
18-49	250 (47.6)	598 (73.5)	588 (36.3)	421 (73.2)		187 (48.5)	366 (69.9)	341(30.5)	123 (70.7)	
≥ 50	126 (24.0)	216 (26.5)	357 (22.1)	154 (26.8)		99 (25.6)	158 (330.1)	163 (14.5)	51 (29.3)	
Total	574	911	1801	626		398	589	1439	183	

Relative Vaccine effectiveness

Table 2 shows results of the Cox regression analyses for symptomatic infection and pneumonia by Delta and Omicron variants. For both variants, univariate analysis shows that being male and booster vaccination were associated with reduced risk of symptomatic infection. Age was associated with symptomatic infection, especially among subjects ≥50 years. Cox regression adjusting for age group, gender, and vaccination status were similar in magnitude for symptomatic infection risk from Delta vs Omicron. Hazard ratios among those ≥50 years differed in direction between Delta and Omicron (2.75 and 0.56), and relative protection increased from 24% to 59% in boosted subjects. After removing subjects < 20 years (primarily the school outbreak students) from the Cox regression analysis, primary vaccination <180 days and booster vaccination were both associated with protection from Delta and Omicron symptomatic infections.

For pneumonia, the relation with age was more pronounced than was the case for symptomatic infection, and more so with Delta than Omicron. Hazard ratios for pneumonia were consistent in direction, showing greater protection associated with primary vaccination <180 days and booster dose administration, regardless of variant. After excluding subjects < 20 years from the Cox regression analysis, hazard ratios against pneumonia change little, except for an increase in protection (from 17% to 35%) among subjects who received primary vaccination within 180 days. Survival curve analysis results for pneumonia for each variant by vaccination status group are shown in Figure 2. Although the three vaccination groups were statistically significantly different for Delta pneumonia, there was no statistically significant difference between the two primary vaccination groups for Omicron pneumonia, although both were different from the boosted group.

There were few severe infections in the two transmission chains. There were 12 severe cases in the Delta chain, with five included in Cox analysis (2 with primary vaccination ≥180 days group, 3 cases with primary vaccination< 180 days, and none in the booster vaccination group. There were no severe cases in the Omicron transmission chain.

Table 2. Cox regression analysis by vaccination status and by outcomes of SARS-CoV-2 infection

Covariates	Delta infection for all				Omicron infection for all				Omicron infection for ⩾20 yrs	
	Crude HR (95%CI)	p value	Adjusted HR (95%CI)	p value	Crude HR (95%CI)	p value	Adjusted HR (95%CI)	p value	Adjusted HR (95%CI)	p value
Symptomatic infection										
Gender										
Female	Ref		Ref		Ref		Ref		Ref	
Male	0.80 (0.64 - 1.00)	0.05	0.79 (0.63 - 0.98)	0.04	0.80 (0.65 – 0.99)	0.04	0.73 (0.59 - 0.90)	0.01	0.52(0.33 - 0.80)	0.003
Age group(age)										
< 18	Ref		Ref		Ref		Ref			
18-49	1.17 (0.84 - 1.63)	0.36	1.26 (0.87 - 1.81)	0.22	0.65 (0.52 – 0.81)	<0.01	0.92(0.72 - 1.18)	0.5	Ref (20-49 yrs)	
≥ 50	2.58 (1.86 - 3.60)	<0.01	2.75 (1.94 - 3.91)	<0.01	0.40 (0.28 – 0.56)	<0.01	0.56 (0.39 - 0.81)	0.01	1.33(0.89 - 2.00)	0.166
Vaccination status										
Primary vaccination≥180 days	Ref		Ref		Ref		Ref		Ref	
Primary vaccination<180 days	0.92 (0.72 - 1.18)	0.51	1.04 (0.79 - 1.36)	0.79	2.11 (1.60 – 2.78)	<0.01	1.95 (1.43 - 2.65)	<0.01	0.79(0.52 - 1.20)	0.261
Booster vaccination	0.75 (0.53 - 1.06)	0.11	0.76 (0.54 - 1.07)	0.11	0.41 (0.20 – 0.87)	0.02	0.41(0.20 - 0.86)	0.02	0.39(0.18 - 0.86)	0.019
Pneumonia										
Gender										
Female	Ref		Ref		Ref		Ref		Ref	
Male	0.65 (0.47 - 0.90)	0.01	0.65 (0.47 - 0.90)	0.01	0.96 (0.60 - 1.52)	0.85	0.93 (0.58 - 1.49)	0.77	0.77(0.39 - 1.54)	0.457
Age group (yrs)										
< 18	Ref		Ref		Ref		Ref			
18-49	8.61 (2.70 - 27.43)	<0.01	9.11 (2.81 - 29.5)	<0.01	0.88 (0.52 - 1.50)	0.63	0.89 (0.48 - 1.67)	0.73	Ref (20-49 yrs)	
≥ 50	28.00 (8.88 - 88.40)	<0.01	29.50 (9.26 - 94.0)	<0.01	1.11 (0.59 - 2.07)	0.75	1.13 (0.56 - 2.27)	0.74	1.70(0.87 - 3.32)	0.123
Vaccination status										
Primary vaccination≥180 days	Ref		Ref		Ref		Ref		Ref	
Primary vaccination<180 days	0.60 (0.43 - 0.83)	0.01	0.86 (0.61 - 1.20)	0.37	0.84 (0.51 - 1.37)	0.48	0.83 (0.46 - 1.50)	0.53	0.65(0.32 - 1.32)	0.231
Booster vaccination	0.38 (0.22 - 0.64)	<0.01	0.38 (0.23 - 0.66)	<0.01	0.13 (0.02 - 0.97)	0.047	0.13 (0.02 - 0.97)	0.047	0.15(0.02 - 1.08)	0.059

DISCUSSION

We used a 748-case, two-variant COVID-19 outbreak in Henan province to determine the relative vaccine effectiveness of the vaccines used in China to protect against symptomatic infection and pneumonia. Our study found an rVE of 62% against Delta pneumonia and 87% against Omicron pneumonia among homologous inactivated vaccine booster-dose recipients compared with individuals who received complete primary vaccination greater than 180 days prior to exposure to SARS-CoV-2. Relative VE was lower for individuals receiving primary vaccination less than 180 days prior to exposure than among boosted individuals, demonstrating an effectiveness advantage of the homologous booster dose. Results from our study support the current COVID-19 booster vaccination strategy in China in which everyone 18 years and older is recommended to receive a booster dose six months after their primary series.

Our study also found a higher breakthrough infection rate in the Omicron transmission chain than the Delta chain (22% vs 10%) and found no severe Omicron cases and only 12 severe Delta cases, representing 3% of the Delta outbreak cases. The low rate of severe infection provides information valuable for projection of health care resource needs in the future.

In licensure clinical trials for vaccines produced in China estimates of efficacy against symptomatic COVID-19 were 50% to 78% [15],[16]. Our relative VE estimates are not directly comparable, since efficacy estimates are absolute rather than relative estimates. A relative VE estimate only indicates additional VE above and beyond an unmeasured absolute VE of the comparison group. There have been several real-world assessments of VE of the China-produced vaccines [8],[9],[10],[11], but none that compare rVE against Delta and Omicron in simultaneous outbreaks, and few studies of relative VE from a booster dose of China-produced vaccine.

As of September 7, 2022, 603 million confirmed cases of COVID-19 and 6.4 million COVID-19 deaths were reported worldwide to the World Health Organization (WHO) [[17]. To stop the virus from raging around the world, vaccines had high hopes. In less than a year after SARS-CoV-2 emergence, COVID-19 vaccines were developed via several technologies [18] and have been approved by regulators and WHO for emergency use. WHO approved the two inactivated vaccines that comprised the vast majority of COVID-19 vaccines used in China and included in our study.

In the real world, several studies reported high effectiveness of mRNA-based vaccines against SARS-CoV-2 infection, with a breakthrough infection of less than 1% of symptomatic SARS-CoV-2 infections, and a ~0.1% rate of hospitalization or death[19],[20]. However, rapid decrease of neutralizing antibody levels in the first 3-month after the second dose was observed [21], accompanied by the significant decline of protection six month after completion of two-dose regimen [22],[23]. However, a third dose could significantly restore protection, especially protection against severe COVID-19-related outcomes. In large observational studies conducted in Israel, compared with two doses regimen completed at least 5 months previously, adding a third dose was estimated to be > 90% effective in preventing severe outcomes of SARS-CoV-2 infections [24],[25]. Also in Israel, among residents of long-term care facilities, a relative reduction of 71% and 80% on preventing SARS-CoV-2 infection and hospitalization were observed after receiving third doses [26]. In China, inactivated vaccines were implemented widely, and a similar decline of neutralizing titers was also observed. Immunogenicity of homologous booster doses of inactivated vaccine has been illustrated in clinical trials [7], [27],

and the likely mechanism for booster dose immunogenicity and corresponding effectiveness is activation of memory B cells induced by primary series vaccination. However, due to high primary-series COVID-19 vaccine coverage in China, it is challenging to measure absolute vaccine effectiveness because measuring absolute VE requires an unvaccinated comparison group. This challenge is greater for estimating absolute VE against the Omicron variant since the Omicron infections were more recent than the ancestral and Delta variant infections.

The number of studies of COVID-19 VE against Omicron is growing. VEs of mRNA vaccines and adenovirus vector vaccines against Omicron were significantly lower than against Delta. At the end of 2021, a real world study on VE against Omicron pneumonia in South Africa showed that VE of Pfizer mRNA vaccine was 70% [2]. VE against infection was limited and VE against hospitalization decreased significantly with time since vaccination (82% within 14 days, 52% between 15 and 179 days, and 38% over 180 days). However, after a homologous booster dose, VE against hospitalization caused by Delta and Omicron increased to 94% and 90%. Although our study measured relative VE, the booster dose impact appears consistent, showing that booster vaccination improves protective effectiveness of the vaccines [3],[28].

We found a higher breakthrough infection rate for Omicron than Delta exposure. A likely explanation is that most Omicron transmission was in a large boarding middle school. The crowded student dormitories, classrooms, and canteens may greatly increase pathogen exposure, leading to reduced protection [29]. After receiving boosters, we observed significantly lower breakthrough rates for Delta (22% vs 8%) and Omicron exposure (10% vs 5%). Immunity elicited by COVID-19 vaccines wanes over time [30], and giving booster doses is necessary for restoration [4],[31],[32].

Consistent with what is well known about COVID-19, older age was risk factor for pneumonia in our study. The hazard ratio among people over 50 years old was higher than in people under 18 years old for Delta pneumonia. Hypo-responsiveness among the elderly has been reported from clinical studies of COVID-19 vaccines [19],[33],[34]. Due to immunosenescence, elderly have a lower ability to fight respiratory infections and are hyporesponsive to vaccination [35],[36].

There are several limitations in our study. First, the age distributions in the Delta and Omicron transmission chains were different. Delta transmission occurred in a community, while Omicron transmission was concentrated in a middle school. The imbalance in age did not appear to influence the relative VE of booster doses against Delta and Omicron in age-based sensitivity analysis. Second, we did not have data on comorbidities of most subjects. We therefore could not use comorbidities in the Cox regression model. Comorbidity data were available in a small subgroup, however, and these data indicated that more than 80% of comorbidity occurred in people ≥ 50 years. We therefore used 50 years of age as a cut-off for age group aggregation. Third, because coverage was very high at 90%, there were too few unvaccinated people to serve as control to measure absolute vaccine effectiveness. The small number of unvaccinated individuals are likely to be significantly different than vaccinated people, making them an unreliable control group. We therefore excluded subjects who did not complete primary vaccination, and instead used the numerous subjects who completed the primary vaccination ≥ 180 days as reference to measure the relative VE throughout the analysis. Finally, the outbreak was too small and the subjects too few to assess rVE for the different vaccines. Since almost all of the vaccine used in Henan (and China) are the two inactivated vaccines in our study, we believe it is reasonable to conclude that we assessed rVE for China's inactivated vaccines, especially the homologous

booster dose, and that our results can generalize to the rest of mainland China. However, our study results cannot generalize to other countries.

Conclusion

COVID-19 vaccination in China provided good protection against symptomatic COVID-19 and COVID-19 pneumonia caused by Delta and Omicron variants. Protection declined 6 months after primary series vaccination but was restored by homologous inactivated booster doses given 6 months after the primary series.

Acknowledgements

We are very grateful for the data collection efforts by local CDC and infectious hospital staff of Zhengzhou, Yuzhou, and Anyang cities in Henan province. We are very grateful to Yaowen Zhang, Yang Liu (Beijing Institute of Biological Products CO., LTD, SINOPHARM), and Xiaobin Cao and Yupeng Liang (Sinovac Research & Development Co., Ltd) for help with data extraction and running SAS code for data analysis.

Contributors

ZDY, ZYW, XYW, XYL and YMS acquired funding and contributed to the study's conception and design. ABW, RZ, ZHQ, FZW, CH, ZJA, HFW, and YY conceptualized the study and prepared the original study protocol, which was subsequently reviewed by LER. DW, LT, and CH developed the statistical methods. DW, CH and XYW wrote and tested the SAS code for the data analysis and drafted the manuscript. YY, HFW, YYZ, JJP, YFL, MXL, CSW and YTM collected data from local CDCs and abstracted the data. DW, LT, LER ZJA, ZDY and YMS interpreted the results and revised the manuscript and critically reviewed the manuscript. All authors approved the final submitted version.

Funding

This work was supported by the Operation of Public Health Emergency Response Mechanism of Chinese Center for Disease Control and Prevention (131031001000150001) and the National Key Research and Development Program of China(2021YFC2301600).

Competing interests

All authors declare no competing interests.

Ethical approval

COVID-19 is a class A notifiable infectious disease according to the Law on the Prevention and Control of Infectious Diseases (SCSNPC, 1989) in China; case reporting and investigation are mandatory. This study used data from COVID-19 surveillance and control and COVID-19 vaccination records available to public health officials; individual informed consent is not required or possible for routine surveillance data collection for a class A notifiable infectious disease. This study was approved by the Institutional Review Board of Chinese Center for Disease Control and Prevention (Approval Notice:202101-01).

Data sharing

The data can be assessed from the China Information System for Disease Control and Prevention by researchers who meet the criteria for access to confidential data (for the criteria for access and details of how to request access see https://www.phsciencedata.cn/Share/en/index.jsp).

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Figure titles and legends

Figure 1.

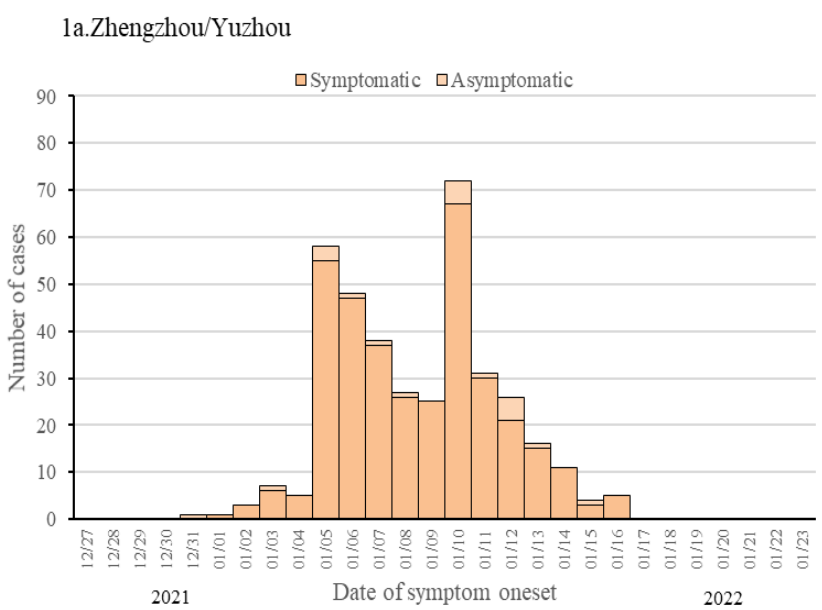
Title: Epidemic curves of SARS-CoV-2 infections in Zhengzhou/Yuzhou and Anyang between December 26, 2021 and January 23, 2022.

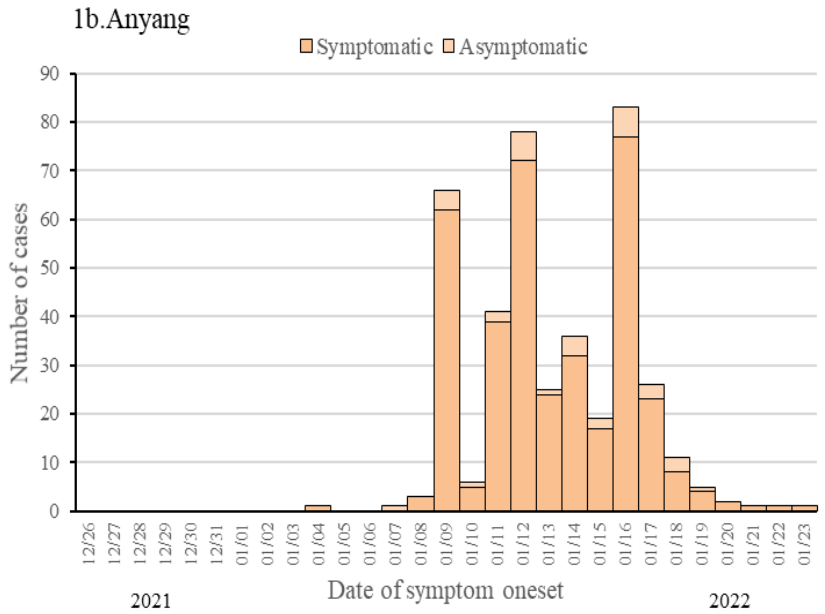
Legend: Figure 1a shows the COVID-19 epidemic curve with the number of cases plotted by date of symptom onset from December 26, 2021 to January 16, 2022 in the Delta transmission chain. Confirmed and asymptomatic cases are stacked to show total daily cases by date of symptom onset. The peak onset of symptomatic infection occurred between January 5 and 10., 2022. Figure 1b shows the COVID-19 epidemic curve for confirmed cases only, with number of cases plotted by date of symptom onset of from January 04, 2022 to January 23,2022 in the Omicron transmission chain. The confirmed cases onset of illness peaked between January 9 and 16.

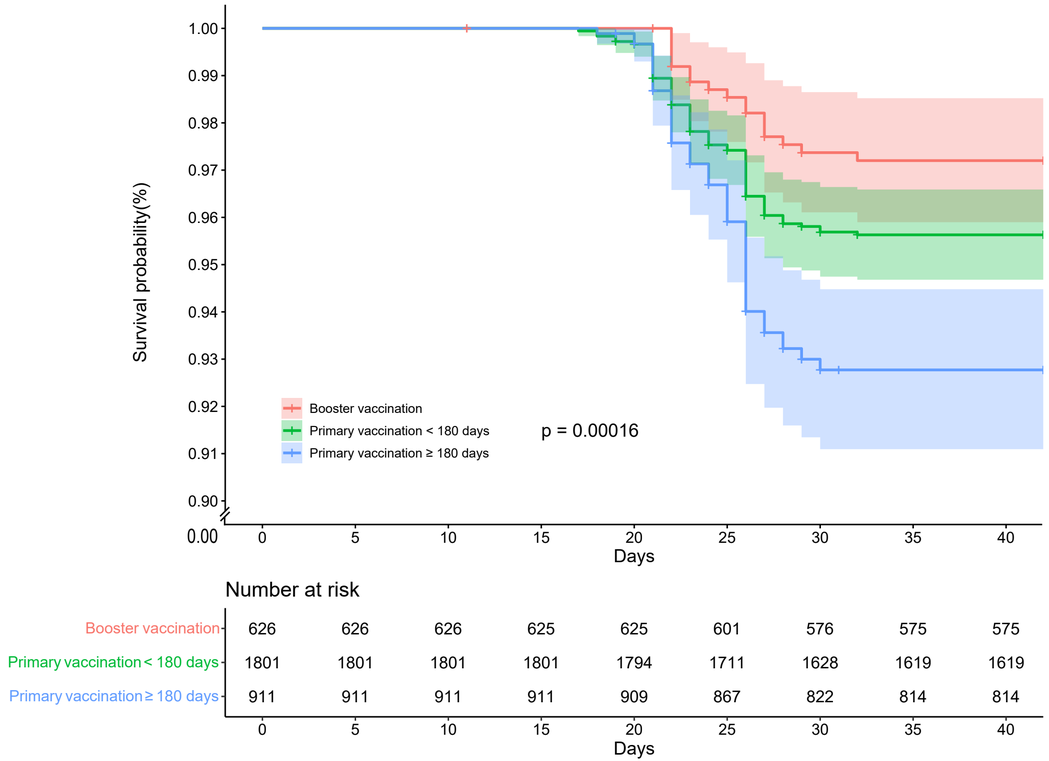
Figure 2.

Title: Survival curves of pneumonia caused by Delta and Omicron variants.

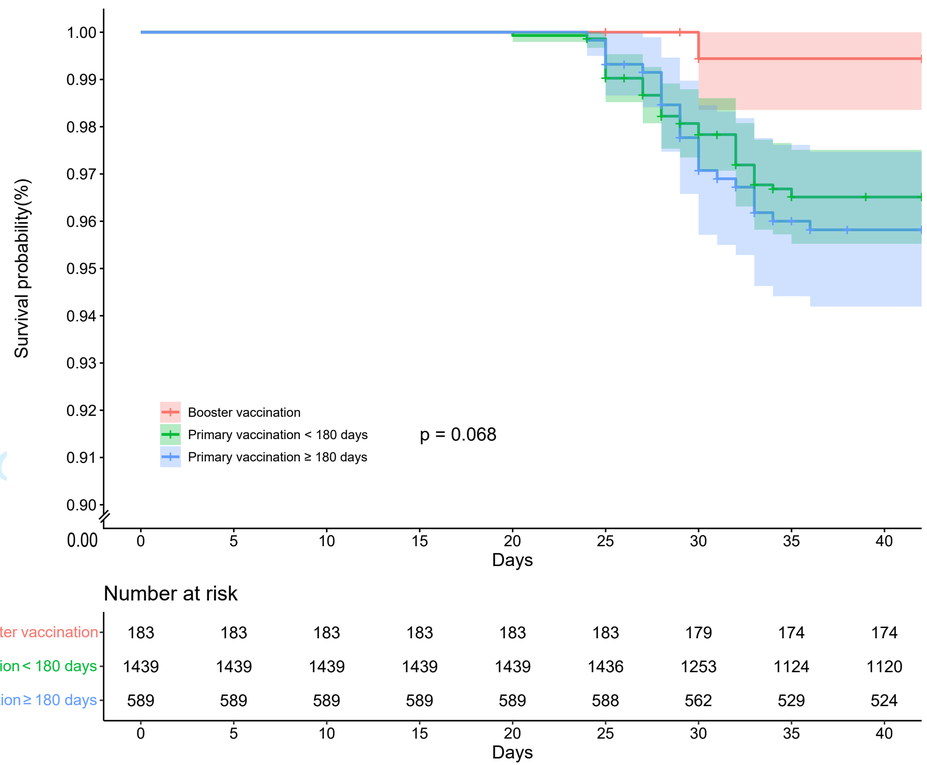
Legend: Figures 2a and 2b show Cox model estimates of the survival probability of pneumonia with the Delta and Omicron variant of SARS-CoV-2 according to vaccination status, adjusting gender and age, starting from December 15, 2021. Time zero is two weeks before the first case.


1a.Zhengzhou/Yuzhou
Symptomatic
Asymptomatic
Number of cases
Date of symptom oneset
2021
2022


1b.Anyang
Symptomatic
Asymptomatic
Number of cases
Date of symptom oneset
2021
2022



2a. Delta



2b. Omicron

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-7 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	7 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9 Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not possible
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			11 and 2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.