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Sumário

Artigo

1. Em surto da delta na China, cerca de 20% dos casos foram em crianças e adolescentes; vacinados com CoronaVac não registraram casos críticos

ESTUDO: *"Transmission and containment of the SARS-CoV-2 Delta variant of concern in Guangzhou, China: A population-based study"*

REVISTA: *PLOS Neglected Tropical Disease*

DATA DE PUBLICAÇÃO: *5/1/2022*

Em estudo publicado na última quarta (5) na revista PLOS Neglected Tropical Disease, pesquisadores chineses da Universidade Médica do Sul de Guangzhou (Cantão) e do Centro de Controle e Prevenção de Doenças da província, apontaram que um em cada cinco casos do surto da variante delta do vírus SARS-CoV-2 que se abateu sobre a região entre maio e junho de 2021 acometeu menores com idade pré-escolar (1 a 5 anos) e estudantes de 6 a 18 anos. Além disso, dos 153 casos de Covid-19 do surto, cerca de 85% ocorreu entre não vacinados. Durante o período do estudo, houve sete casos assintomáticos e 146 sintomáticos. Destes, 24 (15,7%) foram considerados leves, 113 (73,9%) moderados, e nove (5,9%) foram considerados críticos. Não houve nenhum caso grave. Dos 153 casos, 116 (84,7%) aconteceram em indivíduos sem cobertura vacinal e 21 (15,3%) em pessoas com esquema de vacinação parcial ou completo da CoronaVac, imunizante do Butantan e da farmacêutica chinesa Sinovac, ou Sinopharm, imunizante chinês que também conta com a tecnologia de vírus inativado. Foram excluídos 16 casos com estado vacinal indeterminado.

"Os sintomas clínicos foram mais leves nos casos com vacinação parcial ou total do que naqueles que não foram vacinados. Notavelmente, nenhum caso crítico foi observado naqueles que foram parcial ou totalmente vacinados, enquanto os nove casos críticos ocorreram todos entre pessoas não vacinadas", ressaltaram os pesquisadores no estudo.

Do total de casos de Covid-19 do surto, 28 (18,3%) foram entre menores de 18 anos, 72 (47,1%) entre pessoas de 19 a 59 anos, 19 (12,4%) na população de 60 a 70 anos e 34 (22,2%) em idosos acima dos 70 anos. Crianças em idade pré-escolar responderam por 3,3% dos casos.

Intensificação da vacinação após surto

Em 21 de maio de 2021, foi relatado o primeiro caso da variante delta em Guangzhou. Em resposta ao ressurgimento da Covid-19 na província, o governo local implementou uma série de medidas de contenção e iniciou a vacinação emergencial de toda a população. No fim de junho, quando o surto acabou, 10,7 milhões dos 15,3 milhões de habitantes haviam sido vacinados com CoronaVac ou Sinopharm (sendo que 8,7 milhões haviam completado o esquema vacinal de duas doses), estendendo a cobertura vacinal para 67% da população da província.

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Transmission and containment of the SARS-CoV-2 Delta variant of concern in Guangzhou, China: A population-based study

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OPEN ACCESS

Citation: Li L, Han Z-G, Qin P-Z, Liu W-H, Yang Z, Chen Z-Q, et al. (2022) Transmission and containment of the SARS-CoV-2 Delta variant of concern in Guangzhou, China: A population-based study. PLoS Negl Trop Dis 16(1): e0010048. https://doi.org/10.1371/journal.pntd.0010048

Editor: Susanna Kar Pui Lau, The University of Hong Kong, HONG KONG

Received: July 22, 2021

Accepted: December 3, 2021

Published: January 5, 2022

Data Availability Statement: The datasets generated and/or analysed during the current study are not publicly available due to the regulations of Guangzhou Center for Disease Control and Prevention. Permission can be requested by contacting Guangzhou Center for Disease Control and Prevention (http://www.gzcdc.org.cn).

Funding: This work was supported by National Natural Science Foundation of China [81973140, 82003555] to CQO and L LI, China Postdoctoral Science Foundation [2020M672744, 2020TQ0135]

Abstract

Background

The first community transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant of concern (VOC) in Guangzhou, China occurred between May and June 2021. Herein, we describe the epidemiological characteristics of this outbreak and evaluate the implemented containment measures against this outbreak.

Methodology/Principal findings

Guangzhou Center for Disease Control and Prevention provided the data on SARS-CoV-2 infections reported between 21 May and 24 June 2021. We estimated the incubation period distribution by fitting a gamma distribution to the data, while the serial interval distribution was estimated by fitting a normal distribution. The instantaneous effective reproductive number (R_t) was estimated to reflect the transmissibility of SARS-CoV-2. Clinical severity was compared for cases with different vaccination statuses using an ordinal regression model after controlling for age. Of the reported local cases, 7/153 (4.6%) were asymptomatic. The median incubation period was 6.02 (95% confidence interval [CI]: 5.42–6.71) days and the means of serial intervals decreased from 5.19 (95% CI: 4.29–6.11) to 3.78 (95% CI: 2.74–4.81) days. The incubation period increased with age ($P<0.001$). A hierarchical prevention and control strategy against COVID-19 was implemented in Guangzhou, with R_t decreasing from 6.83 (95% credible interval [CrI]: 3.98–10.44) for the 7-day time window ending on 27 May 2021 to below 1 for the time window ending on 8 June and thereafter. Individuals with partial or full vaccination schedules with BBIBP-CorV or CoronaVac accounted for 15.3% of the COVID-19 cases. Clinical symptoms were milder in partially or fully vaccinated cases than in unvaccinated cases (odds ratio [OR] = 0.26 [95% CI: 0.07–0.94]).

to L LI, the Key Project of Medicine Discipline of Guangzhou [2021–2023-11] to L LUO, and the Basic Research Project of Key Laboratory of Guangzhou [202102100001] to L LUO. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusions/Significance

The hierarchical prevention and control strategy against COVID-19 in Guangzhou was timely and effective. Authorised inactivated vaccines are likely to contribute to reducing the probability of developing severe disease. Our findings have important implications for the containment of COVID-19.

Author summary

On 11 May 2021, the WHO reclassified the B.1.617.2 variant as a "variant of concern" (VOC) from being a "variant of interest", considering its global public health significance. On 21 May 2021, the first local case infected with the Delta variant (i.e. lineage B.1.617.2) in Guangzhou, China, was reported. In response to the resurgence of COVID-19, the local government implemented a series of containment measures. This provides a valuable opportunity to understand the characteristics of the Delta variant and to evaluate the performance of inactivated COVID-19 vaccines (BBIBP-CorV and CoronaVac) and other interventions. We estimated that the median incubation period was 6.02 days and the means of serial intervals decreased from 5.19 to 3.78 days. The incubation period increased with age. The vaccination coverage in the COVID-19 cases was 15.3%. Clinical symptoms were milder in cases with partial or full vaccination than in those who were unvaccinated (odds ratio [*OR*] = 0.26). We found that the effective reproductive number decreased from 6.83 for the 7-day time window ending on 27 May 2021 to below 1 for the time window ending on 8 June and thereafter. Our findings have important implications for the containment of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is a serious threat to public health. Globally, there have been over 186 million confirmed cases and 4.0 million deaths as of 11 July 2021 [1], and many efforts, such as non-pharmaceutical interventions (NPIs) and vaccination, have been implemented to prevent and contain COVID-19. The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants has accelerated the spread of COVID-19 [2]. In 2021, explosive surges of SARS-CoV-2 occurred in India. Circulation of the Delta variant (i.e. lineage B.1.617.2), which was first identified in India, may have contributed to the devastating second wave of COVID-19 in India [3]. On 11 May 2021, the WHO reclassified the B.1.617.2 variant as a "variant of concern" (VOC) from being a "variant of interest", considering its global public health significance [4]. The variant has invaded more than 110 countries, territories, and areas [1]. Meanwhile, this variant accounts for a large proportion of the newly sequenced and genotyped SARS-CoV-2 cases in some locations, such as England (>90%) [5]. Understanding the epidemiological characteristics and clinical severity of the SARS-CoV-2 Delta variant would help inform targeted interventions for containing the spread of COVID-19.

Population movement is a critical influential factor of COVID-19 transmission [6]. Guangzhou is an important transportation hub in southern China, with over 15 million permanent residents and mass population mobility. In the first five months of 2021, around 2,000 passengers were arriving in Guangzhou from abroad each day. The city is at high risk for COVID-19

transmission from imported cases from abroad [7]. There were, on average, eight COVID-19 cases imported from abroad every day and no local case was reported between 1 January and 20 May 2021. On 21 May, a local case infected with the Delta variant was reported in Guangzhou [8]. In response to the resurgence of COVID-19, the local government implemented a series of containment measures, including vaccination programs, case finding through mass tests for COVID-19, case isolation, as well as other social distancing interventions. Timely assessment of the epidemiological features of the cases of SARS-CoV-2 infection and the prevention and control measures would provide better preparedness for the COVID-19 outbreak caused by highly infectious variants [9].

Several studies have reported promising vaccine efficacy results based on data collected from clinical trials. More real-world data are needed to elucidate vaccine effectiveness [10]. As of 31 May, over 10 million residents (vaccination coverage: around 67%) in Guangzhou had received COVID-19 vaccines (BBIBP-CorV or CoronaVac), among whom, more than three million residents had been fully vaccinated [11]. This provides a valuable opportunity to evaluate the performance of the authorised inactivated COVID-19 vaccines. Herein, we describe the epidemiological characteristics of the cases infected with SARS-CoV-2 Delta VOC in Guangzhou and evaluate the implemented containment measures.

Methods

Ethics statement

This study was approved by the Research Ethics Committee of Guangzhou CDC (No: GZCDC-ECHR-2020P0019). Consent to participate was waived since anonymous information was used.

Data collection

The Guangzhou Center for Disease Control and Prevention (CDC) provided the individual data of all SARS-CoV-2 infections reported between 21 May and 24 June 2021 in Guangzhou. Nasal and throat swabs were collected for COVID-19 tests. Cases were confirmed to be SARS--CoV-2 infections using real-time reverse transcription-polymerase chain reaction (rRT-PCR, S1 File). The individual information included sex, age, occupation class (people who have retired and the unemployed, preschool children, students, healthcare workers, others), possible infection date, type of exposure (family, having been at the same restaurant with a confirmed case, others), type of detection (tracing of close contacts, mass screening, hospital screening), date of illness onset (the date of symptom onset for the symptomatic cases and the date of sample collection for the first positive test of asymptomatic cases), clinical severity (asymptomatic, mild, moderate, severe, and critical according to the criteria proposed by the National Health Commission of the People's Republic of China [12], S1 Table).

Seventy-five cases who did not have information on the exact infection date and who did not have symptoms were excluded when estimating the incubation period (i.e. the time delay from infection to symptom onset) distribution in the main analysis. A transmission pair was defined as two confirmed COVID-19 cases that had clear epidemiological links with each other, i.e. one case (infectee) was infected by the other (infector). Asymptomatic infectees and the infectees whose infectors were asymptomatic were excluded when estimating the serial interval (i.e. the delay between symptom onset dates of successive cases in transmission pairs) distribution. Symptom onset dates of 67 transmission pairs were used to estimate the serial interval distribution (S1 Fig).

Statistical analysis

The median and range were calculated for the continuous variable of age, and proportions were provided for categorical variables. We estimated the incubation period distribution by fitting a lognormal, gamma, and Weibull distribution to the data using the maximum likelihood method and selected the distribution with the smallest value of Akaike Information Criteria (AIC). The serial interval distributions were estimated by fitting normal distributions [13,14]. We estimated the distributions of serial intervals for the entire study period and for nine different time windows (i.e. eight running time windows with a fixed length of 14 days and the last one was from 26 May through 24 June, making sure that all of the time windows contained at least 30 data points of serial intervals). We assessed the association between age and incubation period using a gamma regression model with a log link (according to the selected distribution for incubation period), while the associations between age (of infector and infectee) and serial interval were examined in linear regression models, after controlling for the effects of calendar time.

Previous studies have suggested that the instantaneous reproductive number is a better choice to examine the effectiveness of control measures compared with the case reproductive number [15]. In this study, we estimated the instantaneous effective reproductive number R_t (the average number of secondary cases arising from a typical primary infection [16]) to reflect the transmissibility of SARS-CoV-2 and to evaluate the performance of interventions implemented during this outbreak. The R_t was estimated as:

$$R_t = \frac{I_t}{\sum_{s=1}^{t} I_{t-s} w_s}$$

where I_t was the number of incident cases at time t and w_s was estimated with the time-varying distributions of serial intervals [17]. When the time step of data is small, the estimates of R_t can be highly variable and it would be difficult to interpret the results. To deal with this problem, we estimated the R_t over a 7-day time window assuming that the R_t remains constant within the same time window. Such estimate reflects the average transmissibility for the time window of one week. We present the R_t for the time window ending on 27 May and thereafter, since the estimates may be unstable at the very beginning of the outbreak with few cases [15].

We categorized the COVID-19 cases into two groups based on their vaccination status (Group 1: unvaccinated; Group 2: partially or fully vaccinated [infection occurred $\geq$21 days after dose 1]; 16 cases with indeterminate vaccination status [infection occurred $<$21 days after dose 1 or the time interval between the infection date and the vaccination date was unclear] were excluded). The differences in the clinical severity of the local cases by vaccination status were evaluated using an ordinal logistic regression model after controlling for the potentially confounding effect of age.

Sensitivity analysis was conducted to check the robustness of (1) the estimate of incubation period distribution (1a) assuming that the incubation period followed the distributions which were not corresponding to the smallest AIC; (1b) including seven additional cases with the information of possible exposure dates or exposure windows; (2) the association between age and incubation period using the models with three independent variables of age, calendar time, and one potentially influential factor (i.e. occupation, type of exposure or clinical severity) which was statistically significant in bivariate regression models (with calendar time and one potentially influential factor as the independent variables). All analyses were conducted using R software (version 4.1.0; R Foundation for Statistical Computing).

Results

On 18 May 2021, a 75-year-old woman (Case #1) showed symptoms and sought professional help in a hospital. Later, on 21 May, the woman was confirmed to be infected with the Delta VOC. She was the first local case infected with this variant in Guangzhou (Fig 1). SARS-CoV-2 was transmitted from the woman to her friend Case #3 and a waitress (reported outside Guangzhou) when they were having a meal in a restaurant. Her husband was also infected. Case #3 brought SARS-CoV-2 to seven family members and eight friends when having a meal in a restaurant and dancing with friends. Case #19, who infected as many as 16 residents, was

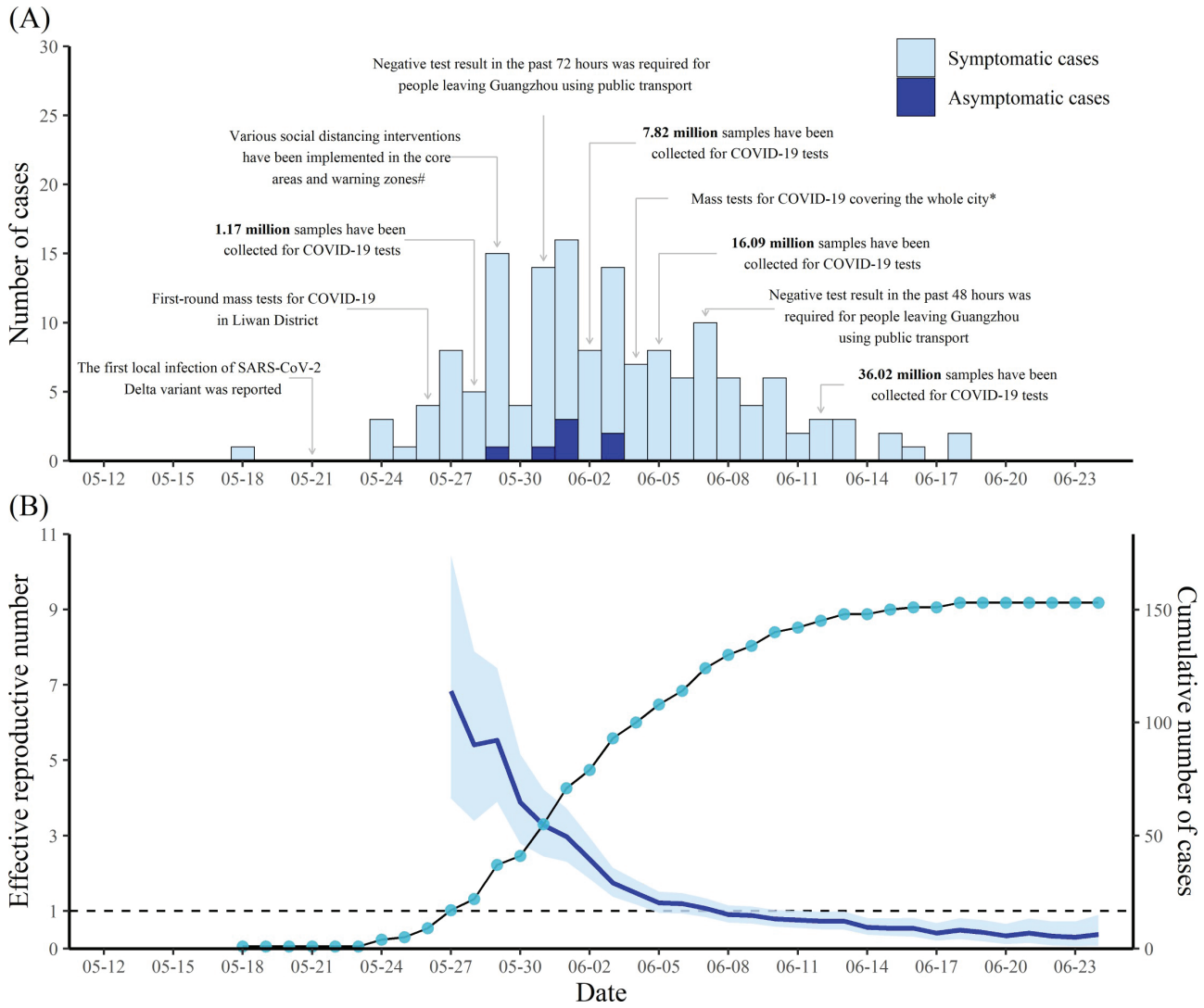

Fig 1. Number of COVID-19 cases by date of illness onset and effective reproductive number in Guangzhou, China. (A) Number of COVID-19 cases by date of illness onset. (B) Estimated effective reproductive number by ending date of 7-day time window and cumulative number of cases by date of illness onset. The blue line shows the point estimates of the effective reproductive number and the light blue region represent the 95% credible intervals. Points represent the daily cumulative number of cases. # Social distancing interventions included school closure, banning of public gatherings, traffic control, prohibition of dining in restaurants. * Mass tests for COVID-19 was done from 4 to 6 June 2021.

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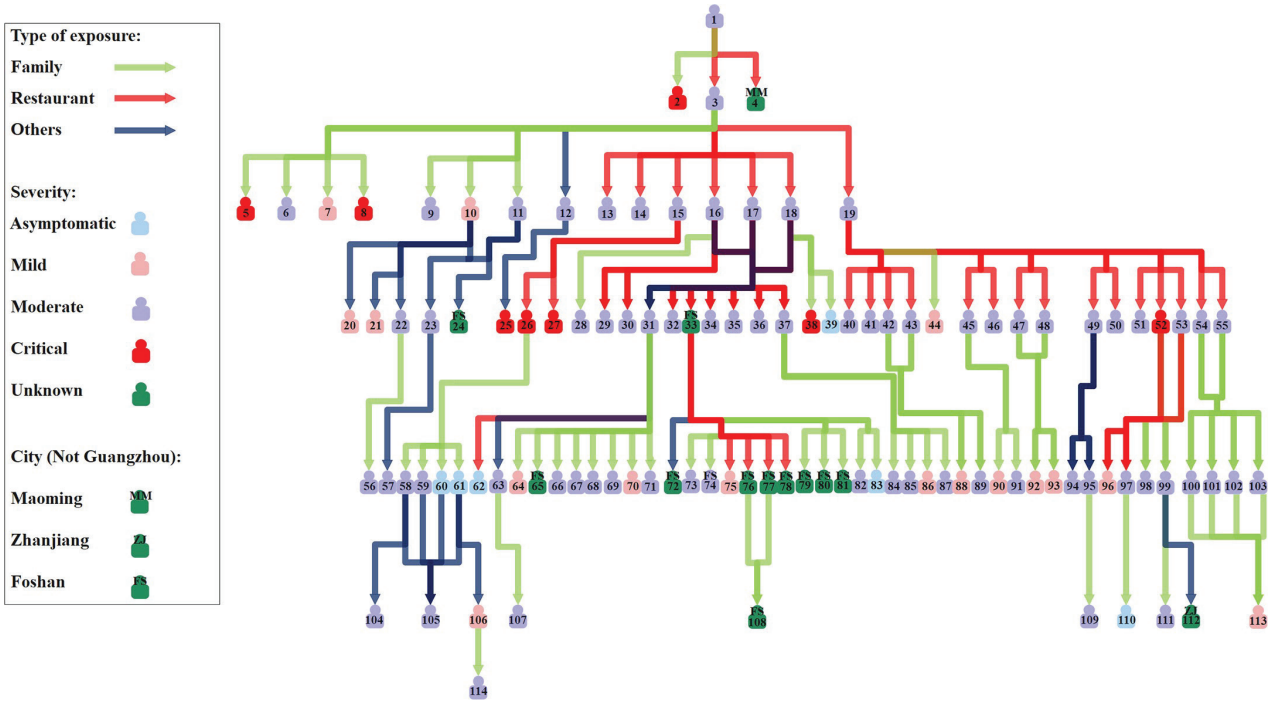


Fig 2. Transmission network of the infections of the SARS-CoV-2 Delta variant. A total of 101 and 13 cases reported in Guangzhou and other cities with information for determining the generation are presented. Cases without a clear epidemiological link with the confirmed cases and the ones whose infector did not have a clear exposure history were not included.

https://doi.org/10.1371/journal.pntd.0010048.g002

one of Case #3's friends (Fig 2). In this outbreak, a total of seven generations were found to be associated with the transmission chain initiated by the first infection of the Delta variant (Fig 2). The number of cases increased gradually from the start of this outbreak and peaked on 1 June with 16 residents showing symptoms or testing positive for SARS-CoV-2 on that day. Thereafter, the number of cases fluctuated and showed a decreasing trend (Fig 1). From 19 June through 24 June 2021, no local case has been reported in Guangzhou.

From 21 May to 24 June 2021, there were 153 local cases reported in Guangzhou (symptomatic cases: 146 [95.4%]; asymptomatic infections: 7 [4.6%]). The median age of the local cases was 48 (range: 1–94) years, and males accounted for 41.2% of these cases (Table 1). More than half of the cases were people who had retired and the unemployed. Preschool children, students, healthcare workers, and others represented 3.3%, 16.3%, 2.6%, and 26.8% of the local cases, respectively. During the study period, 24 (15.7%), 113 (73.9%), 0 (0.0%), and 9 (5.9%) of the patients had mild, moderate, severe, and critical disease severity, respectively (Table 1).

We identified 103 cases with a clear exposure history: 53 (51.5%) were observed within family households, 36 (35.0%) took place in restaurants, and 14 (13.6%) were linked via other exposures (Table 1). Results suggested that the gamma distribution fitted best to the incubation period in terms of AIC (S2 Table). The mean and median incubation periods and were 6.50 (95% confidence interval [CI]: 5.86–7.20) and 6.02 (95% CI: 5.42–6.71) days, respectively. The 95th percentile of the incubation periods was 12.27 (95% CI: 10.68–13.84) days. As for the serial interval, the mean and standard deviation were 4.24 (95% CI: 3.35–5.14) and 3.95 (95% CI: 3.23–4.61) days, respectively (Fig 3) for the entire study period. In addition, we found that the means of serial intervals of different time windows decreased gradually from 5.19 (95% CI:

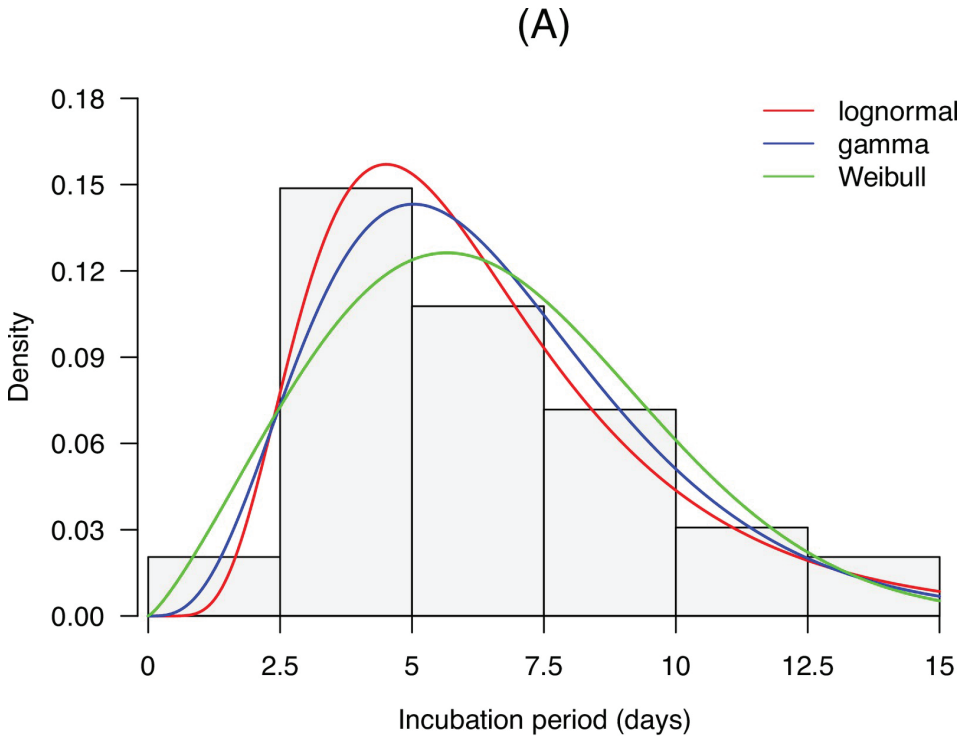
Table 1. The characteristics of the COVID-19 cases in Guangzhou, China, reported from 21 May through 24 June 2021.

Characteristics	Cases (n = 153)
Male sex—no. (%)	63/153 (41.2)
Median age (range)—years	48 (1, 94)
Age group (years)—no. (%)	
≤18	28/153 (18.3)
19–59	72/153 (47.1)
60–70	19/153 (12.4)
≥70	34/153 (22.2)
Occupation—no. (%)	
People who have retired at home and the unemployed	78/153 (51.0)
Preschool children	5/153 (3.3)
Students	25/153 (16.3)
Healthcare workers	4/153 (2.6)
Others	41/153 (26.8)
Type of exposure—no. (%)	
Family	53/103 (51.5)
Exposure to the same restaurant with a confirmed case	36/103 (35.0)
Others	14/103 (13.6)
Type of detection—no. (%)	
Tracing of close contacts	99/153 (64.7)
Mass screening	46/153 (30.1)
Hospital screening	8/153 (5.2)
Clinical severity—no. (%)	
Asymptomatic	7/153 (4.6)
Mild	24/153 (15.7)
Moderate	113/153 (73.9)
Severe	0/153 (0.0)
Critical	9/153 (5.9)

https://doi.org/10.1371/journal.pntd.0010048.t001

4.29–6.11) to 3.78 (95% CI: 2.74–4.81) days (S3 Table). The incubation period was positively associated with age ($P<0.001$, S4 Table), while the associations between age (of infector and infectee) and serial interval were statistically non-significant (S5 and S6 Tables).

In response to the COVID-19 outbreak, the local government formulated a hierarchical prevention and control strategy to suppress community transmission. Generally speaking, Guangzhou was divided into three areas according to the risk level of SARS-CoV-2 transmission. The core areas were the cluster areas in which many COVID-19 cases were reported. The warning zones were the places in which sporadic cases have been found. Other areas were low-risk areas. The level of response to COVID-19 increased with the risk level, with the most rigorous interventions taking place in the areas with the highest level of transmission risk. A series of NPIs and vaccinations were implemented during this outbreak (Fig 1 and S7 Table). Notably, one of the most important measures was case finding through mass tests for COVID-19 among residents in the core areas, warning zones and then the low-risk areas. By 6 June 2021, the entire population of the city had been tested for COVID-19. As of 12 June, over 36 million samples had been collected for SARS-CoV-2 tests. In the core areas and warning zones, multiple rRT-PCR tests have been performed. Vaccination is another important measure for the containment of COVID-19. On 31 May, mass vaccination was stopped and the focus was shifted to case finding through mass tests for COVID-19. However, vaccination was


(A)
lognormal
gamma
Weibull
Density
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0.15
0.12
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15
Incubation period (days)

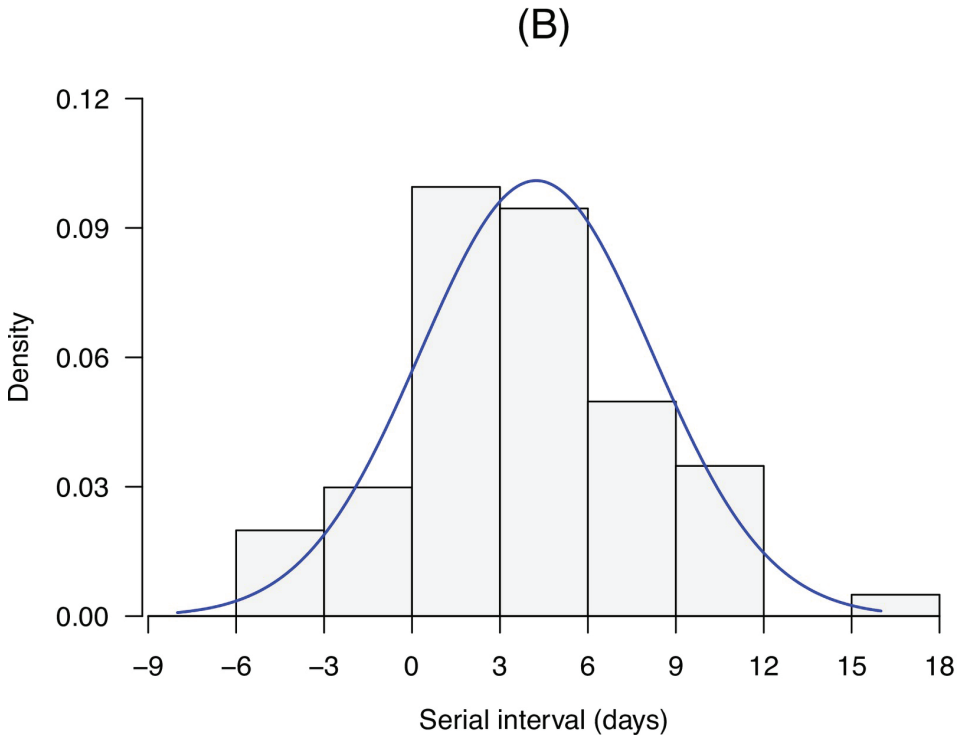
(B)
Density
0.12
0.09
0.06
0.03
0.00
−9
−6
−3
0
3
6
9
12
15
18
Serial interval (days)

Fig 3. Incubation period and serial interval distributions of the SARS-CoV-2 Delta variant in Guangzhou, China. The blue lines represent the estimated distribution densities. Data of 78 cases and 67 transmission pairs were used to estimate the incubation period and serial interval distributions, respectively.

https://doi.org/10.1371/journal.pntd.0010048.g003

restarted on 6 June for individuals who did not live in the core areas and had received one shot 21 days before 6 June. By 24 June, 10.77 million residents had been vaccinated, among whom, 8.72 million had been fully vaccinated. Other interventions included quarantine for high-risk groups, rigorous inspection (e.g. requiring residents to show health codes, measuring body temperature), requiring wearing masks, limiting public gatherings, etc (S7 Table). In this outbreak, 99 cases (64.7%) were in close contact with confirmed cases, while 46 (30.1%) were detected through mass screening (Table 1). With these efforts, R_t decreased rapidly from 6.83 (95% credible interval [CrI]: 3.98–10.44) for the 7-day time window ending on 27 May 2021 to below 1 for the time window ending on 8 June and thereafter (Fig 1).

We found that 21 cases were partially or fully vaccinated before infection (15.3%) among the 137 cases (excluding the 16 cases with indeterminate vaccination status, Table 2). Clinical symptoms were milder in the partially or fully vaccinated cases than the unvaccinated group (odds ratio [*OR*] = 0.26 [95% CI: 0.07–0.94], Table 3). Notably, no critical cases were observed in those who had been partially or fully vaccinated, while 9/116 of the unvaccinated cases were critical cases (Table 2).

Results of sensitivity analysis suggested that the estimates of mean, median and 95th percentile of incubation periods were similar to the ones in the main analysis (S8 Table). The associations of incubation period with occupation and type of exposure were statistically significant in bivariate regression models (S9 Table). Age was positively associated with incubation period in the model with an additional inclusion of occupation and the one with type of exposure (S10 and S11 Tables).

Discussion

In this study, we provided a detailed description of the first community transmission of the SARS-CoV-2 Delta VOC in Guangzhou, China, providing important epidemiological parameters of this outbreak. We found that 4.6% of the cases during the study period were asymptomatic, a figure lower than the 15.6% reported in a previous systematic review [18]. The difference in age structure and definitions of asymptomatic and symptomatic cases may explain the variation in the proportion of asymptomatic infections. We estimated that the mean and median incubation periods were 6.50 and 6.02 days, respectively, which were slightly longer than the pooled estimates of the mean (6.3 days) and median incubation periods (5.4 days) of preexisting strains reported in a systematic review and meta-analysis [19]. The

Table 2. Clinical severity of COVID-19 cases by vaccination status.

Clinical severity	Unvaccinated (n = 116)	Partially or fully vaccinated (n = 21)
Asymptomatic	6 (5.2)	1 (4.8)
Mild	19 (16.4)	5 (23.8)
Moderate	82 (70.7)	15 (71.4)
Severe	0 (0.0)	0 (0.0)
Critical	9 (7.8)	0 (0.0)

Note. Numbers in brackets were proportions. 16 cases with indeterminate vaccination status (infection occurred <21 days after dose 1 or the time interval between infection date and vaccination date was unclear) were excluded.

https://doi.org/10.1371/journal.pntd.0010048.t002

Table 3. Results of an ordinal logistic regression model assessing the association between vaccination status and clinical severity.

Variables	Odds ratio (95% confidence interval)	*t*	*P*
Age	1.11 (1.08–1.15)	5.940	<0.001
Vaccination status			
Unvaccinated	Reference		
Partially or fully vaccinated	0.26 (0.07–0.94)	-2.025	0.043

Note. Sample size was 137.

https://doi.org/10.1371/journal.pntd.0010048.t003

difference may be due to not only the biological discrepancy in the circulating strains, but also the definitions of symptom onset date and possible infection date, and the approach of estimation [19,20,21,22]. Consistent with a prior study in Singapore [21], we found that the incubation period was positively associated with age. The longer incubation period observed in the old cases probably resulted from a slower immune response in the elderly [21,23]. The higher proportion of old cases (22.2% of the local cases were aged 70 years and older) in this outbreak may in part contribute to a longer incubation period than that for the transmission in 2020 in 30 provinces of China [24]. Older age of the subjects in the present study may also explain why our estimate of the mean of incubation period was larger than 5.8 days which was reported in a study of the Delta variant [25]. We found that the maximum incubation period was 15 days, which indicated that longer quarantine periods (>14 days) would be required for extreme cases [26].

Seven generations were found to be associated with the transmission chain initiated by the first infection of the Delta variant in approximately 20 days, which indicated that this variant may be transmitted rapidly. A previous study in the United Kingdom reported that the household transmission rate associated with the Delta variant was higher than that of the Alpha variant, which was found to have a 43–90% higher reproductive number than the preexisting strains [27,28]. In England, the first confirmed case of the Delta variant was detected in late March 2021, and this variant accounted for more than 90% of all new cases at the end of May 2021 [28,29], which also suggested its potential for high transmissibility. Our study estimated that the mean and standard deviation of serial intervals were 4.24 and 3.95 days, respectively for the entire study period. A substantial fraction of secondary transmission was likely to occur prior to illness onset given the shorter serial interval compared with the incubation period [30]. Our estimate of the mean serial interval was larger than that for the strains circulating in early 2020 in China (3.66 days for the locally infected) [14] and the Delta variant circulating in Daejeon, South Korea (3.26 days) [31]. In addition, we estimated that the means of serial intervals of different time windows decreased from 5.19 to 3.78 days. Shorten estimates of means of serial intervals over time were also reported in previous studies [17,25]. The estimate of R_t is influenced by the mean and standard deviation of serial interval. A larger mean of serial interval may lead to a higher R_t, while a larger standard deviation may result in a R_t which is closer to 1 [17]. Therefore, estimating R_t for the Delta VOC using the estimate of preexisting strains may introduce bias.

In this study, we estimated the R_t based on the time-varying distributions of serial intervals and found that R_t declined from 6.83 for the time window ending on 27 May 2021 to below 1 for the time window ending on 8 June and thereafter, which suggested that the interventions in Guangzhou were timely and effective. It is worth noting that the estimated R_t should be interpreted in the context of reduced transmission with great efforts, including social distancing interventions and mass vaccination programs in Guangzhou.

In this outbreak, 94.8% of COVID-19 cases were detected among close contacts of confirmed cases and through mass screening of residents. This finding suggests that case finding through mass tests for COVID-19 and case isolation are of great importance for the control of COVID-19 when the implementation is feasible. It is recommended to implement mass screening to detect the COVID-19 cases when some cases of unknown origin occur and it seems that the pathogen spreads.

Vaccination is an important intervention for the prevention and control of infectious diseases. Randomized-controlled trials and observational studies have revealed vaccine efficacy/effectiveness ranging from 50–95% against symptomatic COVID-19 caused by preexisting strains, including the Alpha variant [10,32,33]. A recent study in the United States indicated that the adjusted effectiveness of the authorised mRNA vaccines in preventing SARS-CoV-2 infection was 91% and 81% with full vaccination and partial vaccination, respectively, when administered in real-world conditions [34]. In Chile, the effectiveness of CoronaVac was 65.9%, 87.5%, and 90.3% for the prevention of infection, hospitalization, and ICU admission for the individuals with fully immunized [35]. In Guangzhou, the vaccination coverage of the whole population (67%) was approximately 2.4 times higher than the coverage of COVID-19 cases (15.3%). In this study, we found that the partially or fully vaccinated cases generally had milder symptoms than those in the unvaccinated group after controlling for age. In addition, Li et al. conducted a test-negative case-control study to assess the effectiveness of inactivated vaccines among residents aged 18–59 in Guangzhou using the close contacts of confirmed cases as controls [36]. Results suggested that the overall vaccine effectiveness for two-dose vaccination was 59.0% against COVID-19 and 70.2% against moderate COVID-19. These data further implied that the authorised inactivated vaccines are probably capable of protecting people from the Delta VOC, and vaccination can reduce the probability of the occurrence of severe disease. In Guangzhou, the target population of vaccination was mainly residents aged 18–59 years without contraindications during the study period. Currently, the vaccination is free for residents aged 12 years of age and older in China, as more evidence has proved that the authorised inactivated COVID-19 vaccines are safe and effective [37–40]. Mass screening and vaccination are labour-intensive, especially when the two measures are implemented at the same time. In China, community health centers and hospitals organize the mass screening and vaccination, with great support from volunteers.

We found that 37 vaccinated individuals were infected in this outbreak. Vaccine breakthrough infections were also reported in other locations [41,42,43]. Nevertheless, the vaccine breakthrough infections only occurred in a small percentage of vaccinated individuals, meanwhile, these cases merely represented a small fraction of COVID-19 cases [41]. COVID-19 vaccination is still an effective measure to prevent infection, severe illness, and death [42]. Given that the infections can occur in vaccinated individuals, personal protection measures, such as wearing masks in indoor public settings where the transmission risk of COVID-19 is high, are still needed [42].

We found that 51.5% of the transmission pairs had a family bound. Consistently, transmission within family households was the most frequent in the first wave of COVID-19 in Guangzhou and Hong Kong [44,45]. SARS-CoV-2 transmission in restaurants has been reported previously [46]. Improving ventilation and increasing the distance between tables may reduce the infection risk [46]. Eating at restaurants was restricted in this outbreak, which has in part mitigated the transmission of COVID-19.

Our study had some limitations. First, our analysis mainly focused on the characteristics of the cases of SARS-CoV-2 infection reported in Guangzhou, since some important information (e.g. symptom onset date, clinical severity, and vaccination status) of the cases reported in other cities was not available. Second, the infection and symptom onset dates were reported by

the patients and the infection dates were not clear for some COVID-19 cases. Also, some transmission pairs were not determined. Potential bias may influence the estimates of the incubation period, serial interval, and R_t. Third, we did not account for pre-symptomatic transmission when estimating R_t. This will be addressed in future studies. Next, we did not evaluate a specific intervention in this study but the combination of various control measures, since these interventions were implemented simultaneously, and it was difficult to distinguish their effects. In addition, it would be more informative if averted number of COVID-19 cases attributable to the interventions can be provided. Further studies will quantify the effects using mathematical and statistical models. Last, possibly insufficient sample size can affect the statistical power and the conclusion. For instance, the sample size for the inference of the effect of vaccination status on clinical severity may be not sufficient. More solid evidence will be available with real-world data from a large sample size.

In conclusion, the hierarchical prevention and control strategy against COVID-19 in Guangzhou was timely and effective. Case finding through mass tests for COVID-19 and case isolation are important for the containment of SARS-CoV-2 transmission if the implementation is feasible. Receiving the authorised inactivated vaccines may reduce the probability of developing severe disease after infection. It is recommended that eligible individuals be vaccinated to better protect themselves against COVID-19. Our findings have important implications for the containment of COVID-19.

Supporting information

S1 File. Real-time reverse transcription-polymerase chain reaction.
(DOCX)

S1 Fig. Data on incubation period and serial interval used in the main analysis.
(TIF)

S1 Table. Definitions of cases with different clinical severity.
(XLSX)

S2 Table. Values of Akaike Information Criteria (AIC) for three distributions fitted to incubation periods.
(XLSX)

S3 Table. Estimates of means and standard deviations of serial intervals for different time windows.
(XLSX)

S4 Table. Results of the model which assessed the association between age and incubation period in the main analysis.
(XLSX)

S5 Table. Results of the model which examined the association between age of infector and serial interval.
(XLSX)

S6 Table. Results of the model which evaluated the association between age of infectee and serial interval.
(XLSX)

S7 Table. Interventions for the areas of different transmission risk of SARS-CoV-2.
(XLSX)

S8 Table. Estimates of the means, medians and 95th percentiles of incubation periods in the sensitivity analysis.
(XLSX)

S9 Table. Results of bivariate regression models for incubation period.
(XLSX)

S10 Table. Results of the model which assessed the association between age and incubation period with an adjustment of occupation.
(XLSX)

S11 Table. Results of the model which examined the association between age and incubation period with an adjustment of type of exposure.
(XLSX)

Acknowledgments

We thank staff members of Guangzhou Center for Disease Control and Prevention for administrative work and data collection.

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2. CoronaVac em adolescentes com doenças reumáticas causa três vezes menos efeitos adversos do que vacinas de RNA mensageiro

ESTUDO: *"Early experience of COVID-19 vaccine-related adverse events among adolescents and young adults with rheumatic diseases: A single-center study"*

REVISTA: *International Journal of Rheumatic Diseases*

DATA DE PUBLICAÇÃO: *3/1/2022*

Um grupo de pesquisadores da Faculdade de Medicina da Universidade de Istambul, na Turquia, concluiu que em jovens que recebem a CoronaVac, vacina do Butantan e da farmacêutica chinesa Sinovac contra a Covid-19, o índice de efeitos adversos após a imunização é três vezes menor do que em quem toma vacinas feitas com a tecnologia de RNA mensageiro. O resultado foi descrito em estudo publicado no International Journal of Rheumatic Diseases, e baseado no acompanhamento, ao longo de um ano, de 246 adolescentes com idade média de 15 anos.

Dos 145 participantes da pesquisa que haviam tomado a vacina de RNA mensageiro, 107 (74%) experimentaram eventos adversos relacionados à imunização. Dos 32 que tomaram CoronaVac, apenas sete (22%) relataram efeitos adversos. Os sintomas mais comuns foram fadiga, cefaleia, mialgia, artralgia e febre.

Três indivíduos relataram eventos adversos graves, uma vez que necessitaram de hospitalização e tratamento adicional. Uma garota de 20 anos desenvolveu hipertensão após a segunda dose, uma garota de 12 anos apresentou erupção cutânea grave após a primeira dose, e um adolescente de 13 desenvolveu pré-síncope por hipotensão após a primeira dose. Nenhum deles havia tomado CoronaVac.

Esses resultados comprovam, novamente, que a vacina do Butantan e da Sinovac é a que tem o melhor perfil de segurança dentre os imunizantes atualmente em uso contra a Covid-19, seja em adultos, idosos, crianças ou adolescentes.

No grupo investigado havia 126 pacientes com doenças autoinflamatórias, 54 pacientes com artrite idiopática juvenil, 30 pacientes com doença do tecido conjuntivo, nove com vasculite e quatro com febre reumática aguda. O grupo controle foi composto por 23 adolescentes saudáveis. Dos voluntários, 214 pacientes receberam a vacina de RNA mensageiro, 28 tomaram a CoronaVac e quatro tomaram as

duas. Antes da imunização, 44 indivíduos haviam contraído Covid-19 e se recuperado, sendo que quatro deles apresentaram infecção assintomática e o restante só sintomas leves. A grande maioria tomava regularmente medicação antes da imunização e continuou após receber a vacina.

De acordo com os pesquisadores, "nosso estudo indica um perfil de segurança aceitável das vacinas contra Covid-19 disponíveis em nosso país [Turquia] e incentiva as crianças com doenças reumáticas a serem vacinadas".

Nos primeiros dias da pandemia, as crianças eram consideradas como tendo um curso assintomático ou leve de Covid-19, em contraste com os adultos. No entanto, um número crescente de casos pediátricos com síndrome inflamatória multissistêmica em crianças, causada pelo SARS-CoV-2, têm sido descritos com consequências devastadoras, como internação em unidade de terapia intensiva ou até óbito. Portanto, estratégias de vacinação precisam ser bem estabelecidas para crianças, assim como para adultos.

Received: 5 November 2021 | Revised: 21 December 2021 | Accepted: 22 December 2021

DOI: 10.1111/1756-185X.14279

International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

Early experience of COVID-19 vaccine-related adverse events among adolescents and young adults with rheumatic diseases: A single-center study

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Abstract

Objective: Considering the concerns regarding the coronavirus disease-2019 (COVID-19) vaccine safety among pediatric patients with inflammatory rheumatic diseases (IRD) due to a lack of data, an urgent need for studies evaluating safety profiles of vaccines emerged.

Methods: Among participants vaccinated by CoronaVac inactive SARS-CoV-2 or BNT162b2 messenger RNA (mRNA) COVID-19 (Pfizer-BioNTech) vaccine, healthy children under 18 and patients under 21 with an at least 1-year follow-up period in our department for a childhood-onset rheumatic disease were included into this cross-sectional study.

Results: Overall, 246 subjects (141 [57.3%] females) (biologic group: 43, non-biologic group: 180, healthy control group: 23) were eligible for the study. The median age was 15.34 (12.02-20.92) years. The most common adverse events were fatigue (n = 68, 27.6%), headache (n = 44, 17.9%), myalgia (n = 38, 15.4%), arthralgia (n = 38, 15.4%), and fever (n = 35, 14.2%). Only 3 subjects (2 patients with familial Mediterranean fever, and one healthy child) were considered to experienced serious adverse events, since they required hospitalization. Local reactions were seen in 20 (8.13%), and 27 patients (12.1%) had disease flares within 1 month after the vaccines. Although it was significantly higher in those who received the BNT162b2 mRNA vaccine ($P < .001$), there was no significant relationship between adverse event frequency and age, gender, the existing diseases, ongoing treatment regimens and pre-vaccination COVID-19 histories.

Conclusion: Although immunogenicity studies for efficacy of the vaccines and long-term follow-up studies for adverse events monitoring are required, our study indicates an acceptable safety profile of COVID-19 vaccines and encourages children with IRD to be vaccinated.

KEYWORDS
COVID-19, pediatrics, rheumatology, SARS-CoV-2, vaccines

1 | INTRODUCTION

For almost 2 years, our planet has been suffering from coronavirus disease-2019 (COVID-19) caused by a novel coronavirus named severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2). Although scientists worldwide are mainly focused on the pandemic, there is still no available therapeutic option that may provide sufficient cure, and COVID-19 remains a significant global health concern. Thus, preventive strategies such as face masks, social distancing, personal hygiene, and vaccination come into prominence. Recently, several studies have shown newly developed vaccines to be effective and safe tools for the fight against COVID-19.[1,2]

In the early days of the pandemic, children were considered to have an asymptomatic or a mild COVID-19 disease course in contrast to adults.[3] However, a growing number of pediatric cases with multi-system inflammatory syndrome in children (MIS-C) caused by SARS-CoV-2 have been described with devastating consequences such as intensive care unit admission or even death.[4,5] Therefore, vaccination strategies are needed to be well-established for children, as well as for adults.

There is a vulnerable group such as immunocompromised patients among the pediatric population that merits to be prioritized for the vaccination. Patients with inflammatory rheumatic diseases (IRD) are considered to be in this group, due to their immune-disturbed conditions caused by their medications and chronic inflammatory states. However, it is still debated whether IRD increases the risk of severe COVID-19 due to conflicting findings of current studies.[6-11]

Although patients with IRD and those under immunosuppressive treatment were mainly excluded from the clinical trials of recent vaccines, they were widely vaccinated.[12] Since they may be at increased risk of worse outcomes from vaccine-preventable diseases, and due to limited source of vaccines in most of the developing countries, they were considered to be a prioritized group by authorities.[13,14] Yet there is no sufficient safety data, particularly for the vaccination of children with IRD.

There are 2 different kinds of COVID-19 vaccines, CoronaVac inactive SARS-CoV-2 and BNT162b2 messenger RNA (mRNA) COVID-19 (Pfizer-BioNTech), which are currently available in our country. Considering the concerns regarding COVID-19 vaccine safety among pediatric patients with IRD due to a lack of data, an urgent need for studies evaluating safety profiles of vaccines emerged. We designed this cross-sectional study to examine the vaccine-related adverse events among this group of patients.

2 | MATERIALS AND METHODS

2.1 | Patients and data collection

In our country, in January 2021, healthcare professionals, and in February 2021, patients with chronic health conditions, those older than 18, were started to be vaccinated by 2 doses of CoronaVac inactive SARS-CoV-2 with a 1-month interval. Afterward, the third dose was allowed for both groups in July 2021. Citizens were able to choose their vaccine type, as CoronaVac inactive SARS-CoV-2 or BNT162b2 mRNA COVID-19 (Pfizer-BioNTech). Finally, the fourth dose was approved for both groups in August 2021. Again, individuals were free to prefer their vaccine type.

In mid-August 2021, CoronaVac inactive SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccines started being administered to children older than 12 with chronic medical conditions and healthy children older than 15 in our country. Then, at the beginning of September 2021, vaccine administration against the novel coronavirus was launched for all children under 12, regardless of their underlying disease.

We conducted a web-based survey in mid-September 2021. Questionnaires regarding the data of the rheumatic diseases, COVID-19 vaccination status, disease flares within 1 month after the vaccines, and experienced adverse events (due to vaccines) of the participants were prepared in Google Forms and circulated through several social media platforms.

Healthy children under 18 and patients under 21 with an at least 1-year follow-up period in our department for a childhood-onset rheumatic disease were included in the study. While data of the rheumatic patients were verified by their medical records, data of COVID-19 vaccination status and experienced adverse events of the participants were verified by phone calls and national registries. Subjects whose data could not be verified by phone calls, registries or medical records were excluded from the study due to a lack of data.

Redness, warmth, regional pain, and tenderness at the injection site due to COVID-19 vaccines were considered as local reactions. While permanent disabilities, hospitalization or an extended hospital stay (if vaccinated while in the hospital), life-threatening illness, birth defects (congenital anomalies), and death were considered severe adverse events, the rest of the adverse events were considered non-severe adverse events, based on the recommendations of Vaccine Adverse Event Reporting System (VAERS) which is co-managed by the Centers for Disease Control and Prevention and the US Food and Drug Administration.[15]

Subjects were categorized into 3 different groups. Children with no underlying disease were considered the healthy control group. While rheumatic patients who were receiving at least one of the biologic agents such as etanercept, infliximab, adalimumab, anakinra, canakinumab, tocilizumab, and rituximab during their vaccination periods were considered the biologic group, the rest of the rheumatic patients were considered the non-biologic group.

The institutional ethics committee of our center approved the study protocol (03/09/21-29430533-903.99-175245). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. At least one of the family members of all the participants provided informed consent.

2.2 | Statistical analysis

The statistical analysis was performed using SPSS for Windows, version 21.0 (SPSS Inc). Categorical variables were expressed as numbers (percentages). Ages of the patients were given as median

(minimum-maximum), based on their distribution which was measured by using the Kolmogorov-Smirnov test. Categorical variables were compared by using Chi-square test or Fisher's exact test, when available. Ages of the patients were compared using the Mann-Whitney *U* or Kruskal-Wallis test, when appropriate. Statistical significance was defined as $P < .05$. Prism software (Prism 8, GraphPad Software) was used to analyze and graph data.

3 | RESULTS

3.1 | Study population

Following the link of our web-based survey that was shared on our clinic's online social media platforms, 466 participants fulfilled the questions. Those who stated that they were not vaccinated (n = 181) were not included in the study. Among those who stated they were vaccinated, those who could not be reached by phone (n = 19), whose follow-up period was <1 year (n = 8) and whose data could not be verified via the national registries, medical records of our department or phone calls (n = 12) were excluded.

Finally, 246 subjects (141 females) were eligible for the study. The median age was 15.34 (12.02-20.92) years. Twenty-three participants whose parents stated in the survey that they did not have any chronic diseases, and whose medical records were checked and confirmed by phone calls that they did not have any underlying disease or long-term medication were considered the healthy control (HC) group.

In the study group there were 126 patients with autoinflammatory diseases (AID) (familial Mediterranean fever [FMF], 123; cryopyrin-associated periodic syndrome [CAPS], 2; Blau syndrome [BS]), 54 patients with juvenile idiopathic arthritis (JIA) (oligoarticular JIA [oJIA], 43; juvenile spondylarthritis [jSPA], 8; polyarticular JIA [pJIA]), 30 patients with connective tissue disease (CTD) (systemic lupus erythematosus [SLE], 16; dermatomyositis [DM], 10; scleroderma, 3; Sjögren's syndrome, 1), 9 patients with vasculitis (Behçet's disease [BD], 2; deficiency of adenosine deaminase 2 [DADA2], 2; Takayasu arteritis [TA], 2; granulomatous polyangiitis [GPA], 1; Henoch-Schönlein purpura [HSP], 2; Kawasaki disease [KD]) and 4 patients with acute rheumatic fever (ARF) (Table 1).

During their vaccination periods, 128 patients were receiving colchicine (FMF, 123; CAPS, 2; BD, 2; DADA2, 1); 49 conventional disease-modifying antirheumatic drugs (cDMARDs) (methotrexate [MTX], 22 [JIA, 12; DM, 7; scleroderma, 2; SLE, 1]; hydroxychloroquine [HCQ], 21 [SLE, 16; DM, 3; Sjögren, 1; scleroderma, 1]; leflunomide, 10 [JIA; 9; SLE, 1]; mycophenolate mofetil [MMF]; 6 [SLE, 3; scleroderma, 2; DM, 1]; cyclosporine; 3 [DM; 3]; cyclophosphamide, 1 [SLE; 1]), 43 biologic disease-modifying antirheumatic drugs (bDMARDs) (etanercept, 16 [JIA, 12; DM, 2; DADA2, 2]; adalimumab, 10 [JIA, 10]; canakinumab, 8 [FMF, 7; CAPS, 1]; tocilizumab, 6 [JIA; 2; TA, 2; scleroderma, 2]; anakinra, 2 [FMF, 1; CAPS, 1]; rituximab, 1 [SLE, 1]); 21 systemic steroids (JIA, 10; SLE, 6; DM, 2; DADA2, 1; BD, 1; scleroderma, 1); and 6 patients were receiving acetyl-salicylic acid (SLE, 5; DADA2, 1) (Table 1). Four patients with ARF were under penicillin prophylaxis. Twenty-two patients with IRD excluding the ARF were in remission, and they were not receiving any treatment except non-steroidal anti-inflammatory drugs.

Before their vaccinations, 44 subjects recovered from COVID-19 (FMF, 18; JIA, 9; HC, 7; SLE, 5; ARF, 3; DM, 1; GPA, 1) (Table 1). While 4 of the recovered ones (HC, 2; JIA, 1; SLE, 1) had asymptomatic infection, the rest had mild COVID-19 symptoms. None of them had a severe clinical course.

While 214 subjects received BNT162b2 mRNA vaccine (FMF, 106; JIA, 49; HC, 19; SLE, 14; DM, 10; ARF, 4; CAPS, 2; scleroderma, 2; KD, 1; HSP, 1; BD, 1; DADA2, 1; Sjögren, 1; TA, 1; GPA, 1; BS, 1), 28 received inactivated SARS-CoV-2 vaccine (FMF, 16; JIA, 5; HC, 3; SLE, 2; DADA2, 1; scleroderma, 1), and 4 received both (FMF, 1; BD, 1; TA, 1; HC, 1) (Table 1).

Out of 246 subjects, 145 received a single dose of BNT162b2 mRNA vaccine, 19 received a single dose of inactivated SARS-CoV-2 vaccine, 69 received double doses of BNT162b2 mRNA vaccine, 8 received double doses of inactivated SARS-CoV-2 vaccine, 3 received double doses of inactivated SARS-CoV-2 vaccine plus a single dose of BNT162b2 mRNA vaccine, 1 received double doses of inactivated SARS-CoV-2 vaccine plus double doses of BNT162b2 mRNA vaccine, and 1 received 3 doses of inactivated SARS-CoV-2 vaccine.

3.2 | Adverse events

COVID-19 vaccine-related adverse events reported by the participants and their families were as follows: fatigue (n = 68, 27.6%), headache (n = 44, 17.9%), myalgia (n = 38, 15.4%), arthralgia (n = 38, 15.4%), fever (n = 35, 14.2%), nausea-vomiting (n = 19, 7.7%), diarrhea (n = 16, 6.5%), anorexia (n = 16, 6.5%), chest pain (n = 14, 5.7%), abdominal pain (n = 11, 4.5%), rhinorrhea (n = 8, 3.3%), arthritis (n = 8, 3.3%), cough (n = 8, 3.3%), dyspnea (n = 6, 2.4%), throat ache (n = 5, 2%), rash (n = 3, 1.2%), anosmia (n = 2, 0.8%), hypertension (n = 1, 0.4%), and hypotension (n = 1, 0.4%) (Figure 1).

Three subjects were considered to have severe adverse events, since they required hospitalization and additional treatment: 20.2 years-aged female patient with FMF who developed hypertension (2 weeks remained) after the second dose of BNT162b2 mRNA vaccine; 12.1 years-aged female with no underlying disease who experienced severe rash after the first dose of BNT162b2 mRNA vaccine; and 13.7 years-aged male patient with FMF who developed pre-syncope due to hypotension after the first dose of BNT162b2 mRNA vaccine.

All the adverse events but hypertension recovered in THE first 4 days. There was no adverse event after the administration of the second dose of CoronaVac inactive SARS-CoV-2 vaccine. Adverse event frequencies according to days and vaccine doses are given in Figure 2. Local reactions after the vaccines were seen in 20 subjects (JIA, 8; FMF, 7; HC, 3; DM, 1; BS, 1). Local reaction frequencies according to vaccine doses are also given in Figure 2.

Twenty-seven patients experienced disease flare within 1 month after the vaccination (after the first dose of BNT162b2 mRNA

TABLE 1 Baseline characteristics of the study population

	Healthy controls (n = 23)	Patients with AID (n = 126)	Patients with JIA (n = 54)	Patients with CTD (n = 30)	Patients with vasculitis (n = 9)	Patients with ARF (n = 4)
Age, y (median, min-max)	15.67 (12.04-19.94)	15.09 (12.06-20.72)	15.41 (12.06-20.64)	16.89 (12.49-20.64)	15.58 (12.02-20.92)	15.42 (13.71-18.1)
Gender						
Female, n (%)	10 (43.5%)	68 (54%)	35 (64.8%)	19 (63.3%)	6 (66.7%)	3 (75%)
Male, n (%)	13 (56.5%)	58 (46%)	19 (35.2%)	11 (36.7%)	3 (33.3%)	1 (25%)
Diagnoses (n)	-	FMF (123) CAPS (2) BS (1)	oJIA (43) jSPA (8) pJIA (3)	SLE (16) DM (10) Scleroderma (3) Sjögren (1)	BD (2) DADA2 (2) TA (2) GPA (1) HSP (1) KD (1)	-
Ongoing treatments						
Colchicine, n (%)	-	125 (99.2%)	-	-	3 (33.3%)	-
Steroid, n (%)	-	-	10 (18.5%)	9 (30%)	2 (22.2%)	-
ASA, n (%)	-	-	-	5 (16.7%)	1 (11.1%)	-
bDMARDs						
Anakinra, n (%)	-	2 (1.6%)	-	-	-	-
Canakinumab (n, %)	-	8 (6.3%)	-	-	-	-
Tocilizumab, n (%)	-	-	2 (3.7%)	2 (6.7%)	2 (22.2%)	-
Etanercept, n (%)	-	-	12 (22.2%)	2 (6.7%)	2 (22.2%)	-
Adalimumab, n (%)	-	-	10 (18.5%)	-	-	-
Rituximab, n (%)	-	-	-	1 (3.3%)	-	-
cDMARDs						
MTX, n (%)	-	-	12 (22.2%)	10 (33.3%)	-	-
Leflunomide, n (%)	-	-	9 (16.7%)	1 (3.3%)	-	-
Cyclosporine, n (%)	-	-	-	3 (10%)	-	-
Cyclophosphamide, n (%)	-	-	-	1 (3.3%)	-	-
HCQ, n (%)	-	-	-	21 (70%)	-	-
MMF, n (%)	-	-	-	6 (20%)	-	-
COVID-19 history before vaccination, n (%)	7 (30.4%)	18 (14.1%)	9 (17.3%)	6 (20%)	1 (11.1%)	3 (75%)
Vaccination info						
Vaccination type						
mRNA, n (%)	19 (82.6%)	109 (86.5%)	49 (90.7%)	27 (90%)	6 (66.7%)	4 (100%)

TABLE 1 (Continued)

	Healthy controls (n = 23)	Patients with AID (n = 126)	Patients with JIA (n = 54)	Patients with CTD (n = 30)	Patients with vasculitis (n = 9)	Patients with ARF (n = 4)
Inactive, n (%)	3 (13%)	16 (12.7%)	5 (9.3%)	3 (10%)	1 (11.1%)	-
Mix, n (%)	1 (4.3%)	1 (0.8%)	-	-	2 (22.2%)	-
Adverse events						
None, n (%)	12 (52.2%)	68 (54%)	33 (61.1%)	21 (70%)	3 (33.3%)	2 (50%)
Non-severe, n (%)	10 (435%)	56 (44.4%)	21 (38.9%)	9 (30%)	6 (66.7%)	2 (50%)
Severe, n (%)	1 (4.3%)	2 (1.6%)	-	-	-	-
Local reactions, n (%)	3 (13%)	8 (6.3%)	8 (14.8%)	1 (3.3%)	-	-
Disease flare within 1 month						
Yes, n (%)	-	15 (11.9%)	10 (18.5%)	2 (6.7%)	-	-
No, n (%)	-	111 (88.1%)	44 (81.5%)	28 (93.3%)	9 (100%)	4 (100%)

Abbreviations: AID, autoinflammatory diseases; ARF, acute rheumatic fever; ASA, acetylsalicylic acid; BD, Behçet disease; bDMARDs, biologic disease-modifying antirheumatic drugs; BS, Blau syndrome; CAPS, cryopyrin-associated periodic syndromes; cDMARDs, conventional disease-modifying antirheumatic drugs; CTD, connective tissue disease; DADA2, deficiency of adenosine deaminase 2; DM, dermatomyositis; FMF, familial Mediterranean fever; GPA, granulomatous polyangiitis; HCQ, hydroxychloroquine; HSP, Henoch-Schönlein purpura; JIA, juvenile idiopathic arthritis; jSPA, juvenile spondylarthritis; KD, Kawasaki disease; MMF, mycophenolate mofetil; MTX, methotrexate; oJIA, oligoarticular juvenile idiopathic arthritis; pJIA, polyarticular juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TA, Takayasu arteritis.

vaccine, 17; after the second dose of BNT162b2 mRNA vaccine, 7; after the first dose of CoronaVac inactive SARS-CoV-2 vaccine, 3) (FMF, 15; JIA, 10; SLE, 2). Among those who experienced disease flare, all patients with FMF presented with typical attacks (fever, abdominal pain, chest pain, and/or arthralgia), and all JIA patients developed new-onset arthritis. In addition to increased inflammatory markers, 1 of 2 patients with SLE had cutaneous involvement, and bicytopenia was seen in the other.

3.3 | Comparison of the participant groups

There were no significant differences between the HC group, biological group and non-biological group in terms of age, gender, vaccine types, and frequencies of pre-vaccination COVID-19 histories, local reactions and adverse events. Moreover, the frequency of disease flares within 1 month after vaccines was not different between the biological group and the non-biological group. Detailed data Are given in Table 2.

3.4 | Assessment of the risk factors for vaccine-related adverse events

There was no significant relationship between adverse event frequency and age, gender, the existing diseases, ongoing treatments (except acetylsalicylic acid [ASA]) and pre-vaccination COVID-19 histories. While the adverse event frequency was significantly lower in those who were receiving ASA during their vaccination period ($P = .037$), it was significantly higher in those who received the BNT162b2 mRNA vaccine ($P < .001$). Detailed data were given in Table 3.

4 | DISCUSSION

Out of 246 participants, 107 (43.5%) experienced COVID-19 vaccine-related adverse events in this study. Adverse events were seen after vaccine administration in 100 of 218 mRNA vaccines and 7 of 32 inactive vaccines. Since they required hospitalization, 2 patients with FMF under colchicine treatment and a healthy child were considered to have severe adverse events, and the remaining 104 were non-severe. All 3 occurred due to mRNA vaccines, and none of those with severe adverse events were under bDMARDs or cDMARDs treatment.

There was no significant differences between HC, non-biologic, and biologic groups with regard to the frequencies of vaccine-related adverse events and local reactions. However, the non-biologic group in the study was highly heterogeneous because it included patients in remission and patients receiving therapies that potentially alter the vaccine responses due to their B cell depletion effects, such as CYC or MMF.[16-18] Thus, sub-analyses were not possible in this study due to low number of patients.

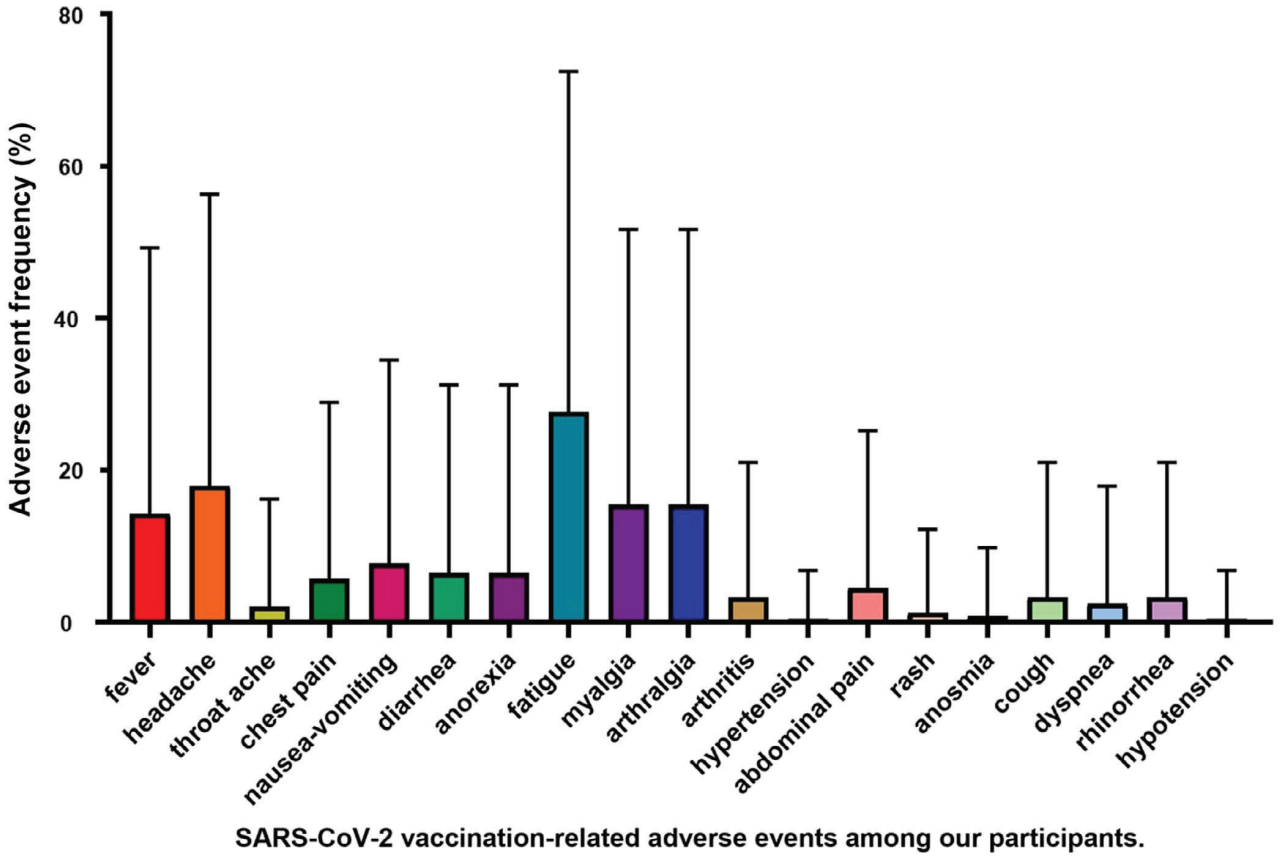

FIGURE 1 SARS-CoV-2 vaccination-related adverse events among our participants

While adverse events were significantly more common among the subjects who received the mRNA vaccine than those who received the inactive vaccine, there was no significant impact of age, gender, the existing diseases, ongoing treatments including DMARDs, and pre-vaccination COVID-19 histories on the adverse event frequency. The most common adverse events were fatigue, headache, myalgia, arthralgia, and fever, respectively. Local reactions were seen in 20 (8.13%) participants. Consistent with our findings, fatigue, headache, and muscle or joint pain were the most common vaccine-related systemic symptoms in the studies that enrolled adult patients with IRD.[19,20] Similarly, to the original phase 3 trial of the BNT162b2 COVID-19 mRNA vaccine, local pain in the injection site, fatigue and headache were the most common adverse events in a study that involved healthy adults and adult patients with SLE and rheumatoid arthritis. While reactogenicity was more frequent in the patient group, adverse events were not more severe than in the control group.[21]

Out of 27 (11%) patients who had disease flare within a 1-month period after the vaccines, those with JIA and MCTD required treatment modification, unlike 15 patients with FMF. Moreover, disease flare frequency was not different between biologic and non-biologic groups. Among the studies conducted in adult patients with IRD, while disease flare rate was 13.4% in the COVID-19 Global Alliance of Rheumatology Vaccine Study, it was reported as 5% in a study supported by the European League Against Rheumatism COVID-19 Vaccine Registry.[19,22] For accurate data regarding the disease flares, studies involving disease activity scores in all age groups are required.

Frequencies of local and systemic reactions caused by BNT162b2 COVID-19 mRNA vaccines were noted as 74% and 19%, respectively, in a recent study that involved 21 adolescents with JIA aged 16-21 years under anti-tumor necrosis factor (anti-TNF) treatment. Disease flares or serious adverse events were seen in none of the subjects. Although this study had a limited count of patients, it provided the first data on the vaccination of adolescent with IRD.[23] In our cohort, adverse events were seen in 10 of 26 patients under anti-TNF treatment and 21 of 54 patients with JIA, and similarly, none of them were serious.

In a phase 4 trial that evaluated immunogenicity and safety of the CoronaVac inactivated vaccine in adult patients with IRD, the most common systemic reactions were somnolence, headache, fatigue, and arthralgia, and none of them were moderate or severe. Systemic reaction frequencies after the first and second dose of the vaccine were 43.3%, and 33.4%, respectively.[24] Apart from local reactions, adverse events such as diarrhea, myalgia, arthritis, anosmia, anorexia, abdominal pain, rash, chest pain, and headache were seen in 7 of 32 CoronaVac inactivated vaccine administrations in our study. None of them remained for more than 2 days, and none of them were seen after the second dose. Consistent with the

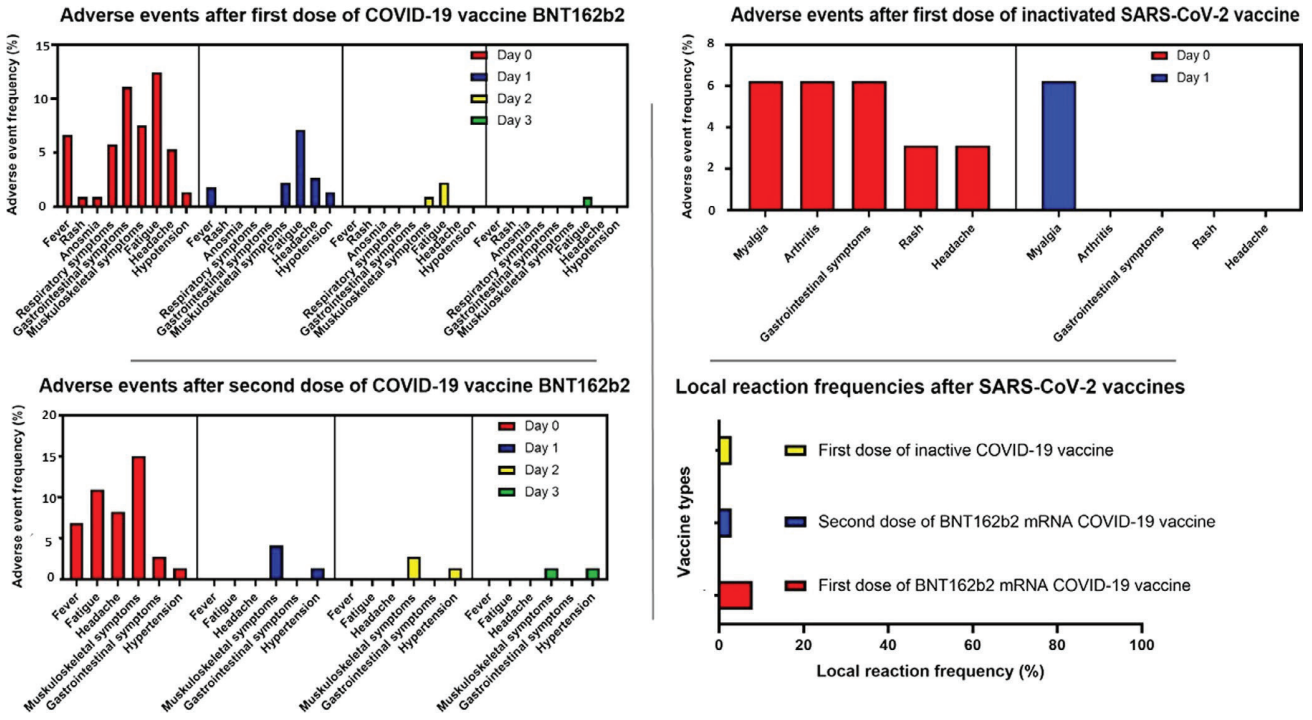

FIGURE 2 Adverse event frequencies according to days and vaccine types

TABLE 2 Comparison between the characteristics of healthy children, biologic group, and non-biologic group

	Healthy control group (n = 23)	Non-biologic group (n = 180)	Biologic group (n = 43)	*P*
Age, y (median, min-max)	15.67 (12.04-19.94)	15.14 (12.02-20.72)	16.09 (12.19-20.92)	.124
Gender				
Female, n (%)	10 (43.5%)	106 (58.9%)	25 (58.1%)	.369
Male, n (%)	13 (56.5%)	74 (41.1%)	18 (41.9%)	
Pre-vaccination COVID-19 history				
Yes, n (%)	7 (30.4%)	28 (15.6%)	9 (20.9%)	.182
No, n (%)	16 (69.6%)	152 (84.4%)	34 (79.1%)	
Vaccination type				
mRNA, n (%)	19 (82.6%)	160 (88.9%)	35 (81.4%)	.301
Inactive, n (%)	3 (13.0%)	18 (10.0%)	7 (16.3%)	
Mix, n (%)	1 (4.3%)	2 (1.1%)	1 (2.3%)	
Local reaction				
Yes, n (%)	3 (13.0%)	14 (7.8%)	3 (7.0%)	.581
No, n (%)	20 (87.0%)	166 (92.2%)	40 (93.0%)	
Disease flare within 1 month[a]				
Yes, n (%)	-	21 (11.7%)	6 (14.0%)	.680
No, n (%)	-	159 (88.3%)	37 (86.0%)	
Adverse events				
None, n (%)	12 (52.2%)	101 (56.1%)	26 (60.5%)	.579
Non-severe, n (%)	10 (43.5%)	77 (42.8%)	17 (39.5%)	
Severe, n (%)	1 (4.3%)	2 (1.1%)	0 (0.0%)	

[a]Healthy control group was not included into this analysis.

TABLE 3 Comparison of the patients with and without COVID-19 vaccine-related adverse events according to the baseline characteristics

	Adverse events		
	Yes (n = 107)	No (n = 139)	*P*
Age, y (median, min-max)	15.55 (12.02-20.92)	15.11 (12.18-20.72)	.376
Gender			
Female, n (%)	65 (60.7%)	76 (54.7%)	.340
Male, n (%)	42 (39.3%)	63 (45.3%)	
Disease			
Healthy control, n (%)	11 (10.3%)	12 (8.6%)	.323
Patients with AID, n (%)	58 (54.2%)	68 (48.9%)	
FMF, n	57	66	
CAPS, n	1	1	
BS, n	-	1	
Patients with JIA, n (%)	21 (19.6%)	33 (23.7%)	
oJIA, n	15	28	
jSPA, n	4	4	
pJIA, n	2	1	
Patients with CTD, n (%)	9 (8.4%)	21 (15.1%)	
SLE, n	4	12	
DM, n	4	6	
Scleroderma, n	1	2	
Sjögren, n	-	1	
Patients with vasculitis, n (%)	6 (5.6%)	3 (2.2%)	
BD, n	2	-	
DADA2, n	1	1	
TA, n	1	1	
GPA, n	1	-	
HSP, n	-	1	
KD, n	1	-	
Patients with ARF, n (%)	2 (1.9%)	2 (1.4%)	
Presence of a rheumatic disease, n (%)	96 (89.7%)	127 (%91.4)	.827
Ongoing treatments			
Colchicine, n (%)	60 (56.1%)	68 (48.9%)	.266
Steroid, n (%)	10 (9.3%)	11 (7.9%)	.819
ASA, n (%)	0 (0.0%)	6 (4.3%)	**.037**
bDMARDs, n (%)	17 (15.9%)	26 (18.7%)	.684
Anakinra, n	-	2	
Canakinumab, n	4	4	
Tocilizumab, n	3	3	
Etanercept, n	5	11	
Adalimumab, n	5	5	
Rituximab, n	-	1	
cDMARDs, n (%)[a]	18	31	
MTX, n	11	11	
Leflunomide, n	3	7	

TABLE 3 (Continued)

	Adverse events		
	Yes (n = 107)	No (n = 139)	P
Cyclosporine, n	3	-	
Cyclophosphamide, n	1	-	
HCQ, n	5	16	
MMF, n	3	3	
COVID-19 history before vaccination, n (%)			
Yes, n (%)	19 (17.8%)	25 (%18)	1
No, n (%)	88 (82.2%)	114 (%82)	
Vaccination type[b]			
mRNA, n	100	118	<.001
Inactive, n	7	25	

Abbreviations: AIDs, autoinflammatory diseases; ARF, acute rheumatic fever; ASA, acetylsalicylic acid; BD, Behçet disease; bDMARDs, biologic disease-modifying antirheumatic drugs; BS, Blau syndrome; CAPS, cryopyrin-associated periodic syndromes; cDMARDs, conventional disease-modifying antirheumatic drugs; CTD, connective tissue disease; DADA2, Deficiency of Adenosine Deaminase 2; DM, dermatomyositis; FMF, familial Mediterranean fever; GPA, granulomatous polyangiitis; HCQ, hydroxychloroquine; HSP, Henoch-Schönlein purpura; JIA, juvenile idiopathic arthritis; jSPA, juvenile spondylarthritis; KD, Kawasaki disease; MMF, mycophenolate mofetil; MTX, methotrexate; oJIA, oligoarticular juvenile idiopathic arthritis; pJIA, polyarticular juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TA, Takayasu arteritis.

[a]Total of cDMARDs rows are not equal to cDMARDs columns due to several patients being under poly-cDMARDs treatment.

[b]Four patients received both vaccination types; 3 experienced adverse events after mRNA vaccination, and 1 did not experience any adverse events.

previously mentioned phase 4 trial, none of them were considered serious. Although inactive vaccines are generally safe, there are concerns regarding the sufficient immunogenicity in patients with IRD, based on current findings.[25]

In order to achieve sufficient immunogenicity, although not contraindicated, the American College of Rheumatology (ACR) currently recommended withholding MTX, MMF and cyclophosphamide for 1-2 weeks following each COVID-19 dose in patients with well-controlled disease. This approach is mainly based on data from previous studies conducted with other vaccines, such as influenza and pneumococci.[14] However, findings of a recent study do not support temporarily cessation of MTX during vaccination in terms of seropositivity.[26] Due to the lack of data in the first days of the mass vaccination schedules and the concerns of the families regarding the disease activities, none of our patients discontinued their medication during the vaccination process. Adverse events per vaccine administration rates of the patients under treatment with MTX, MMF and cyclophosphamide were 11/22, 3/6, and 1/1, respectively. Although there was no safety issue in these patients because none of the adverse events were severe, further studies evaluating acceptable immunogenicity by measuring antibody levels are required.

Due to its B cell depletion effect, rituximab is another medical option that was recommended to be stopped during vaccination in the current ACR guidelines. It was proposed that, if the disease activities allow, the next rituximab cycle for patients must be delayed to 2-4 weeks after the final vaccine dose, to achieve acceptable antibody levels.[14] A recent study verified these suggestions by showing significantly impaired immunogenicity in patients receiving rituximab.[26] However, since both T cells and B cells have a pivotal role in the fight against SARS-CoV-2, it remains unclear whether vaccines may protect patients with an impaired humoral response.[27,28] Moreover, rituximab was shown to be significantly associated with severe COVID-19 disease course.[29]

In our cohort, there was only one patient under rituximab treatment during the vaccination period. He was a 16-year-old partially controlled SLE patient. In addition to rituximab, he was receiving MMF and HCQ. He had a COVID-19 infection history with mild to moderate symptoms before the vaccination. Therefore, he and his family had enormous concerns regarding re-infection with severe symptoms. He was vaccinated by double dose of CoronaVac inactivated vaccine based on his choice, and neither disease flares nor any adverse events were seen. Although he received his regular rituximab schedule with 1-month delay in line with current recommendations, we planned to examine him in terms of immunogenicity.

Vaccine hesitancy rapidly raised due to growing number of cases who developed vaccine-related severe or permanent adverse events such as myocarditis, hypertension, acute respiratory failure, septic shock, sudden hearing loss, and thromboembolic events.[30-33] Therefore, studies like ours that present a well-documented safety profile even in patients with IRD as a vulnerable group may ameliorate the concerns.

There are notable limitations in our study. First, dosages of immunosuppressive treatments of our patients are not available. Second, we did not assess the exact duration of the patients' medications and their disease activities. Third, given that the survey method was used as the first step for gathering data, selection bias may have occurred due to the possible willingness of the individuals who experienced adverse events for filling the questionnaire. Fourth, considering the

difficulty of sub-analyses due to a low number of patients, although CYC and MMF are known to potentially alter vaccine response, they were included in the non-biologic group. Although we did not assess the intervals between vaccination times and COVID-19 infection histories of the subjects, we know that our Ministry of Health regulations do not allow infected individuals to be vaccinated within the first 6 months. The main strength of the study is that this is the first one which evaluates adolescents and young adults with a broad spectrum of IRD in terms of vaccine-related adverse events.

In conclusion, our study indicates an acceptable safety profile of COVID-19 vaccines available in our country and encourages children with IRD to be vaccinated. Thus, prospective immunogenicity studies evaluating the efficacy of the vaccines and long-term follow-up studies for adverse events monitoring are required.

ACKNOWLEDGEMENTS

None

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article.

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How to cite this article: Haslak F, Gunalp A, Cebi MN, et al. Early experience of COVID-19 vaccine-related adverse events among adolescents and young adults with rheumatic diseases: A single-center study. *Int J Rheum Dis*. 2022;00:1–11. doi:10.1111/1756-185X.14279

Artigo

3. Estudo mostra que CoronaVac é segura e imunogênica para crianças com idades entre sete meses e cinco anos

ESTUDO: *"Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in inadvertently vaccinated healthy children"*

REVISTA: *Revista do Instituto de Medicina Tropical de São Paulo*

DATA DE PUBLICAÇÃO: *6/12/2021*

Um estudo de vacinação com a CoronaVac realizado por cientistas do Instituto Adolfo Lutz, do Instituto de Infectologia Emílio Ribas e da Secretaria de Estado da Saúde de São Paulo concluiu que a CoronaVac é segura e imunogênica para crianças. A pesquisa foi realizada com 27 brasileiros, com idades entre sete meses e cinco anos, que receberam a vacina do Butantan e da farmacêutica chinesa Sinovac de modo inadvertido nas cidades de Diadema e Itirapina, no estado de São Paulo. Apenas uma delas apresentou sintomas leves, sem outros eventos adversos importantes registrados durante o acompanhamento de 30 dias.

As crianças participantes do estudo buscaram unidades básicas de saúde (UBS) para tomar a vacina da influenza, mas acabaram recebendo por engano a CoronaVac. O evento foi imediatamente comunicado às secretarias de saúde de cada município e, em relação ao evento adverso, ao sistema de vigilância vacinal. O Centro de Vigilância Epidemiológica da Secretaria de Estado da Saúde de São Paulo (CVE) e o Instituto Adolfo Lutz atenderam as secretarias de Itirapina e Diadema.

As 27 crianças vacinadas com uma única dose foram monitoradas por pediatras, que coletaram amostras de soro na primeira consulta (nove dias após a vacinação) e após 30 dias da imunização. A única criança que relatou efeitos adversos tinha dois anos e apresentou coriza na primeira consulta após a vacinação.

Todas as crianças foram testadas para sorologia SARS-CoV-2 S1 com proteína Ortho IgG anti-S1 total e Cpass, um método que permite a rápida detecção de anticorpos neutralizantes totais. Cinco delas tinham título de proteína IgG total superior a 1.0 (testes de reagentes) entre três e nove dias após a vacinação. Do total, 19 tiveram o sangue coletado 30 dias depois da aplicação e também apresentaram títulos totais de proteína IgG spike superior a 1.0. Quatro das cinco crianças que apresentaram teste reagente na primeira consulta foram testadas novamente um mês depois da imunização e apresentaram aumento da proteína spike IgG anti S1 total, passando de uma média de 10,4 para 20,5.

Os objetivos do estudo eram descrever a resposta da saúde pública a um erro programático e monitorar a segurança, tolerabilidade e soroconversão da vacina por meio da detecção da quantidade total de anticorpos IgG contra a proteína spike SARS-CoV-2 S1 após a vacinação de crianças com CoronaVac.

REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO
JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

BRIEF COMMUNICATION

http://doi.org/10.1590/S1678-9946202163083

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in inadvertently vaccinated healthy children

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ABSTRACT

Twenty-seven children aged seven months to 5 years were inadvertently vaccinated with a COVID-19 vaccine, the CoronaVac (Sinovac, China), an inactivated SARS-CoV-2 vaccine, in two different cities of Sao Paulo State, Brazil. After the event, these children were monitored by local pediatricians and serum samples were collected at the first visit and 30 days after vaccination and tested for SARS-CoV-2 S1 serology with Ortho total IgG anti-S1 protein and Cpass, an ACE2 receptor binding domain inhibition assay. Only one child had a mild symptom after vaccination, with no other adverse events documented up to the 30 days follow-up. Of 27 children tested 3-9 days after vaccination, 5 (19%) had positive serology suggesting a previous natural SARS-CoV-2 infection, with all 19 tested on day 30 after vaccination and presenting with positive tests, with an increment of antibody titers in those initially positive. A low Cpass binding inhibition was observed in the first collection in 11 seronegative cases, with high titers among those anti-S1 positive. All children showed an important increase in antibody titers on day 30. The event allowed the documentation of a robust serological response to one dose of CoronaVac in this small population of young children, with no major adverse effects. Although it was an unfortunate accident, this event may contribute with future vaccine strategies in this age group. The data suggest that CoronaVac is safe and immunogenic for children.

KEYWORDS: COVID-19 vaccines. Adverse events. Brazil.

INTRODUCTION

On May 22nd, 2021, 27 healthy children were inadvertently vaccinated with a COVID-19 vaccine CoronaVac, instead of receiving the influenza vaccine in a primary health care unit in Itirapina, a small city in the countryside of Sao Paulo State, Brazil. One day later (May the 23rd), the same error happened in Diadema, a city located in the metropolitan area of Sao Paulo city, where five children were also inadvertently vaccinated with CoronaVac.

CoronaVac is an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (Beijing, China), which has been used among adults aged ≥18 years in Brazil, since January 2021. This vaccine is produced by Sinovac in partnership with the local public vaccine manufacturer Butantan[1]. Over 40 million doses of CoronaVac had already been administered by the end of June 2021 all over the country[2].

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Received: 13 August 2021

Accepted: 4 October 2021

The vaccination error was promptly reported to the health department of each municipality and, in relation to adverse events, to the vaccination surveillance system. The Epidemiological Surveillance Center of Sao Paulo State (CVE) and the Adolfo Lutz Institute assisted the health departments of Itirapina and Diadema. The objectives were to describe the public heath response to a programmatic error and to monitor the vaccine safety, tolerability and seroconversion by detecting the total amount of IgG antibodies against SARS-CoV-2 S1 spike protein after the vaccination of children with CoronaVac.

MATERIALS AND METHODS

The children who had been inadvertently vaccinated with CoronaVac (Sinovac Life Sciences, Beijing, China) were monitored by pediatricians in primary health care units for 30 days, to receive medical assistance if any sign or symptom appeared. Reports of their health conditions were sent to the health department of each municipality. Three visits were scheduled for medical evaluation, right after the event recognition (error in the vaccine used), at 15th and 30th day after vaccination. To inform the families and local health workers caring for these children of their serological status, two registered assays, available at State public laboratories were used. Blood samples were taken on the first medical evaluation (3-9 days after the event) and on the 30th day after the vaccination event. The presence of antibodies for SARS-CoV-2 were detected using (i) a chemiluminescent microparticle assay (VITROS® Anti-SARS-CoV2, Ortho Clinical Diagnostics, United Kingdom) which detects the domain of the S1 (spike) antigen, considering sororeactive for SARS-CoV-2 antibodies samples with titers >1.0 and; (ii) the evaluation of antibodies able to interfere with the RBD-ACE2 interaction (RBI), measured by cPass (SARS-CoV-2 Neutralization Antibody Detection kit, GenScript, USA), both test performed following the manufacturer's instructions. The test was considered positive for the presence of neutralizing antibodies for SARS-CoV-2 when an inhibition titer ≥ 20% is obtained, and samples are assigned as presenting with low inhibition when percentages from 5% to 20% inhibition are detected.

All clinical information and laboratory tests results were registered in each case, reporting the clinical manifestations of adverse events to the health departments and to the programmatic error surveillance system.

The approach to these children occurred only after the detection of the error in the type of vaccine used, when their parents were contacted and informed about the vaccination error. All children were evaluated by local health workers and upon demand of parents and local health authorities, blood samples were collected to perform the serological assays. Those that agreed to participate in the serological evaluation were oriented to return after 30 days after vaccination for retesting. The present investigation was the official response to a public health crisis, thus it did not require the approval of an ethical council.

RESULTS

Table 1 shows the characteristics of CoronaVac vaccinated children. From the total of 27 children, 52% were male, with ages ranging from 7 months to 5 years. Only one 2-years-old child presented a symptom (running nose) during the first visit, nine days after vaccination. No other symptoms were reported among the infants in the 30 days following the vaccination.

All children (n=27) were tested at the first visit for S1 antibodies and 5 (18.5%) had total S1 spike protein IgG titer higher than 1.0 (reagent tests) 3-9 days after vaccination. Nineteen had blood collected 30 days after vaccination and all of them had total S1 spike protein IgG titers higher than 1.0 (reagent tests). Four of the five children who presented reagent tests at the first visit were retested on the 30th day after vaccination, all showing an increased total IgG anti S1 spike protein, going from a mean of 10.4 to a mean value of 20.5. About half (47%, 9/19) tested for the receptor binding domain inhibition (RBI) showed results above 20%, but most had a low binding inhibition (5-20%), with only three cases, all S1 seropositive, with high titers (over 90% inhibition). On the 30th day, 12/13 tested children had titers above 30%, with a median titer of 45% (IQR 36-65). Titers of S1 have also increased from the initial collection up to the 30th day, from 0.1 (IQR 0-0.3) to 7.9 (5.5-11.2).

DISCUSSION

No COVID-19 vaccines are authorized in Brazil, so far, for use in children under the age of 12 years. However, a phase 2 study has already assessed the safety, tolerability and immunogenicity of CoronaVac in the population aged 3 to 17 years[3].

We presented a response to a programmatic error situation. Despite the vaccination error, all monitored children did not show adverse events following the immunization. The analyses from phase 1–3 trials have shown that CoronaVac was safe in adults aged 18 years and older[4]. A Phase 1-2 study evaluated children and adolescents aged 3 to 17 years vaccinated with CoronaVac and showed that 27% of the vaccinated participants reported at least one adverse event within 28 days of vaccination[3]. All adverse

Table 1 - Demographic and serological results from children inadvertently vaccinated with CoronaVAc (one dose), Sao Paulo State, Brazil, 2021.

Sex	Age (months)	DV 1	DV 2	S1 Ab 1	S1 Ab 2	RBI 1	RBI 2
Female	22	4	NA	0.01	NA	5.00	NA
Female	28	4	30	0.00	6.49	19.61	30.95
Female	42	4	30	3.11	19.00	39.90	NA
Female	69	4	NA	0.01	NA	NA	NA
Female	44	4	30	0.00	7.53	-6.89	45.22
Female	30	4	NA	11.30	NA	NA	NA
Female	3	6	30	0.01	7.73	9.07	62.34
Female	60	7	NA	0.01	NA	NA	NA
Female	7	3	33	0.00	10.10	21.83	64.87
Female	37	3	33	0.00	3.03	3.60	33.04
Female	60	3	33	0.00	7.94	8.73	51.00
Female	54	9	NA	0.02	NA	NA	NA
Male	52	4	NA	0.01	NA	-0.69	NA
Male	31	4	NA	0.00	NA	NA	NA
Male	23	4	30	0.00	3.77	NA	22.05
Male	22	4	NA	0.03	NA	NA	NA
Male	60	4	30	5.17	20.50	91.50	96.8
Male	31	4	30	0.00	3.00	27.12	35.84
Male	46	4	30	0,.00	10.20	-10.54	38.68
Male	10	4	30	0.00	8.90	22.99	68.12
Male	13	4	30	0.00	11.20	22.50	68.96
Male	49	4	30	0.01	4.19	13.21	35.79
Male	35	4	30	0.03	5.48	23.48	38.06
Male	32	4	41	0.01	9.73	NA	NA
Male	18	3	33	19.00	24.10	97.07	NA
Male	54	5	34	0.17	6.95	19.48	57.98
Male	23	9	30	13.30	18.60	97.36	NA

DV 1 = days after the 1st dose of vaccine and first blood sampling ; DV 2 = days after the 1st dose of vaccine and 2nd blood sampling; S1 Ab 1= antibody titers against the SPIKE domain S1 at the time of the 1st blood sampling ; S1 Ab 2 = antibody tites against the SPIKE domain S1 at the time of the 2nd blood sampling ; RBI 1 = percentage of receptor binding inhibition at the time of the 1st blood sampling ; RBI 2 = percentage of receptor binding inhibition at the time of the 2st blood sampling ; NA = not available.

events were non-severe, and the most common reactions were pain at the injection site and fever[3].

All tested children showed an increase in total S1 spike protein IgG antibodies 30 days following the vaccination. Although some children already had antibodies at the time of the initial blood collection, presumably due to previous asymptomatic, unrecognized infection by SARS-CoV-2. When these previously positive children were tested 30 days after the vaccination, they showed an increment in IgG binding antibody units at the second blood sampling. As no infection during the observation period was documented, and if they had occurred, they would unlikely affect all children, one can assume that the immunological response was generated by the vaccine. The receptor binding inhibition, a functional assay to evaluate the ability of serum samples to interfere with the binding of the viral receptor binding domain of the S1 protein with the cellular receptor ACE-2, showed some inhibition (from 5 to 20%) in 11 children that did not had total anti S1 IgG antibodies[5]. The titers were however low and may represent either unspecific reactivity or a previous exposure to other coronaviruses. The limited information of the test in particular in this age group, does not allow us to come to any conclusion, but all retested children on the 30th day after vaccination showed important increments in RBI titers, with only one case below 30% inhibition as can be seen in Table 1. These two assays have been evaluated in comparison with other diagnostic tests and have shown an adequate performance[6]. Although

limited to a serological response to S1 antigens, either total IgG to the viral S1 protein binding inhibition to the major SARS-CoV-2 receptor, the data suggest an anti-spike response after one dose of the vaccine. In other words, one dose of CoronaVac was immunogenic in children[3].

Wrong vaccine administration is the most reported vaccination error[7,8]. CoronaVac and influenza vaccines used in the Brazilian public health system come from the same local producer (Butantan) and they have the multiple dose presentation, which could favor the confusion. However, the label and the color of the bottle cap are different. The current high number of different vaccines available in the Brazilian immunization schedule demands well trained health professionals. Vaccination errors may harm patients and cause a negative impact on the population's confidence on vaccination, which in turn will negatively impact the vaccination coverage[8].

This study has some limitations. Firstly, it is a response to an unexpected event, justifying the small sample size that does not allow us to rule out the occurrence of rare adverse events or even to definitely conclude on the duration of the seroconversion observed after the first dose. Secondly, children did not receive the second dose and were not evaluated after the end of the proposed immunization. Thirdly, the cellular immunity was not evaluated. Finally, the monitoring period (30 days) was short to determine long-term immunogenicity and also for a complete evaluation of safety.

Children infected with SARS-CoV-2 mainly have mild disease or are asymptomatic, when compared with adults. However, a small number of children, especially those with health comorbidities, might be at risk of severe COVID-19[9,10]. Furthermore, the SARS-CoV-2 infection can lead to a serious, although rare complication called the multisystem inflammatory syndrome in children[11]. Finally, children can be transmitters of SARS-CoV-2 in communities[12]. A vaccine against SARS-CoV-2 for children and adolescents will contribute decisively to the control of the COVID-19 pandemic. Our investigation suggests that CoronaVac is well tolerated and safe and can induced humoral responses in children, but proper safety and effectiveness studies must be performed before expanding the vaccination to young children.

ACKNOWLEDGMENTS

The authors would like to thank all the collaborators from the Health Departments of Diadema and Itirapina, the GVE – Santo Andre and Piracicaba (regional surveillance offices), and the regional laboratories of Santo Andre and Rio Claro, Instituto Adolfo Lutz.

AUTHORS' CONTRIBUTIONS

EGF, HKS, NVDLA, MLBRN, and LFMB conducted the investigation together with the technicians of the municipality of Diadema and Itirapina; GISL, VOS, RY, KCRM, JFG, JAL, and LFMB performed the laboratory assay; EGF drafted the initial manuscript. GISL, HKS, NVDLA, and LFMB reviewed the manuscript. All authors approved the final manuscript as submitted.

CONFLICT OF INTERESTS

None.

FUNDING

None.

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Artigo

4. Revisão sistemática de estudos científicos atesta segurança e eficácia da CoronaVac para crianças e adolescentes

ESTUDO: *"Safety, Immunogenicity, and Efficacy of COVID-19 Vaccines in Children and Adolescents: A Systematic Review"*

REVISTA: *Vaccines*

DATA DE PUBLICAÇÃO: *29/9/2021*

Pesquisadores chineses realizaram uma revisão sistemática sobre estudos controlados e randomizados, estudos de caso e seriados com o objetivo de estimar a segurança, imunogenicidade e eficácia da vacinação de crianças e adolescentes contra a Covid-19. A pesquisa foi conduzida por cientistas da Universidade Médica de Chongqing, da Universidade de Lanzhou e do Centro Nacional de Pesquisa Médica sobre Saúde e Doenças Infantis da China e publicado no periódico Vaccines em meados de setembro de 2021.

Os pesquisadores investigaram estudos publicados até 23/7/2021 nas plataformas PubMed, Web of Science, no database sobre Covid-19 da Organização Mundial da Saúde (OMS) e no Instituto Nacional da China para Infraestrutura do Conhecimento (CNKI, na sigla em inglês).

Foram incluídos na revisão oito estudos publicados, envolvendo um total de 2.852 crianças, e 28 estudos clínicos em andamento. Uma das principais pesquisas analisadas foi o ensaio clínico randomizado controlado de fase 1 e 2 do uso da CoronaVac entre crianças de três a 17 anos realizado na China. Os demais papers são referentes a vacina desenvolvida com a tecnologia de RNA mensageiro.

Segundo a revisão, o ensaio clínico da CoronaVac mostrou que a vacina tem bom perfil de segurança e é imunogênica para crianças e adolescentes. Em relação à segurança, a maioria dos eventos adversos foi leve ou moderado, como dor no local da injeção, fadiga, dor de cabeça e dor no peito. Quanto à imunogenicidade, tanto na fase 1 quanto na fase 2, a soroconversão de anticorpos neutralizantes após a segunda dose foi de 100%.

"Nossa revisão encontrou altos níveis de imunogenicidade e eficácia vacinal em crianças e adolescentes. Esse é um claro indicador de que as vacinas são efetivas, e os estudos controlados randomizados também não se depararam com grandes questões em relação a segurança", concluem os pesquisadores.

A vacina é a forma mais eficaz de prevenir e controlar infecções por Covid-19, além de estimular o sistema imunológico a produzir anticorpos. Promover a vacinação de crianças e adolescentes é crucial para barrar a propagação do coronavírus, já que esse grupo representa um quarto da população mundial.

vaccines

MDPI

Systematic Review

Safety, Immunogenicity, and Efficacy of COVID-19 Vaccines in Children and Adolescents: A Systematic Review

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Abstract: Aim: To identify the safety, immunogenicity, and protective efficacy of COVID-19 vaccines in children and adolescents. Methods: We conducted a systematic review of published studies and ongoing clinical studies related to the safety, immunogenicity, and efficacy of COVID-19 vaccine in children or adolescents (aged < 18 years). Databases including PubMed, Web of Science, WHO COVID-19 database, and China National Knowledge Infrastructure (CNKI) were searched on 23 July 2021. International Clinical Trials Registry Platform (ICTRP) was also searched to identify ongoing studies. Results: Eight published studies with a total of 2852 children and adolescents and 28 ongoing clinical studies were included. Of the eight published studies, two were RCTs, two case series, and four case reports. The investigated COVID-19 vaccines had good safety profiles in children and adolescents. Injection site pain, fatigue, headache, and chest pain were the most common adverse events. A limited number of cases of myocarditis and pericarditis were reported. The RCTs showed that the immune response to BNT162b2 in adolescents aged 12–15 years was non-inferior to that in young people aged 16–25 years, while with 3 μg CoronaVac injection the immune response was stronger than with 1.5 μg. The efficacy of BNT162b2 was 100% (95% CI: 75.3 to 100), based on one RCT. Of the 28 ongoing clinical studies, twenty-three were interventional studies. The interventional studies were being conducted in fifteen countries, among them, China (10, 43.5%) and United States(9, 39.1%) had the highest number of ongoing trials. BNT162b2 was the most commonly studied vaccine in the ongoing trials. Conclusion: Two COVID-19 vaccines have potential protective effects in children and adolescents, but awareness is needed to monitor possible adverse effects after injection. Clinical studies of the COVID-19 vaccination in children and adolescents with longer follow-up time, larger sample size, and a greater variety of vaccines are still urgently needed.

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Citation: Lv, M.; Luo, X.; Shen, Q.; Lei, R.; Liu, X.; Liu, E.; Li, Q.; Chen, Y. Safety, Immunogenicity, and Efficacy of COVID-19 Vaccines in Children and Adolescents: A Systematic Review. *Vaccines* **2021**, *9*, 1102. https://doi.org/10.3390/vaccines9101102

Academic Editor: François Meurens

Received: 1 August 2021
Accepted: 24 September 2021
Published: 29 September 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Keywords: COVID-19; vaccine; children; adolescents; systematic review

1. Background

One and a half year have passed since the beginning of the coronavirus disease 2019 (COVID-19) pandemic. Yet the epidemic is still not under control. With over 200 million confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and over 4 million COVID-19 related deaths, COVID-19 has brought great suffering and devastation to people worldwide.

Vaccines, as an effective way to prevent and control disease infections, stimulate the human immune system to produce antibodies, thus increasing immunity to the disease and generating protection for the immunized individual [1]. Vaccination aims to curb the spread of the disease and helps to potentially achieve herd immunity. As of 18 September 2021, twenty-two COVID-19 vaccines worldwide have been approved [1]. However, we have little knowledge of the efficacy and safety of COVID-19 vaccines in children and adolescents. Given that children and adolescents account for approximately one quarter of the world's population [2], promoting vaccination of children and adolescents is also crucial to end the spread of COVID-19.

The development of COVID-19 vaccine has been in full swing since the COVID-19 outbreak. Studies have shown that the current COVID-19 vaccines are effective and safe in adults [3–6]. Several international organizations and countries have also developed guidelines for different aspects of COVID-19 vaccination, including vaccination of special populations, management of adverse reactions, and cautions for vaccination [7–9]. However, the efficacy of protection and adverse effects of COVID-19 vaccines in children and adolescents remains unclear despite a large number of clinical trials being conducted. Furthermore, children and adolescents have less severe COVID-19 symptoms than adults [10], and they likely play a limited role in spreading the infection to others. Therefore, more high-quality clinical studies are still needed to determine whether COVID-19 vaccination should be recommended for children at the moment [11]. In addition, children are a population group with special needs and features, and the attitude of parents or guardians toward the COVID-19 vaccine is also an essential factor affecting children's vaccination. To explore and promote COVID-19 vaccination in children and adolescents, The National Clinical Research Center for Child Health and Disorders (Chongqing, China) initiated an international guideline for the management of COVID-19 in children and adolescents [12] that also contains the question of whether and how children and adolescents should be vaccinated against COVID-19. To answer this question, we conducted a systematic review to estimate the safety, immunogenicity, and protective efficacy of the COVID-19 vaccine in children and adolescents, covering both completed and ongoing studies and trials.

2. Methods

We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (see Supplementary Table S1 for PRISMA checklist) [13] and the Cochrane Handbook for Systematic Reviews of Interventions [14]. We have registered this systematic review at OSF REGISTRIES (DOI:10.17605/OSF.IO/JC32H, accessed on 3 August 2021).

2.1. Inclusion and Exclusion Criteria

We included published studies and ongoing clinical studies related to the safety, immunogenicity, and efficacy of COVID-19 vaccine in children or adolescents (aged < 18 years). The study design was limited to primary studies, including randomized clinical trials (RCTs), non-randomized trials, and observational studies. We also included ongoing studies registered at the International Clinical Trials Registry Platform (ICTRP).

We excluded articles from which we could not extract data specifically on children or adolescents or if we could not access the full text, conference proceedings, and study protocols. For ongoing studies, we only included registration records if the aim of the study was to determine the safety, immunogenicity, or efficacy of COVID-19 vaccine in children and adolescents.

2.2. Search Strategy

We systematically searched Medline (via PubMed), Web of Science, World Health Organization (WHO) COVID-19 database, and China National Knowledge Infrastructure (CNKI), from their inception to 23 July 2021 to identify studies that met our eligibility criteria. The search strategy combined terms from three themes: (1) COVID-19, (2) vaccine, and (3) children and adolescents (see detailed search strategy in Supplementary Table S2). All search strategies were developed and retrieved independently by two investigators (ML and XL) and then cross-checked. We first developed a search strategy for Medline, and after reaching agreement adapted this strategy for other databases. In addition to the literature databases, we searched ICTRP to identify ongoing studies. We also searched Google Scholar and reference lists of identified articles to avoid missing potentially relevant literature.

2.3. Literature Screening

The screening process included three phases. First, one investigator removed duplicates from the retrieved records. Following this, four investigators (ML, XL, RL, and QS) screened all identified records independently by reading titles and abstracts. If the information in the title and abstract was insufficient, the full text was obtained for review. Disagreements were solved by consensus with the senior researcher (YC). We used Endnote 20.0.1 software in the entire screening process.

2.4. Data Extraction

The following data were extracted from the completed studies: (1) basic information: publication date, country, study design, name of the vaccine; (2) information of the participants: age, sample size, sex distribution; and (3) outcome information: safety, immunogenicity, and efficacy of COVID-19. For the ongoing clinical studies, we extracted the registration date, country, recruitment status, participants' age, target sample size, intervention, and primary outcome. All data were independently extracted by two investigators (ML and XL) using a predesigned extraction sheet.

2.5. Risk of Bias Assessment

Two investigators (ML and XL) assessed the methodological quality of the original studies to ensure the reliability of the findings. We used the Risk of Bias tool recommended by Cochrane Collaboration [15] to assess randomized trials. The tool consists of six domains of bias (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias). For case-control and cohort studies we used the Newcastle-Ottawa Scale (NOS) [16].; for case series and case reports the checklist proposed by Murad et al. [17]; and for cross-sectional studies the checklist of the Joanna Briggs Institute (JBI) [18].

2.6. Data Analysis

We descriptively presented the main findings on safety, immunogenicity, and efficacy of COVID-19 vaccine in children or adolescents. Microsoft Excel 16.51 (2019) was used for data processing and analysis. We considered to conduct a quantitative meta-analysis if at least two studies were included and the heterogeneity between the studies in terms of outcomes, population characteristics, and type of vaccine was low ($I^2 \leq 50\%$). For ongoing clinical studies, we also presented the numbers of trials by country and type of vaccine. Adobe Illustrator was used to visually present the number of ongoing clinical trials of COVID-19 vaccine in children or adolescents worldwide.

3. Results

3.1. Literature Search

Our initial search revealed 3092 records, of which 931 were excluded as duplicates. After screening the titles and, if necessary, full texts, eight published studies [19–26] with 2852 children or adolescents and 28 ongoing clinical studies targeting to recruit a total of 122,442 participants were included. The study selection process is shown in detail in Figure 1.

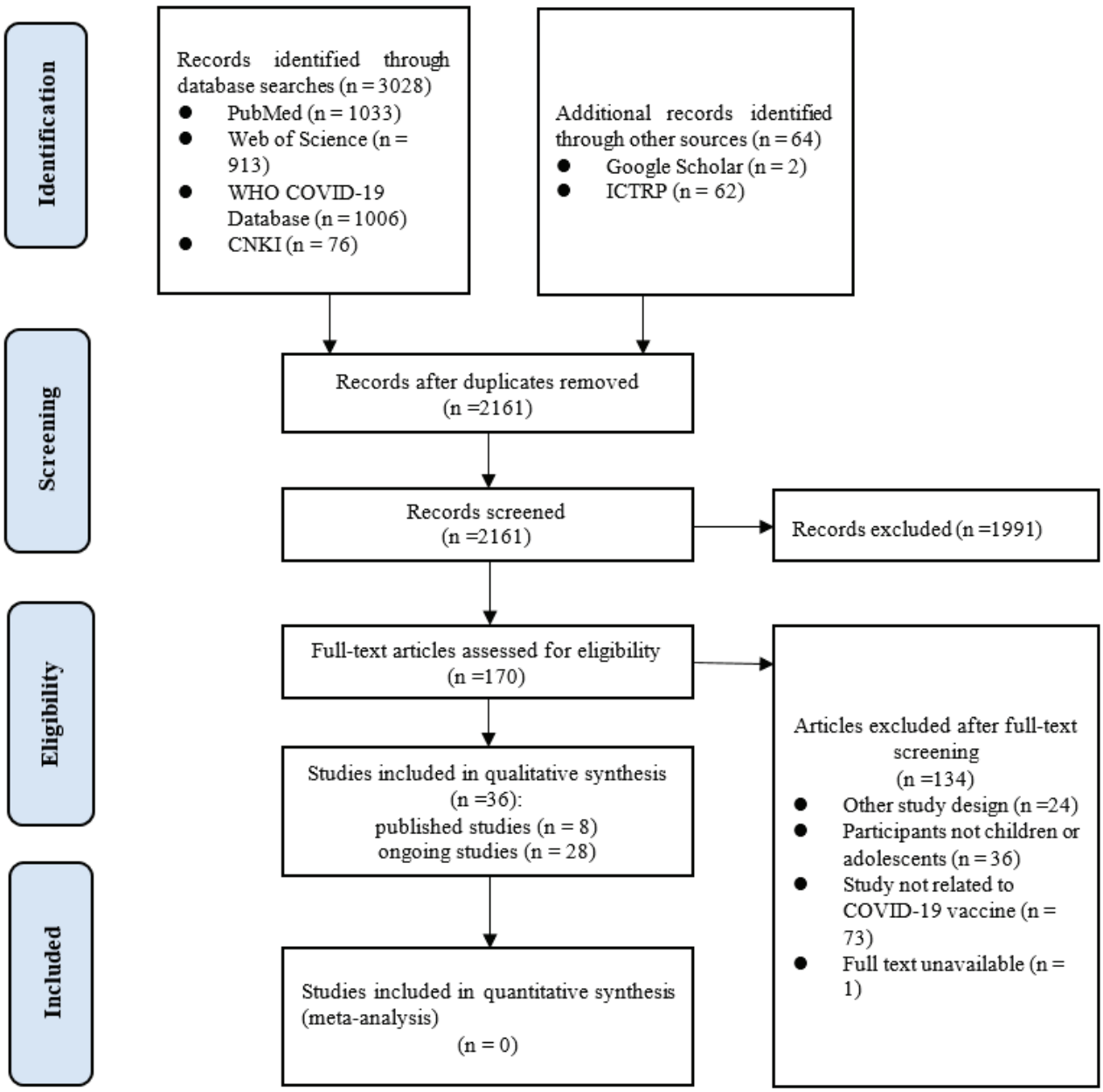

Figure 1. Study selection process (WHO: World Health Organization; COVID-19: coronavirus disease 2019; CNKI: China National Knowledge Infrastructure; ICTRP: International Clinical Trials Registry Platform).

3.2. Characteristics of the Included Clinical Studies

Among the eight published studies included, two were RCTs [19,20], two were case series [21,22], and four were case reports [23–26]. Five studies were conducted in the United States, and one in China, France, and Israel each. The studies were restricted to adolescents with the exception of one RCT that included children aged between 3 and 17 years. In one study the participants received CoronaVac COVID-19 vaccine developed by Sinovac Life Sciences, and in the other seven the participants received BNT162b2 mRNA COVID-19 vaccine developed by Pfizer-BioNTech. The characteristics of the included studies are summarized in Table 1.

Table 1. Basic characteristics of included clinical studies (n = 8).

Name of Vaccine	Participants	Sample Size	Follow-Up Duration	Study Design	Country	Funding	Reference
CoronaVac	Healthy children and adolescents aged 3–17 years	552	4.1 months	RCT Phase 1–2	China	Public/nonprofit (Chinese National Key Research and Development Program and Beijing Science and Technology Program)	Han et al., 2021 [19]
BNT162b2	Adolescents aged 12–15 years with no previous COVID-19 diagnosis or SARS-CoV-2 infection	2264	4.7 months	RCT Phase 3	USA	Private (BioNTech and Pfizer)	Frenck et al., 2021 [20]
BNT162b2	Adolescents and young adults aged 16 years with solid tumor older than	9	NR *	Case series	France	NR *	Riviere et al., 2021 [21]
BNT162b2	Adolescents aged 16–18 years	7	NR *	Case series	Israel	None	Snapiri et al., 2021 [22]
BNT162b2	An adolescent aged 17 years	1	2 weeks	Case report	USA	NR *	Minocha et al., 2021 [23]
BNT162b2	A previously healthy adolescent aged 16 years	1	2 weeks	Case report	USA	NR *	McLean et al., 2021 [24]
BNT162b2	Healthy adolescents 14–18 years	5	unclear	Case report	USA	None	Marshall et al., 2021 [25]
BNT162b2	Children and adolescents aged 12–17 years	13	3 months	Case report	USA	NR *	Schauer et al., 2021 [26]

* NR: not reported.

3.3. Quality of Included Studies

The overall methodological quality of the two included RCTs was high and the risk of bias low (Table 2). In the rest of the studies (case series and case reports), we did not assess two of the eight items of the Murad et al. [17] checklist, "Was there a challenge/rechallenge phenomenon" and "Was there a dose-response effect?", because they were not applicable. One study complied with five of the remaining six items, three with four items, one with three items, and one with two items. The method of case selection was unclear in all

included case series and case reports. Only two case reports or case series reported the item "were other alternative causes that may explain the observation ruled out?", and in three studies the follow-up time was not long enough for outcomes to occur.

Table 2. Quality assessment of included studies.

Risk of Bias in the Included Rcts Assessed by the Risk of Bias Tool							
Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Study
Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally pre-specified	
low	low	low	low	low	low	low	Han et al., 2021 [19]
low	low	low	low	unclear	low	low	Frenck et al., 2021 [20]

Methdological quality in the case series and case reports assessed by Murad et al. checklist								
Selection	Ascertainment		Causality				Reporting	Study
Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	Was the exposure adequately ascertained?	Was the outcome adequately ascertained?	Were other alternative causes that may explain the observation ruled out?	Was there a challenge/rechallenge phenomenon?	Was there a dose-response effect?	Was follow-up long enough for outcomes to occur?	Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	
0	1	1	0	N/A	N/A	0	0	Revon-Riviere et al., 2021 [21]
0	1	1	0	N/A	N/A	0	1	Snapiri et al., 2021 [22]
0	1	1	0	N/A	N/A	1	1	Minocha et al., 2021 [23]
0	1	1	0	N/A	N/A	1	1	McLean et al., 2021 [24]
0	1	1	1	N/A	N/A	0	1	Marshall et al., 2021 [25]
0	1	1	1	N/A	N/A	1	1	Schauer et al., 2021 [26]

0 = no; 1 = yes; N/A: Not applicable.

3.4. Safety of COVID-19 Vaccines

The most common adverse event in the two RCTs was injection site pain [20,21]. Besides that, fever, headache, and fatigue were also frequently reported. Most adverse events were not severe. No deaths were reported. A case series [22] that included 13 patients with solid tumor also showed that mild-to-moderate injection site pain was the most frequent adverse event (6 patients).

Besides, a few diagnosed myocarditis and/or pericarditis cases related to COVID-19 vaccine were reported in some studies. All cases occurred following the second dose of BNT162b mRNA COVID-19 vaccination. We summarized the basic information of 27 cases from included studies (Table 3). The median age was 16 years (range, 12–17 years). Most patients were male (26, 96.3%). Median time of onset was 3 days after receiving the vaccine (range, 1–4 days). All patients had chest pain.

Table 3. Basic information of diagnosed myocarditis and/or pericarditis cases (n = 27).

Vaccination	Age	Sex	Symptoms	Diagnosis	Time of Onset (Days Since Vaccination)	Length of Hospitalization (Days)	Study
BNT162b2, second dose	17	M	Chest pain	Perimyocarditis	3	4	Snapiri et al., 2021 [22]
BNT162b2, second dose	16	M	Chest pain	Perimyocarditis	1	6	Snapiri et al., 2021 [22]
BNT162b2, second dose	16	M	Chest pain, cough	Perimyocarditis	2	6	Snapiri et al., 2021 [22]
BNT162b2, second dose	16	M	Chest pain, nausea	Perimyocarditis	3	4	Snapiri et al., 2021 [22]
BNT162b2, second dose	17	M	Chest pain, headache	Perimyocarditis	1	5	Snapiri et al., 2021 [22]
BNT162b2, second dose	16	M	Chest pain, dyspnea, diarrhea, fever	Perimyocarditis	2	5	Snapiri et al., 2021 [22]
BNT162b2, second dose	17	M	Chest pain, dyspnea	Perimyocarditis	3	3	Snapiri et al., 2021 [22]
BNT162b2, second dose	17	M	Chest pain, fever, body aches,	Myocarditis	1	6	Minocha et al., 2021 [23]
BNT162b2, second dose	16	M	Chest pain	Myopericarditis	2.5	6	McLean et al., 2021 [24]
BNT162b2, second dose	16	M	Chest pain, bilateral arm pain, fever, fatigue, nausea, vomiting, anorexia, headache	Myocarditis	2	6	Marshall et al., 2021 [25]
BNT162b2, second dose	17	M	Chest pain, bilateral arm pain, numbness, paresthesia	Myopericarditis	2	2	Marshall et al., 2021 [25]
BNT162b2, second dose	17	M	Chest pain, bilateral arm pain, abdominal pain, fever, nausea, vomiting, anorexia, SOB, palpitations	Myocarditis	4	5	Marshall et al., 2021 [25]
BNT162b2, second dose	16	M	Chest pain, SOB	Myocarditis	3	3	Marshall et al., 2021 [25]
BNT162b2, second dose	14	M	Chest pain, fever, SOB	Myopericarditis	2	4	Marshall et al., 2021 [25]
BNT162b2, second dose	16	M	Chest pain, fever, chills, myalgias, headache, SOB	Myopericarditis	2	1	Schauer et al., 2021 [26]
BNT162b2, second dose	16	M	Chest pain, fever, myalgias	Myopericarditis	2	1	Schauer et al., 2021 [26]
BNT162b2, second dose	16	M	Chest pain, myalgias, headache	Myopericarditis	3	3	Schauer et al., 2021 [26]
BNT162b2, second dose	17	M	Chest pain, fever, malaise	Myopericarditis	3	1	Schauer et al., 2021 [26]
BNT162b2, second dose	15	M	Chest pain, myalgias, SOB	Myopericarditis	2	2	Schauer et al., 2021 [26]
BNT162b2, second dose	15	F	Chest pain, vomiting	Myopericarditis	3	1	Schauer et al., 2021 [26]
BNT162b2, second dose	15	M	Chest pain, fevers, SOB	Myopericarditis	3	3	Schauer et al., 2021 [26]
BNT162b2, second dose	15	M	Chest pain, chills	Myopericarditis	3	3	Schauer et al., 2021 [26]
BNT162b2, second dose	12	M	Chest pain	Myopericarditis	3	2	Schauer et al., 2021 [26]
BNT162b2, second dose	14	M	Chest pain, fever, headache	Myopericarditis	3	3	Schauer et al., 2021 [26]
BNT162b2, second dose	14	M	Chest pain, malaise, SOB	Myopericarditis	4	2	Schauer et al., 2021 [26]
BNT162b2, second dose	16	M	Chest pain, SOB	Myopericarditis	2	2	Schauer et al., 2021 [26]
BNT162b2, second dose	15	M	Chest pain	Myopericarditis	3	2	Schauer et al., 2021 [26]

M: male; F: female; SOB: shortness of breath.

3.5. Immunogenicity of the COVID-19 Vaccines

The two included RCTs indicated that the investigated COVID-19 vaccines, CoronaVac and BNT162b2, were immunogenic in children and adolescents. Frenck et al. [20] reported that the immune response to BNT162b2 in 12–15 year old adolescents was noninferior to that in young adults aged 16–25 (geometric mean ratio (GMR) = 1.75, 95% CI: 1.47~2.10), indicating even a better response in 12–15 years group than in young adults. Han et al. [19] found that in Phase 1, the seroconversion of neutralizing antibody after the second dose was 100% both in 1.5 μg group and 3.0 μg group with geometric mean titer (GMT) of 55.0 (95% CI 38.9–77.9) and 117.4 (87.8–157.0), respectively (p = 0.0012). In Phase 2, the seroconversion rates were 96·8% (95% CI: 93.1–98.8) and 100% (95% CI: 98.0–100.0) in the 1.5 μg group and the 3.0 μg group, respectively (p = 0.030).

3.6. Efficacy of the COVID-19 Vaccines

The RCTs on BNY162b2 [20] showed that the efficacy of the vaccine in children and adolescents was 100% (95% CI: 75.3~100). The other RCT on CoronaVac did not assess vaccine efficacy.

3.7. Ongoing Clinical Studies

We identified 28 ongoing clinical studies with a total target sample size of 122,442 (see Supplementary Table S3 for ongoing clinical trials on COVID-19 vaccination in children and adolescents). Twenty-three were interventional studies (including one Phase 1 trial; six Phase1/2 trials; six Phase 2 trials; four Phase 2/3 trials; three Phase 3 trials; one Phase 4 trial; and one where the phase was not clear) and five were observational studies. The minimum age of eligible participants was 6 months. Twenty-seven studies reported the name of vaccine they planned to use and there were a total of 15 different vaccine candidates of the following five major types: mRNA (13 studies), inactivated (7 studies), protein subunit (four studies), non-replicating viral vector (four studies), and replicating viral vector (one studies).

The interventional clinical trials were being conducted in 15 countries, the highest numbers of planned trials being in China (10 trials, 43.5%) and the United States (9 trials, 39.1%). BNT162b2 was the most common vaccine (6 trials, 26.1%). Figure 2 shows the countries with ongoing clinical trials and vaccines used in trials.

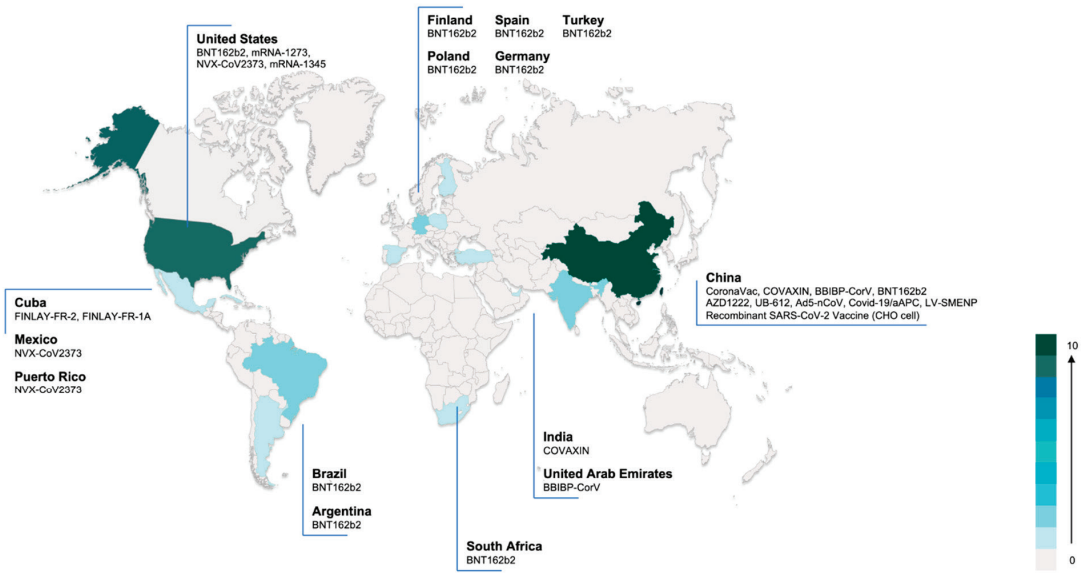

Figure 2. Ongoing interventional COVID-19 vaccine trials in children and adolescents worldwide. Color in the figure indicates the number of ongoing vaccine trials in each country.

4. Discussion

4.1. Principal Findings

Our review identified eight completed studies and 28 ongoing clinical studies of COVID-19 vaccines in children and adolescents. The investigated COVID-19 vaccines had good safety profiles, most adverse effects were mild or moderate, such as injection site pain, fatigue, headache, and chest pain. Some studies reported a few cases of myocarditis and pericarditis. The immune response to the BNT162b2 vaccine in adolescents aged 12–15 years was non-inferior to that in young people aged 16–25 years, and CoronaVac injection had a stronger immune response with a 3.0 μg than 1.5 μg dose. According to the one RCT on BNT162b2, no cases of COVID-19 in adolescents aged 12–15 years were detected. Clinical trials on children and adolescents are being conducted all over the world with a large number of different vaccines.

Children and adolescents, as a special population, present many influencing factors to consider when administering vaccines. Vaccine efficacy and safety are the most important considerations for children and their parents [27]. It is therefore important to demonstrate that vaccines are safe and protective before they are administered to children and adolescents. During an average influenza season, approximately 9.8% of children aged 0–14 year present with influenza [28]. After vaccination against influenza A (H1N1), 90.3% of children and adolescents aged 10–17 years developed protective antibodies, and no serious adverse reactions were seen [29,30]. Similarly, when the COVID-19 outbreak emerged, researchers actively promoted the development of vaccines with the expectation that vaccination could protect healthy population. Our study showed that two vaccines have shown to be effective and safe in pediatric populations. However, the evidence for both vaccines was based on single RCTs, and these two studies both had limitations such as the small sample size and lack of long-term data on safety and immunogenicity data. In particular, the risk of myocarditis and pericarditis should be closely monitored. Most cases of myocarditis and pericarditis associated with the COVID-19 vaccine were mild, and mostly affected children were male. Schauer et al. [26] estimated an incidence of myopericarditis of 0.008% in adolescents 16–17 years of age and 0.01% in those aged 12 through 15 years following the second dose.

Another important factor to consider for vaccination of children and adolescents is the risk of multisystemic inflammatory syndrome in children (MIS-C). In April 2020, children infected with SARS-CoV-2 presenting symptoms similar to incomplete Kawasaki disease (KD) or toxic shock syndrome were documented in the UK [31]. Since then, children with similar symptoms have been reported in other parts of the world as well [32–34]. This condition was subsequently named as MIS-C. The overall mortality of MIS-C is approximately 1–2% [35]. The decision to vaccinate should be made by weighing the risk of exposure, reinfection, and severe disease following infection against the uncertain safety of vaccination in such individuals. Whereas no directly relevant studies have confirmed the association of MIS-C with COVID-19 vaccination, a systematic review published in 2017 [36] identified 27 observational studies and case reports of KD. These showed that diphtheria-tetanus-pertussis (DTP)-containing vaccines, Haemophilus influenzae type b (Hib) conjugate vaccine, influenza vaccine, hepatitis B vaccine, 4-component meningococcal serogroup B (4CMenB) vaccine, measles-mumps-rubella (MMR)/MMR-varicella vaccines, pneumococcal conjugate vaccine (PCV), rotavirus vaccine (RV), yellow fever vaccine, and Japanese encephalitis vaccine did not increase the risk of KD. Thus, children and adolescents at high risk of severe COVID-19 or those with specific comorbidities should be considered to be prioritized in vaccination. More research is needed to clarify to what extent COVID-19 vaccines can mitigate the risks and bring benefits.

To date, 22 COVID-19 vaccines have been approved throughout the world, more than 1/3 of which are inactivated, and 138 vaccines are under development and exploitation. More than 300 clinical trials of COVID-19 vaccines have been registered or published [37,38]. Studies have shown that most COVID-19 vaccines are safe and effective in adults aged $\geq$ 18 years. Overall, in phase 2 and 3 RCTs, mRNA- and adenoviral vector-based COVID-19

vaccines had 94.6% (95% CI 0.936–0.954) and 80.2% (95% CI 0.56–0.93) efficacy, respectively [3–5], with good acceptability [6] and safety [39]. Only two RCTs on children and adolescents have been published in peer-reviewed journals so far, both of which found that the respective vaccines, BNT162b2 and CoronaVac, are safe and effective. Institutions including WHO, Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Canadian Pediatric Society have already authorized emergency use of BNT162b2 in children and adolescents aged 12 years and above [40–43]. European Medicines Agency (EMA) has also approved the Spikevax (previously COVID-19 Vaccine Moderna) vaccine for adolescents aged 12 to 17 years, based on the evidence from an ongoing study [44]. Although these guidelines gave recommendations on vaccinating children or adolescents from the perspective of Western countries, we still need to wait for more evidence from more countries and regions to better understand how COVID-19 vaccines work in different populations. With the more than twenty ongoing clinical trials, their findings may continue to offer clues of better protecting younger generations from COVID-19.

Public health authorities in countries that have approved COVID-19 vaccine in children and adolescents should also consider multiple aspects in their decision-making. European Centre for Disease Prevention and Control issued a set of eight interim considerations from the view of the overall potential public health impact of COVID-19 vaccination of adolescents [45]. Opel et al. suggested nine criteria to consider when evaluating antigens for inclusion in mandatory school immunization programs, which were categorized into vaccine-related, disease-related, and implementation-related [11]. We currently know however too little about the performance of COVID-19 vaccines or the epidemiology of SARS-CoV-2 in children to make any definitive judgment about whether COVID-19 vaccine should be mandatory in children, especially those under 12. Authorities should closely monitor and continually assess the benefits and potential risks of vaccination in children and adolescents. In addition, the acceptability of the COVID-19 vaccine among both the children themselves as well as their parents and guardians is a major influencing factor on the likelihood of children getting vaccinated. Studies have shown that approximately 80% of parents were reluctant to enroll their children in clinical studies of the COVID-19 vaccine [46] and approximately half of Chinese parents showed hesitancy on taking the COVID-19 vaccine for their children [47]. Therefore, it is necessary to educate parents and children about the vaccine to increase vaccination rates while ensuring the efficacy and safety of vaccines [48]. Furthermore, factors such as national policy, religion, culture, and other routine immunization procedures need to be taken into account in the administration of COVID-19 vaccine to children.

4.2. Potential Impact for Future Research and Practice

Our study included only two RCTs on COVID-19 vaccination in children and adolescents, one investigating CoronaVac developed by Sinovac and one BNT162b2 developed by Pfizer/BioNTech. For the vast majority of vaccines clinical studies are either ongoing but not completed, or not yet planned. For future research, we recommend paying attention to the following three aspects. First, more clinical studies on the protective efficacy and safety of COVID-19 vaccine in children and adolescents need to be conducted. Second, systematic reviews of factors affecting COVID-19 vaccination in children and adolescents, willingness to be vaccinated, and methods to promote vaccination, are needed. This includes also updating this systematic review when more studies, in particular RCTS, on COVID-19 in children and adolescents become available. Third, evidence-based guidelines for COVID-19 vaccination in children and adolescents are needed to promote and standardize vaccination in children and adolescents. Policymakers should develop policies for COVID-19 vaccination in children and adolescents based on the best current evidence in the future, and parents and guardians should be guided by policies that actively encourage and support their children to be vaccinated against COVID-19.

4.3. Strengths and Limitations

This paper is, to the best of our knowledge, the first systematic review on the safety, immunogenicity, and protective efficacy of COVID-19 vaccination in children and adolescents. We systematically searched key databases and websites to conduct a comprehensive evaluation and analysis of published studies and registry data records. However, this paper also has some limitations. First, we did not conduct a meta-analysis in this study, because of the heterogeneity in participant characteristics, outcomes, and study designs. Second, this study only included articles published in English. However, as the amount of evidence published so far is known to be limited, it is reasonable to expect that the studies we included covered most of the knowledge up to now. Finally, some studies that included children and adolescents did not report the age and outcome among these age groups separately. Given the limited time, we excluded these studies instead of contacting authors to request access to original data.

5. Conclusions

Our review found high rates of immunogenicity and vaccine efficacy in children and adolescents. This is a clear indicators that the vaccines are effective, and the RCTs also did not find any major issues with safety. Nevertheless, awareness is needed to monitor the possible adverse effects. Although most adverse events observed in the trials were mild, we identified a limited number of cases of myocarditis and pericarditis among the vaccinated children and adolescents, from several different studies. This shows also that particularly in the current situation where RCTs are still limited, it is important to include all existing evidence, also from individual case reports, in systematic reviews. Real-world data can also reveal findings that may not be observed in the well-controlled RCT settings. It is crucial that more clinical studies with sufficiently long follow-up time, large sample size, and using different types of vaccine are conducted in the future. Evidence-based guidelines are urgently needed to inform policymakers, children and adolescents, and their parents and guardians about the benefits and risks of vaccination against COVID-19.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/vaccines9101102/s1, Table S1: PRISMA checklist, Table S2: detailed search strategy, Table S3: ongoing clinical trials on COVID-19 vaccination in children and adolescents.

Author Contributions: Conceptualization: Y.C., E.L. and Q.L.; study design: Y.C. and Q.L.; literature search: M.L. and X.L. (Xufei Luo); figures and table: M.L. and X.L. (Xiao Liu); data collection: R.L., Q.S., X.L. (Xufei Luo) and M.L.; data analysis: M.L. and X.L. (Xufei Luo); data interpretation: Y.C., Q.L., E.L. and M.L.; writing: M.L., X.L. (Xufei Luo) and Y.C.; supervision: Y.C., E.L. and Q.L. All authors provided input regarding the direction of the study and the content of the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used during the current study are available from the corresponding author on reasonable request.

Acknowledgments: We appreciate Janne Estill for providing comments and language editing for this review.

Conflicts of Interest: The authors declare no conflict of interest.

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Artigo

5. Estudo com mais de dez milhões de chilenos maiores de 16 anos mostra que efetividade da CoronaVac é superior a 86%

ESTUDO: *"Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile"*

REVISTA: *The New England Journal of Medicine*

DATA DE PUBLICAÇÃO: *2/9/2021*

A efetividade da CoronaVac entre adolescentes já é um fato comprovado desde setembro, quando pesquisadores chilenos publicaram o artigo "Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile" no periódico científico The New England Journal of Medicine, um dos mais prestigiosos do mundo. O estudo, realizado entre fevereiro e maio de 2021 com 10,2 milhões de pessoas, investigou a eficácia da vacina no "mundo real" contra casos de Covid-19 e no combate às variantes do SARS-CoV-2 então circulantes no país – gama e alfa, principalmente.

O estudo de coorte (pesquisa observacional que acompanha indivíduos ao longo de um período de tempo para determinar características e evolução do grupo) contou com participantes acima dos 16 anos cadastrados no Fundo Nacional de Saúde (FONASA), programa nacional de saúde chileno que cobre cerca de 80% da população. O esquema vacinal aplicado no país é de duas doses da CoronaVac com intervalo de 28 dias.

A pesquisa mostrou que a proteção da vacina do Butantan e da Sinovac foi de 65,9% contra infecções por Covid-19, de 87,5% contra hospitalizações, de 90,3% contra internações em Unidades de Terapia Intensiva (UTI) e de 86,3% contra mortes.

Participaram do estudo 708.676 jovens de 16 a 19 anos, o equivalente a 7% do total de voluntários do coorte. Destes, 8.192 (1,2%) receberam uma dose de CoronaVac e 30.033 (4,2%) receberam duas doses. Os demais 670.451 consistiam em grupo controle ou pessoas que haviam tido Covid-19 (14.871). Vale ressaltar que, no Chile, assim como no Brasil, a vacinação foi iniciada pelos idosos, considerados mais vulneráveis à Covid-19.

O país andino tem as taxas mais elevadas de realização de testes para detecção da Covid-19 na América Latina e um sistema padronizado de informação pública para estatísticas vitais ao estudo. Na época, o Ministério da Saúde chileno já havia utilizado 13,98 milhões de doses da CoronaVac desde o começo da campanha de vacinação, em fevereiro.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 2, 2021 VOL. 385 NO. 10

Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile

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ABSTRACT

BACKGROUND

Mass vaccination campaigns to prevent coronavirus disease 2019 (Covid-19) are occurring in many countries; estimates of vaccine effectiveness are urgently needed to support decision making. A countrywide mass vaccination campaign with the use of an inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine (CoronaVac) was conducted in Chile starting on February 2, 2021.

METHODS

We used a prospective national cohort, including participants 16 years of age or older who were affiliated with the public national health care system, to assess the effectiveness of the inactivated SARS-CoV-2 vaccine with regard to preventing Covid-19 and related hospitalization, admission to the intensive care unit (ICU), and death. We estimated hazard ratios using the extension of the Cox proportional-hazards model, accounting for time-varying vaccination status. We estimated the change in the hazard ratio associated with partial immunization (≥14 days after receipt of the first dose and before receipt of the second dose) and full immunization (≥14 days after receipt of the second dose). Vaccine effectiveness was estimated with adjustment for individual demographic and clinical characteristics.

RESULTS

The study was conducted from February 2 through May 1, 2021, and the cohort included approximately 10.2 million persons. Among persons who were fully immunized, the adjusted vaccine effectiveness was 65.9% (95% confidence interval [CI], 65.2 to 66.6) for the prevention of Covid-19 and 87.5% (95% CI, 86.7 to 88.2) for the prevention of hospitalization, 90.3% (95% CI, 89.1 to 91.4) for the prevention of ICU admission, and 86.3% (95% CI, 84.5 to 87.9) for the prevention of Covid-19–related death.

CONCLUSIONS

Our results suggest that the inactivated SARS-CoV-2 vaccine effectively prevented Covid-19, including severe disease and death, a finding that is consistent with results of phase 2 trials of the vaccine. (Funded by Agencia Nacional de Investigación y Desarrollo and others.)

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This article was published on July 7, 2021, and updated on July 13, 2021, at NEJM.org.

N Engl J Med 2021;385:875-84.
DOI: 10.1056/NEJMoa2107715

The coronavirus disease 2019 (COVID-19) pandemic has imposed an enormous disease burden worldwide, with more than 159 million cases and approximately 3.3 million deaths reported as of May 10, 2021.[1] Covid-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and the severity ranges from mild symptoms to life-threatening disease.[2] Older age and underlying conditions substantially increase the case fatality rate.[3,4] Nonpharmaceutical interventions, such as social distancing, face masks, and contact tracing, have so far been the mainstay of health policy strategies to reduce viral spread and limit demands on health care.[5,6] New Covid-19 vaccines are beginning to change this situation. On December 2, 2020, the first vaccine tested in a large, randomized clinical trial was approved in the United Kingdom,[7,8] although some countries began vaccinations before clinical results were available. Several effective vaccines against Covid-19 have been developed and approved in record time,[8-12] and numerous new vaccines are in the final stages of clinical trials.[13]

Mass vaccination campaigns to prevent Covid-19 are now occurring in many countries.[14] Preliminary results of the effectiveness of other Covid-19 vaccines across different populations have been published, including studies at the national level in Israel[15] and Scotland[16] and studies involving essential frontline workers at specific locations in the United States.[17-19] Estimates of vaccine effectiveness in the prevention of Covid-19 are essential because they reflect real-world challenges, such as logistics, cold chains, vaccination schedules, and follow-up, and also involve more diverse populations than those selected in randomized clinical trials, such as older or immunocompromised persons or those with coexisting conditions. Despite being the standard for assessing vaccine efficacy, phase 3 clinical trials have some limitations, such as restrictive inclusion criteria and implementation under strict experimental conditions that may not resemble a mass vaccination rollout.[20] Thus, large observational studies to estimate the effectiveness of new vaccines in real-world settings are an essential complement to randomized, controlled trials.[21]

Existing vaccine-effectiveness estimates have focused on the BNT162b2 messenger RNA (mRNA) vaccine (Pfizer–BioNTech), the ChAdOx1 nCoV-19 vaccine (Oxford–AstraZeneca), and the mRNA-1273 vaccine (Moderna).[15-19] Several countries are conducting vaccination campaigns with the use of an inactivated SARS-CoV-2 vaccine (CoronaVac) amid a record surge of Covid-19 cases worldwide.[1,13] A total of 22 primarily low- and middle-income countries have approved the CoronaVac vaccine for emergency use. Despite its global importance, limited evidence is available on the efficacy or effectiveness of this vaccine.

Phase 1–2 trials of the CoronaVac vaccine[22] were carried out in China among participants 18 to 59 years of age[23] and in participants 60 years of age or older.[24] The findings suggested that the vaccine was safe and immunogenic in most patients 14 days after receipt of the second dose. Phase 3 clinical trials are taking place in Brazil, Chile, Indonesia, and Turkey (ClinicalTrials.gov numbers, NCT04456595, NCT04651790, NCT04508075, and NCT04582344, respectively). Efficacy results from these trials have not yet been published, but reported efficacy estimates from the manufacturers with regard to mild Covid-19 have varied substantially among the sites: 50.7% (95% confidence interval [CI], 35.6 to 62.2) in Brazil, 65.3% in Indonesia, and 83.5% (95% CI, 65.4 to 92.1) in Turkey.[25-28] In addition, preliminary estimates from an observational study involving vaccinated health care workers (from a preprint server) suggested that at least one dose of the CoronaVac vaccine was 49.6% (95% CI, 11.3 to 71.4) effective against Covid-19 in Manaus, Brazil, a location where the P.1 (or gamma) variant, which is considered to be a variant of concern by the Centers for Disease Control and Prevention,[29] is predominant (occurred in approximately 75% of the test results).[30] No estimates of the effectiveness of the CoronaVac vaccine with regard to preventing Covid-19 in the general population or in persons who have received full vaccination are publicly available.

On February 2, 2021, Chile began a mass vaccination campaign with the CoronaVac vaccine (Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[31] The Public Health Institute of Chile approved the CoronaVac vaccine for emergency use on January 20, 2021; the vaccine is to be administered in a two-dose schedule, with doses separated by 28 days. The vaccination campaign prioritized older adults, beginning at 90 years of age or older; frontline health care workers; and persons with underlying conditions. The government relied on the existing health care infrastructure to roll the vaccines out to the eligible

population where they lived. Vaccination rollout was organized by means of a publicly available national schedule that assigned specific dates to eligible groups. Eligible persons needed to show up at the nearest vaccination site with their identification; they did not need to make an appointment (Figs. S3 and S4). A national immunization registry keeps track of the vaccination schedules. As of May 10, 2021, the Ministry of Health has administered 13.98 million doses of the CoronaVac vaccine (7.62 million first doses and 6.36 million second doses).[32] Vaccine introduction and scale-up of the campaign occurred during a period with the highest incidence rates of Covid-19 since the beginning of the pandemic in Chile.

We used a rich administrative observational data set to provide estimates of the effectiveness of the CoronaVac vaccine in preventing Covid-19 and related hospitalization, admission to the intensive care unit (ICU), and death in the Chilean population. We estimated the effectiveness of the administration of one vaccine dose and of two doses (the complete schedule), with adjustment for relevant demographic and clinical confounders of the association between vaccination and Covid-19 outcomes. We conducted robustness checks to test whether vaccine effectiveness would be affected by differences in health care access between the vaccinated and unvaccinated groups, and we provide vaccine-effectiveness estimates among persons 16 to 59 years of age and among those 60 years of age or older.

METHODS

STUDY POPULATION AND DESIGN

We used a prospective observational cohort at the national level. The study cohort included participants 16 years of age or older who were affiliated with Fondo Nacional de Salud (FONASA), the national public health insurance program, which includes approximately 80% of the Chilean population. A detailed description of the vaccination campaign is provided in the Supplementary Appendix. Eligibility criteria included an age of 16 years or more, affiliation with FONASA, and receipt of at least one dose of the CoronaVac vaccine between February 2 and May 1, 2021, or no receipt of any Covid-19 vaccination. We excluded participants with a probable or confirmed SARS-CoV-2 infection, as assessed by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay or antigen testing, on or before February 2, 2021, and persons who had received at least one dose of the BNT162b2 vaccine. We did not focus on the effectiveness of the BNT162b2 vaccine because these estimates have been provided elsewhere.[15,17] We focused on the results regarding the CoronaVac vaccine because they are the mainstay of the vaccination strategy in Chile. However, we provide estimates of the effectiveness of the BNT162b2 vaccine in the Supplementary Appendix as a validation of the procedures used here.

All persons 16 years of age or older are eligible to receive the vaccine, according to the national vaccination schedule. We classified participants into three groups: those who were not vaccinated, those who were partially immunized (≥14 days after receipt of the first vaccine dose and before receipt of the second dose), and those who were fully immunized (≥14 days after receipt of the second dose).

The study team was entirely responsible for the design of the study and for the collection and analysis of the data. The authors vouch for the accuracy and completeness of the data. The first, second, and last authors wrote the first draft of the manuscript.

OUTCOMES AND COVARIATES

We estimated vaccine effectiveness using four primary outcomes: laboratory-confirmed Covid-19, hospitalization for Covid-19, admission to the ICU for Covid-19, and Covid-19–related death. For all the outcomes, we considered the time from the beginning of follow-up (February 2, 2021) to the onset of symptoms as the end point. Vaccine-effectiveness estimates regarding Covid-19 cases included the more severe outcomes. All suspected cases of Covid-19 in Chile are notified to health authorities by means of an online platform and are confirmed by laboratory testing. In our study, cases of Covid-19 and related deaths were those in persons with laboratory-confirmed infection, which corresponds to code U07.1 in the *International Classification of Diseases, 10th Revision.*

We controlled for several patient characteristics that could confound the association between vaccination and outcomes, including age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19. These conditions included chronic kidney disease, diabetes, cardiovascular disease, stroke, chronic obstructive pulmonary disease, hematologic dis-

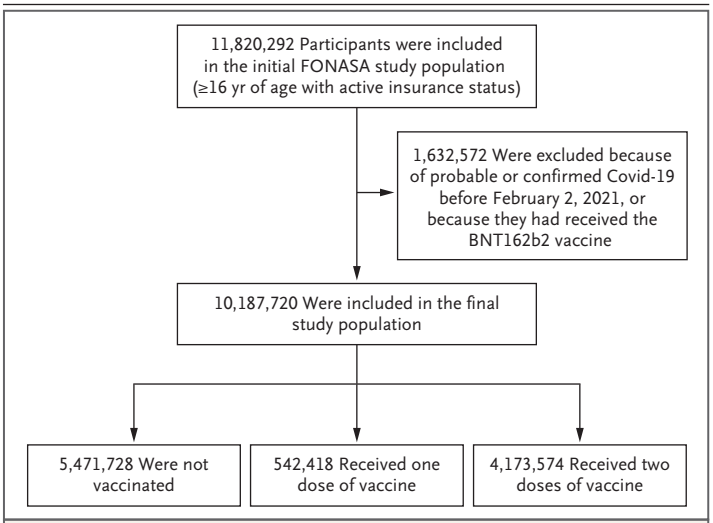

Figure 1. Study Participants and Cohort Eligibility.

Participants were at least 16 years of age, were affiliated with Fondo Nacional de Salud (FONASA; the national public health care system in Chile), and either had received at least one dose of the CoronaVac vaccine between February 2 and May 1, 2021, or had not received any vaccination. We excluded persons who had probable or confirmed coronavirus disease 2019 (Covid-19) according to reverse-transcriptase–polymerase-chain-reaction assay for severe acute respiratory syndrome coronavirus 2 and all persons who had been immunized with the BNT162b2 vaccine.

ease, autoimmune disease, human immunodeficiency virus infection, and Alzheimer's disease and other dementias.[4,33-35]

STATISTICAL ANALYSIS

Our analysis was broadly based on the analytic methods of Thompson et al.[17] for estimating vaccine effectiveness in the United States. We determined vaccine effectiveness by estimating the hazard ratio between the vaccinated and unvaccinated groups. On the basis of the observed information regarding the time to symptom onset from February 2, 2021, we estimated hazard ratios using the extension of the Cox proportional-hazards model, which allowed us to account for a time-varying vaccination status of the persons in the study. We evaluated the robustness of the model assumptions by fitting a stratified version of the extended Cox proportional-hazards model using the available predictors. Inference was based on a partial likelihood approach (Section S2).[17] We estimated the change in the hazard associated with partial immunization and full immunization, and both time-to-event analyses were performed separately. Because the immunity status induced by the CoronaVac vaccine is unknown during the 13 days between vaccine administration and partial or full immunization, those periods were excluded from the at-risk person-time in our analyses.[17]

We estimated the vaccine effectiveness as 1 minus the corresponding hazard ratio, obtained from a model including the previously described covariates, which was expressed as a percentage. We also provide the results with adjustment for the effect of sex and age only. To evaluate whether our effectiveness results were affected by potentially different access to health care between vaccinated persons and unvaccinated persons and according to the age distribution, we performed subgroup analyses involving the subgroup of persons with access to RT-PCR or antigen testing for SARS-CoV-2 and subgroups of persons 60 years of age or older and persons 16 to 59 years of age. Statistical analyses were conducted with the use of the survival package of R software, version 4.0.5.[36,37]

RESULTS

STUDY POPULATION AND VACCINATION ROLLOUT

Figure 1 shows the flow diagram of the study cohort. Of the 11,820,292 persons 16 years of age or older who were affiliated with FONASA, 10,187,720 were eligible for inclusion in the study. Table 1 shows the descriptive statistics for the approximately 10.2 million participants included in the study cohort. There were significant differences according to geographic region, sex, age, income group, nationality, and presence of underlying medical conditions, both in the incidence of Covid-19 and according to vaccination status (unvaccinated, vaccinated with only one dose, or vaccinated with two doses). Laboratory confirmation of infection was by RT-PCR assay in 98.1% of the cases and by antigen testing in 1.9%. Figure 2A shows the rapid rollout of the vaccination campaign, which started on February 2, 2021. Details of the vaccination campaign are provided in Section S1 and Figures S5 through S8. Figure 2B shows the crude cumulative incidence of Covid-19 during the study period among persons who had received one or two doses of vaccine or were unvaccinated.

VACCINE EFFECTIVENESS

There were approximately 615 million person-days in the unvaccinated group, 70 million person-days in the partially immunized group, and 92 million

Table 1. Characteristics of the Study Cohort, Overall and Those with Laboratory-Confirmed Covid-19, According to Vaccination Status.*

Characteristic	Cohort Participants		Persons with Covid-19		P Value	Unvaccinated Persons		Persons Vaccinated with One Dose		Persons Vaccinated with Two Doses		P Value
	no.	%	no.	%		no.	%	no.	%	no.	%	
Total	10,187,720	100	248,645	2.4	—	5,471,728	53.7	542,418	5.3	4,173,574	41.0	—
Sex												<0.001
Female	5,469,202	54.0	135,311	2.5	<0.001	2,775,436	50.8	272,044	5.0	2,421,722	44.3	
Male	4,718,518	46.0	113,334	2.4		2,696,292	57.1	270,374	5.7	1,751,852	37.1	
Age group												<0.001
16–19 yr	708,676	7.0	14,871	2.1	<0.001	670,451	94.6	8,192	1.2	30,033	4.2	
20–29 yr	2,017,676	20.0	59,645	3.0		1,655,595	82.1	55,854	2.8	306,227	15.2	
30–39 yr	1,867,491	18.0	54,480	2.9		1,446,544	77.5	59,166	3.1	361,781	19.4	
40–49 yr	1,423,770	14.0	39,993	2.8		851,622	59.8	165,487	11.6	406,661	28.6	
50–59 yr	1,457,564	14.0	37,539	2.6		434,694	29.8	184,268	12.6	838,602	57.5	
60–69 yr	1,365,940	13.0	23,669	1.7		221,738	16.2	41,693	3.1	1,102,509	80.7	
70–79 yr	870,082	8.5	11,778	1.4		111,592	12.8	16,412	1.9	742,078	85.3	
≥80 yr	476,521	4.7	6,670	1.4		79,492	16.7	11,346	2.4	385,683	80.9	
No. of coexisting conditions†												<0.001
0	6,880,426	68.0	168,401	2.4	0.04	4,447,684	64.6	394,030	5.7	2,038,712	29.6	
≥1	3,307,294	32.0	80,244	2.4		1,024,044	31.0	148,388	4.5	2,134,862	64.6	<0.001
Nationality												
Chilean	9,497,058	93.2	233,572	2.5	<0.001	4,913,208	51.7	513,604	5.4	4,070,246	42.9	
Non-Chilean	690,662	6.8	15,073	2.2		558,520	80.9	28,814	4.2	103,328		

* The study cohort included eligible persons who were affiliated with Fondo Nacional de Salud, the national public health insurance program, which collects, manages, and distributes funds for the public health care system in Chile. The model also included individual-level income and location (16 regions). Additional details are provided in Table S1. Covid-19 denotes coronavirus disease 2019.

† Coexisting conditions included chronic kidney disease, diabetes, cardiovascular disease (hypertension or myocardial infarction), stroke, chronic obstructive pulmonary disease, hematologic disease (lymphoma, leukemia, or myeloma), autoimmune disease (rheumatoid arthritis, juvenile idiopathic arthritis, or systemic lupus erythematosus), human immunodeficiency virus infection, and Alzheimer's disease and other dementias.

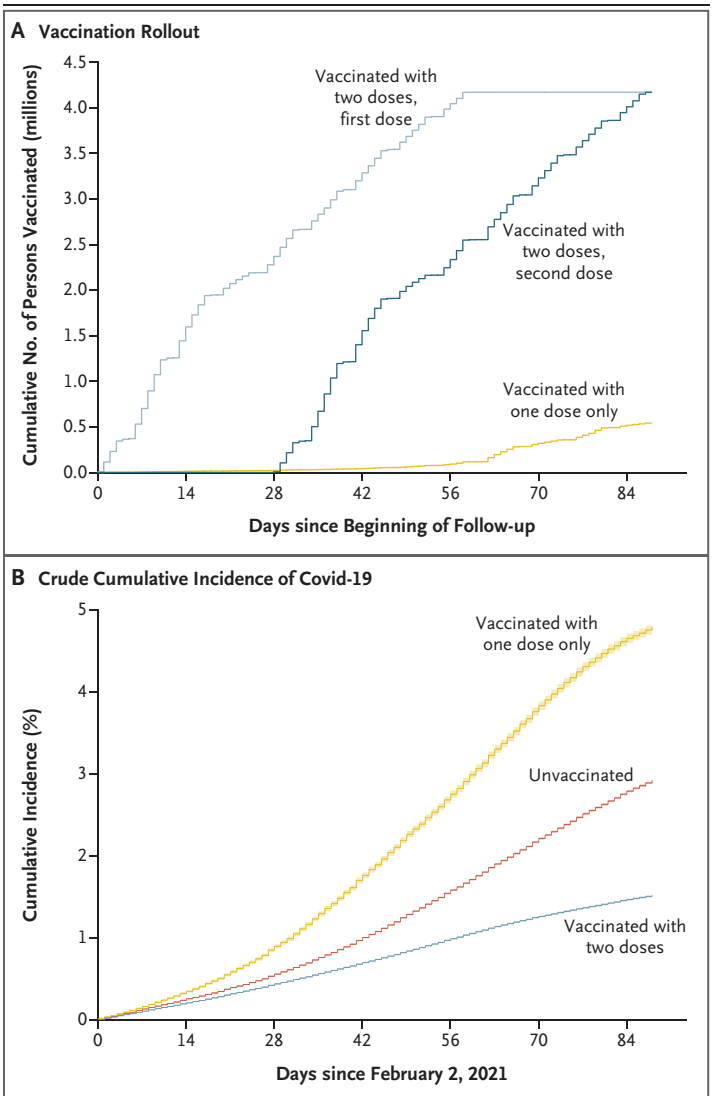

Figure 2. Vaccination Rollout and Crude Cumulative Incidence of Covid-19 in the Study Cohort.

Panel A shows the pace and coverage of the vaccination program among persons who received both doses of vaccine (first and second doses shown separately) or only one dose during the study period (February 2 through May 1, 2021). Panel B shows the crude cumulative incidence of Covid-19 during the study period among unvaccinated persons, among persons who had received only one dose of vaccine, and among persons who had received both doses of vaccine. The relatively high cumulative incidence of Covid-19 in the one-dose group should be interpreted with caution. As shown in Panel A, this group initiated vaccination approximately 40 days after the beginning of the vaccination campaign on February 2, 2021. Therefore, the incidence curve includes all cases that occurred from before vaccination up to 13 days after receipt of the first dose. Shading on the lines indicates 95% confidence intervals.

person-days in the fully immunized group during the study period (Table 2). We documented 218,784 cases of Covid-19, as well as 22,866 hospitalizations, 7873 ICU admissions, and 4042 deaths.

We estimated that the vaccine effectiveness among partially immunized persons (14 to 28 days after receipt of the first dose) was 15.5% (95% CI, 14.2 to 16.8) for the prevention of Covid-19 and 37.4% (95% CI, 34.9 to 39.9) for the prevention of hospitalization, 44.7% (95% CI, 40.8 to 48.3) for the prevention of admission to the ICU, and 45.7% (95% CI, 40.9 to 50.2) for the prevention of Covid-19–related death. In the fully immunized group, the estimated adjusted vaccine effectiveness was 65.9% (95% CI, 65.2 to 66.6) for the prevention of Covid-19 and 87.5% (95% CI, 86.7 to 88.2) for the prevention of hospitalization, 90.3% (95% CI, 89.1 to 91.4) for the prevention of ICU admission, and 86.3% (95% CI, 84.5 to 87.9) for the prevention of Covid-19–related death (Table 2). The vaccine-effectiveness estimates in the stratified model were consistent with these results.

We estimated that the adjusted vaccine effectiveness in the subgroup of fully immunized persons 60 years of age or older was 66.6% (95% CI, 65.4 to 67.8) for the prevention of Covid-19 and 85.3% (95% CI, 84.3 to 86.3) for the prevention of hospitalization, 89.2% (95% CI, 87.6 to 90.6) for the prevention of ICU admission, and 86.5% (95% CI, 84.6 to 88.1) for the prevention of Covid-19–related death (Table 3). Vaccine-effectiveness estimates among persons 16 to 59 years of age are provided in Table S3.

To address a potential concern that the observed vaccine effectiveness may have been driven by health care access, we conducted an analysis in the subgroup of persons who had undergone testing with an RT-PCR assay (98.1%) or antigen test (1.9%) during the analysis period. The results, conditional on whether testing was performed, showed larger effects for vaccination than when we included the complete cohort. Among fully immunized persons in this subgroup, the adjusted vaccine effectiveness was 72.9% (95% CI, 72.3 to 73.4) for the prevention of Covid-19 and 89.2% (95% CI, 88.5 to 89.8) for the prevention of hospitalization, 91.6% (95% CI, 90.5 to 92.5) for the prevention of ICU admission, and 87.8% (95% CI, 86.2 to 89.2) for the prevention of Covid-19–related death (Table S4).

DISCUSSION

We provide estimates of the effectiveness of administration of the CoronaVac vaccine in a countrywide mass vaccination campaign for the prevention of laboratory-confirmed Covid-19 and related hospitalization, admission to the ICU, and

Table 2. Effectiveness of CoronaVac Vaccine in Preventing Covid-19 Outcomes in Overall Study Cohort, According to Immunization Status.*

Outcome and Immunization Status	Study Cohort	Persons with Covid-19		Vaccine Effectiveness (95% CI)		
	No. of Person-Days	No. of Persons	Incidence Rate	Analysis Adjusted for Sex and Age	Analysis Adjusted for All Covariates†	Stratified Analysis‡
			no. of events/ 1000 person-days		*percent*	
Covid-19						
Unvaccinated	614,868,240	185,633	0.3019	—	—	—
Partially immunized	69,788,352	20,865	0.2990	8.0 (6.5–9.4)	15.5 (14.2–16.8)	17.2 (15.8–18.6)
Fully immunized	91,671,797	12,286	0.1340	61.2 (60.3–62.0)	65.9 (65.2–66.6)	63.7 (62.8–64.6)
Hospitalization						
Unvaccinated	620,894,706	18,034	0.0290	—	—	—
Partially immunized	70,690,796	3,370	0.0477	31.4 (28.6–34.0)	37.4 (34.9–39.9)	40.3 (37.6–42.8)
Fully immunized	92,445,333	1,462	0.0158	86.0 (85.1–86.8)	87.5 (86.7–88.2)	86.5 (85.6–87.4)
Admission to ICU						
Unvaccinated	621,226,431	6,359	0.0102	—	—	—
Partially immunized	70,836,597	1,154	0.0163	37.5 (33.1–41.5)	44.7 (40.8–48.3)	45.3 (41.2–49.2)
Fully immunized	92,622,083	360	0.0039	88.8 (87.4–90.0)	90.3 (89.1–91.4)	90.2 (88.9–91.4)
Confirmed death						
Unvaccinated	621,426,477	2,786	0.0045	—	—	—
Partially immunized	70,854,187	847	0.0120	39.8 (34.4–44.7)	45.7 (40.9–50.2)	46.0 (40.7–50.8)
Fully immunized	92,514,261	409	0.0044	84.4 (82.4–86.2)	86.3 (84.5–87.8)	86.7 (84.9–88.3)

* Participants were classified into three groups: those who were unvaccinated, those who were partially immunized (≥14 days after receipt of the first vaccine dose and before receipt of the second dose), and those who were fully immunized (≥14 days after receipt of the second dose). The 13 days between vaccine administration and partial or full immunization were excluded from the at-risk person-time. ICU denotes intensive care unit.

† The analysis was adjusted for age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19.

‡ A stratified version of the extended Cox proportional-hazards model was fit to test the robustness of the estimates to model assumptions, with stratification according to age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19.

death. Among fully immunized persons, the adjusted vaccine effectiveness was 65.9% for Covid-19 and 87.5% for hospitalization, 90.3% for ICU admission, and 86.3% for death. The vaccine-effectiveness results were maintained in both age-subgroup analyses, notably among persons 60 years of age or older, independent of variation in testing and independent of various factors regarding vaccine introduction in Chile.

The vaccine-effectiveness results in our study are similar to estimates that have been reported in Brazil for the prevention of Covid-19 (50.7%; 95% CI, 35.6 to 62.2), including estimates of cases that resulted in medical treatment (83.7%; 95% CI, 58.0 to 93.7) and estimates of a composite end point of hospitalized, severe, or fatal cases (100%; 95% CI, 56.4 to 100).[27] The large confidence intervals for the trial in Brazil reflect the relatively small sample (9823 participants) and the few cases detected (35 cases that led to medical treatment and 10 that were severe). However, our estimates are lower than the vaccine effectiveness recently reported in Turkey (83.5%; 95% CI, 65.4 to 92.1),[27,28] possibly owing to the small sample in that phase 3 clinical trial (10,029 participants in the per-protocol analysis), differences in local transmission dynamics, and the predominance of older adults among the fully or partially immunized participants in our study. Overall, our results suggest that the CoronaVac vaccine had high effectiveness against severe disease, hospitalizations, and death, findings that underscore the

Table 3. Effectiveness of CoronaVac Vaccine in Preventing Covid-19 Outcomes among Cohort Participants 60 Years of Age or Older, According to Immunization Status.

Outcome and Immunization Status	Subgroup Cohort	Persons with Covid-19		Vaccine Effectiveness (95% CI)		
	No. of Person-Days	No. of Persons	Incidence Rate	Analysis Adjusted for Sex and Age	Analysis Adjusted for All Covariates*	Stratified Analysis†
			no. of events/ 1000 person-days		*percent*	
Covid-19						
Unvaccinated	75,707,905	15,597	0.2060	—	—	—
Partially immunized	35,675,604	8,333	0.2336	3.9 (0.9–6.8)	9.7 (6.9–12.4)	12.7 (9.8–15.5)
Fully immunized	66,563,272	7,510	0.1128	63.4 (62.0–64.6)	66.6 (65.4–67.8)	67.2 (66.0–68.4)
Hospitalization						
Unvaccinated	76,047,640	5,304	0.0697	—	—	—
Partially immunized	35,961,593	2,168	0.0603	29.2 (25.1–33.1)	35.0 (31.3–38.6)	38.6 (34.8–42.2)
Fully immunized	66,986,859	1,344	0.0201	83.4 (82.2–84.5)	85.3 (84.3–86.3)	85.4 (84.3–86.4)
Admission to ICU						
Unvaccinated	76,194,648	1,811	0.0238	—	—	—
Partially immunized	36,062,081	672	0.0186	38.2 (31.9–44.0)	44.5 (38.7–49.7)	47.0 (41.2–52.2)
Fully immunized	67,051,769	331	0.0049	87.5 (85.7–89.0)	89.2 (87.6–90.6)	89.3 (87.8–90.7)
Confirmed death						
Unvaccinated	76,169,386	1,999	0.0262	—	—	—
Partially immunized	36,053,806	768	0.0213	39.7 (33.8–45.1)	45.8 (40.4–50.7)	46.1 (40.5–51.2)
Fully immunized	67,045,620	402	0.0060	84.4 (82.3–86.2)	86.5 (84.6–88.1)	86.8 (85.0–88.4)

* The analysis was adjusted for age, sex, region of residence, income, nationality, and whether the patient had underlying conditions that have been associated with severe Covid-19.
† A stratified version of the extended Cox proportional-hazards model was fit to test the robustness of the estimates to model assumptions, with stratification according to sex, age, coexisting conditions, nationality, and income.

potential of this vaccine to save lives and substantially reduce demands on the health care system.

Our study has at least three main strengths. First, we used a rich administrative health care data set, combining data from an integrated vaccination system for the total population and from the Ministry of Health FONASA, which covers approximately 80% of the Chilean population. These data include information on laboratory tests, hospitalization, mortality, onset of symptoms, and clinical history in order to identify risk factors for severe disease. Information on region of residence also allowed us to control for differences in incidence across the country. We adjusted for income and nationality, which correlate with socioeconomic status in Chile and are thus considered to be social determinants of health. The large population sample allowed us to estimate vaccine effectiveness both for one dose and for the complete two-dose vaccination schedule. It also allowed for a subgroup analysis involving adults 60 years of age or older, a subgroup that is at higher risk for severe disease[3] and that is underrepresented in clinical trials. Second, data were collected during a rapid vaccination campaign with high uptake and during a period with one of the highest community transmission rates of the pandemic, which allowed for a relatively short follow-up period and for estimation of the prevention of at least four essential outcomes: Covid-19 cases and related hospitalization, ICU admission, and death. Finally, Chile has the highest testing rates for Covid-19 in Latin America, universal health care access, and a standardized, public reporting system for vital statistics, which limited the number of undetected or unascertained cases and deaths.[14]

Our study has several limitations. First, as an observational study, it is subject to confounding. To account for known confounders, we adjusted the analyses for relevant variables that could affect vaccine effectiveness, such as age, sex, underlying medical conditions, region of residence, and nationality. The risk of misclassification bias that would be due to the time-dependent performance of the SARS-CoV-2 RT-PCR assay is relatively low, because the median time from symptom onset to testing in Chile is approximately 4 days (98.1% of the tests were RT-PCR assays). In this 4-day period, the sensitivity and specificity of the molecular diagnosis of Covid-19 are high.[38] However, there may be a risk of selection bias. Systematic differences between the vaccinated and unvaccinated groups, such as health-seeking behavior or risk aversion, may affect the probability of exposure to the vaccine and the risk of Covid-19 and related outcomes.[39,40] However, we cannot be sure about the direction of the effect. Persons may be hesitant to get the vaccine for various reasons, including fear of side effects, lack of trust in the government or pharmaceutical companies, or an opinion that they do not need it, and they may be more or less risk-averse. Vaccinated persons may compensate by increasing their risky behavior (Peltzman effect).[40] We addressed potential differences in health care access by restricting the analysis to persons who had undergone diagnostic testing, and we found results that were consistent with those of our main analysis.

Second, owing to the relatively short follow-up in this study, late outcomes may not have yet developed in persons who were infected near the end of the study, because the time from symptom onset to hospitalization or death can vary substantially.[3,15] Therefore, effectiveness estimates regarding severe disease and death, in particular, should be interpreted with caution. Third, during the study period, ICUs in Chile were operating at 93.5% of their capacity on average (65.7% of the patients had Covid-19).[32] If fewer persons were hospitalized than would be under regular ICU operation, our effectiveness estimates for protection against ICU admission might be biased downward, and our effectiveness estimates for protection against death might be biased upward (e.g., if patients received care at a level lower than would usually be received during regular health system operation).

Fourth, although the national genomic surveillance for SARS-CoV-2 in Chile has reported the circulation of at least two viral lineages considered to be variants of concern, P.1 and B.1.1.7 (or the gamma and alpha variants, respectively),[41] we lack representative data to estimate their effect on vaccine effectiveness (Table S2). Results from a test-negative design study of the effectiveness of the CoronaVac vaccine in health care workers in Manaus, Brazil, where the gamma variant is now predominant, showed that the efficacy of at least one dose of the vaccine against Covid-19 was 49.6% (95% CI, 11.3 to 71.4).[30] Although the vaccine-effectiveness estimates in Brazil are not directly comparable with our estimates owing to differences in the target population, the vaccination schedule (a window of 14 to 28 days between doses is recommended in Brazil[42]), and immunization status, they highlight the importance of continued vaccine-effectiveness monitoring.

Overall, our study results suggest that the CoronaVac vaccine was highly effective in protecting against severe disease and death, findings that are consistent with the results of phase 2 trials[23,24] and with preliminary efficacy data.[27,28]

The research protocol was approved by the Comité Ético Científico Clínica Alemana Universidad del Desarrollo. The study was considered exempt from informed consent; no human health risks were identified. Research analysts are employees of the Chilean Ministry of Health; our use of data follows Chilean law 19.628 on private data protection.

Presented in part at the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) meeting on coronavirus disease 2019 (Covid-19) vaccines, April 29, 2021, and the WHO Vaccines Prioritization Working Group, April 21, 2021.

Supported by grants from the Agencia Nacional de Investigación y Desarrollo (ANID) Millennium Science Initiative Program, Millennium Nucleus Center for the Discovery of Structures in Complex Data (MIDAS) (NCN17_059, to Dr. Jara), and Millennium Initiative for Collaborative Research in Bacterial Resistance (MICROB-R) (NCN17_081, to Drs. Undurraga and Araos); the Advanced Center for Chronic Diseases, ANID Fondo de Financiamiento de Centros de Investigación en Áreas Prioritarias (FONDAP) (15130011, to Dr. Araos); and the Research Center for Integrated Disaster Risk Management ANID FONDAP (15110017, to Dr. Undurraga).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Owing to data privacy regulations, the individual-level data in this study cannot be shared (Law N19.628). Aggregate data on vaccination and incidence are publicly available at https://github.com/MinCiencia/Datos-COVID19/.

We thank the attendees of the WHO meeting and working group for suggestions and comments; Drs. Ira Longini (University of Florida), Daniel Cohen (Tel Aviv University), Richard Peto (University of Oxford), Elizabeth Miller (Public Health England), and Myron M. Levine (University of Maryland); Drs. Catterina Ferreccio (Pontificia Universidad Católica de Chile), Ximena Aguilera (Universidad del Desarrollo), Maria T. Valenzuela (Universidad de Los Andes), Pablo Vial (Universidad del Desarrollo), Gonzalo Valdivia (Pontificia Universidad Católica de Chile), Fernando Otaiza (Ministerio de Salud), and Alvaro Erazo (Pontificia Universidad Católica de Chile), from the Chilean Covid-19 Advisory Group, for advice on the study design and interpretation of results; and Drs. José R. Zubizarreta (Harvard University) and Erika M.C. D'Agata (Brown University) for thoughtful suggestions.

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Artigo

6. Mortalidade de crianças por Covid é muito maior em países pobres, onde vacinação dos mais novos não está prevista

ESTUDO: *"COVID-19 vaccines for children in LMICs: another equity issue"*

REVISTA: *The New England Journal of Medicine*

DATA DE PUBLICAÇÃO: *2/9/2021*

A mortalidade de crianças por Covid-19 é muito maior em países pobres do que nos países ricos, ou seja, justamente nas nações que ainda não incluíram esse público em seus programas de vacinação. A desigualdade na distribuição de vacinas e no atendimento médico explicam o problema e abrem a discussão de quando e como incluir essa população na vacinação contra Covid-19, escreveram as pesquisadoras Beate Kampmann e Uduak Okomo, da London School of Hygiene &Tropical Medicine, em um artigo na revista científica The Lancet.

As pesquisadoras levantam a tese com base nos resultados de uma meta-análise (método estatístico que analisa dados de dois ou mais estudos) que concluiu que 91,5% das mortes globais de crianças e adolescentes por Covid-19 foram notificadas em países de baixa e média renda, enquanto 83,5% da população pediátrica infectada era proveniente destes países.

O robusto estudo, que revisou mais de 16 mil artigos científicos e 225 relatórios nacionais de 216 países, apontou que a taxa de mortalidade foi significativamente mais alta em países de baixa e média renda do que nos países ricos: 2,77 versus 1,32 a cada 1 milhão de crianças. Os dados compilados por pesquisadores da Universidade de Toronto foram publicados na revista científica PLOS One.

"Esta grande desigualdade impede que os países de baixa e média renda não apenas previnam a morte e doenças graves, mas também implantem vacinas como ferramentas para interromper a transmissão do SARS-CoV-2. A inclusão das crianças e adolescentes não será uma prioridade nestes países mais pobres por um longo tempo por causa das graves deficiências na distribuição das vacinas", descrevem no artigo.

Diante dos dados, as pesquisadoras apontam que a proteção das crianças contra Covid-19 dependerá mais de fatores nacionais e de políticas

públicas, que podem incluir ou não o acesso desse público às vacinas.

"Os impactos da vacinação contra Covid-19 em crianças e adolescentes na dinâmica de transmissão irão variar nacionalmente, levando em conta circunstâncias epidemiológicas, o surgimento de novas variantes do SARS-CoV-2 e estratégias de mitigação de contato com papéis diferentes em lugares diferentes", completam.

Tanta desigualdade desfoca os resultados de estudos com vacinas de vírus inativado, como a CoronaVac, e vacinas de RNA mensageiro, que demonstraram ser seguras e imunogênicas para crianças e adolescentes, na opinião das pesquisadoras.

"Não há razão para acreditar que as vacinas não devam ser igualmente protetoras contra Covid-19 em crianças e adolescentes, como nos adultos. Mais de 30 ensaios internacionais recrutam crianças e adolescentes a partir de seis meses para avaliar a segurança, imunogenicidade, dosagem e distribuição", explicam.

COVID-19 vaccines for children in LMICs: another equity issue


Hindustan Times/Getty Images

Published **Online**
July 30, 2021
https://doi.org/10.1016/
S0140-6736(21)01748-7

Given the success of COVID-19 vaccines in preventing death and severe disease in adults[1] and their impact on community transmission,[2] use in children and young people (CYP) inevitably requires consideration. Although severe COVID-19 is rare in CYP,[3] they are affected by SARS-CoV-2 infection and the impacts of the COVID-19 pandemic, including education, mental health, and general wellbeing.[4]

As of late July, 2021, no COVID-19 vaccine is recommended for children younger than 12 years and safety and efficacy data from phase 3 clinical trials are so far limited: 1131 CYP aged 12–15 years received the Pfizer–BioNTech mRNA vaccine[5] and safety data are available from phase 1 and 2 trials of Sinovac's inactivated CoronaVac vaccine in 438 children aged 3–17 years.[6] Safety data have been reassuring, with published data confirming excellent immunogenicity.[5] There is no reason to believe the vaccines should not be equally protective against COVID-19 in CYP as they are in adults. More than 30 international trials are now recruiting CYP as young as 6 months to assess safety, immunogenicity, dosing, and scheduling questions.[7] Safety data from the Pfizer–BioNTech mRNA vaccine trial proved sufficient for regulatory authorities in the EU, Israel, and North America to issue approval for use of this vaccine in CYP aged 12–15 years. Safety data from the real-life roll-out of COVID-19 vaccines are continuously collected through surveillance systems in high-income countries (HICs)[8,9] and are generally reassuring, although a rare vaccine-associated signal of transient inflammation of the heart muscle in some young adults has raised concerns.[10] On balance, the US Centers for Disease Control and Prevention concluded that benefits outweigh the risks.[11]

Countries are also still calculating what indirect benefits for reduced SARS-CoV-2 transmission in schools and the wider community could be achieved by vaccinating CYP. With children now recognised as part of the chains of community transmission,[4] the discussion about a CYP vaccine programme was perhaps inescapable. Yet the impacts of COVID-19 vaccination in CYP on transmission dynamics will vary nationally, since epidemiological circumstances, novel SARS-CoV-2 variants, and contact mitigation strategies will have different roles in different places.

Most countries have yet to decide whether to include CYP in COVID-19 vaccination programmes. Canada, Israel, some European countries, and the USA have introduced the vaccine for all young people older than 12 years. By contrast, countries such as Germany and the UK are focusing on groups most at risk of severe COVID-19, but are not universally rolling out COVID-19 vaccination to CYP older than 12 years.[12]

Unsurprisingly, low-income and middle-income countries (LMICs) have not yet introduced COVID-19 vaccines for CYP. WHO guidance from July 14, 2021, states: "Children and adolescents tend to have milder disease compared to adults, so unless they are part of a group at higher risk of severe COVID-19, it is less urgent to vaccinate them than older people, those with chronic health conditions and health workers…WHO's Strategic Advisory Group of Experts (SAGE) has concluded that the Pfizer–BioNTech vaccine is suitable for use by people aged 12 years and above. Children aged between 12 and 15 who are at high risk may be offered this vaccine alongside other priority groups for vaccination. Vaccine trials for children are ongoing and WHO will update its recommendations when the evidence or epidemiological situation warrants a change in policy."[13]

Further data from LMICs will aid risk assessments of SARS-CoV-2 in CYP, both for personal health and transmission roles. A recent meta-analysis indicated that the outcome of children admitted to hospital with acute COVID-19 is worse in LMICs than in HICs (case fatality rates 0·29% [95% CI 0·28–0·31%] *vs* 0·03% [0·03–0·03%]).[14] Vaccinating CYP in LMICs may ultimately have more benefit to their health status compared with CYP in HICs.

All vaccines should be given to those who need them most, particularly in the context of a pandemic with limited vaccine supply. Of the more than 4 billion doses of COVID-19 vaccines administered globally in the past 8 months, less than 2% have been given in Africa;[15] on a continent that cannot vaccinate its most vulnerable populations (eg, older people and those with chronic conditions) and highly exposed health-care workers, introducing vaccines for CYP remains a luxury. This gross inequity prevents LMICs from not only preventing death and serious illness,

but also from deploying vaccines as tools to interrupt SARS-CoV-2 transmission. The inclusion of CYP will not be a priority in LMICs for a long time because of the serious shortfalls of vaccines.

What of the WHO motto that "No one is safe till everyone is safe"? HICs have unlimited stocks of COVID-19 vaccines.[16] If a key reason for the use of the COVID-19 vaccines in CYP in HICs is reducing SARS-CoV-2 transmission, surely CYP in LMICs should also be vaccinated? We are far from the vision of the African Union (AU) to vaccinate two-thirds of its members' population. In addition to COVAX, the AU has now partnered with additional vaccine suppliers through the AU's African Vaccine Acquisition Trust, including UNICEF.[17] However, even vaccinating 66% of individuals is unlikely to be sufficient to interrupt transmission chains.

In addition to supply issues and logistics that prevent the use of COVID-19 vaccines in CYP in LMICs, the success of any plans to roll out the vaccines must also ride on the back of acceptance and confidence. Parents in LMICs need reassurance they are doing the right thing for their children, just as has been found in HICs.[18]

During deliberations on the potential benefits of COVID-19 vaccines for CYP, it is important to recognise that this pandemic has already deprived more than 8 million children, primarily in LMICs, from life-saving, routine childhood vaccines.[19] Immunisation services are preoccupied with the implementation of COVID-19 vaccine programmes for adults. At present, greater benefit for children's health globally will be derived by delivering the health interventions we already know will save their lives, such as vaccines against measles and other vaccine-preventable diseases, than by focusing on delivering COVID-19 vaccines to part of a population that does not currently represent a strategic priority in the response to this pandemic. Although maybe not equitable, we believe this approach is more important for the health of CYP at this point in time.

BK has received institutional grants from Pfizer for a maternal immunisation study unrelated to COVID-19; and received personal fees for services to a Data and Safety Monitoring Board from Johnson & Johnson for a COVID-19 vaccine study and for scientific advisory boards from Pfizer, Sanofi, and GlaxoSmithKline for non-COVID-19-related vaccines for use in pregnancy. UO declares no competing interests.

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Artigo

7. CoronaVac é segura e gera forte resposta imune em crianças e adolescentes, confirma estudo

ESTUDO: *"Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial"*

REVISTA: *The Lancet Infectious Diseases*

DATA DE PUBLICAÇÃO: *8/7/2021*

A CoronaVac, vacina contra a Covid-19 desenvolvida pela biofarmacêutica chinesa Sinovac Biotech e produzida no Brasil pelo Butantan, é segura para a população de três a 17 anos de idade e pode induzir uma forte produção de anticorpos no grupo pediátrico. As conclusões foram obtidas nos estudos clínicos de fases 1 e 2 conduzidos pela Sinovac com a aplicação da CoronaVac em crianças e adolescentes. Os resultados foram publicados no periódico científico The Lancet Infectious Diseases.

Este é o primeiro estudo do mundo a avaliar o uso de uma vacina contra a Covid-19 em uma população a partir dos três anos de idade. "Crianças e adolescentes com Covid-19 geralmente têm infecções leves ou assintomáticas em comparação aos adultos. Apesar disso, um pequeno número ainda pode estar em risco de doença grave e essa população ainda pode transmitir o vírus a outras pessoas. Portanto, é vital testar a segurança e a eficácia das vacinas contra a Covid-19 em grupos de idades mais jovens", disse o gerente geral da Sinovac, Gao Qiang, em comunicado publicado no site da farmacêutica.

O estudo randomizado, controlado e duplo-cego avaliou 550 crianças (71 na fase 1 e 479 na fase 2) de três a 17 anos para medir a segurança, a tolerabilidade e a imunogenicidade da aplicação de duas doses da Coronavac com um intervalo de 28 dias entre elas.

Um grupo tomou a vacina enquanto o outro recebeu placebo com hidróxido de alumínio, adjuvante não nocivo ao organismo presente na fórmula do imunizante. As análises apontaram que a vacina foi capaz de gerar anticorpos em 96% dos voluntários 28 dias após a segunda dose. Na fase 1, nenhum dos participantes tinha anticorpos neutralizantes contra o SARS-CoV-2 e, 28 dias após a vacinação, 100% deles apresentaram anticorpos.

Na fase 2, alguns voluntários receberam duas aplicações com dosagens menores (1,5µg) e outros receberam dosagens maiores (3µg). Enquanto no primeiro grupo 95% dos participantes apresentaram anticorpos no sangue, este número foi de 100% no segundo grupo. Por isso, os pesquisadores optaram por seguir apenas com a dosagem mais alta no ensaio clínico de fase 3, que ainda está em andamento.

As reações adversas foram de leves a moderadas, sendo dor no local da aplicação e febre as mais comuns, com desaparecimento dos sintomas em até 48 horas. 27% dos participantes relataram efeitos colaterais. Houve apenas um caso de evento adverso grave, não associado à vacina - uma criança teve pneumonia após receber placebo.

Publicado em: 08/07/2021

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial

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Summary

Background A vaccine against SARS-CoV-2 for children and adolescents will play an important role in curbing the COVID-19 pandemic. Here we aimed to assess the safety, tolerability, and immunogenicity of a candidate COVID-19 vaccine, CoronaVac, containing inactivated SARS-CoV-2, in children and adolescents aged 3–17 years.

Methods We did a double-blind, randomised, controlled, phase 1/2 clinical trial of CoronaVac in healthy children and adolescents aged 3–17 years old at Hebei Provincial Center for Disease Control and Prevention in Zanhuang (Hebei, China). Individuals with SARS-CoV-2 exposure or infection history were excluded. Vaccine (in 0·5 mL aluminum hydroxide adjuvant) or aluminum hydroxide only (alum only, control) was given by intramuscular injection in two doses (day 0 and day 28). We did a phase 1 trial in 72 participants with an age de-escalation in three groups and dose-escalation in two blocks (1·5 μg or 3·0 μg per injection). Within each block, participants were randomly assigned (3:1) by means of block randomisation to receive CoronaVac or alum only. In phase 2, participants were randomly assigned (2:2:1) by means of block randomisation to receive either CoronaVac at 1·5 μg or 3·0 μg per dose, or alum only. All participants, investigators, and laboratory staff were masked to group allocation. The primary safety endpoint was adverse reactions within 28 days after each injection in all participants who received at least one dose. The primary immunogenicity endpoint assessed in the per-protocol population was seroconversion rate of neutralising antibody to live SARS-CoV-2 at 28 days after the second injection. This study is ongoing and is registered with ClinicalTrials.gov, NCT04551547.

Findings Between Oct 31, 2020, and Dec 2, 2020, 72 participants were enrolled in phase 1, and between Dec 12, 2020, and Dec 30, 2020, 480 participants were enrolled in phase 2. 550 participants received at least one dose of vaccine or alum only (n=71 for phase 1 and n=479 for phase 2; safety population). In the combined safety profile of phase 1 and phase 2, any adverse reactions within 28 days after injection occurred in 56 (26%) of 219 participants in the 1·5 μg group, 63 (29%) of 217 in the 3·0 μg group, and 27 (24%) of 114 in the alum-only group, without significant difference (p=0·55). Most adverse reactions were mild and moderate in severity. Injection site pain was the most frequently reported event (73 [13%] of 550 participants), occurring in 36 (16%) of 219 participants in the 1·5 μg group, 35 (16%) of 217 in the 3·0 μg group, and two (2%) in the alum-only group. As of June 12, 2021, only one serious adverse event of pneumonia has been reported in the alum-only group, which was considered unrelated to vaccination. In phase 1, seroconversion of neutralising antibody after the second dose was observed in 27 of 27 participants (100·0% [95% CI 87·2–100·0]) in the 1·5 μg group and 26 of 26 participants (100·0% [86·8-100·0]) in the 3·0 μg group, with the geometric mean titres of 55·0 (95% CI 38·9–77·9) and 117·4 (87·8–157·0). In phase 2, seroconversion was seen in 180 of 186 participants (96·8% [93·1–98·8]) in the 1·5 μg group and 180 of 180 participants (100·0% [98·0–100·0]) in the 3·0 μg group, with the geometric mean titres of 86·4 (73·9–101·0) and 142·2 (124·7–162·1). There were no detectable antibody responses in the alum-only groups.

Interpretation CoronaVac was well tolerated and safe and induced humoral responses in children and adolescents aged 3–17 years. Neutralising antibody titres induced by the 3·0 μg dose were higher than those of the 1·5 μg dose. The results support the use of 3·0 μg dose with a two-immunisation schedule for further studies in children and adolescents.

Funding The Chinese National Key Research and Development Program and the Beijing Science and Technology Program.

Lancet Infect Dis 2021; 21: 1645–53

Published Online June 28, 2021 https://doi.org/10.1016/S1473-3099(21)00319-4

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Introduction

The ongoing COVID-19 pandemic, caused by SARS-CoV-2, has led to more than 174·5 million infections and more than 3·8 million deaths worldwide as of June 11, 2021.[1] Children and adolescents infected with SARS-CoV-2 are mainly mild or asymptomatic compared with adults, but a

Research in context

Evidence before this study

We searched PubMed on Apr 29, 2021, for published research articles, with no language or date restrictions, using the search terms of "SARS-CoV-2", "COVID-19", "vaccine", and "clinical trial". We identified several clinical trials of COVID-19 vaccines across different platforms, including mRNA, viral vector, protein subunit, and inactivated virus. The results from phase 1–3 studies have confirmed that different vaccines were safe, effective, and induced humoral antibody responses in adults. As of April 19, 2020, more than ten COVID-19 candidate vaccines have been rolled out in many countries for general population use. Although vaccine companies have started to assess the safety and efficacy of COVID-19 vaccines in populations of 6 months to 17 years of age, there are currently no authorised vaccines for use among children and adolescents under the age of 16. We previously assessed CoronaVac, an inactivated vaccine developed by Sinovac Life Sciences, in adults aged 18–59 years and those aged 60 years and older, and showed that it was safe and well tolerated. Seroconversion rates ranged from 92% to 100% after two doses of CoronaVac (3·0 μg and 6·0 μg) with two immunisation schedules (on days 0 and 14, or on days 0 and 28) in adults aged 18–59 years. Seroconversion rates were higher than 98% after two doses of CoronaVac (3 μg and 6 μg) with the 0–28 days schedule in patients aged 60 years and older.

Added value of this study

This is, we believe, the first report of an inactivated SARS-CoV-2 vaccine, CoronaVac, tested in children and adolescents aged 3–17 years. CoronaVac was found to be well tolerated and safe in this population. The seroconversion rates of neutralising antibody with both doses (1·5 μg and 3·0 μg) were over 96% after two-dose vaccination and the neutralising antibody titres induced by the 3·0 μg dose were higher than those induced by the 1.5 μg dose. Taken together, the 3·0 μg dose of CoronaVac induced higher immune responses compared with 1·5 μg dose.

Implications of all the available evidence

While a small number of children and adolescents with SARS-CoV-2 infection might be at risk for severe COVID-19 and complicated illnesses, they usually have mild or asymptomatic symptoms compared with adults. Nevertheless, children and adolescents can be important transmitters of SARS-CoV-2 in communities. Therefore, testing the effectiveness of COVID-19 vaccines in this population is important. CoronaVac was well tolerated and immunogenic in healthy children and adolescents aged 3–17 years in this trial, which supports the use of CoronaVac for further studies in this population.

relatively small number of children and adolescents might be at risk for severe COVID-19, especially those with underlying health comorbidities.[2–5] Studies have also found that the SARS-CoV-2 infection can lead to a serious complication called multisystem inflammatory syndrome in children, which includes myocardial dysfunction, shock, and respiratory failure requiring intensive care.[3,6,7] Furthermore, children and adolescents can be important transmitters of SARS-CoV-2 in communities.[8,9] Therefore, testing the effectiveness of COVID-19 vaccines in this population is important. As of June 11, 2021, a total of 287 candidate vaccines are in clinical or preclinical development.[10] The results from phase 3 trials of multiple vaccines across three platforms, including mRNA, viral vector, and inactivated virus, have confirmed that the vaccines are effective in preventing SARS-CoV-2 infection in adults,[11,12] and more than ten vaccines have been rolled out in many countries for general population use. No COVID-19 vaccines are authorised for use among children under the age of 12 years, but vaccine companies have been started to assess the safety and efficacy of various vaccine platforms among the population aged 6 months to 17 years.[13,14] The mRNA vaccine developed by Pfizer has shown 100% efficacy and robust antibody responses in adolescents aged 12–15 years.[15]

Purified inactivated viruses have traditionally been used for vaccine development. CoronaVac is an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (Beijing, China), which provided partial or complete protection in macaques following SARS-CoV-2 challenge, without observable antibody-dependent enhancement of infection.[16] The analyses from phase 1–3 trials have shown that CoronaVac was effective, immunogenic, and safe in adults aged 18 years and older.[12,17–19] Furthermore, another 11 inactivated COVID-19 candidate vaccines are in clinical evaluation, and several studies have also shown that the inactivated vaccines can induce neutralising antibody responses and have good safety profiles.[20–24]

The phase 1/2 trial of CoronaVac in children and adolescents was launched in October, 2020 to assess the safety, tolerability, and immunogenicity. Here we report the results of CoronaVac among healthy participants aged 3–17 years old.

Method

Study design and participants

We have done two phase 1/2 clinical trials of CoronaVac in participants aged 18–59 years and aged 60 years and older.[17,18] The preliminary immunogenicity and safety results supported the expansion of the trial to children and adolescents. We subsequently did a single-centre, randomised, double-blind, controlled, phase 1/2 trial to evaluate the safety, tolerability, and immunogenicity of CoronaVac in children and adolescents aged 3–17 years. On the basis of the results of previous trials and considering the low weight of this population, two different doses—1·5 μg and 3·0 μg—were adopted in this study.

This trial was run at Hebei Provincial Center for Disease Control and Prevention in Zanhuang (Hebei, China).

The phase 1 trial was an age de-escalation and dose-escalation study of 72 participants. Participants in each age group (3–5 years, 6–11 years, and 12–17 years) were recruited in order from the low-dose stage (block 1) to the high-dose stage (block 2). In block 1, participants were randomly assigned to receive either 1·5 μg vaccine or aluminum hydroxide adjuvant only (alum only, control) and participants in block 2 were randomly assigned to receive either 3·0 μg vaccine or alum only. In phase 1, 7 days of follow-up for safety were required before entering the next stage. The phase 2 trial was initiated only after all the participants in phase 1 had finished and passed a 7-days safety observation period after the first dose, as confirmed by the data monitoring committee. The required safety criteria were: no-life threatening vaccine-related adverse events (adverse reactions), no more than 15% of vaccinated participants reporting severe adverse reactions, and no other safety concerns in the opinion of the data monitoring committee. A total of 480 participants were recruited in phase 2, including 120 aged 3–5 years, 180 aged 6–11 years, and 180 aged 12–17 years.

Eligible participants were healthy children and adolescents aged 3–17 years. The key exclusion criteria included high-risk epidemiology history within 14 days before enrolment (eg, travel or residence history in communities with case reports, or contact history with someone infected with SARS-CoV-2), history of severe acute respiratory syndrome or SARS-CoV-2 infection (as reported by participants), axillary temperature of more than 37·0°, and history of allergy to any vaccine component. A complete list of exclusion criteria is listed in the protocol, which is available online.

Parents provided written informed consents, and participants 8–17 years of age also provided written assents before enrolment. The clinical trial protocol and informed consent form were approved by the Ethics Committee of Hebei CDC (IRB2020-005). The study was done in accordance with the requirements of Good Clinical Practice of China and the International Conference on Harmonisation.

Randomisation and masking

In phase 1, participants of block 1 and block 2 were randomly assigned (3:1) to either vaccine or alum only, and in phase 2, participants were randomly assigned (2:2:1) to either 1·5 μg, 3·0 μg of vaccine, or alum only. The randomisation codes for the phase 1 and phase 2 were generated by the randomisation statistician by means of block randomisation using SAS software (version 9.4). The randomisation code was assigned to each participant in sequence in the order of enrolment, and then the participants received the study vaccine labelled with the same code. The vaccine and alum only were completely identical in appearance, and all participants, investigators, and laboratory staff were masked to group allocation.

Procedures

CoronaVac is an inactivated vaccine candidate against SARS-CoV-2 infection. To prepare the vaccine, SARS-CoV-2 (CN02 strain) was propagated in African green monkey kidney cells (WHO Vero 10-87 Cells). At the end of the incubation period, the virus was harvested, inactivated with β-propiolactone, concentrated, purified, and finally adsorbed onto aluminum hydroxide. The aluminium hydroxide complex was then diluted in sodium chloride, phosphate-buffered saline, and water, before being sterilised and filtered for injection. The control was aluminum hydroxide adjuvant (alum only) with no virus. Both the vaccine and alum only were prepared in the Good Manufacturing Practice-accredited facility of Sinovac Life Science that was periodically inspected by the National Medical Products Administration committee for compliance. The production process of the vaccine in this trial was a highly automated bioreactor (ReadyToProcess WAVE 25, GE, Umea, Sweden), which was consistent with the production process of vaccine used in the phase 2 trial of adults aged 18–59 years and in the phase 1/2 trial of older adults aged at least 60 years.[17,18] Vaccine doses of 1·5 μg, or 3·0 μg in 0·5 mL of aluminium hydroxide diluent per dose and alum only in ready-to-use syringes were administered intramuscularly to participants on day 0 and day 28.

Participants were observed in the study site for at least 30 min after vaccination. For the first 7 days after each dose, parents or guardians of participants were required to record any injection-site adverse events (eg, pain, swelling, erythema), or systemic adverse events (eg, allergic reaction, cough, fever) on the diary cards. From day 8 to day 28 after each dose, safety data were collected by spontaneous report from the participants combined with the regular visit (which occurred on day 3, day 8 and day 28 after each dose in phase 1, and on day 8 and day 28 in phase 2). Solicited adverse events were recorded for 7 days after each dose and unsolicited adverse events for 28 days. The serious adverse events are recorded throughout the study and follow-up will continue until 12 months after the second dose. The reported adverse events were graded according to the China National Medical Products Administration guidelines.[25] The causal relationship between adverse events and vaccination was established by the investigators.

In the phase 1 trial, blood and urine samples were taken on day 3 after each dose and tested to investigate any abnormal changes of the haematology, biochemistry, and urine routine indexes. Blood samples were collected on day 0, 28, and 56 from participants in phase 1, and on day 0 and 56 in phase 2 to evaluate the neutralising antibody titres. The neutralising antibody titres to

For more on **exclusion criteria** see http://www.hebeicdc.cn/kygz/25011.jhtml

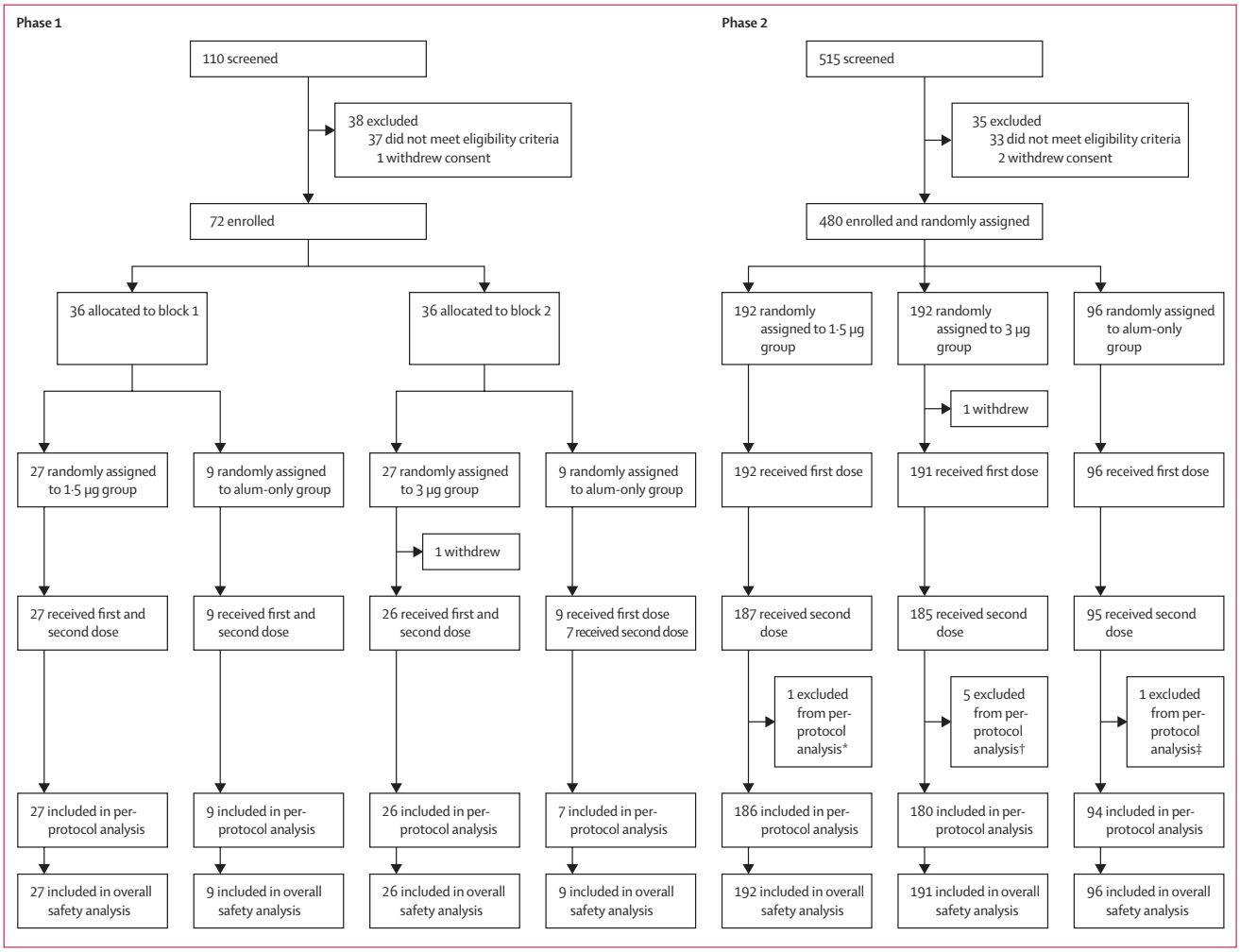

Figure 1: **Trial profile**
*One participant in the 1·5 µg group was excluded from the per-protocol analysis because he received tetanus immunoglobulin at day 14 after the second dose. †One participant in the 3 µg group was excluded from the per-protocol analysis because blood collection after vaccination was outside of the specified time window, and four did not have a blood sample taken 28 days after the second dose. ‡One participant in the alum only group was excluded from the per-protocol analysis because he did not have a blood sample taken 28 days after the second dose.

See Online for appendix

live SARS-CoV-2 (virus strain: SARS-CoV-2/human/CHN/CN1/2020, genebank number MT407649.1) was quantified by means of the microcytopathogenic effect assay.[26] Serum samples were inactivated at 56° for 30 min and serially diluted with cell culture medium in two-fold steps. The diluted serum samples were incubated with equal volume (50 µL) of the live SARS-CoV-2 virus suspension, with a 50% cell culture infective dose of 100 for 2 h at 37·0°. Vero cells (1·0–2·0×10^5 cells per mL) were then added to the serum–virus suspensions in microplates in duplicate and incubated at 36·5° for 5 days. Cytopathic effects were recorded under microscopes and the neutralising antibody titre was calculated by the dilution number of 50% protective condition. Detection was done by the National Institute for Food and Drug Control. Further information on the method has been provided in the appendix (p 1).

Outcomes

The primary safety endpoint was any vaccine-related adverse events (adverse reactions) within 28 days after the administration of each dose of the study vaccine or alum only. Secondary safety endpoints were serious adverse events and any abnormal changes in laboratory measurements at day 3 after each dose. Laboratory index tests were prespecified only in the phase 1 trial. The primary immunogenic endpoint was the seroconversion rate of neutralising antibodies to live SARS-CoV-2 at day 28 after the second dose. Secondary immunogenic endpoints were geometric mean titre (GMT) of neutralising antibodies to

live SARS-CoV-2, as well as seropositive rates and geometric mean increase. Seroconversion was defined as a change from seronegative at baseline to seropositive or a four-fold titre increase if the participant was seropositive at baseline. The positive cutoff of the titre for neutralising antibodies to live SARS-CoV-2 was 1/8.

Statistical analysis

We assessed the safety endpoints in the safety population, which included all participants who had received at least one dose of vaccine or alum only. We assessed the immunogenicity endpoints in the per-protocol population, which included all participants who had randomly received two doses of vaccine or alum only, had antibody results available, and did not violate the trial protocol.

We did not determine the sample sizes on the basis of a statistical power calculation, but followed the requirements of the China National Medical Products Administration and Chinese Technical Guidelines for Clinical Trials of Vaccines—ie, recruitment of at least 20–30 participants in phase 1 and 300 participants in phase 2 trial.

We used the Pearson χ^2 test or Fisher's exact test for the analysis of categorical outcomes. We calculated the 95% CIs for all categorical outcomes using the Clopper-Pearson method. We calculated GMTs and corresponding 95% CIs on the basis of the standard normal distribution of the log-transformation antibody titre. We used the ANOVA method to compare the log-transformed antibody titres. When the comparison among all groups showed significant difference, we then did pairwise comparisons. Hypothesis testing was two-sided and we considered a p value of less than 0·05 to be significant.

An independent data monitoring committee consisting of one independent statistician, one clinician, and one epidemiologist was established before commencement of the study. Safety data were assessed and reviewed by the committee to ensure further proceeding of the study. We used SAS (version 9.4) for all analyses. This trial is registered with ClinicalTrials.gov, NCT04551547.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Employees of Sinovac Life Sciences and Sinovac Biotech, listed as the authors, contributed to the study design, data interpretation, clinical trial monitoring, writing or revising the manuscript.

Results

Between Oct 31, 2020, and Dec 2, 2020, 110 individuals were screened and 72 were enrolled in phase 1. Between Dec 12 and Dec 30, 2020, 515 individuals were screened and 480 were enrolled in phase 2. 550 (>99%) of

	Phase 1			Phase 2		
	1·5 μg group (n=27)	3 μg group (n=26)	Aluminium hydroxide only group (n=18)	1·5 μg group (n=192)	3·0 μg group (n=191)	Aluminium hydroxide only group (n=96)
Age, years	8·4 (4·2)	8·2 (4·0)	8·3 (4·0)	9·3 (3·9)	9·2 (3·8)	9·1 (4·0)
3–5	9 (33%)	9 (35%)	6 (33%)	48 (25%)	47 (25%)	24 (25%)
6–11	9 (33%)	9 (35%)	6 (33%)	72 (38%)	72 (38%)	36 (38%)
12–17	9 (33%)	8 (31%)	6 (33%)	72 (38%)	72 (38%)	36 (38%)
Sex						
Male	10 (37%)	12 (46%)	8 (44%)	105 (55%)	108 (57%)	54 (56%)
Female	17 (63%)	14 (54%)	10 (56%)	87 (45%)	83 (43%)	42 (44%)
Han ethnicity	27 (100%)	26 (100%)	18 (100%)	192 (100%)	191 (100%)	96 (100%)
Height, m	1·3 (0·2)	1·3 (0·3)	1·3 (0·3)	1·4 (0·2)	1·4 (0·2)	1·4 (0·2)
Weight, kg	34·3 (15·7)	35·0 (14·9)	34·9 (17·7)	40·4 (19·0)	37·9 (16·9)	39·2 (18·9)

Data are mean (SD) or n (%).

Table 1: **Baseline characteristics**

	1·5 μg group (n=219)	3·0 μg group (n=217)	Aluminium hydroxide only group (n=114)	Total (n=550)	p value*
Solicited adverse reactions within 0–7 days					
Any	51 (23%)	59 (27%)	22 (19%)	132 (24%)	0·28
Grade 1	39 (18%)	51 (24%)	15 (13%)	105 (19%)	0·065
Grade 2	16 (7%)	19 (9%)	9 (8%)	44 (8%)	0·82
Grade 3	2 (1%)	0	0	2 (<1%)	0·36
Injection site adverse reactions					
Pain	36 (16%)	35 (16%)	2 (2%)	73 (13%)	<0·0001
Grade 1	34 (16%)	35 (16%)	2 (2%)	71 (13%)	<0·0001
Grade 2	2 (1%)	0	0	2 (<1%)	0·36
Swelling	3 (1%)	6 (3%)	1 (1%)	10 (2%)	0·50
Grade 1	0	4 (2%)	0	4 (1%)	0·053
Grade 2	3 (1%)	3 (1%)	1 (1%)	7 (1%)	1·0
Induration	0	2 (1%)	0	2 (<1%)	0·20
Grade 1	0	2 (1%)	0	2 (<1%)	0·20
Erythema	0	1 (<1%)	0	1 (<1%)	0·60
Grade 1	0	1 (<1%)	0	1 (<1%)	0·60
Pruritus	3 (1%)	2 (1%)	0	5 (1 %)	0·64
Grade 1	3 (1%)	2 (1%)	0	5 (1%)	0·64
Systematic adverse reactions					
Fever	9 (4%)	11 (5%)	5 (4%)	25 (5%)	0·93
Grade 1	3 (1%)	2 (1%)	2 (2%)	7 (1%)	0·89
Grade 2	4 (2%)	10 (5%)	3 (3%)	17 (3%)	0·22
Grade 3	2 (1%)	0	0	2 (<1%)	0·36
Cough	5 (2%)	8 (4%)	5 (4%)	18 (3%)	0·47
Grade 1	1 (<1%)	4 (2%)	3 (3%)	8 (1%)	0·19
Grade 2	4 (2%)	4 (2%)	2 (2%)	10 (2%)	1·0
Headache	6 (3%)	4 (2%)	3 (3%)	13 (2%)	0·82
Grade 1	3 (1%)	3 (1%)	1 (1%)	7 (1%)	1·0
Grade 2	4 (2%)	1 (<1%)	2 (2%)	7 (1%)	0·39
Anorexia	3 (1%)	4 (2%)	2 (2%)	9 (2%)	0·92
Grade 1	1 (<1%)	3 (1%)	2 (2%)	6 (1%)	0·52
Grade 2	3 (1%)	1 (<1%)	0	4 (1%)	0·54

(Table 2 continues on next page)

	1·5 µg group (n=219)	3·0 µg group (n=217)	Aluminium hydroxide only group (n=114)	Total (n=550)	p value*
(Continued from previous page)					
Diarrhoea	2 (1%)	2 (1%)	4 (4%)	8 (1%)	0·16
Grade 1	2 (1%)	2 (1%)	4 (4%)	8 (1%)	0·16
Nausea	3 (1%)	2 (1%)	2 (2%)	7 (1%)	0·89
Grade 1	3 (1%)	2 (1%)	2 (2%)	7 (1%)	0·89
Mucocutaneous eruption	2 (1%)	2 (1%)	1 (1%)	5 (1%)	1·0
Grade 1	1 (<1%)	1 (<1%)	0	2 (<1%)	1·0
Grade 2	1 (<1%)	1 (<1%)	1 (1%)	3 (1%)	1·0
Vomiting	3 (1%)	1 (<1%)	1 (1%)	5 (1%)	0·85
Grade 1	3 (1%)	1 (<1%)	1 (1%)	5 (1%)	0·85
Muscle pain	4 (2%)	0	0	4 (1%)	0·078
Grade 1	2 (1%)	0	0	2 (<1%)	0·36
Grade 2	2 (1%)	0	0	2 (<1%)	0·36
Fatigue	1 (<1%)	1 (<1%)	1 (1%)	3 (1%)	1·0
Grade 1	1 (<1%)	1 (<1%)	1 (1%)	3 (1%)	1·0
Grade 2	1 (<1%)	0	0	1 (<1%)	1·0
Hypersensitivity	0	0	1 (1%)	1 (<1%)	0·21
Grade 1	0	0	1 (1%)	1 (<1%)	0·21
Unsolicited adverse reactions within 0–28 days					
Any	11 (5%)	15 (7%)	9 (8%)	35 (6%)	0·52
Grade 1	2 (1%)	3 (1%)	3 (3%)	8 (1%)	0·43
Grade 2	10 (5%)	12 (6%)	7 (6%)	29 (5%)	0·75
Overall adverse reactions within 0–28 days					
Any	56 (26%)	63 (29%)	27 (24%)	146 (27%)	0·55
Grade 1	40 (18%)	52 (24%)	18 (16%)	110 (20%)	0·16
Grade 2	22 (10%)	24 (11%)	15 (13%)	61 (11%)	0·67
Grade 3	2 (1%)	0	0	2 (<1%)	0·36

Data are n (%), representing the total number of participants who had adverse reactions (ie, adverse events related to vaccination). Results are broken down by dose and age group in the appendix (pp 2–10). *For differences across all groups.

Table 2: **Adverse reactions reported within 28 days after the first and the second dose of vaccine or alum only in phase 1 and phase 2**

552 enrolled participants received the first dose of vaccine or alum only (71 in phase 1 and 479 in phase 2) and were included in the safety population (figure 1). 69 (96%) participants in phase 1 received the second dose and all were eligible for the immunogenic evaluation at day 28 after the second dose (per-protocol population; figure 1). In phase 2, 467 (97%) participants received the second dose and 460 (96%) were included in the per-protocol population (figure 1). Seven participants were excluded because one received tetanus immunoglobulin at day 14 after the second dose, five did not have a blood sample taken at 28 days after the second dose, and one took a blood sample outside of the specified time window. The demographic characteristics of the participants were similar in terms of sex, mean age, height, weight, and ethnicity among groups. The mean age of study participants was 8·3 years (SD 4·0) in phase 1, including 24 (34%) of 71 participants aged 3–5 years, 24 (34%) aged 6–11 years, and 23 (32%) aged 12–17 years. The mean age of study participants was 9·2 years (3·9) in phase 2, including 119 (25%) of 479 participants aged 3–5 years, 180 (38%) aged 6–11 years, and 180 (38%) aged 12–17 years (table 1).

The safety data of the phase 1 and phase 2 trial were combined for analysis because the same batches of the vaccine and alum only and the same safety observation method were used. 146 (27%) of 550 participants reported at least one adverse reaction within 28 days of either vaccination, and the proportions of participants with any adverse reactions were similar across groups. Most adverse reactions were mild (grade 1) and moderate (grade 2) in severity. Only two (<1%) of 550 had grade 3 adverse reactions. Most adverse reactions occurred within 7 days after vaccination and participants recovered within 48 h. The most common reactions were injection site pain (73 [13%] participants) and fever (25 [5%]). Except for a higher prevalence of injection site pain in two vaccine groups than that in alum-only group, there

	1·5 µg group		3·0 µg group		Aluminium hydroxide only group		p value	
	Rate	% (95%) CI	Rate	% (95%) CI	Rate	% (95%) CI	Three groups	1·5-µg vs 3·0-µg group
Phase 1								
Total	27/27	100·0% (87·2–100·0)	26/26	100·0% (86·8–100·0)	0/16	0·0% (0·0–20·6)	<0·0001	1·0
3–5 years	9/9	100·0% (66·4–100·0)	9/9	100·0% (66·4–100·0)	0/5	0·0% (0·0–52·2)	<0·0001	1·0
6–11 years	9/9	100·0% (66·4–100·0)	9/9	100·0% (66·4–100·0)	0/6	0·0% (0·0–45·9)	<0·0001	1·0
12–17 years	9/9	100·0% (66·4–100·0)	8/8	100·0% (63·1–100·0)	0/5	0·0% (0·0–52·2)	<0·0001	1·0
Phase 2								
Total	180/186	96·8% (93·1–98·8)	180/180	100·0% (98·0–100·0)	0/94	0·0% (0·0–3·9)	<0·0001	0·030
3–5 years	46/46	100·0% (92·3–100·0)	45/45	100·0% (92·1–100·0)	0/24	0·0% (0·0–14·2)	<0·0001	1·0
6–11 years	68/69	98·6% (92·2–100·0)	68/68	100·0% (94·7–100·0)	0/35	0·0% (0·0–10·0)	<0·0001	1·0
12–17 years	66/71	93·0% (84·3–97·7)	67/67	100·0% (94·6–100·0)	0/35	0·0% (0·0–10·0)	<0·0001	0·059

Data are n/N (% [95% CI]).

Table 3: **Seroconversion rates of neutralising antibody responses to live SARS-CoV-2 28 days after the second dose**

were no significant differences in the prevalence of other solicited or unsolicited reactions among the three groups (table 2). In an exploratory analysis by age, the prevalence of adverse reactions was highest in participants aged 12–17 years (72 [35%] of 203 participants) followed by 3–5 years (37 [26%] of 143 participants) and 6–11 years (37 [18%] of 204 participants; appendix pp 8–10). As of June 12, 2021, only one participant in the alum-only group has reported one serious adverse event (pneumonia; appendix p 15), which was considered to be unrelated to vaccination. Additionally, only two (3%) of 71 participants at day 3 after the first dose and two (3%) of 69 participants after the second dose in phase 1 had a significant increase of laboratory indicator (appendix p 11).

In phase 1, none of the participants had any detectable neutralising antibody response against live SARS-CoV-2 at baseline (appendix p 12). The seroconversion rates at day 28 after the second dose were 27 (100%) of 27 participants in the 1·5 µg group (GMT 55·0 [95% CI 38·9–77·9]) and 26 (100%) of 26 in the 3·0 µg group (117·4 [87·8–157·0]). The GMT of the 3·0 µg group was significantly higher than that of the 1·5 µg group (p=0·0012; table 3, figure 2, appendix p 12). Testing for neutralising antibodies in all alum-only recipients was negative after vaccination (appendix p 12). In an exploratory analysis by age, seroconversion rates at day 28 after the second dose of 1·5 µg or 3·0 µg vaccine were all 100% in participants aged 3–5 years, 6–11 years, and 12–17 years, with the GMTs ranging from 45·9 to 212·6 (figure 2, appendix p 14).

In phase 2, none of the participants had any detectable neutralising antibody response at baseline (appendix p 13). After the second dose of vaccination, the seroconversion rates were 180 (95% CI 96·8% [93·1–98·8]) of 186 participants in the 1·5 µg group (GMT 86·4 [73·9–101·0]) and 180 (100·0% [98·0–100·0]) of 180 participants in the 3·0 µg group (142·2 [124·7–162·1]). The seroconversion rate and GMT of the 3·0 µg group were higher than those of the 1·5 µg group (p=0·030 and p<0·0001; table 3, figure 2, appendix p 13). Neutralising antibodies in all alum-only recipients were negative after vaccination (appendix p 13). In an exploratory analysis by age, the seroconversion rates at day 28 after the second dose were higher than 93% in the 1·5 µg and 3·0 µg groups for participants aged 3–5 years, 6–11 years, and 12–17 years, with the GMTs ranging from 78·3 to 146·0 (figure 2, appendix p 14).

Discussion

To our knowledge, this is the first report of immunogenicity and safety of COVID-19 candidate vaccine among children as low as 3 years old. We found that two

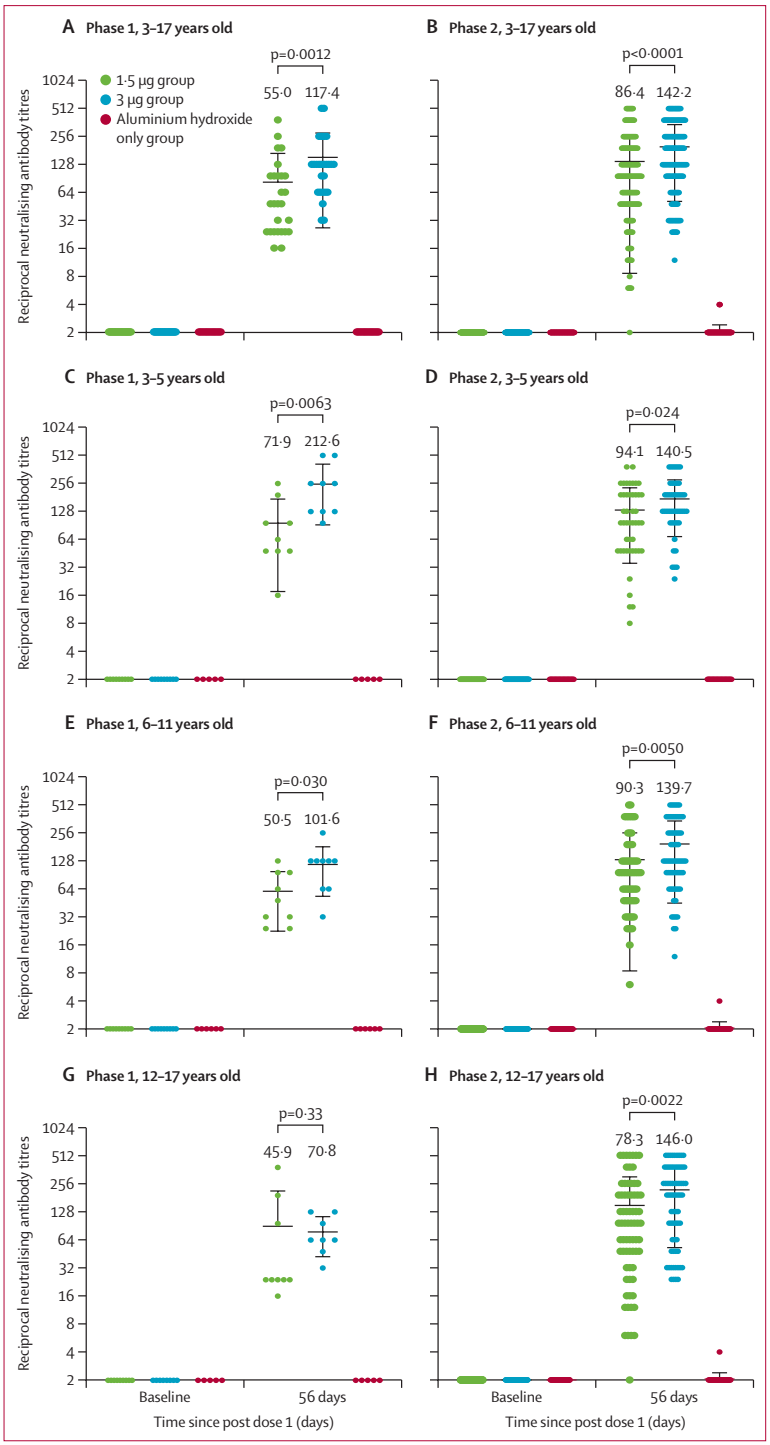

Figure 2: **Antibody titres of neutralising antibodies to live SARS-CoV-2 induced after two doses of CoronaVac or aluminium hydroxide diluent only in phase 1 and phase 2 trials**

GMT=geometric mean titre.The error bars indicate the 95% CI of the GMT and the spots indicate the individual antibody titres, with the number above the spots showing the GMT estimate. Only p values between 1·5 µg and 3·0 µg groups after the second vaccination are shown in the figure. All p values for all data are in the appendix (pp 12–13)

doses of the CoronaVac were safe and well tolerated at doses of 1·5 μg and 3·0 μg among children and adolescents aged 3–17 years old. The prevalence of adverse reactions in different dose groups was similar, indicating that there was no dose-related concern on safety. Most reactions were mild to moderate in severity and transient. Injection-site pain was the most reported symptom. The results were similar to our study of adults and elderly.[17,18] Furthermore, the higher grade 1 injection site pain reported by adolescents aged 12–17 years was the main reason for the higher prevalence of adverse reactions in this population compared with children aged 3–5 years and 6–11 years. None of the serious adverse events reported during the trial was related to vaccination.

CoronaVac was immunogenic in children and adolescents aged 3–17 years. The seroconversion rates of neutralising antibody in children and adolescents with both doses were over 96% after the two-dose vaccination. The GMTs of 142·2 in the 3·0 μg groups were higher than that of 86·4 in the 1·5 μg group in phase 2; however, even the GMT of 86·4 induced better immunogenicity compared with adults aged 18–59 years (44·1) and those aged 60 years and older (42·2) who received a 3·0 μg dose of vaccine with the same immunisation schedule.[17,18] Age plays an important role in antibody response to vaccine.[27] Decreasing responses to vaccination with increasing age have been shown in other vaccines, such as hepatitis B vaccine, seasonal influenza, pneumococcal disease, tetanus, pertussis, and diphtheria.[27,28] The results implied that a lower dose of vaccine could induce higher immune response in children and adolescents.

In an exploratory analysis stratified by age, we did not observe significant differences in neutralising antibody responses between age groups (3–5 years, 6–11 years, and 12–17 years) after the second vaccination (appendix p 14). GMTs in phase 1 decreased with age in recipients of the same vaccine, whereas they were similar in phase 2. Small sample size might account for the change trends of GMT in phase 1. In each age group, there were significant differences in GMTs between the 1·5 μg and 3·0 μg groups after the second dose, except in the group aged 12–17 years old in phase 1. Taken together, the 3·0 μg dose of CoronaVac induced higher immune responses in all age groups compared with the 1·5 μg dose.

Evidence from various studies supports the important role of T-cell responses to SARS-CoV-2 infection,[29] and such responses have been found with use of different vaccine platforms, including mRNA, viral vectors, and recombinant proteins.[30] In this study, T cell responses were not assessed, which was a limitation of the study design. However, a study in Chile found a significant induction of a T-cell response characterised by the secretion of interferon-gamma following vaccination of CoronaVac in a population aged 18 years and older,[19], which was different from the lower response observed in our phase 1 trial among adults aged 18–59 years.[17] Another inactivated SARS-CoV-2 vaccine, BBV152, has also been reported to induced a Th1-biased response.[21,24] Future studies are needed to assess the responses of type 1 and type 2 T-helper cells by inactivated vaccines.

This study has some further limitations. First, the sample size of this study is relatively small per age group and all study populations were of Han ethnicity. Further studies will be done in different regions and multiethnic populations to collect more data to provide scientific evidence for immune strategy. Second, at the time of the report, long-term immunogenicity and safety could not be available, although the participants will be followed up for at least 1 year. Finally, the calculated p values cannot support any powerful statistical conclusions in this study, which are only for reference and should be interpreted with caution.

In conclusion, CoronaVac was well tolerated and safe, and induced humoral responses in children and adolescents aged 3–17 years. Among the two doses evaluated, the neutralising antibody titres induced by a 3·0 μg dose were higher than those of the 1·5 μg dose. The results support the use of 3·0 μg dose with a two-immunisation schedule for further studies in children and adolescents.

Contributors

QL, QG, YZ, BH, and YS designed the trial and study protocol. BH, WY, and ML contributed to the literature search. All authors had access to data, and YS and QL verified the data. BH and WY wrote the first draft manuscript. QG, QL, YS, ML, XL, and YZ contributed to the data interpretation and revision of the manuscript. ZJ and QS contributed to data analysis. LW monitored the trial. QM and WJ were responsible for the site work including the recruitment, follow-up, and data collection, and ZW was the site coordinator. CL were responsible for the laboratory analysis. All the authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

QG and XL are employees of Sinovac Life Sciences. YS, WY, and LW are employees of Sinovac Biotech. All other authors declare no competing interests.

Data sharing

The individual participant-level data that underlie the results reported in this Article will be shared after de-identification (text, tables, figures, and appendices). This clinical trial is ongoing, and all the individual participant data will not be available until the immune persistence evaluation is completed. The data will be available immediately after publication and finalisation of the completed clinical study report for at least 6 months. Supporting clinical documents including the study protocol and statistical analysis plan and the informed consent form will be available immediately following publication of this Article for at least 1 year. Information on how to access the supporting clinical documents is available online. Researchers who provide a scientifically sound proposal will be allowed to access to the de-identified individual participant data. Proposals should be sent to the corresponding author. These proposals will be reviewed and approved by the sponsor, investigators, and collaborators on the basis of scientific merit. To gain access, data requestors will need to sign a data access agreement.

Acknowledgments

This study was funded by the National Key Research and Development Program and Beijing Science and Technology Program.

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