Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Effectiveness of inactivated COVID-19 vaccines against severe illness in B.1.617.2 (Delta) variant–infected patients in Jiangsu, China

Zhiliang Hu1,2,*, Bilin Tao2,*, Zhongqi Li2,*, Yan Song1, Changhua Yi1, Junwei Li1, Meng Zhu2, Yongxiang Yi1,*, Peng Huang2, a,*, Jianming Wang2, b, **

1 Nanjing Public Health Medical Center, the Second Hospital of Nanjing, Nanjing University of Chinese Medicine, Nanjing, 210003 China
2 Department of Epidemiology, Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing, 211166 China

A R T I C L E   I N F O

Article history:
Received 11 November 2021
Revised 12 January 2022
Accepted 13 January 2022

Keywords:
COVID-19
SARS-CoV-2
Delta variant
vaccine
effectiveness
severe illness

A B S T R A C T

Background: The SARS-CoV-2 B.1.617.2 (Delta) variant has caused a new surge in the number of COVID-19 cases. The effectiveness of inactivated vaccines against this variant is not fully understood.

Methods: Using data from a recent large-scale outbreak of B.1.617.2 SARS-CoV-2 infection in Jiangsu, China, we conducted a real-world study to explore the effect of inactivated vaccine immunization on the course of disease in patients infected with the Delta variant.

Results: Of 476 patients with B.1.617.2 infection, 184 were unvaccinated, 105 were partially vaccinated, and 187 were fully vaccinated. A total of 42 (8.8%) patients developed severe illness, of whom, 27 (14.7%), 13 (12.4%), and 2 (1.1%) were unvaccinated, partially vaccinated, and fully vaccinated, respectively (P <.0001). All 15 (3.2%) patients who required mechanical ventilation were unvaccinated. After adjusting for age, sex, and comorbidities, fully vaccinated patients had an 88% reduced risk of progressing to severe illness (ORadjuned*: 0.12, 95% CI: 0.02-0.45). However, this protective effect was not observed in partially vaccinated patients (ORadjuned*: 1.11, 95% CI: 0.51-2.36). Full immunization offered 100% protection from severe illness among women. The effect of the vaccine was potentially affected by underlying medical conditions (ORadjuned*: 0.26, 95% CI: 0.03-1.23).

Conclusion: Full vaccination with inactivated vaccines is highly effective in preventing severe illness in Delta variant–infected patients. However, partial vaccination does not offer clinically meaningful protection against severe disease.

© 2022 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

According to the World Health Organization (WHO) estimation, as of January 5, 2022, the global cumulative number of confirmed COVID-19 cases has risen to more than 293 million and more than 5.4 million people have died from it (WHO 2021). There is no doubt that vaccination is a vital measure to contain the COVID-19 pandemic. Different COVID-19 vaccines, including inactivated, adenovirus vector, and messenger RNA vaccines, have been authorized or are in the laboratory development and clinical utility evaluation stage (Folegatti et al. 2020, Jara et al. 2021, Kandeil et al. 2021, Polack et al. 2020). As of August 5, 2022, more than 9.1 billion doses of the COVID-19 vaccines have been administered globally (WHO 2021). These vaccines can effectively induce immune responses against SARS-CoV-2 infection (Sadarangani et al. 2021, Xia et al. 2021, Zhang et al. 2021). Clinical trials outside China demonstrated that vaccine efficacy in preventing symptomatic COVID-19 ranged from 65.9% to 83%, and severe illness or intensive care unit (ICU) admission ranged from 90% to 100% (Al Kaabi et al. 2021, Jara et al. 2021, Tanriover et al. 2021). In China, people are generally vaccinated with inactivated vaccines. Accumulated evidence suggests that an inactivated COVID-19 vaccine could efficiently, although not wholly, protect against SARS-CoV-2 infection and, more importantly, prevent severe illness progression. However, it is difficult to confirm in mainland China because there...
was no large-scale local outbreak after the first epidemic wave in 2020. Moreover, the protective effect of the inactivated vaccine on the pathogenesis of SARS-CoV-2 mutant strains is not clear.

On July 20, 2021, 9 domestic COVID-19 cases were first identified through regular screening at the Nanjing Lukou International Airport, China (Polack et al. 2020). The outbreak at the airport spread rapidly to the surrounding areas, leading to outbreaks in Nanjing, Yangzhou, and Zhangjiajie. Genome sequencing confirmed that the etiologic agent was the SARS-CoV-2 B.1.617.2 (Delta) variant, which was first identified in Maharashtra, India, in late 2020 and now has spread globally (Voysey et al. 2021). Compared with the original type of SARS-CoV-2, the Delta variant has significantly increased virulence and transmissibility (Burki 2021, Liu et al. 2021, Zhang et al. 2021). Furthermore, in many studies, the protective effect of vaccines against Delta variant infection has been shown to be weakened (Chen et al. 2021, Christensen et al. 2021, Lopez Bernal et al. 2021, Nasreen et al. 2021, Sheikh et al. 2021).

In the case of more than 200 million doses of COVID-19 vaccine administered in China, whether the widely used inactivated vaccine is still effective against the Delta variant is a question worthy of discussion. Thus, we performed a real-world study using patients’ clinical and epidemiologic data in a designated hospital in Nanjing. They were all linked to the outbreak of COVID-19 at the Nanjing Lukou International Airport. Our study aimed to describe what extent the inactivated vaccine could prevent COVID-19 from progressing to severe illness in patients infected with the SARS-CoV-2 Delta variant.

Methods

Study design and population

We recruited 476 patients with confirmed COVID-19 treated in the isolation wards of Nanjing Public Health Medical Center from July to August 2021. The inclusion criteria were: (1) patients aged more than 18 years; (2) confirmed by SARS-CoV-2 nucleic acid polymerase chain reaction (PCR) test; (3) linked to the recent outbreak of COVID-19 originating in Nanjing Lukou International Airport; and (4) infected with the Delta variant. China has adopted a dynamic zero–COVID-19 policy. With this strategy, the surveillance system could efficiently track all the related cases whenever there was a local outbreak of COVID-19. In our study, samples from patients with COVID-19 were sequenced by the local Centers for Disease Control and Prevention if the SARS-CoV-2 PCR cycle threshold (Ct) value was less than 30. All subjects were confirmed to have an epidemiologic link with the sequencing-confirmed cases infected with the Delta variant.

The Nanjing Public Health Medical Center is the only designated hospital that provides medical services for patients with COVID-19 in Nanjing. Of the 476 patients recruited in this study, 189 lived in Nanjing, 273 lived in Yangzhou, 12 lived in Huai'an, and 2 lived in Suqian. We collected data from each patient, including demographic characteristics, medical history, vaccine status, comorbidities, clinical features, laboratory tests, treatments, and outcomes. The onset date was defined as when symptoms first appeared or when asymptomatic patients were detected for the first time with SARS-CoV-2 nucleic acid positivity. The diagnosis of severe illness was based on the Guideline of COVID-19 Diagnosis and Treatment (Trial Version 8) issued by the National Health Council of China. This study was approved by the ethics committee of Nanjing Public Health Medical Center (2020-LS-ky003). Written informed consent was waived by the Ethics Commission.

Vaccination status

Information regarding the time of vaccination and the type of vaccine was obtained from the electronic health information system. The time interval between the last dose of vaccination and the onset of disease was calculated. Because 2 weeks were needed after the second dose to develop protective immune responses against SARS-CoV-2 infection, a vaccine shot was considered effective only when the time interval between the second shot and disease onset was at least 14 days. We categorized patients into 3 groups: unvaccinated, partially vaccinated, and fully vaccinated, according to immunization history. Patients were also considered unvaccinated if they had received 1 dose but the time interval between the first shot and illness onset was less than 14 days. Similarly, patients who had received 2 vaccine shots, for whom the time interval between the second shot and illness onset was less than 14 days, were considered partially vaccinated (Figure 1) (Li et al. 2021).

Outcomes

The primary outcome of interest was the progression to severe illness in patients infected with the Delta variant. As defined by the Guideline of COVID-19 Diagnosis and Treatment (Trial Version 8) in China, severe illness of COVID-19 for adult patients must meet 1 of the following criteria: (1) respiratory rate ≥ 30 breaths/min; (2) oxygen saturation measured by finger pulse oximeter during air inhalation ≤ 93% while at rest; (3) arterial partial pressure of oxygen (PaO2)/oxygen uptake concentration (FiO2) ≤ 300 mm Hg; and (4) aggravated clinical symptoms and pulmonary imaging showing that the lesion progressed more than 50% within 24–48 hours. Patients with critical COVID-19 were those who had developed respiratory failure and required mechanical ventilation or had evidence of shock or other organ dysfunction that needed transfer to the ICU. The most severe condition of the patients during hospitalization was recorded. In this study, we analyzed both severe and critical cases.

Covariates

Covariates that have been confirmed in or possibly have a role in disease progression were considered, including age, sex, comorbidities, vaccination status, baseline SARS-CoV-2 viral load, and therapies (corticosteroids, intravenous immunoglobulin, and aerosol interferon alfa). Age was categorized into 2 groups: 18–59 years and ≥60 years. Clinical parameters such as blood lymphocyte counts, C-reactive protein (CRP), interleukin 6 (IL-6), D-dimer, lactate dehydrogenase (LDH), and pulmonary involvement were more appropriate as an index of disease severity rather than risk factors and were therefore not included in the multivariable regression analysis. All cases involved in this study were vaccinated with the inactivated vaccine.

Statistical analysis

Categorized variables were expressed as frequencies, and continuous variables were described as medians (interquartile ranges [IQRs]). As appropriate, comparisons were made using the Kruskal-Wallis test, Mann-Whitney U test, chi-square test, or Fisher exact test. Factors related to severe illness were analyzed by univariate and multivariate regression analysis, and the relationship was expressed with odds ratios (ORs) and 95% confidence intervals (95% CIs). Furthermore, we performed a subgroup analysis by stratifying age, sex, and underlying medical conditions. The significance level was set at 0.05. All analyses were performed using R software for Windows version 4.0.5 (https://www.r-project.org/).
Results

Characteristics of the patients

A total of 476 hospitalized patients were included in the analysis, of whom, 184 (38.6%), 105 (22.1%), and 187 (39.3%) were unvaccinated, partially vaccinated, and fully vaccinated, respectively. The inactivated vaccines used were from CoronaVac (Sinovac Biotech, Beijing, China), BBIBF-CorV (Sinopharm, Beijing, China), and KCONVAC (BioKangtai, Shenzhen, China), accounting for 73.3%, 26.5%, and 0.2% of the vaccination shots, respectively. As shown in Table 1, although sex and CRP levels were similar among patients with different vaccination statuses, most of the variables were significantly different. Compared with unvaccinated patients, fully vaccinated patients were younger, less likely to have underlying illness, and had lower levels of IL-6 and lactate dehydrogenase. There was no statistical significance of the viral load between unvaccinated and fully vaccinated patients, either represented by the PCR Ct value of the ORF1ab gene (P = 0.441) or the N gene (P = 0.265).

Estimating the efficacy of inactivated SARS-CoV-2 vaccine

A total of 42 (8.8%) patients developed severe illness, of whom, 27 (14.7%), 13 (12.4%), and 2 (1.1%) were unvaccinated, partially vaccinated, and fully vaccinated, respectively (P < 0.001; Table 1). Fifteen (3.2%) patients required mechanical ventilation, all of whom were unvaccinated. The characteristics of the individuals categorized by severity of the disease are shown in Supplemental Table 1. As predefined in the Methods, patients who had received 1 dose of vaccine and had acquired Delta variant infection within 14 days were deemed unvaccinated. This 14-day elapsed time was also applicable to the second dose vaccination. There was no significant difference in the proportion of severe illness between patients who did not receive any COVID-19 vaccine and patients who received 1 dose within 14 days (15.6% vs 12.2%, P = 0.750) or between patients who did not receive any COVID-19 vaccine and patients who received the second dose within 14 days (12.8% vs 11.1%, P = 1.000). Therefore, our estimation of the effectiveness of vaccines would not be significantly biased by the definition of vaccination status.

Compared with the unvaccinated group, the fully vaccinated group had a significantly decreased risk of severe illness (OR: 0.06, 95% CI: 0.01-0.21, P < 0.001; risk reduction: 94%, 95% CI: 79%-99%). The risk of severe illness was also decreased for the partially vaccinated patients, but the difference was not significant (OR: 0.82, 95% CI: 0.39-1.64, P = 0.588) (Table 2). After adjusting for potential confounders, such as sex, age, and underlying medical conditions, the protective effect of full vaccination remained significant (ORAdjusted: 0.12, 95% CI: 0.02-0.45, P = 0.006; adjusted risk reduction: 88%, 95% CI: 55%-98%). No significant effect was found for partial vaccination (ORAdjusted: 1.11, 95% CI: 0.51-2.36, P = 0.783) (Table 2).

Subgroup analysis

The risk of progressing to severe illness was 0 in fully vaccinated persons without underlying medical conditions, age ≥60 years, or female sex. Only 14 older patients were fully vaccinated; therefore, the protection may be overestimated in this subgroup. The protective effect against severe illness remained significant for 18- to 59-year-old fully vaccinated persons (ORAdjusted: 0.12, 95% CI: 0.02-0.61, P = 0.016; risk reduction: 88%, 95% CI: 39%-98%) and fully vaccinated males (ORAdjusted: 0.19, 95% CI: 0.03-0.86, P = 0.049; risk reduction: 81%, 95% CI: 14%-97%). The effect of the vaccine was potentially affected by underlying medical conditions, resulting in the reduced protective effect of full vaccination (ORAdjusted: 0.26, 95% CI: 0.03-1.23). Partial vaccination had no significant protective effect on severe illness in any subgroup (P > 0.05) (Table 3).

Discussion

Mutations of SARS-CoV-2 have attracted significant public attention, with variants of concern leading to increased transmissibility, impaired immune protection from the vaccine, more severe disease, or compromised diagnostic capacity (Khateeb et al. 2021). The Delta variant, which was first identified in India, is more transmissible than other lineages of SARS-CoV-2 and is now becoming the major strain driving the COVID-19 pandemic (Campbell et al. 2021, Singh et al. 2021, Vaughan 2021). Vaccine breakthrough caused by the Delta variant has been increasingly reported, even in massively vaccinated regions (Mizrahi et al. 2021, 206
Table 1
Baseline characteristics and disease outcomes among 476 SARS-CoV-2 Delta variant-infected patients with different vaccination statuses

| Variables                     | Unvaccinated (n = 184) | Partially vaccinated (n = 105) | Fully vaccinated (n = 187) | P value |
|-------------------------------|------------------------|-------------------------------|---------------------------|---------|
| Sex                           |                        |                               |                           | 0.213   |
| Female, n (%)                 | 115 (62.5)             | 92 (53.3)                     | 185 (63.1)                |         |
| Male, n (%)                   | 69 (37.5)              | 49 (46.7)                     | 69 (36.9)                 |         |
| Age (years)                   |                        |                               |                           |         |
| 18-59, n (%)                  | 56 (30.4)              | 69 (65.7)                     | 173 (92.5)                | <.0001  |
| ≥60, n (%)                    | 128 (69.6)             | 36 (34.3)                     | 14 (7.5)                  |         |
| Comorbidity                   | 83 (45.1)              | 35 (33.7)                     | 33 (17.6)                 | <.0001  |
| Hypertension, n (%)           | 62 (33.7)              | 24 (23.1)                     | 23 (12.3)                 | <.0001  |
| Diabetes, n (%)               | 24 (13.0)              | 10 (9.6)                      | 9 (4.8)                   | 0.021   |
| Heart disease, n (%)          | 14 (7.6)               | 5 (4.8)                       | 2 (1.1)                   | 0.005   |
| Cancer, n (%)                 | 7 (3.8)                | 3 (2.9)                       | 1 (0.5)                   | 0.074   |
| COPD, n (%)                   | 3 (1.6)                | 0 (0.0)                       | 0 (0.0)                   | 0.180   |
| Asthma, n (%)                 | 6 (3.3)                | 1 (1.0)                       | 2 (1.1)                   | 0.344   |
| Autoimmune disease, n (%)     | 2 (1.1)                | 1 (1.0)                       | 2 (1.1)                   | 0.001   |
| Time from illness onset to hospitalization, median (IRQ) days | 3.0 (2.0, 5.0) | 3.0 (1.0, 4.0) | 2.0 (1.0, 4.0) | <.0001 |
| Symptoms                      |                        |                               |                           |         |
| Fever, n (%)                  | 75 (40.8)              | 38 (36.5)                     | 51 (27.3)                 | 0.021   |
| Cough, n (%)                  | 96 (52.2)              | 50 (48.1)                     | 98 (52.4)                 | 0.748   |
| Shortness of breath, n (%)    | 13 (7.1)               | 7 (6.7)                       | 3 (1.6)                   | 0.020   |
| Abdominal pain or diarrhea, n (%) | 12 (6.5) | 4 (3.8)                      | 12 (6.4)                  | 0.635   |
| Loss of smell or taste, n (%) | 5 (2.7)                | 2 (1.9)                       | 12 (6.4)                  | 0.120   |
| Stuffy nose or runny nose, n (%) | 16 (8.7) | 16 (15.2)                    | 35 (18.7)                 | 0.020   |
| Pharyngeal discomfort, n (%)  | 33 (17.9)              | 27 (25.7)                     | 43 (23.0)                 | 0.257   |
| Laboratory findings          |                        |                               |                           |         |
| C-reactive protein, median (IRQ) mg/L | 5.6 (1.8, 15.0) | 7.8 (2.5-20.9) | 5.7 (2.1, 14.3) | 0.248  |
| >10, n (%)                    | 66 (35.9)              | 47 (44.8)                     | 65 (34.8)                 | 0.205   |
| Interleukin 6, median (IRQ) pg/mL | 183 (9.4, 32.5) | 117 (4.9, 24.9) | 61 (1.5, 13.6) | <.0001  |
| Neutrophil count, median (IRQ) × 10⁹/L | 2.9 (2.0, 3.6) | 3.0 (2.3, 4.2) | 3.2 (2.3, 4.2) | 0.047   |
| Lymphocyte count, median (IRQ) × 10⁹/L | 1.1 (0.8, 1.4) | 1.3 (0.9, 1.7) | 1.2 (0.9, 1.6) | 0.004   |
| LDH, median (IRQ) U/L         | 240.5 (214.8, 289.0)   | 240.0 (204.0, 268.0)         | 231.0 (199.0, 260.0)      | 0.007   |
| ALT, median (IRQ) U/L         | 18.9 (13.8, 28.5)      | 20.7 (13.1, 32.1)            | 16.6 (11.4, 26.3)         | 0.024   |
| Viral load (CT value)         | 23.0 (20.0, 27.0)      | 25.0 (21.0, 29.0)            | 22.0 (19.0, 27.5)         | 0.016   |
| SARS-CoV-2 antibody, S/CO     | 0.07 (0.00, 0.36)      | 0.71 (0.15, 3.49)            | 0.34 (0.11, 1.24)         | <.0001  |
| IgM, median (IRQ)             | 0.11 (0.06, 0.37)      | 1.50 (0.2, 33.6)             | 5.49 (2.3, 35.0)          | <.0001  |
| IgG, median (IRQ)             | 0.11 (0.06, 0.37)      | 1.50 (0.2, 33.6)             | 5.49 (2.3, 35.0)          | <.0001  |
| Severe illness, n (%)         | 27 (14.7)              | 13 (12.4)                     | 2 (1.1)                   | <.0001  |
| Mechanical ventilation, n (%) | 15 (8.2)               | 0 (0.0)                       | 0 (0.0)                   | <.0001  |

Data were expressed as median (interquartile range [IRQ]) or number (percentage). Comparisons among groups were made using the Kruskal-Wallis test, chi-square test, or Fisher exact test, as appropriate. The Ct value was used to represent the viral load. COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; Ct, cycle threshold; S/CO, signal to cutoff.

Table 2
Univariable and multivariable analysis for factors associated with severe illness

| Variables                     | Univariable model | Multivariable model |
|-------------------------------|-------------------|---------------------|
|                              | Crude OR (95% CI) | P value             | Adjusted OR (95% CI) | P value |
| Sex                           |                   |                     |                     |         |
| Female                       | 1                 |                     |                     |         |
| Male                         | 1.45 (0.76-2.75)  | 0.249               | 1.48 (0.76-2.87)    | 0.247   |
| Age (years)                  |                   |                     |                     |         |
| 18-59                        | 1                 | 1                   | 1                   |         |
| ≥60                          | 4.83 (2.46-10.07) | <.0001              | 2.37 (1.08-5.47)    | 0.036   |
| Comorbidity                  |                   |                     |                     |         |
| No                           | 1                 |                     |                     |         |
| Yes                          | 2.33 (1.23-4.43)  | 0.009               | 1.33 (0.67-2.65)    | 0.415   |
| Vaccination status           |                   |                     |                     |         |
| Unvaccinated                 | 1                 |                     |                     |         |
| Partially vaccinated         | 0.82 (0.39-1.64)  | 0.588               | 1.11 (0.51-2.36)    | 0.783   |
| Fully vaccinated             | 83 (0.06-0.21)    | <.0001              | 0.72 (0.02-0.45)    | 0.006   |
| Time from illness onset to hospitalization (per day) | 1.06 (0.94-1.17) | 0.309              | -                  | -       |
| Ct value (N gene)            | 0.99 (0.94-1.04)  | 0.649               | -                  | -       |

OR, odds ratio; CI, confidence interval; Ct, cycle threshold.
 Vaughan 2021). Therefore, concern has been raised regarding whether herd immunity bolstered by inactivated vaccines in China could protect against the Delta variant.

In late May, the first attack by this new virus occurred in Guangzhou, China, with approximately 160 cases involved (Lopez Bernal et al. 2021). A real-world study on 74 patients and 292 negative controls calculated that the overall effect for 2-dose vaccination was 59.0% protective against SARS-CoV-2 infection and 100% protective against severe illness (Li et al. 2021). The current study focusing on 476 hospitalized patients demonstrated that the risk of progression to severe illness substantially decreased in fully vaccinated patients. After adjusting for age, sex, and underlying medical conditions, the risk reduction remained significant at 88%. Moreover, in our study, inactivated vaccines provided 100% protection against mechanical ventilation. This is the largest real-world study to confirm the effectiveness of inactivated vaccines in preventing severe illness caused by the Delta variant in China.

It is well known that underlying comorbidities and old age are risk factors for severe illness in SARS-CoV-2–infected patients (Jordan et al. 2020). This is consistent with the findings in our study. Severe illness did not occur in fully vaccinated patients without underlying medical conditions (100% protection). Both fully vaccinated patients who developed severe illness had underlying diseases. Interestingly, 100% protection was also found in older patients who had been fully vaccinated. Because only 14 older patients were fully vaccinated, the protective effect of inactivated vaccines might be overestimated in this study. Fully vaccinated women were 100% protected against progression to severe illness, whereas fully vaccinated men had a reduced risk of 81%. Whether sex disparities exist in COVID-19 vaccine efficacy needs to be further explored.

Although an entire course of vaccination could efficiently prevent progression to severe illness in patients with COVID-19, the protective effect could not be identified in partially vaccinated patients. This may be due to a relatively high viral burden and decreased immune protection in patients infected with Delta variant (Christensen et al. 2021, Lopez Bernal et al. 2021, Nasreen et al. 2021). The baseline viral load in this study, as represented by the Ct value of the real-time quantitative reverse transcription polymerase chain reaction (RT-PCR), was 20 (IQR: 16-25), which is much higher than that (median: 30; IQR: 25-34) in our previous data during the first outbreak of COVID-19 in 2020 (Hu et al. 2020). In the context of Delta variant infection, relatively higher immunity may be necessary, which would generally be achieved after full vaccination (Sadarangani et al. 2021). It is worth noting that, in addition to personal protection and vaccination, enhancing the ability of countries or regions to respond to public health concerns is also crucial for COVID-19 control (Ji et al. 2021).

There are some limitations to our study. First, we confirmed the protective effect of inactivated vaccines in preventing the progression to severe illness, but we could not estimate vaccine efficacy against Delta variant infection because all participants were confirmed COVID-19 cases. Second, because individuals who have been protected from the disease would not develop a severe illness related to COVID-19, the effectiveness of inactivated vaccines against severe disease in our study based on infected cases would be, to some extent, an underestimation of the effectiveness of inactivated vaccines against severe disease based on the whole population.

In conclusion, we found that complete course immunization with inactivated vaccines could effectively protect against severe illness caused by the Delta variant in China. The protective effect is affected by underlying medical conditions. Partial vaccination does not offer clinically meaningful protection against severe illness. Our study highlights the importance of continuous efforts in encouraging a full course of vaccination.

Contributions

Jianming Wang, Peng Huang, and Yongxiang Yi conceived and designed the study. Yongxiang Yi, Zhiliang Hu, Yan Song, Changhua Yi, and Junwei Li contributed to the recruitment of participants. Jianming Wang, Zhiliang Hu, Peng Huang, Bilin Tao, and Zhongqi Li led the data collection, data analysis, and data interpretation. Zhiliang Hu, Bilin Tao, and Zhongqi Li drafted the manuscript. All authors provided critical review and final approval of the manuscript. The corresponding author attests that all listed authors meet the authorship criteria and that no one meeting the criteria have been omitted.
Declaration of Competing Interests

All authors have no conflict of interest to declare.

Acknowledgements

We would like to thank all the heroic people who actively participated in ending this COVID-19 outbreak.

Funding

This study was supported by Key Research and Development Program of Department of Health of Jiangsu (ZDB2020036), Project of Nanjing Infectious Disease Clinical Medical Center Construction (NA2021062071), and Nanjing Major Science and Technology Project (2021-11005). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.01.030.

References

Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdurrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. JAMA 2021;326(1):35–45. doi:10.1001/jama.2021.8563

Burki TK. Lifting of COVID-19 restrictions in the UK and the Delta variant. Lancet Respir Med 2021;9(8):e85. doi:10.1016/S2213-2600(21)00328-3.

Campbell F, Archer B, Laurentsen-Schafer H, Jinjin Y, Konings F, Battr N, et al. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill 2021;26(24). doi:10.2861/jsem-1560-7917.ES.2021.26.24.2100059.

Chen LQ, Lu L, Chio CY, Cai JP, Tsai HW, Chu AW, et al. Impact of SARS-CoV-2 variant-associated RBD mutations on the susceptibility to serum antibodies elicited by COVID-19 infection or vaccination. Clin Infect Dis 2021;ciab656. doi:10.1093/cid/ciab656.

Christensen PA, Ollem RJ, Long SW, Subedi S, Davis JJ, Hodjat P, et al. Delta Variants of SARS-CoV-2 Cause Significantly Increased Vaccine Breach in COVID-19 Cases in Houston, Texas. Am J Pathol 2021. doi:10.1016/j.ajpath.2021.03.019.

Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Bell-Jama-Ramsterforst A, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1, single-blind, randomised controlled trial. Lancet 2020;396(10249):467–78. doi:10.1016/S0140-6736(20)31604-4.

Hu Z, Lv Y, Xu C, Sun W, Chen W, Peng Z, et al. Clinical Use of Short-Course and Low-Dose Corticosteroids in Patients With Non-severe COVID-19 During Pneumonia Progression. Front Public Health 2020;8(355):355. doi:10.3389/fpubh.2020.00355.

Jara A, Udhirraga EA, Gonzalez C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med 2021;385(10):875–84. doi:10.1056/NEJMoa2107715.

Ji Y, Shao J, Tao B, Song H, Li Z, Wang J. Are we ready to deal with a global COVID-19 pandemic? Rethinking countries’ capacity based on the Global Health Security Index. Int J Infect Dis 2021;106:289–94. doi:10.1016/j.ijid.2021.03.089.

Jordan RE, Adab P, Cheng XK, Covid-19: risk factors for severe disease and death. BMJ 2020;368:m1198. doi:10.1136/bmj.m1198.

Kandell A, Mostafa A, Hegazy RR, El-Shesheny R, El-Taweel A, Comama MR, et al. Immunogenicity and Safety of an Inactivated SARS-CoV-2 Vaccine: Preclinical Studies. Vaccines (Basel) 2021;9(3):214. doi:10.3390/vaccines9030214.

Khateeb J, Li Y, Zhang H. Emerging SARS-CoV-2 variants of concern and potential intervention approaches. Crit Care 2021;25(1):244. doi:10.1186/s13054-021-03962-x.

Liu XN, Huang Y, Wang W, Jing QL, Zhang CH, Qin FZ, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. Emerg Microbes Infect 2021;10(1):1751–9. doi:10.1002/2222.1751202109329.

Liu Q, Yang D, Qu B, Martinez L, Ji YX, Song H, et al. Drug resistance gene mutations and treatment outcomes in MDR-TB: A prospective study in Eastern China. PLoS Negl Trop Dis 2021;15(1):e0009068.

Lopez Beruald J, Andrews N, Gower C, Gallagher E, Simmons R, Threlfall E, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021;385(7):585–94. doi:10.1056/NEJMoa2010889.

Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2-breakthrough infections to time-from-vaccine. Nat Commun 2021;12(1):6379. doi:10.1038/s41467-021-26672-3.

Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchanan SA, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada. medRxiv 2021;2021.2006.2028.21235942preprint. doi:10.1101/2021.06.28.21235942.

Polack PF, Thompson SJ, Kitchin N, Absalon J, Gurman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603–15. doi:10.1056/NEJMoa2043577.

Sadrzadani M, Marchant A, Kollmann T. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol 2021;21(8):475–84. doi:10.1038/s41577-021-00578-z.

Sheikh A, McMenamin J, Taylor B, Robertson CF, Public Health S and the EIRC. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet 2021;397(10293):2461–2. doi:10.1016/S0140-6736(21)01358-1.

Singh J, Rahman SA, Elshamsi NZ, Hira S, Hasnain SE. SARS-CoV-2 variants of concern are emerging in India. Nat Med 2021;27(7):1131–3. doi:10.1038/s41591-021-01397-4.

Tanneiro MD, Doganay HL, Akovala M, Guner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virus SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021;398(10296):213–22. doi:10.1016/S0140-6736(21)01429-X.

Vaughan A. Delta to dominate world. New Sci 2021;250(3341):9. doi:10.1016/j.smc.2021.05.012.

Voysey M, Clemens SAC, Madhu SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397(10269):99–111. doi:10.1016/S0140-6736(21)02661-3.

WHO. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/ (2021 25th August 2021).

Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled study. Lancet 2021;397(10269):23–33. doi:10.1016/S0140-6736(21)02669-0.

Zhang Y, Zeng G, Fan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21(2):181–92. doi:10.1016/S1473-3342(20)30843-4.