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ORIGINAL ARTICLE

Effectiveness of Inactivated SARS-CoV-2 Vaccines During a Delta Variant Outbreak in Hunan Province, China: A Retrospective Cohort Study

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Abstract

Objective: This study was aimed at investigating the effectiveness of inactivated COVID-19 vaccines against the Delta variant.

Methods: We performed a retrospective cohort study of close contacts of people with laboratory-confirmed SARS-CoV-2 infections in Hunan province, China, from July to August 2021. Mixed-effect logistic regression was used to estimate vaccine effectiveness (VE), and analyze the effects of the vaccination status of index cases and the exposure risk level on VE estimation.

Results: A total of 1,685 close contacts of 126 index cases were included; 835 (49.6%) had received two doses of inactivated vaccines, and the median interval between the 2nd dose and exposure was 48 days (IQR: 41 to 56 days). Full vaccination was defined as two doses at least 14 days before exposure. Adjusted VE estimates for full vaccination were 54.8% (95% CI: 7.7 to 77.9) and 68.4% (95% CI: 8.5 to 89.1) against symptomatic and moderate-to-severe COVID-19, respectively. VE for inactivated vaccines was difficult to observe if index cases had been fully vaccinated. The estimated VE with respect to infection protection was lower among household than non-household contacts.

Conclusion: Complete primary immunization of two-dose inactivated COVID-19 vaccines protected against SARS-CoV-2 Delta variant infection. Infection risk was higher among vaccinated household contacts than vaccinated non-household contacts.

Key words: SARS-CoV-2, Delta, inactivated vaccine, vaccine effectiveness, close contact

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INTRODUCTION

The emergence of SARS-CoV-2 variants has exacerbated the COVID-19 pandemic's substantial burden on healthcare resources and social activities worldwide [1,2]. Mass immunization has been used to decrease suffering and death in the pandemic, but the relatively lower COVID-19 vaccine-induced immunity against variants of concern than the original strain [3,4] and waning immunity over time [5,6] challenge the effectiveness of vaccines. In China, inactivated COVID-19 vaccines (BBIBP-CorV manufactured by Sinopharm and CoronaVac manufactured by Sinovac) have been widely administered since

December 2020 in a two-dose regimen with an interval of 21 days [7]. Under China's dynamic Zero-COVID policy, after the emergency-use vaccination of people at occupational risk of infection, such as healthcare workers, China's COVID-19 Vaccination Program began vaccinating adults 18–59 years of age, and was subsequently expanded to older adults in March 2021 and to children 3–17 years of age in October 2021 [8,9].

Several observational studies have shown that inactivated vaccines are effective against illness caused by SARS-CoV-2 variants, particularly severe outcomes. A test negative case-control study in Brazil has reported an effectiveness estimate of 46.8% (95%CI: 38.7 to 53.8) against symptomatic illness, and estimates of 55.5% (95%CI: 46.5 to 62.9) and 61.2% (95%CI: 48.9 to 70.5) against hospitalization and death among older adults have been observed during a Gamma variant epidemic [10]. In outbreaks in China [11,12], among people ≥18 years of age, vaccine effectiveness (VE) ranges from 50.5% (95%CI: 27.6 to 66.2) to 60.4% (95%CI: 31.8 to 88.9) against symptomatic infection and 61.4% (95%CI: 36.1 to 76.7) to 78.4% (95%CI: 56.9 to 99.9) against pneumonia caused by the Delta strain. During the Omicron variant wave in Brazil, the effectiveness of two-dose CoronaVac against severe outcomes (i.e., hospital admission or death) was estimated to be 88.4% (95% CI: 77.9 to 93.9) and 90.7% (95% CI: 89.5 to 91.8), whereas the effectiveness against symptomatic infection was 46.0% (95% CI: 42.6 to 49.2) and 36.2% (95% CI: 34.9 to 37.4) over a vaccination duration of 2 to 19 weeks and 20 or more weeks, respectively [13]. COVID-19 VE against severe disease remains high, though it did decrease somewhat 6 months after full vaccination, and is less affected by variants and waning immunity than the VE against mild illness [14]. Although existing real-world evidence on the effectiveness of inactivated COVID-19 vaccines has indicated considerable protection, these effectiveness estimates apply to differing conditions with respect to participants, dominant variants and times after vaccination. Additional evidence of the effectiveness of inactivated vaccines is greatly needed.

In late July 2021, a Delta (B.1.617.2) variant outbreak occurred in Hunan. During the outbreak response, more than 10,000 people were traced, identified as being at risk and quarantined. At-risk populations included people living in the same residential communities, studying at the same school, sharing a workplace, hospitalized in the same ward, taking public transportation or attending entertainment venues with an infected individual. We used this outbreak to evaluate the effectiveness of inactivated vaccines against the Delta variant and to explore potential vaccine protection effects due to the vaccination status of the index case (defined as the first infected individual who had been to a risk region or had contact with an imported infection before the onset of symptoms or confirmation of SARS-CoV-2 infection) and the exposure risk.

METHODS

Study design and participants

We conducted a retrospective cohort study to assess the effectiveness of inactivated vaccines among the close contacts of index cases during a Delta outbreak in Hunan from July to August 2021. Close contacts were individuals with unprotected close contact with a confirmed index case within 4 days before to 14 days after illness onset or, for asymptomatic index cases, within 4 days before to 14 days after the first positive sample of the asymptomatic case [15]. Unprotected close contacts were individuals exposed to an infected person without any personal protective equipment, such as a surgical mask or protective clothing. Close contacts underwent mandatory, centrally managed quarantining, during which they were periodically tested for SARS-CoV-2 infection with reverse transcriptase polymerase chain reaction assays. Close contacts ≥18 years of age with a clear vaccination history were eligible for participation in the study. Those under 18 years of age, who had prior SARS-CoV-2 infection or who had received a COVID-19 vaccine other than an inactivated vaccine (BBIBP-CorV/WIBP-CorV manufactured by Sinopharm, CoronaVac manufactured by Sinovac and KCONVAC manufactured by Biokangtai) were excluded. Relevant demographic data, exposure histories, and clinical records were obtained from the provincial Center for Disease Control (CDC) through their field epidemiology investigation.

Vaccination status

Vaccination data were obtained through interviews and verified with electronic records in the Hunan Immunization Information System, which included vaccine type, vaccination date, vaccination dose and vaccine manufacturer. Participants were categorized into three groups: non-vaccinated, partially vaccinated and fully vaccinated. Non-vaccinated individuals received no vaccines or received their first vaccine dose less than 14 days before the last exposure. Partially vaccinated individuals received their first dose more than 14 days before the last exposure and received either no second dose or a second dose less than 14 days before the last exposure. Fully vaccinated individuals received a second dose at least 14 days before the last exposure (S1 Fig).

Outcomes

VE was estimated against four laboratory-confirmed SARS-CoV-2 outcomes: any SARS-CoV-2 infection (symptomatic or asymptomatic), symptomatic COVID-19 (including confirmed cases of any severity), mild COVID-19 or moderate-to-severe COVID-19. We used case definitions consistent with China's Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (eighth edition) [16], as shown in S1 Table.

Statistical analysis

We used percentages to describe participant characteristics, and median and interquartile range (IQR) values to

describe the age and time between the last dose and the last exposure. Crude VE was estimated as 1 minus the risk ratio (RR) of each outcome with respect to the secondary attack rate (SAR) of the unvaccinated group. Adjusted RRs and 95% confidence intervals (CIs) were estimated by inclusion of all measured covariates in mixed-effect regression models; the rates of SARS-CoV-2 infection and COVID-19-associated outcomes in the fully and partially vaccinated groups were compared with the unvaccinated group as a reference. Multivariable model covariates included age group (18–29, 30–39, 40–49, 50–59, 60–69 or ≥70 years), sex, transmission setting (household or non-household) and vaccination status of the index case (non-vaccinated, partially vaccinated or fully vaccinated). A clustering index was introduced as a random effect. The robustness of the model was evaluated by random selection of one index case for close contacts with multiple exposures (S2 Table). For all models, VE was calculated as (1-RR)×100%. Subgroup analyses were conducted by age group (18–59 and ≥60 years), sex, vaccination status of index cases (not fully vaccinated or fully vaccinated), transmission setting (household or non-household) and vaccine manufacturer (Sinopharm or Sinovac). To explore the duration of inactivated vaccine protection among fully vaccinated participants, intervals between the 2nd vaccine dose and the last exposure were stratified into 14–90 day and >90 day groups and analyzed. All statistical analyses were performed in R software, version 4.1.1.

Ethical review

The study was reviewed and approved by the Hunan provincial CDC and prevention ethical committee review (No. IRB2020005).

RESULTS

Outbreak and participant characteristics

During the outbreak, 10,971 individuals were identified as being at-risk. Through contact tracing, 1,685 close contacts of the index cases were identified and found to be eligible for inclusion (Fig 1). Among the close contacts,

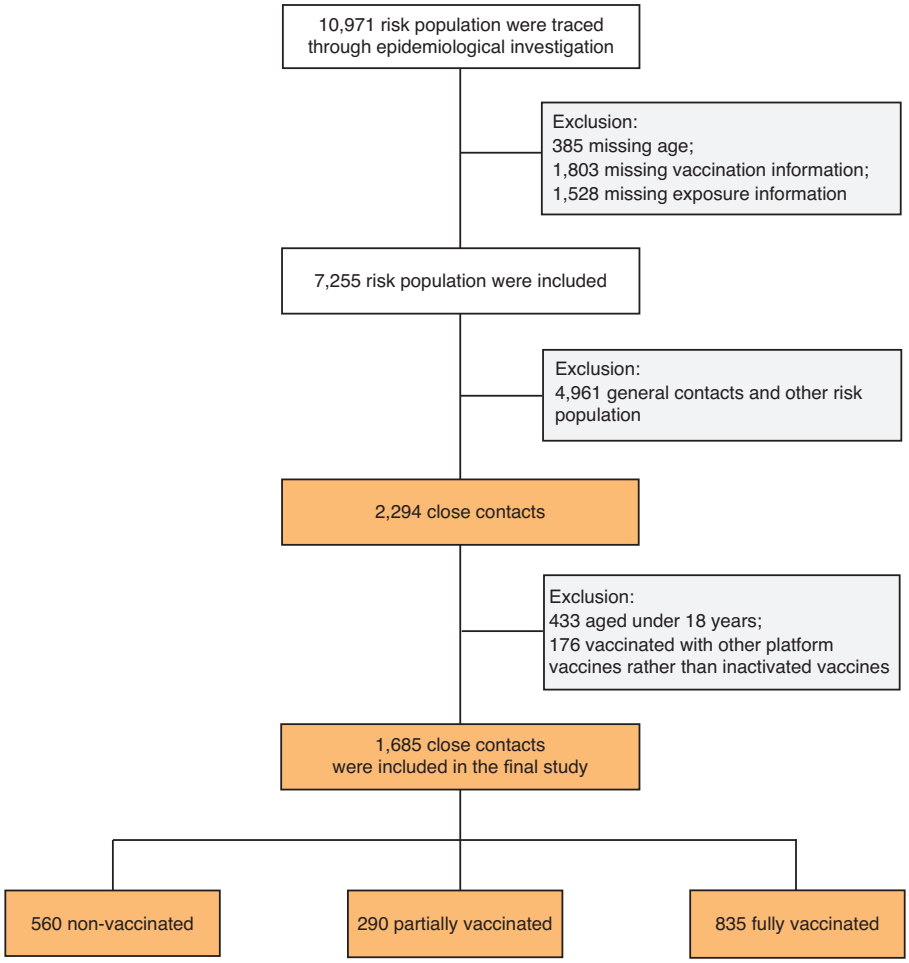

FIGURE 1 | Study flowchart. The at-risk population includes close contacts, general contacts and other high-risk populations. General contacts are those who had contact with a person with confirmed or suspected SARS-CoV-2 infection on public transportation; who were living, studying or working together; or those who sought medical assistance, but did not meet the criteria for a close contact. The other risk population refers to secondary close contacts (i.e., close contacts of primary close contacts) and people who shared the same public space but did not have direct contact with an infected person.

560 (33.2%) were unvaccinated, 290 (17.2%) were partially vaccinated, and 835 (49.6%) were fully vaccinated; most were 18–59 years old and female, particularly among the fully vaccinated. A total of 55 secondary cases and asymptomatic infections were reported among close contacts. One severe case was identified in an unvaccinated person older than 60 years. Among unvaccinated cases, 13 (61.9%) involved moderate-to-severe COVID-19; among fully vaccinated cases, only 7 (41.2%) involved moderate COVID-19 and no severe COVID-19. Most close contacts (83.4%) were exposed through social engagement, transportation, work or service contacts. Among fully vaccinated individuals, most had finished vaccination 1–2 months before exposure (Table 1).

TABLE 1 | Study population characteristics by vaccination status (n, %).

Characteristics	Non- vaccinated (n=560)	Partially vaccinated (n=290)	Fully vaccinated (n=835)	All close contacts (n=1685)
Age, years				
Median (IQR)	37 (28, 52)	39 (30, 52)	38 (31, 48)	38 (30, 50)
Age group				
18–59	471 (84.1)	267 (92.1)	813 (97.4)	1551 (92.0)
≥60	89 (15.9)	23 (7.9)	22 (2.6)	134 (8.0)
Sex				
Male	256 (45.7)	146 (50.3)	288 (34.5)	690 (40.9)
Female	304 (54.3)	144 (49.7)	547 (65.5)	995 (59.1)
Clinical outcome				
Non-infection	537 (95.9)	276 (95.2)	817 (97.8)	1630 (96.7)
Asymptomatic infection	2 (0.4)	1 (0.3)	1 (0.1)	4 (0.2)
Symptomatic cases	21 (3.8)	13 (4.5)	17 (2.0)	51 (3.0)
Mild	8 (38.1)	4 (30.8)	10 (58.8)	22 (43.1)
Moderate	12 (57.1)	9 (69.2)	7 (41.2)	28 (54.9)
Severe	1 (4.8)	0 (0.0)	0 (0.0)	1 (2.0)
Vaccination history				
Time interval between last dose and last known exposure, days				
Median (IQR)	-	25 (21, 28)	48 (41, 56)	-
Vaccine manufacturer				
BBIBP-CorV/WIBP-CorV	-	137 (47.2)	277 (33.2)	414 (36.8)
CoronaVac	-	152 (52.4)	377 (45.1)	529 (47.0)
KCONVAC	-	1 (0.3)	0 (0)	1 (0.1)
Mixed	-	-	181 (21.7)	181 (16.1)
Transmission setting				
Household	44 (7.9)	18 (6.2)	41 (4.9)	103 (6.1)
Social	137 (24.5)	78 (26.9)	161 (19.3)	376 (22.3)
Workplace	76 (13.6)	26 (9.0)	251 (30.1)	353 (20.9)
Healthcare facility	23 (4.1)	9 (3.1)	24 (2.9)	56 (3.3)
School	21 (3.8)	3 (1.0)	5 (0.6)	29 (1.7)
Transportation	149 (26.6)	70 (24.1)	138 (16.5)	357 (21.2)
Community	1 (0.2)	0 (0.0)	8 (1.0)	9 (0.5)
Service	83 (14.8)	68 (23.4)	169 (20.2)	320 (19.0)
Multiple exposures	26 (4.6)	18 (6.2)	38 (4.6)	82 (4.9)

Abbreviations: IQR denotes interquartile range.

Vaccine effectiveness

The adjusted VE for full vaccination was 47.5% (95% CI: -7.4 to 74.3) against SARS-CoV-2 infection, 54.8% (95% CI: 7.7 to 77.9) against symptomatic COVID-19, 26.1% (95% CI: -103.3 to 73.2) against mild COVID-19 and 68.4% (95% CI: 8.5 to 89.1) against moderate-to-severe COVID-19. The adjusted partial VE estimates were all lower than the corresponding full-schedule VE estimates (Table 2).

When index cases and their close contacts were both fully vaccinated, the adjusted VEs were 41.6% (95% CI: -115 to 84.2), 35.9% (95% CI: -130.4 to 82.2) and 55.0% (95% CI: -93.8 to 89.6) against SARS-CoV-2 infection, symptomatic COVID-19 and moderate-to-severe COVID-19, respectively. These VE estimates were lower than those when the index case was not fully vaccinated (Table 3). The adjusted VEs of full vaccination among household contacts were 37%–38% against any clinical outcome, and the adjusted VEs among non-household contacts were higher (Table 4). Among adults 18–59 years of age, the adjusted full-schedule VEs were 44.3% (95% CI: -15.9 to 73.2), 46.2% (95% CI: -12.1 to 74.2), 15.2% (95% CI: -138.1 to 69.8) and 61.0% (95% CI: -16.1 to 86.9) against SARS-CoV-2 infection, symptomatic COVID-19, mild COVID-19 and moderate-to-severe COVID-19, respectively (S4 Table). The adjusted full-schedule VEs among females against SARS-CoV-2 infection (61.6%, 95% CI: 0.4 to 85.2), symptomatic COVID-19 (65.3%, 95% CI: 11.3 to 86.4) and moderate-to-severe COVID-19 (76.5%, 95% CI: 14.0 to 93.6) were higher than those among males (S5 Table). BBIBP-CorV/WIBP-CorV (Sinopharm) and CoronaVac (Sinovac) provided similar levels of protection (S6 Table).

The VE according to the time since vaccination was estimated by dividing participants into subgroups with 14–90 days or >90 days between vaccination and exposure. In the fully vaccinated group, the median interval between the 2nd dose and exposure was 48 days (IQR: 41 to 56 days); the longest interval was 192 days. Most participants (692/835, 82.87%) received the 2nd dose no more than 3 months before exposure. The adjusted full-schedule VE against infection was 52.3% (95% CI: -2.9 to 77.9) in the first 3 months and 46.6% (95% CI: -107.3 to 86.2) for longer intervals (S7 Table).

DISCUSSION

Our study during the Hunan outbreak indicated that full-schedule inactivated COVID-19 VE estimates against SARS-CoV-2 Delta-variant infection and symptomatic, mild and moderate-to-severe COVID-19 were 47.5% (95% CI: -7.4 to 74.3), 54.8% (95% CI: 7.7 to 77.9), 26.1% (95% CI: -103.3 to 73.2) and 68.4% (95% CI: 8.5 to 89.1), respectively. Full-schedule VE estimates, regardless of severity, were lower for close contacts of fully vaccinated index cases than non-vaccinated or partially vaccinated index cases; VE estimates were lower among household contacts than non-household

TABLE 2 | Effectiveness of inactivated vaccines in preventing COVID-19 outcomes, according to vaccination status.

Outcome and vaccination status	SAR (%, a/n)	Unadjusted VE (95% CI)	Adjusted VE (95% CI)
SARS-CoV-2 infection			
Non-vaccinated	4.3 (24/561)	-	-
Partially vaccinated	4.5 (13/289)	-5.1 (-103.4, 45.6)	-4.2 (-127.9, 52.4)
Fully vaccinated	2.2 (18/835)	49.6 (8, 72.4)	47.5 (-7.4, 74.3)
Symptomatic COVID-19			
Non-vaccinated	3.9 (22/559)	-	-
Partially vaccinated	4.2 (12/288)	-5.9 (-110.8, 46.8)	4.8 (-108.4, 56.5)
Fully vaccinated	2 (17/834)	48.2 (3.4, 72.2)	54.8 (7.7, 77.9)
Mild COVID-19			-
Non-vaccinated	1.6 (9/546)	-	-
Partially vaccinated	1.1 (3/279)	34.8 (-139, 82.2)	10 (-224.3, 75)
Fully vaccinated	1.2 (10/827)	26.6 (-79.4, 70)	26.1 (-103.3, 73.2)
Moderate to severe COVID-19			-
Non-vaccinated	2.4 (13/550)	-	-
Partially vaccinated	3.2 (9/285)	-33.6 (-208.8, 42.2)	-30.7 (-249.3, 51.1)
Fully vaccinated	0.8 (7/824)	64.1 (10.5, 85.6)	68.4 (8.5, 89.1)

Abbreviations: SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2; COVID-19 denotes coronavirus disease 2019; SAR denotes secondary attack rate; VE denotes vaccine effectiveness; CI denotes confidence interval.

TABLE 3 | Effectiveness of inactivated vaccines in preventing different COVID-19 outcomes, according to the vaccination status of the index case.

Outcome	Vaccination status	Not fully vaccinated index cases[a]			Fully vaccinated index cases		
		SAR (%, a/n)	Unadjusted VE (95% CI)	Adjusted VE (95% CI)	SAR (%, a/n)	Unadjusted VE (95% CI)	Adjusted VE (95% CI)
SARS-CoV-2 infection	Non-vaccinated	6.8 (21/307)	-	-	4 (13/322)	-	-
	Partially vaccinated	7 (12/172)	-2 (-102.2, 48.5)	-6.5 (-172.3, 58.4)	4.3 (6/139)	-6.9 (-175.5, 58.5)	30.3 (-221.5, 84.9)
	Fully vaccinated	2.8 (12/432)	59.4 (18.7, 79.7)	52 (-15.5, 80)	2.4 (11/456)	40.2 (-31.7, 72.9)	41.6 (-115, 84.2)
Symptomatic COVID-19	Non-vaccinated	5.9 (18/304)	-	-	4 (13/322)	-	-
	Partially vaccinated	7 (12/172)	-17.8 (-138.7, 41.8)	-1.7 (-154.5, 59.4)	4.3 (6/139)	-6.9 (-175.5, 58.5)	25.2 (-247.8, 83.9)
	Fully vaccinated	2.6 (11/431)	56.9 (10.1, 79.3)	55.3 (-5.5, 81.1)	2.4 (11/456)	40.2 (-31.7, 72.9)	35.9 (-130.4, 82.2)
Mild COVID-19	Non-vaccinated	2.7 (8/294)	-	-	1.3 (4/313)	-	-
	Partially vaccinated	2.4 (4/164)	10.4 (-193.2, 72.6)	-1.5 (-297.4, 74.1)	0.7 (1/134)	41.6 (-417.6, 93.4)	100[b]
	Fully vaccinated	1.9 (8/428)	31.3 (-81, 73.9)	37.9 (-98.2, 80.6)	1.3 (6/451)	-4.1 (-265.9, 70.4)	-2317.1[b]
Moderate to severe COVID-19	Non-vaccinated	3.4 (10/296)	-	-	2.8 (9/318)	-	-
	Partially vaccinated	4.8 (8/168)	-41 (-250.3, 43.3)	-90.3 (-588.7, 47.4)	3.6 (5/138)	-28 (-275, 56.3)	20.5 (-312.6, 84.7)
	Fully vaccinated	0.7 (3/423)	79 (24.4, 94.2)	75.4 (-12.6, 94.6)	1.1 (5/450)	60.7 (-16, 86.7)	55.0 (-93.8, 89.6)

[a]Not fully vaccinated index cases included those in people who were not vaccinated or were partially vaccinated.
[b]The confidence interval could not be estimated because of the small sample size.
Abbreviations: SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2; COVID-19 denotes coronavirus disease 2019; SAR denotes secondary attack rate; VE denotes vaccine effectiveness; CI denotes confidence interval.

TABLE 4 | Effectiveness of inactivated vaccines in preventing different COVID-19 outcomes, according to the transmission setting

Outcome	Vaccination status	Non-household contact			Household contact		
		SAR (%, a/n)	Unadjusted VE (95% CI)	Adjusted VE (95% CI)	SAR (%, a/n)	Unadjusted VE (95% CI)	Adjusted VE (95% CI)
SARS-CoV-2 infection	Non-vaccinated	3.1 (16/514)	-	-	21.3 (13/61)	-	-
	Partially vaccinated	3 (8/269)	4.5 (-120.4, 58.6)	-1 (-168.2, 62)	30.4 (7/23)	-42.8 (-212.7, 34.8)	-78.9 (-655.3, 57.6)
	Fully vaccinated	1.5 (12/788)	51.1 (-2.6, 76.7)	48.3 (-22.9, 78.2)	14.3 (8/56)	33 (-49.6, 70)	38.3 (-130.5, 83.5)
Symptomatic COVID-19	Non-vaccinated	2.9 (15/513)	-	-	20 (12/60)	-	-
	Partially vaccinated	3 (8/269)	-1.7 (-136.9, 56.3)	-17.4 (-199.3, 53.9)	27.3 (6/22)	-36.4 (-218.9, 41.7)	4.6 (-341.5, 79.4)
	Fully vaccinated	1.4 (11/787)	52.2 (-3.2, 77.9)	49.2 (-20.4, 78.6)	14.3 (8/56)	28.6 (-61.7, 68.5)	36.8 (-133.9, 82.9)
Mild COVID-19	Non-vaccinated	1.4 (7/505)	-	-	7.7 (4/52)	-	-
	Partially vaccinated	1.1 (3/264)	18 (-214.4, 78.6)	-8 (-415.6, 77.4)	5.9 (1/17)	23.5 (-538.3, 90.8)	99.6[a]
	Fully vaccinated	1 (8/784)	26.4 (-101.8, 73.1)	19.7 (-185.4, 77.4)	7.7 (4/52)	0 (-278.7, 73.6)	97.8[a]
Moderate to severe COVID-19	Non-vaccinated	1.6 (8/506)	-	-	14.3 (8/56)	-	-
	Partially vaccinated	1.9 (5/266)	-18.9 (-259.8, 60.7)	-2.2 (-285.1, 72.9)	23.8 (5/21)	-66.7 (-352.4, 38.6)	-178.4 (-1370.3, 47.3)
	Fully vaccinated	0.4 (3/779)	75.6 (8.6, 93.5)	70.6 (-25.1, 93.1)	7.7 (4/52)	46.2 (-68.3, 82.8)	37.7 (-194.9, 86.9)

[a]The confidence interval could not be estimated because of the small sample size.

Abbreviations: SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2; COVID-19 denotes coronavirus disease 2019; SAR denotes secondary attack rate; VE denotes vaccine effectiveness; CI denotes confidence interval.

contacts. Partial vaccination provided insufficient protection against the Delta strain.

Our VE estimates against symptomatic COVID-19 caused by the Delta variant were consistent with those reported in other real-world studies [11,12]. An outbreak investigation on the effectiveness of COVID-19 inactivated vaccines in Henan, China, has reported protection rates against symptomatic infection and COVID-19-associated pneumonia of 50.5% (95% CI: 27.6 to 66.2) and 61.4 (95% CI: 36.1 to 76.7), respectively [12], with the same definition and a comparable age profile of the study participants. The VE against infection in our study was lower than that reported in a test-negative case-control study in Guangdong, China (59%, 95% CI: 16.0 to 81.6) [17], possibly because the longer interval from vaccination to exposure might have led to diminished immunity. A study [18] in Thailand during the Delta variant-dominant period has reported a VE of two-dose CoronaVac against infection of 60% (95% CI: 49–69%), a value higher than the estimate in our study. This difference may be attributable to inadequate surveillance capacity to detect COVID-19 cases with mild symptoms, thus resulting in underreporting of asymptomatic and mild cases in the Thailand epidemic. The VE of inactivated vaccine against moderate COVID-19 and COVID-19 pneumonia (including moderate, severe and critical cases with evidence of pneumonia) observed in the Guangdong outbreak [11,17] has been reported to be 70.2 (95% CI: 29.6 to 89.3) and 78.4 (95% CI: 56.9 to 99.9), respectively, in agreement with the results in our study. Therefore, the COVID-19 vaccines appear to be protective against severe outcomes caused by the Delta variant.

Our finding that one dose provided little protection against any clinical outcome is consistent with findings that inactivated vaccines are immunogenic in most patients 14 days after receipt of a second dose [19]. However, studies have shown that a single vaccination of CoronaVac is effective in preventing severe/fatal cases, with a VE as high as 60.9% (95% CI: 40.6 to 74.3) among people 20–59 years of age [20,21]. Studies with larger sample sizes should be conducted to explore the effectiveness of different immunization regimens.

VEs against the Omicron (B.1.1.529) variant are lower than those against other variants [22-24], particularly those against infection and symptomatic illness. A study in the United States [25] has reported VEs of two doses of an mRNA vaccine of 46% (95% CI, 25 to 61) against Omicron infection, but 65% (95%CI, 49 to 76) against Delta infection among frontline workers. A study in Hong Kong [20] has found that although two doses of CoronaVac or BNT162b2 provided limited protection against mild/moderate disease across all age groups during the fifth wave of the Omicron BA.2 lineage (18%, 95% CI: -18.0 to 42.9 and 31%, 95% CI: 1.6 to 51.7), the VE for two doses against severe/critical illness was 91.7% (95% CI: 87.8 to 94.4) and 95.2% (95% CI: 92.9 to 96.8) among people 20–59 years of age, and that for three doses exceeded 95% against severe/fatal illness, regardless of age group, for both vaccines. Araos and colleagues [26] have reported the effectiveness of two-dose CoronaVac in children 3–5 years of age during an Omicron SARS-CoV-2 outbreak in Chile, and estimated the VEs to be 38.2% (95%CI, 36.5 to 39.9) against COVID-19, 64.6% (95%CI, 49.6 to 75.2) against hospitalization and 69.0% (95%CI, 18.6 to 88.2) against intensive care unit admission, thus suggesting effective protection by inactivated vaccines against illness due to the Omicron variant in children. More research is needed to determine and monitor VE against emerging variants.

Our results suggested that inactivated vaccines may decrease transmission to contacts. The index cases were likely to be less infectious if they had completed primary immunization. Studies have shown that the likelihood of household transmission is approximately 40%–50% lower in vaccinated index patients than unvaccinated index patients [27], and that unvaccinated people with Delta infections are more likely to transmit infection to their contacts than those who have completed primary immunization [28,29]. However, the vaccination of index cases was not randomized in the study, thus potentially introducing bias. More studies are needed to assess the effects of the vaccine in decreasing infectivity. We also found that the protection conferred by inactivated vaccines was lower among household than non-household contacts, possibly because of a higher exposure risk [30,31], thus indicating that isolating infected individuals and maintaining social distancing are necessary to prevent viral spread.

Our study provided limited evidence on people 60 years or older and on the persistence of protection, because of the limited sample size in the outbreak and the timing of the outbreak with respect to the start of Hunan's vaccination campaign. We found higher VEs against the Delta strain in females than in males, a finding potentially associated with stronger immune responses induced by vaccines in females [32,33]. Sex, an important biological factor would largely affect pathogenesis and host immune responses against SARS-CoV-2 infection and vaccination. Some studies [34,35] have demonstrated that females have lower levels of innate immune cytokines and induce more robust virus-specific T cell response than males. Given the potential confounders and limited sample size in this study, more in-depth and comprehensive studies are needed to evaluate sex-specific differences in response to vaccination.

The findings in our study have several limitations. Our analyses were constrained by the small sample size, particularly among people ≥60 years of age, thus precluding subgroup analyses and generalization of the findings. Because the sample size of the study was limited by the outbreak scale, the small sample size increased the likelihood of type II error skewing the results, thus slightly decreasing the power of the study. Because this was an observational study, the results might potentially have been biased by unmeasured confounders, such as comorbidities, exposure

risks of participants and compliance with personal protective measures. We included the transmission setting as household and non-household to control the exposure risk of the participants and therefore mitigate the bias caused by different exposure risk. The outbreak occurred within several months of the vaccination campaign, thus precluding determination of VE over longer periods of time. Further studies evaluating VE over longer periods will be crucial to optimize vaccination strategy.

CONCLUSIONS

Two doses of inactivated vaccines effectively prevent illness caused by the Delta strain, and particularly protect against serious clinical outcomes. The somewhat lower level of protection in high-risk settings suggests the need for continuing public health interventions. Mass vaccination programs to increase population immunity are essential to limit morbidity and mortality from SARS-CoV-2 variant infections.

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CONFLICTS OF INTEREST

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