The effectiveness of primary series CoronaVac vaccine in preventing COVID-19 illness: a prospective cohort study among health workers in Azerbaijan, May–November, 2021

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Abstract

Background Healthcare workers (HCWs) have suffered considerable morbidity and mortality during the COVID-19 pandemic. Few studies have evaluated Coronavac vaccine effectiveness (VE), particularly in eastern Europe, where the vaccine has been widely used. Methods We conducted a prospective cohort study among HCWs in seven hospitals in Baku, Azerbaijan between May 17 to December 1, 2021, to evaluate primary series (two-dose) CoronaVac VE against symptomatic SARS-CoV-2 infection. Participants completed weekly symptom questionnaires, provided nasal swabs for SARS-CoV-2 RT-PCR testing when symptomatic, and provided serology samples at enrolment that were tested for anti-spike and anti-nucleocapsid antibodies. We estimated VE as (1 – hazard ratio)*100 using a Cox proportional hazards model with vaccination status as a time-varying covariate. Results We enrolled 1582 HCWs. At enrolment, 1040 (66%) had received two doses of CoronaVac; 421 (27%) were unvaccinated. During the study period, 72 PCR-positive SARS-CoV-2 infections occurred; 36/39 (92%) sequenced samples were classified as delta variant. The adjusted primary series VE against COVID-19 illness was 29% (95% CI:-51%;67%). For the delta-predominant period, adjusted primary series VE was 19% (95% CI:-81%;64%). For the entire analysis period, adjusted primary series VE was 39% (95% CI:-40%;73%) for HCW vaccinated within 14–149 days, and 19% (95%CI:-81;63) for those vaccinated [?]150 days. Conclusions During a delta-predominant period in Azerbaijan, point estimates suggest that primary series CoronaVac protected nearly 1 in 3 HCWs against COVID-19, but this finding was not statistically significant. Our findings underscore the need to consider booster doses in individuals who have received primary series CoronaVac.

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Abstract

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Methods

We conducted a prospective cohort study among HCWs in seven hospitals in Baku, Azerbaijan between May 17 to December 1, 2021, to evaluate primary series (two-dose) CoronaVac VE against symptomatic SARS-CoV-2 infection. Participants completed weekly symptom questionnaires, provided nasal swabs for SARS-CoV-2 RT-PCR testing when symptomatic, and provided serology samples at enrolment that were tested for anti-spike and anti-nucleocapsid antibodies. We estimated VE as (1 – hazard ratio)*100 using a Cox proportional hazards model with vaccination status as a time-varying covariate.

Results

We enrolled 1582 HCWs. At enrolment, 1040 (66%) had received two doses of CoronaVac; 421 (27%) were unvaccinated. During the study period, 72 PCR-positive SARS-CoV-2 infections occurred; 36/39 (92%) sequenced samples were classified as delta variant. The adjusted primary series VE against COVID-19 illness was 29% (95% CI:-51%;67%). For the delta-predominant period, adjusted primary series VE was 19% (95% CI:-81%;64%). For the entire analysis period, adjusted primary series VE was 39% (95% CI:-40%;73%) for HCW vaccinated within 14–149 days, and 19% (95%CI:-81;63) for those vaccinated [?]150 days.

Conclusions

During a delta-predominant period in Azerbaijan, point estimates suggest that primary series CoronaVac protected nearly 1 in 3 HCWs against COVID-19, but this finding was not statistically significant. Our findings underscore the need to consider booster doses in individuals who have received primary series CoronaVac.

Keywords: COVID-19; vaccine effectiveness; vaccination; healthcare workers; Azerbaijan; CoronaVac

INTRODUCTION:

COVID-19 vaccination has been shown to be a critical intervention to reduce morbidity and mortality from COVID-19. Protecting health workers (HCWs) through COVID-19 immunization is essential for effective control of the COVID-19 pandemic; HCWs are highly exposed to infection, have frequent contact with vulnerable patients, and are essential to the ongoing function of health services.

While many observational studies have evaluated the effectiveness of mRNA and viral vector vaccines, much less is known about the real-world effectiveness of whole inactivated virus vaccines. Inactivated whole-virus vaccines, which have potential advantages of being easier to produce and store, and also presenting a wider range of viral antigens to the immune system, accounted for nearly half of the 7.3 billion COVID-19 vaccine doses delivered globally, as of October 2021. Most of these doses have been used in low- and middle-income countries (LMICs), where few studies have evaluated the effectiveness of COVID-19 vaccines in general.

In LMICs, differences in population demographics and differences in operational aspects of the vaccination campaign could potentially impact real-world vaccine effectiveness (VE).

CoronaVac (Sinovac, Beijing), a newly-developed inactivated vaccine authorized for emergency use by WHO in June 2021, has been widely used in countries in Central Asia and other countries in the eastern part of the European Region of the World Health Organization (WHO); however only one study from the region – a study of HCWs in Turkey conducted during a period of alpha variant predominance – has evaluated the effectiveness of this vaccine.

In Azerbaijan, an upper-middle income country in the European region of WHO with a population of approximately 10 million people, the COVID-19 vaccination campaign began on January 18, 2021. Populations considered most at risk, including HCWs, were prioritized for early vaccination. CoronaVac was the main vaccine available at the beginning of the vaccination campaign.

We conducted a prospective cohort study of COVID -19 vaccine effectiveness in HCWs in Azerbaijan. In this interim analysis of the study, we aimed to estimate the early VE of primary series (two-dose) CoronaVac against PCR-confirmed SARS-CoV-2 illness during March-November, 2021.

MATERIALS AND METHODS

Study setting and population

The study design and analysis were guided by the WHO European Region HCW VE guidance document, and the study was conducted within the framework of WHO's Unity platform.

From May 3 to July 17, 2021, we enrolled HCWs at seven hospitals in the Baku United Hospital network in Baku, the capital city of Azerbaijan, into a prospective cohort. We selected hospitals based on accessibility by the study team in the context of quarantine-related restrictions to travel at the time. At the time of enrolment and during the study period, all sites admitted patients with COVID-19.

We offered enrolment to all HCWs employed by participating hospitals for whom COVID-19 vaccination was not contra-indicated by previous allergy to vaccinations. National guidance at the time required HCWs to wait 6 months from PCR-confirmed infection before receiving the first dose. The national vaccination schedule recommended administration of the second dose of CoronaVac 14-21 days after the first.

Lists of all HCWs employed at study sites were provided by hospital directors to guide recruitment. We invited all HCWs to participate, including physicians, nurses, clinical support staff, and custodial workers, regardless of their COVID-19 vaccination status, intention to get vaccinated in future, or history of previous infection with SARS-CoV-2. At the time of enrolment, and throughout the analysis period, HCWs were required to have COVID-19 vaccination in order to work in hospitals in Azerbaijan; however, because of limited availability of the vaccine in much of the first half of 2021, this requirement was not strictly enforced.

Data collection and management

At enrolment, participants completed a questionnaire that included questions about demographics, comorbidities, previous SARS-CoV-2 infection and SARS-CoV-2 vaccination history. Study staff then contacted participants weekly, using a standard questionnaire, to ask participants if they had experienced any symptoms in the past week (fever, cough, general weakness, fatigue, headache, muscle ache, sore throat, runny nose, shortness of breath, lack of appetite, nausea, vomiting, diarrhoea, altered mental status, loss of taste, or loss of smell), and to ask about the details of any new COVID-19 vaccines participants had received.

We advised all participants who became symptomatic to attend testing facilities at the study hospitals, where trained nurses collected nasopharyngeal swabs, which were tested at on-site government-accredited laboratories or other Ministry of Health laboratories for SARS-CoV-2 by RT-PCR. Symptomatic participants completed an additional survey that included information about date of symptom onset, clinical care-seeking, and details of PCR testing and results. PCR-positive participants were interviewed again 30 days after their

positive test, at which time further details about their course of illness, medical care, hospitalization, and complications were collected.

Data from interviewer-led questionnaires and laboratory records were entered and stored securely using the Sorgular.az platform (Azerbaijan Public Health Reform Center). Participants' reports of positive PCR results were verified using the two national SARS-CoV-2 laboratory databases – the Etabib electronic medical records database, and the Ministry of Health (MoH)/Mandatory Health Insurance database – to which all SARS-CoV-2 PCR tests performed in public and private laboratories in the country are required to be reported. Participants' COVID-19 vaccination history was verified using the national vaccine registry (Rendezvous, Azerbaijan Ministry of Health). Study staff contacted participants to resolve discrepancies between data from questionnaires and those from national databases, and to complete questions from study questionnaires that had not been answered.

Laboratory testing

Blood was collected from all participants at enrolment, and serum was stored at -20degC until testing. Sera samples were tested for anti-spike antibodies with Wantai SARS-CoV-2 total antibody ELISA (Beijing Wantai Biological Pharmacy, Beijing, China) and for anti-nucleocapsid antibodies using Platelia SARS-CoV-2 total antibody ELISA (Bio-Rad Laboratories, Hercules, CA) in the InterDiagnostic Clinic Laboratory, Baku. The manufacturer's recommended controls and thresholds were used to define seropositivity. For participants who had haemolysed or insufficient specimens, repeat blood draws were performed within 30 days of enrolment.

A subset of SARS-CoV-2 PCR-positive study samples was sent to the Charite University Institute of Virology laboratory in Berlin, Germany, for whole genome sequencing (WGS).

Vaccine effectiveness analysis

For our primary study outcome, we measured two-dose CoronaVac VE against symptomatic PCR-confirmed COVID-19 for the overall cohort.

Statistical model

VE was estimated as (1 – hazard ratio)*100. Hazard ratios comparing vaccinated and unvaccinated were estimated using Cox proportional hazards models with vaccination as a time-varying exposure; the vaccination status of some individuals changed over time from unvaccinated to vaccinated, and therefore the same participant could contribute person-time to both exposure categories. Study time was used as the underlying time scale in the Cox regression model. Participants were considered fully vaccinated 14 days after they received their second vaccine dose.

We calculated unadjusted and adjusted VE estimates. We categorized hospitals into two groups based on geographical location; three hospitals in central Baku were considered "central," while four hospitals located on the outskirts of Baku were considered "peripheral." Both unadjusted and adjusted VE estimates included hospital group and prior infection as fixed effects. We assessed other potential confounders (e.g., month, age, sex, occupation, hands-on care, smoking, household size, any chronic condition, BMI) if they changed the VE estimate by more than 5% using step-wise backward selection.

We defined previous infection as a PCR-confirmed infection prior to enrolment documented in either the Etabib database or the MoH/Mandatory Health insurance database. Participants who were unvaccinated at enrolment and had PCR-confirmed SARS-CoV-2 infection prior to enrolment began to contribute person-time on the date they became eligible for vaccination (six months after their last positive test). Participants who were vaccinated at enrolment and who had PCR-confirmed COVID-19 infection prior to enrolment were included in the analysis at the time point they were considered "at risk" of reinfection, which we defined as 90 days after their most recent positive PCR test.

Participants contributed person-time from enrolment, or, for individuals with prior PCR-confirmed SARS-CoV-2 infection, from the start of time at risk, until the earliest of outcome or exit from the study. Person-

time ended at whichever came first of the following outcomes: 1) the day of the first SARS-CoV-2 infection, 2) the day of receipt of a second COVID-19 vaccination if it occurred before the recommended interval between the first and second dose 3) the day of receipt of a third vaccine dose, or 4) the day of the last weekly questionnaire before complete loss to follow-up, withdrawal from the study, transfer or retirement from their hospital of employment, death, or censor date for the analysis period (1 December 2021). Participants were also censored from the primary analysis upon receiving a dose of any COVID-19 vaccine other than CoronaVac.

Further analyses and sensitivity analyses

We only conducted VE analyses for CoronaVac because few other vaccines were used in the study population. We evaluated VE during the overall study period and separately for the period in which SARS-CoV-2 B.1.617.2 (delta variant) was predominant (1 July 2021 - 1 December 2021), which we defined using WGS data from study samples along with publicly available data from GISAID. We also performed these two analyses excluding participants who had a PCR-confirmed SARS-CoV-2 infection prior to enrolment. In addition, we examined VE since time since vaccination by comparing VE in the period from 14 – 149 days since the second vaccine dose to VE [?]150 days since the second vaccine dose.

We performed two sensitivity analyses. For the first, because reinfection can occur earlier than 90 days, we changed the definition of "time at risk" from 90 days after infection to 60 days after infection. For the second, because individuals may be protected as early as 7 days after their second dose, we defined "fully vaccinated" as 7 days after the second dose rather than 14 days after the second dose.

Ethical considerations

The study was approved by the Research Ethics Committees of WHO (protocol: CERC.0097C) and the Ethics Committee of Azerbaijan State Academy of Physical Culture and Sport (03 March 2021; Protocol #3/21). All participants provided informed, written consent. The study is registered in the clinicaltrails.gov registry (NCT050694).

RESULTS:

We enrolled 1,582 HCWs, which comprised 38.5% of eligible HCWs in participating hospitals. Three participants were excluded because no follow-up data were obtained after enrolment. Supplementary Figure 1 shows the flow of participants through study.

Of the 1582 HCWs enrolled, 1473 (93%) were female, the median age was 49 (IQR: 39-57); 408 (26%) were physicians, 591 (37%) were nurses, and 583 (37%) were other HCWs (Table 1). In all, 644 (41%) participants had at least one comorbidity, and 46 (3%) and 14 (1%) participants said they smoked currently or previously, respectively. A total of 458 (29%) HCWs had received the influenza vaccine in the 2019-2020 influenza season. Overall, 582 HCWs (37%) were from central hospitals in Baku, while 1000 (63%) HCWs were from peripheral Baku hospitals.

At enrolment, 1040 (66%) participants had received primary series CoronaVac, 121 (8%) participants had received only one dose of CoronaVac, and 421 (27%) were unvaccinated (Table 1). No participants had received other COVID-19 vaccines at enrolment. Among those vaccinated with the primary series before enrolment, the median time since receipt of the second dose was 99 days (IQR 74-112). Overall, 248 HCWs (16%) had a PCR-positive COVID-19 infection documented prior to enrolment. Compared to unvaccinated participants, participants who had received primary series vaccine before enrolment worked more commonly in central hospitals (39% vs 29%), had more chronic condition (38% vs 48%) and had less PCR-confirmed infections prior to enrolment (6% vs 40%). Differences in participants by vaccination status at enrolment have been previously reported.

In total, 963/1040 (93%) participants who had received primary series vaccine were seropositive at enrolment for either anti-nucleocapsid or the anti-spike protein antibodies; 903 (90%) were seropositive for anti-spike antibodies, while 827 (83%) were seropositive for anti-nucleocapsid antibodies. Among unvacci-

nated participants, 363/421 (86%) were seropositive to at least one of the two antibodies (Table 1). Of the 197 unvaccinated participants who did not report a previous PCR infection at enrolment, 136 (69%) were seropositive at enrolment by one of the two assays.

During the follow-up period, 10 (<1%) participants received primary series vaccination with vaccines other than CoronaVac (9 received Pfizer, and 1 received Sputnik) and were excluded from the analysis. At their exit from analysis, 1485 (95%) participants had received primary series CoronaVac, 41 (3%) had received one dose of CoronaVac, and 43 (3%) remained unvaccinated. Changes in the vaccination status of the enrolled population over the course of the study are illustrated in Figure 1. At study exit, participants who had received the primary series were similar to unvaccinated participants in terms of median age, sex, smoking status and self-assessed health status; however, compared to participants who had received primary series vaccine, unvaccinated participants were more commonly medical doctors (47% vs 25%) and less unvaccinated participants received influenza vaccine during the previous season (70% vs. 81%) (Supplementary Table 1).

Unvaccinated HCWs contributed a total of 24,745 person-days to the 30-week study period, while participants vaccinated with the primary series of CoronaVac contributed 172,457 person-days. During this time period, 380 participants were symptomatic, of whom 201 (53%) provided a respiratory sample that was tested for SARS-CoV-2 by PCR. Overall, 72 participants (5%) had symptomatic PCR-confirmed COVID-19, including 64 vaccinated participants and 8 unvaccinated participants. Cases peaked in August, but incidence remained high through the end of the analysis period; the trajectory of cases in the study mostly mirrored the national trends of COVID-19 incidence during the summer of 2021 in Azerbaijan (Figure 2). Of the 39 samples for which WGS data were available, 36/39 (92%) were delta variant (Supplementary Figure 2).

During the course of the analysis period, in the 30 days following their positive test, 44 participants with PCR-confirmed COVID-19 illness sought medical care (4 unvaccinated and 40 fully vaccinated), and 29 participants went to an emergency room (3 unvaccinated and 26 fully vaccinated). Three participants with PCR-confirmed COVID-19 illness were hospitalized (1 unvaccinated and 2 fully vaccinated). No deaths occurred among participants with PCR-confirmed COVID -19 illness. VE could not be calculated against these more severe outcomes because of the small number of events among unvaccinated participants.

For the overall cohort, the adjusted two-dose VE was 29% (95% CI -51% to 67%) (Table 2, Figure 3a). For the delta-predominant period, adjusted two-dose VE was 19% (95% CI -81% to 64%). VE was adjusted for previous infection only; no other potential confounders changed the VE estimates in more than 5%. For the overall cohort analysis, vaccinated participants had received their second dose a median of 90 days (IQR: 75-112) prior to the beginning of the study period, while during the period of delta circulation, vaccinated participants had received their second dose a median of 108 days (IQR: 106-132) prior to the analysis period.

When we excluded participants who had PCR-confirmed SARS-CoV-2 infection prior to enrolment, unadjusted VE was 37 (95% CI -33 to 70), and unadjusted VE during the delta-predominant period was 29 (95% CI -57 to 68).

For the overall cohort, adjusted VE was 39% (95% CI -40% to 73%) for participants who had received their second CoronaVac vaccine within 14-149 days, and 19% (95%CI -81.5 to 63.4) for participants who had received their second CoronaVac vaccine [?]150 days prior (Table 3 and Figure 3b).

In sensitivity analyses, when we decreased the period after infection that participants were considered not at risk from 90 to 60 days, results were very similar (<1% difference) to the 90-day analysis (Table 4). When we considered a participant to be fully vaccinated at 7 days instead of 14 days, VE differed by < 2% from the results of the primary analysis.

DISCUSSION

We found that during a delta-predominant period in Azerbaijan, point estimates suggest that primary series CoronaVac vaccine protected nearly 1 in 3 HCWs against COVID-19, but this finding was not statistically significant. Our findings are the first to describe COVID-19 VE in the South Caucasus region—an area of the WHO European region that continues to have much lower rates of vaccination compared to Western

and Central Europe . As of November 2022, less than half to the adult population (48%) in Azerbaijan had completed primary series vaccination for COVID-19, and less than 10% had completed a booster dose.

Our primary course Coronavac VE point estimates of 29%, and 37% when we excluded participants who had previous PCR-confirmed infection, are similar to previous studies of Coronac VE against symptomatic infection and all infections. A study of HCWs in Turkey without previous infection, the only published study of CoronaVac VE in the European Region of WHO, found that adjusted two-dose VE against SARS-CoV-2 infection was 39% (HR 0.61, 95% CI 0.46–0.80) during a period of alpha variant circulation. That same study reported an unadjusted two-dose CoronaVac VE of 48% (95% CI 29–61%) against symptomatic infection. Studies outside of the European region that have evaluated two-dose CoronaVac VE during periods of predominant delta circulation showed a range of results that varied in part according to time since vaccination. A study from Brazil that included individuals who were 60-179 days and >180 days after their second dose found two-dose VE against symptomatic disease of 37.6% (36.1-39.1) and 34% (32.3-35.7), respectively, in a delta-predominant period. In contrast, two studies from Asia found higher two-dose VE against illness and infection during periods of delta-predominant circulation, but these studies included individuals who had mostly been recently vaccinated. A study from Thailand that used the test-negative design reported two-dose CoronaVac effectiveness of 60% (95% CI, 49–69) against infection; vaccinated participants in that study had received their last dose a mean of 81 days (Range: 60-91 days) prior to the analysis period. A study related to an outbreak of SARS-CoV-2-delta variant in China reported two-dose CoronaVac VE against illness of 73.0 (95% CI 22.3–90.6) among individuals who had mostly received their second vaccine dose within the previous three months.

Primary series VE against infection during delta-predominant periods has been shown to be mostly higher for mRNA and viral vector vaccines compared to Coronavac. However, against omicron, two-dose VE against has been much lower against symptomatic infection, and, to a lesser extent, severe disease, across vaccine products. Booster doses have been shown to increase protection against both mild and severe COVID-19 illness from delta and omicron. In Azerbaijan, booster doses were recommended for HCWs from September 2021. Both Coronavac and Cominarty (Pfizer/Biontech) have been offered, without a preferential recommendation. To date, few studies have evaluated VE of a heterologous booster compared to a homologous booster following primary series vaccination with Coronavac. In Brazil, during an Omicron-predominant period, for individuals who had received tprimary series CoronaVac, heterologous booster with Cominarty had higher VE than homologous booster with CoronaVac against both symptomatic infection [56.8% (56.3-57.3) vs. -2.9% (-5.2–0.6)] and severe disease [86% (84.5-87.4) vs. 73.6% (63.9-80.7)] for those vaccinated 8-59 days prior to the analysis period. Differences persisted for those boosted >59 days prior. However, in Hong Kong, also during a period of Omicron BA.2 circulation, VE against mortality and severe complications was mostly similar for individuals who had received a primary series of CoronaVac followed by Cominarty a booster compared to those who had received three doses of CoronaVac. Both studies showed increased VE against all endpoints for booster doses compared to primary series. In Azerbaijan, where less than 10% of the adult population has received a booster vaccine., conveying the important benefits of booster doses to the public is critical.

Our study population likely had high rates of previous infection at enrolment. Because vaccination with inactivated vaccine leads to seroconversion in both anti-spike and anti-nucleocapsid antibody tests, we could not use antibody testing to determine previous infection among participants who had been vaccinated prior to enrolment. However, 69% of unvaccinated HCWs who did not report a previous infection were seropositive by at least one of the two antibody tests at enrolment, and these findings likely reflect the extent of previous infection in the overall study population. Despite more than two of every three participants likely having been previously infected, we still found some benefit, albeit not statistically significant, to primary series vaccination with CoronaVac. The added benefit of primary COVID-19 vaccination and booster doses in previously infected individuals (hybrid immunity) has been widely demonstrated in other studies.

In our study we found a trend towards decreased VE among participants for whom more than 5 months had passed since their second CoronaVac vaccine. Waning VE with increased time since COVID-19 vaccination

has been described for CoronaVac and other COVID-19 vaccines.[7] The waning effectiveness of primary series vaccination again underscores the importance of booster doses to increase protection.

Our study has a number of strengths. Because we enrolled and systematically followed a discrete cohort of HCWs, we were able to obtain data about vaccination status, SARS-CoV-2 test results, and clinical outcomes, information which would not have been discernible from routinely collected data. The protocol was followed rigorously; participants completed more than 95% of weekly symptom questionnaires during the study period. Only 34 (2%) participants were lost to follow-up. Finally, the use of serology at enrolment allowed us to estimate the prevalence of prior infections among unvaccinated participants, and also provided information on seroconversion rates of HCWs who received the inactivated CoronaVac vaccine.

Our study also has some limitations. The study was not powered to estimate VE against severe outcomes like hospitalization and death – critical endpoints for vaccine evaluation. The study may have suffered from selection bias since enrolment was voluntary. In our study, while there were no differences in age and sex between unvaccinated and vaccinated participants, there were more unvaccinated physicians at the end of the study period. In addition, few participants remained unvaccinated at the end of the study, and these unvaccinated participants may differ from vaccinated participants in ways that we did not measure, including likelihood of exposure to SARS-CoV-2 and other parameters. More unvaccinated participants (40%) than vaccinated participants (6%) had a PCR-confirmed SARS-CoV-2 infection prior to enrolment – likely the result of the Azerbaijan MoH recommendation to defer vaccinated in individuals who had been infected with SARS-CoV-2. While differential rates of previous infection in the two arms could bias VE estimates, we accounted for this difference by including only participants eligible for vaccination, according to the recommendations, and including previous SARS-CoV-2 infection as a confounding variable. Finally, because of the relatively low number of events, the relatively low amount of person-time among unvaccinated participants, and the relatively low VE, our VE estimates had wide confidence intervals.

In conclusion, during a period of mainly delta circulation in Baku, Azerbaijan, we found that primary series CoronaVac VE protected approximately one in three HCWs against symptomatic PCR-confirmed infection, although the results were not statistically significant. HCWs in our cohort had high rates of previous infection and had mostly receive their second vaccine three months previously. These findings reaffirm previous findings about the limited durability of protection of primary series CoronaVac and other vaccines in preventing symptomatic infection, and thus should provide further support for the consideration of booster doses. Our findings also support the utility of COVID-19 vaccination even among individuals who have been previously infected, a policy that is currently promoted in Azerbaijan and elsewhere, and that will be critical to continue as more of the population in Azerbaijan and globally has experienced at least one COVID-19 infection. As this is an ongoing cohort study, future analyses will evaluate VE in the context of booster doses and omicron infection in Azerbaijan.

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DISCLOSURE STATEMENT

The authors report there are no competing interests to declare.

FUNDING DETAILS

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CONTRIBUTORSHIP STATEMENT

GH, MAK, NS, SM and RP conceived the cohort study on which this analysis is based;MADK, NS, MTR, SM, JM, AG, RC, JD, JS, RP, GH, MR and EK planned and implemented the study, including development of study protocols, data quality checks and acquisition of data; MAK, MTR, NS, GH, SM conceived the article; MAK and MTR drafted the manuscript and performed the literature search. MRC performed the data analysis with support from EK, SM, NS, and GH; MRC, and EK directly accessed and verified the raw data and take responsibility for the integrity and accuracy of the analyses. B, and CD performed sequencing of study samples. All authors contributed to the interpretation of the results and critically revised the manuscript. All authors had full access to all the data reported in the study and accept responsibility to submit the paper for publication.

REFERENCES

Figures and Tables

Figure 1. COVID-19 vaccine coverage among study participants, by epidemiologic week, Azerbaijan, 2021.

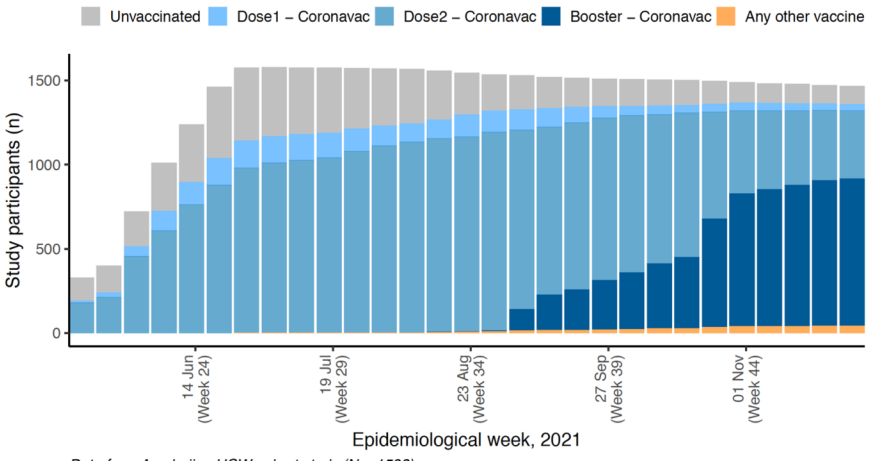


Figure 2. Epicurve showing COVID-19 symptomatic cases by vaccination status in the study population by epidemiologic week, Azerbaijan, May 17 – November 30, 2021

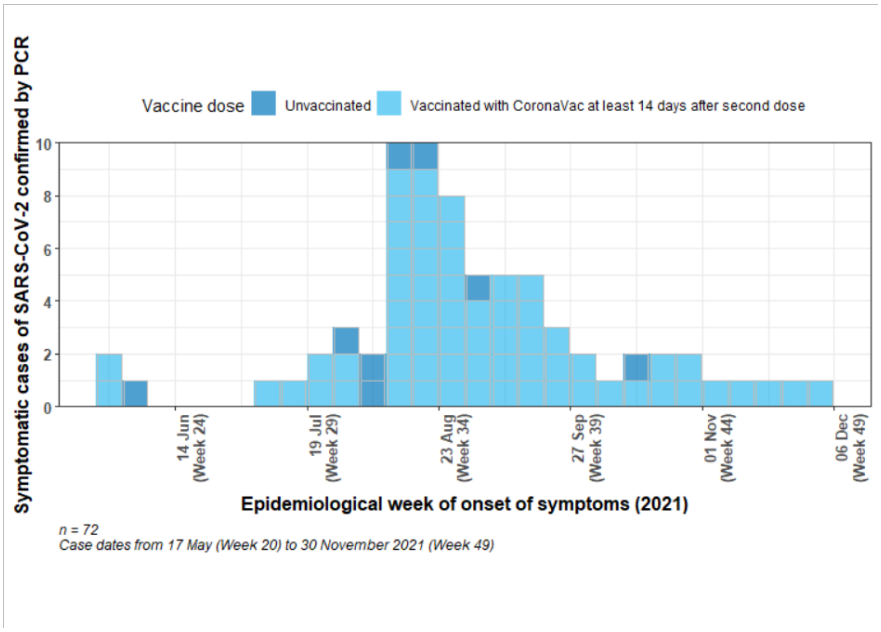


Figure 3a. Forest plot showing overall primary series CoronaVac vaccine effectiveness against PCR-confirmed symptomatic SARS-CoV-2 illness for full cohort and for delta-predominant period only and excluding participants with PCR-confirmed infection prior to enrolment (forest plots show point estimates and 95% CIs).

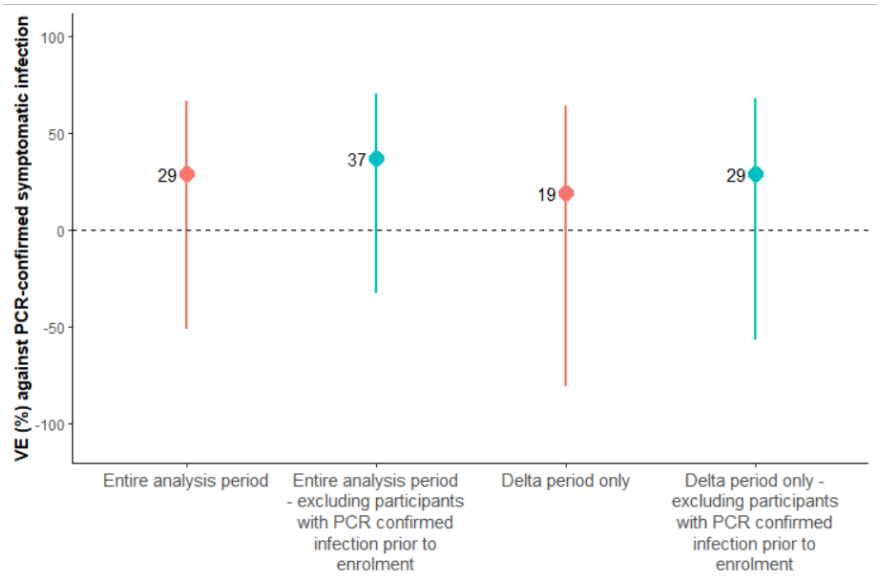


Figure 3b. Forest plot showing overall primary series CoronaVac vaccine effectiveness against PCR-confirmed symptomatic SARS-CoV-2 illness for entire cohort and for Delta-predominant period only, by time from receipt of second vaccine (forest plots show point estimates and 95% CIs)

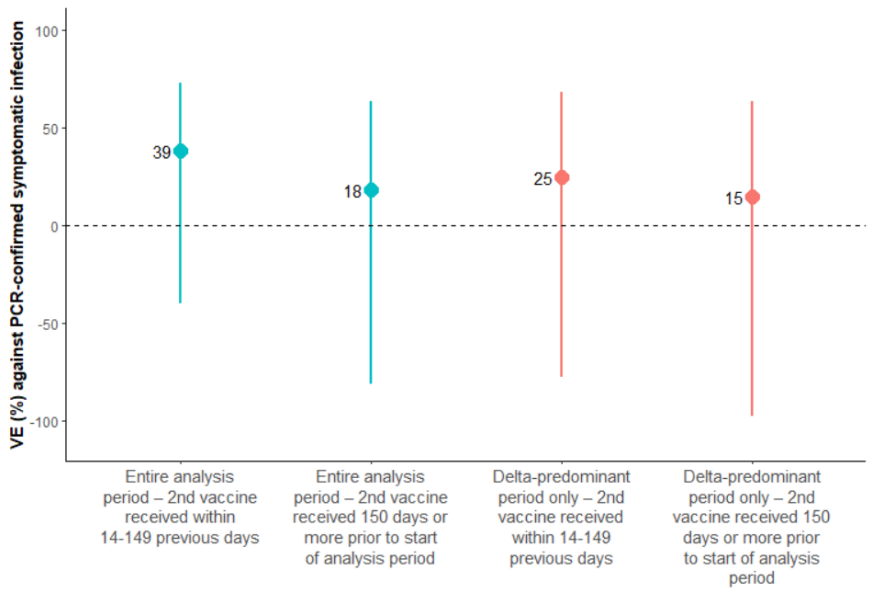


Table 1. Demographic, occupational, and clinical characteristics of participants at enrolment, by site, Azerbaijan, 2021.

Characteristic/Category	Missing	All Participants	Unvaccinated (any vaccine)	Partially vaccinated (1 dose CoronaVac)	Vaccinated (2 doses CoronaVac)
Age	0	n= 1582	n= 421	n= 121	n= 1040
Median (IQR)		49 (39-57)	47 (38-57)	41 (37-54)	50 (40-58)
Age group	0	n= 1582	n= 421	n= 121	n= 1040
20-29, n(%)		84 (5)	27 (6)	14 (12)	43 (4)
30-39, n(%)		322 (20)	102 (24)	33 (27)	187 (18)
40-49, n(%)		426 (27)	104 (25)	37 (31)	285 (27)
50-59, n(%)		476 (30)	111 (26)	26 (21)	339 (33)
60+, n(%)		274 (17)	77 (18)	11 (9)	186 (18)
Sex	0	n= 1582	n= 421	n= 121	n= 1040
F, n(%)		1473 (93)	394 (94)	114 (94)	965 (93)
M, n(%)		109 (7)	27 (6)	7 (6)	75 (7)
Pregnant	1	n= 1472	n= 393	n= 114	n= 965
No, n(%)		1466 (100)	389 (99)	114 (100)	963 (100)
Yes, n(%)		6 (0)	4 (1)	0 (0)	2 (0)
Breastfeeding	1	n= 1472	n= 393	n= 114	n= 965
No, n(%)		1468 (100)	389 (99)	114 (100)	965 (100)
Yes, n(%)		4 (0)	4 (1)	0 (0)	0 (0)
Hospital	0	n= 1582	n= 421	n= 121	n= 1040
Hospital 15, n(%)		131 (8)	8 (2)	9 (7)	114 (11)
Hospital 18, n(%)		230 (15)	47 (11)	10 (8)	173 (17)

Characteristic/Category	Missing	All Participants	Unvaccinated (any vaccine)	Partially vaccinated (1 dose CoronaVac)	Vaccinated (2 doses CoronaVac)
Hospital 23, n(%)		117 (7)	44 (10)	6 (5)	67 (6)
Hospital 24, n(%)		221 (14)	69 (16)	30 (25)	122 (12)
Hospital 26, n(%)		400 (25)	142 (34)	18 (15)	240 (23)
Hospital 29, n(%)		158 (10)	70 (17)	33 (27)	55 (5)
Hospital 7, n(%)		325 (21)	41 (10)	15 (12)	269 (26)
Hospital Location	0	n= 1582	n= 421	n= 121	n= 1040
Central, n(%)		582 (37)	124 (29)	49 (40)	409 (39)
Periphery, n(%)		1000 (63)	297 (71)	72 (60)	631 (61)
Occupation/Role in hospital	0	n= 1582	n= 421	n= 121	n= 1040
Other, n(%)		583 (37)	124 (29)	44 (36)	415 (40)
Nurse or Midwife, n(%)		591 (37)	171 (41)	56 (46)	364 (35)
Medical Doctor, n(%)		408 (26)	126 (30)	21 (17)	261 (25)
Household size	0	n= 1582	n= 421	n= 121	n= 1040
1-3, n(%)		589 (37)	151 (36)	47 (39)	391 (38)
4-5, n(%)		747 (47)	194 (46)	56 (46)	497 (48)
6+, n(%)		246 (16)	76 (18)	18 (15)	152 (15)
Any chronic condition	0	n= 1582	n= 421	n= 121	n= 1040
No, n(%)		938 (59)	220 (52)	78 (64)	640 (62)
Yes, n(%)		644 (41)	201 (48)	43 (36)	400 (38)
Smoking	0	n= 1582	n= 421	n= 121	n= 1040
Never smoked, n(%)		1522 (96)	407 (97)	116 (96)	999 (96)
Currently smokes, n(%)		46 (3)	11 (3)	4 (3)	31 (3)
Previously smoked, n(%)		14 (1)	3 (1)	1 (1)	10 (1)
Self-assessed health status	0	n= 1582	n= 421	n= 121	n= 1040
Excellent, n(%)		106 (7)	20 (5)	7 (6)	79 (8)
Very good, n(%)		122 (8)	23 (5)	8 (7)	91 (9)
Good, n(%)		1046 (66)	268 (64)	73 (60)	705 (68)
Fair, n(%)		276 (17)	93 (22)	30 (25)	153 (15)
Poor, n(%)		32 (2)	17 (4)	3 (2)	12 (1)

Characteristic/Category	Missing	All Participants	Unvaccinated (any vaccine)	Partially vaccinated (1 dose CoronaVac)	Vaccinated (2 doses CoronaVac)
Influenza vaccine 2019-2020	0	n= 1582	n= 421	n= 121	n= 1040
Yes, n(%)		458 (29)	85 (20)	22 (18)	351 (34)
No, n(%)		1124 (71)	336 (80)	99 (82)	689 (66)
Previous PCR-confirmed COVID-19 infection before enrollment	0	n= 1582	n= 421	n= 121	n= 1040
No, n(%)		1334 (84)	253 (60)	99 (82)	982 (94)
Yes, n(%)		248 (16)	168 (40)	22 (18)	58 (6)
Anti-Spike Protein Serology test results at enrolment	59	n= 1523	n= 406	n= 113	n= 1004
Positive, n(%)		1337 (88)	344 (85)	90 (80)	903 (90)
Negative, n(%)		186 (12)	62 (15)	23 (20)	101 (10)
Anti-Nucleocapsid Protein Serology test results at enrolment	65	n= 1517	n= 405	n= 113	n= 999
Positive, n(%)		1240 (82)	329 (81)	84 (74)	827 (83)
Negative, n(%)		261 (17)	70 (17)	27 (24)	164 (16)
Unknown/Equivocal, n(%)		16 (1)	6 (1)	2 (2)	8 (1)
Seropositive at enrolment by either assay	0	n= 1582	n= 421	n= 121	n= 1040
Yes, n(%)		1423 (90)	363 (86)	97 (80)	963 (93)
No, n(%)		159 (10)	58 (14)	24 (20)	77 (7)
Time from receipt of second dose until start of person-time contribution	542	n= 1040	n= 0	n= 0	n= 1040
Median (IQR)		99 (74 - 112) days			99 (74 - 112) days

Table 2 . Two-dose CoronaVac effectiveness against symptomatic PCR-confirmed COVID-19 infection for entire cohort and for entire cohort excluding participants who had a PCR-confirmed SARS-CoV-2 infection prior to enrolment, during the total study period, and for Delta-predominant period only, Azerbaijan, 2021.

	N participants
Total Cohort*	1569
Unvaccinated	415
14d from 2nd dose	1476
Total Cohort, excluding participants with PCR-confirmed infection prior to enrolment**	**1327**
Unvaccinated	253
14d from 2nd dose	1268
DELTA PERIOD (1/07/21-12/1/21)	
Total Cohort*	1565
Unvaccinated	293
14d from 2nd dose	1478
Total Cohort, excluding participants with PCR-confirmed infection prior to enrolment**	**1322**
Unvaccinated	181
14d from 2nd dose	1266

*Adjusted by hospital group

** Adjusted by hospital group and previous infection status

*** Adjusted VE could not be calculated

Table 3 . Two-dose CoronaVac effectiveness against symptomatic PCR-confirmed COVID-19 infection for entire cohort for total study period, and for Delta-predominant period only, by time since receipt of second vaccine, Azerbaijan, 2021.

	N participants	**Total person-time (days)**	**Symptomatic COVID-19**
Total Cohort	1569		
Unvaccinated [ref]	415	57699	8
14d-149d from 2^{nd} dose	1467	196338	24
150d from 2nd dose	1069	143107	40
DELTA PERIOD (1/07/21-1/12/21)			
Total Cohort	1565		
Unvaccinated [ref]	293	34298	7
14d-149d from 2nd dose	1467	163194	22
150d from 2nd dose	1072	117861	40

* Adjusted by hospital group and previous infection status

Table 4 . Two-dose CoronaVac effectiveness against symptomatic PCR-confirmed COVID-19 infection for full cohort for entire study period a) when re-infection could occur 60 days (rather than 90 days) after infection; and b) when participants were considered fully vaccinated 7 days (rather than 14 days) after their second dose

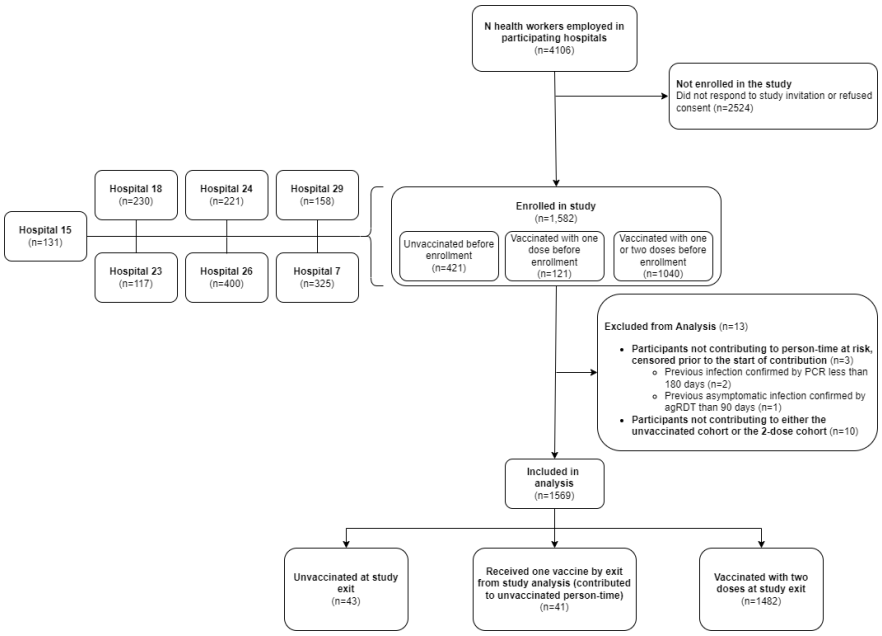
	N p
a. Reinfection definition: 60 days instead of 90 days	
Total Cohort	1569

	N p
Unvaccinated	415
14d from 2nd dose	1476
b. Fully vaccinated with primary series vaccine defined at 7 days after vaccination, instead of 14 days	
Total Cohort	1569
Unvaccinated	415
14d from 2nd dose	1481

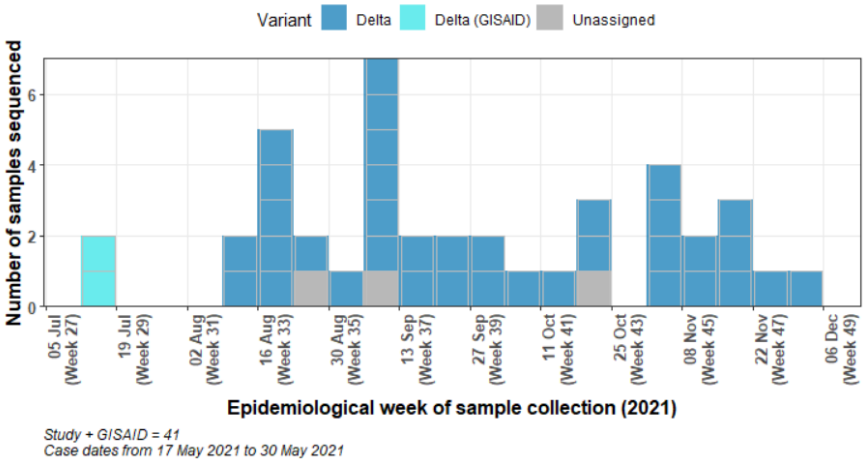
* Adjusted by hospital group and previous infection status

SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Flowchart illustrating the enrollment of healthcare workers in COVID-19 vaccine effectiveness study, Azerbaijan, 2021



Supplementary Figure 2. Whole genome sequencing results of SARS-CoV-2 positive cases from the vaccine effectiveness study (N=39) and from GISAID data for Azerbaijan (N=2) by week during the study period, May 17 – November 30, 2021 (N=41).*



*For whole genome sequencing of PCR-positive study samples, total nucleic acids were extracted using the Roche MagNAP

Supplementary Table 1. Participant demographics and clinical characteristics by COVID-19 vaccination status on the last day of follow-up,* Azerbaijan, 2021

Characteristic/Category	Missing	All Participants	Unvaccinated	Partially vaccina
Age	0	n= 1569	n= 43	n= 41
Median (IQR)		49 (39-57)	51 (36.5-61.5)	42 (38-57)
Age group	0	n= 1569	n= 43	n= 41
20-29, n(%)		84 (5)	5 (12)	1 (2)
30-39, n(%)		319 (20)	11 (26)	15 (37)
40-49, n(%)		423 (27)	4 (9)	8 (20)
50-59, n(%)		471 (30)	8 (19)	11 (27)
60+, n(%)		272 (17)	15 (35)	6 (15)
Sex	0	n= 1569	n= 43	n= 41
F, n(%)		1460 (93)	41 (95)	38 (93)
M, n(%)		109 (7)	2 (5)	3 (7)
Pregnant	1	n= 1459	n= 41	n= 38
No, n(%)		1453 (100)	38 (93)	38 (100)
Yes, n(%)		6 (0)	3 (7)	0 (0)
Breastfeeding	1	n= 1459	n= 41	n= 38
No, n(%)		1455 (100)	39 (95)	38 (100)
Yes, n(%)		4 (0)	2 (5)	0 (0)
Hospital	0	n= 1569	n= 43	n= 41
Hospital 15, n(%)		131 (8)	0 (0)	1 (2)
Hospital18, n(%)		227 (14)	7 (16)	4 (10)
Hospital 23, n(%)		114 (7)	5 (12)	7 (17)

Characteristic/Category	Missing	All Participants	Unvaccinated	Partially vaccina
Hospital 24, n(%)		219 (14)	10 (23)	6 (15)
Hospital 26, n(%)		397 (25)	6 (14)	19 (46)
Hospital 29, n(%)		157 (10)	11 (26)	3 (7)
Hospital 7, n(%)		324 (21)	4 (9)	1 (2)
Hospital Location	0	n= 1569	n= 43	n= 41
Central, n(%)		577 (37)	17 (40)	11 (27)
Periphery, n(%)		992 (63)	26 (60)	30 (73)
Occupation/Role in hospital	0	n= 1569	n= 43	n= 41
Other, n(%)		578 (37)	11 (26)	13 (32)
Nurse or Midwife, n(%)		586 (37)	12 (28)	19 (46)
Medical Doctor, n(%)		405 (26)	20 (47)	9 (22)
Household size	0	n= 1569	n= 43	n= 41
1-3, n(%)		584 (37)	20 (47)	15 (37)
4-5, n(%)		742 (47)	14 (33)	19 (46)
6+, n(%)		243 (15)	9 (21)	7 (17)
Any chronic condition	0	n= 1569	n= 43	n= 41
No, n(%)		933 (59)	27 (63)	23 (56)
Yes, n(%)		636 (41)	16 (37)	18 (44)
Smoking	0	n= 1569	n= 43	n= 41
Never smokes, n(%)		1510 (96)	41 (95)	40 (98)
Currently smokes, n(%)		46 (3)	2 (5)	0 (0)
Previously smokes, n(%)		13 (1)	0 (0)	1 (2)
Self-assessed health status	0	n= 1569	n= 43	n= 41
Excellent, n(%)		105 (7)	2 (5)	5 (12)
Very good, n(%)		121 (8)	2 (5)	4 (10)
Good, n(%)		1039 (66)	28 (65)	24 (59)
Fair, n(%)		274 (17)	9 (21)	6 (15)
Poor, n(%)		30 (2)	2 (5)	2 (5)
Received influenza vaccine during 2019-2020	0	n= 1569	n= 43	n= 41
Yes, n(%)		454 (29)	8 (19)	5 (12)
No, n(%)		1115 (71)	35 (81)	36 (88)

*refers to the end of the person-time included in the analysis for each participant. The person-time ended on: 1) the day of the first infection, 2) the day of receipt of a third vaccine dose, 3) the day of receipt of a second vaccine dose if the interval between first and second dose is shorter than the manufacturer recommendation, 4) the day of the last weekly questionnaire before complete loss to follow-up, withdrawal or censor date, or the last weekly questionnaire before 1 Dec 2021.

**chronic conditions include: cancer, chronic heart disease, high blood pressure/hypertension, chronic kidney disease, chronic liver disease (such as cirrhosis, hepatitis, fatty liver disease), chronic lung disease (such as asthma, COPD), diabetes, immunocompromised (including solid organ transplant and HIV), neurologic disease (including cerebrovascular disease, epilepsy, multiple sclerosis), obesity, autoimmune disorder