SARS-CoV-2 reinfection after previous infection and vaccine breakthrough infection through the second wave of pandemic in India: An observational study

Sachin Dhumal[1,#], Amar Patil[2,#], Ashwini More[3], Sujeet Kamtalwar[3], Amit Joshi[4], Anant Gokarn[4], Sumeet Mirgh[4], Puneeth Thatikonda[2], Prasanth Bhat[2], Vedang Murthy[1], Preeti Chavan[5], Amey Oak[6], Suvarna Gore[6], Atanu Bhattacharjee[6], Nikhil Patkar[7], Sadhana Kannan[8], Nitin Shetty[9], Anjali Rawat[10], Meera Achrekar[10], Bhakti Trivedi[11], Siddhartha Laskar[1], Pankaj Chaturvedi[6,12], Rajendra Badwe[12], Navin Khattry[4], Sudeep Gupta[4,*]

[1] Department of Radiation Oncology, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Tata Memorial Centre, Navi Mumbai, India
[2] Department of Medical Administration, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Tata Memorial Centre, Navi Mumbai, India
[3] Department of Medicine, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Tata Memorial Centre, Navi Mumbai, India
[4] Department of Medical Oncology, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, & Homi Bhabha National Institute, Mumbai, India
[5] Department of Composite Laboratory, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Tata Memorial Centre, Navi Mumbai, India
[6] Centre for Cancer Epidemiology, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Tata Memorial Centre, Navi Mumbai, India
[7] Department of Hematopathology, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Tata Memorial Centre, Navi Mumbai, India
[8] Department of Biostatistics, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Tata Memorial Centre, Navi Mumbai, India
[9] Department of Radiodiagnosis, Advanced Centre for Treatment, Research and Education in Cancer, Kharghar, Tata Memorial Centre, Navi Mumbai, India
[10] Department of Nursing, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, & Homi Bhabha National Institute, Mumbai, India
[11] Department of Anaesthesiology, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, & Homi Bhabha National Institute, Mumbai, India
[12] Department of Surgical Oncology, Tata Memorial Centre, & Homi Bhabha National Institute, Mumbai, India

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ABSTRACT

Background: There are sparse longitudinal data on SARS-CoV-2 infection after previous infection and after partial or full vaccination.

Methods: This study of a cohort of healthcare workers used Kaplan-Meier analysis with appropriate definition of events and censoring and used Cox models to assess outcomes, with data cut-off on June 18, 2021.

Results: A total of 1806 individuals with median age of 32 (18-64) years, 1483 (82.1%) with at least one vaccine dose, 1085 (60.1%) with 2 vaccine doses, 408 (22.6%) with at least one episode of SARS-CoV-2 infection, and 6 (1.47%) with 2 episodes of infection were included in the analysis. At median follow-up of 38.4 weeks after first SARS-CoV-2 infection (n=408), the 52-week probability of reinfection was 2.2% (95% CI, 1.0-4.91%); and at median follow-up of 13.3 weeks after second dose, the 16-week probability of breakthrough infection was 5.6% (95% CI, 4.33-7.23%), which was significantly higher among those without previous SARS-CoV-2 infection versus with previous infection (6.4% vs 1.8%, p=0.016, adjusted Cox HR=3.49, 95% CI, 1.09-11.20, p=0.036) and females versus males (7.9% vs 3.8%, p=0.007, adjusted Cox HR=2.06, 95% CI 1.19-3.56, p=0.01).

* Corresponding author: Sudeep Gupta, MD, DM, Professor Department of Medical Oncology, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India.

E-mail address: sudeepgupta04@yahoo.com (S. Gupta).

# These authors contributed equally.

Conclusions: There was low probability of reinfection after previous SARS-CoV-2 infection and higher vaccine breakthrough infections among females and those without previous infection.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic will shortly complete 2 years since it was first discovered but there is continuing uncertainty about several aspects of this disease. One of the most important questions is the degree and duration of protective immunity by an episode of infection with its causative agent, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Kim et al., 2020; Altawalah, 2021; Huang et al., 2020; Kellam and Barclay, 2020). Several effective vaccines against SARS-CoV-2 infection have been approved from late 2020 onward with well-documented efficacy in controlled clinical trials (Li et al., 2021, Polack et al., 2020, Baden et al., 2021, Voysey et al., 2021, Ella et al., 2021). However, there is a need to collect and report the continuing protection provided by these vaccines in real-world settings, especially in the context of ongoing genetic evolution of SARS-CoV-2. Two vaccines, ChAdOx1 nCoV-19 Coronavirus Vaccine (Recombinant) and whole virion inactivated vaccine (BBV152), have been available in India since early 2021. Empirical data on protective immunity due to previous infection with SARS-CoV-2 and/or vaccination are of fundamental importance in terms of herd immunity and the future course of this pandemic.

Several healthcare institutions, including ours, continued to provide medical care throughout the course of the pandemic. Healthcare workers and other employees of such institutions experienced SARS-CoV-2 infection at variable rates that largely mirrored the ebb and flow of the pandemic in the community. Moreover, workers in healthcare institutions were among the first to receive vaccination against this disease when it became available. Thus, evaluation of SARS-CoV-2 infection data among healthcare institutional employees provides valuable opportunity for longitudinal evaluation of protective immunity due to previous infection and/or vaccination. There are currently sparse data on vaccine breakthrough infections (Bergwerk et al., 2021; Tareq et al., 2021), especially with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant).

We conducted a retrospective, noninterventional, longitudinal study among employees of a single, large, tertiary cancer center in India to study the incidence of SARS-CoV-2 reinfection (after a previous infection) and vaccine breakthrough infection during a period that spanned the occurrence of first and second waves of pandemic in India.

METHODS

This retrospective observational study was conducted to assess the longitudinal incidence of laboratory-confirmed SARS-CoV-2 infection among all healthcare workers in our institution in relation to previous episodes of infection and receipt of a SARS-CoV-2 vaccine. The study was approved by the institutional ethics committee before its initiation and is registered in the Clinical Trials Registry of India (CTRI/2021/08/035655). Informed consent was waived by the ethics committee for subjects whose data could be entirely abstracted from the electronic medical record (EMR). However, for those subjects whose complete data were not available on EMR, the ethics committee approved telephonic contact and telephonic collection of data after obtaining an approved format of telephonic consent. Of the 1806 subjects included in the study, some data were collected through telephone contact after obtaining telephonic consent from 329 individuals.

Data were collected from the EMRs of the institution and its ongoing vaccination program and entered into an electronic database. The eligibility criterion for inclusion in the study was all employees of the institution in permanent or temporary employment as of the date of the start of the pandemic in India. Information on age, sex, dates of first and second doses of vaccine, type of vaccine, date of occurrence of laboratory-confirmed SARS-CoV-2 infection, requirement for hospitalization, number of days of hospitalization, and need for oxygen administration was extracted from the medical records.

Vaccination was given according to government of India guidelines, which were modified from time to time. The ChAdOx1 nCoV-2 vaccine was given initially (January 2021 to March 2021) with an interval of 4-6 weeks between the first and second dose, an interval of 6-8 weeks from April 2021 to May 12, 2021, and an interval of 12-16 weeks from May 13, 2021 onward, based on evolving data (Voysey M, et al., 2021). The BBV-152 vaccine was given at an interval of 4-6 weeks throughout the study period.

Statistical Analysis

The Kaplan-Meier method was used to compute the probability of SARS-CoV-2 infection in each subgroup of interest, with appropriate definition of left and right time boundaries, events and censoring. The Cox proportional hazards method was used for multivariable analysis of impact of covariates on the probability of SARS-CoV-2 infection. Time-dependent covariates were used to test the proportional hazards assumption and an appropriate time-interaction term was entered in the model if this assumption was not met. The period of risk was assumed to start on the date of first lockdown in India on March 24, 2020 and the data cut-off date was June 18, 2021. The following analyses were performed.

The cumulative probability of developing SARS-COV-2 among all healthcare workers since the beginning of pandemic in India (March 24, 2020) until the receipt of first vaccine dose was assessed in the entire employee cohort. The diagnosis of laboratory-confirmed SARS-CoV-2 infection before the date of first vaccine dose in those who received a vaccine or before the cut-off date in unvaccinated individuals constituted an event for this analysis. Those who did not develop SARS-CoV-2 infection were censored on the date of first vaccine dose (if vaccinated) or on data cut-off date (if not vaccinated). Those who died without experiencing the event were also censored on the date of death.

We evaluated the incidence of laboratory-confirmed SARS-CoV-2 reinfection after a previous episode of SARS-CoV-2 infection. Reinfection was defined as RT-PCR positivity for SARS-COV-2 at least 8 weeks after the date of known RT-PCR negativity after first infection or if RT-PCR negativity after previous infection was not documented, at least 8 weeks from the date of joining work after previous infection. The left time boundary for this analysis was assumed to start on the date of laboratory-confirmed diagnosis of the first episode of SARS-CoV-2 infection and an event was defined as diagnosis of a second episode of laboratory-confirmed SARS-CoV-2

Table 1

Characteristics of study population and SARS-CoV-2 infection

Variable	Males (N, %) N=1015	Females (N, %) N=791	P value (Males Vs. Females)	Total (N, %) N=1806
AGE (years)				
Mean	35.6	32.5	P<0.001	34.2
Median	33	30		32
Range	18-64	20-58		18-64
(≥50 years)	96 (9.5%)	28 (3.5%)		124 (6.9%)
VACCINATION STATUS				
Not Vaccinated	151 (14.9%)	172 (21.7%)	P<0.001	323 (17.9%)
At least one dose	864 (85.1%)	619 (78.3%)		1483 (82.1%)
At least one dose after COVID-19	195/227 (85.9%)	133/181 (73.5%)	P<0.001	328/408 (80.4%)
Two doses	624 (61.5%)	461 (58.3%)		1085 (60.1%)
Mean (Median, range) interval between 2 doses (weeks)	6.4 (5.3, 3.6-18.3)	5.8 (4.9, 3.7-20.1)	P<0.001	6.1 (5.0, 3.6-20.1)
Two doses after previous COVID-19	152/227 (67%)	96/181 (52.0%)	P = 0.175	248/408 (60.8%)
ChAdOx1	852 (83.9%)	614 (77.6%)		1466 (81.2%)
BBV152	12 (1.2%)	6 (0.8%)		18 (1.0%)
SARS-CoV-2 INFECTION				
Number with at least one episode of SARS-CoV-2 infection	227 (22.4%)	181 (22.9%)		408 (22.6%)
Number in first wave	177 (17.4%)	117 (14.8%)		294 (16.3%)
Number in second wave	50 (4.9%)	64 (8.1%)		114 (6.3%)
Before vaccination*	193 (19.0%)	139 (17.6%)		332 (18.4%)
After first vaccine dose*	15 (1.5%)	10 (1.3%)		25 (1.4%)
After second vaccine dose*	22 (2.2%)	34 (4.3%)		56 (3.1%)
HOSPITALIZATION FOR SARS-CoV-2				
All with SARS-CoV-2	87/227 (38.3%)	39/181 (21.5%)	P <0.001	126/408 (30.9%)
COVID-19 before first vaccine dose	77/193 (39.9%)	29/139 (20.9%)	P <0.001	106/332 (31.9%)
COVID-19 after first vaccine dose	5/15 (33.3%)	4/10 (40%)	P = 1.0	9/25 (36.0%)
COVID-19 after second vaccine dose	5/22 (22.7%)	7/34 (20.6%)	P = 1.0	12/56 (21.4%)
HOSPITALIZATION DURATION (Days) (Median, Range)				
All hospitalized	8 (1–33)	7 (1–35)		8 (1–35)
COVID-19 before vaccination	9 (1–33)	7 (1–35)		8.5 (1–35)
COVID-19 after first vaccine dose	7 (5–9)	5 (2–8)		7 (2–9)
COVID-19 after second vaccine dose	6 (5–8)	7 (3–10)		7 (3–10)
OXYGEN REQUIREMENT				
All hospitalized	11/87 (12.6%)	1/39 (2.6%)	P = 0.103	12/126 (9.5%)
COVID-19 before vaccination	10/77 (13.0%)	1/29 (3.4%)	P = 0.282	11/106 (10.4%)
COVID-19 after first vaccine dose	0/5 (0%)	0/5 (0%)		0/9 (0%)
COVID-19 after second vaccine dose	1/5 (20%)	0/7 (0%)		1/12 (8.3%)

infection. Employees with 1 episode of infection who did not develop a second infection were censored on the data cut-off date.

The cumulative probability of SARS-CoV-2 was evaluated among employees after receiving first dose and before receiving second dose of vaccine. The left time boundary for this analysis was assumed to start on the date of first vaccine dose and an event was defined as diagnosis of laboratory-confirmed SARS-CoV-2 infection after the first vaccine dose and before the second vaccine dose. Those who did not develop SARS-CoV-2 infection were censored on the date of second vaccine dose (if they received second dose) or on data cut-off date (if they did not receive second dose).

The cumulative probability of SARS-CoV-2 was evaluated among employees after the second dose of vaccine. The left time boundary for this analysis was assumed to start on the date of second vaccine dose and an event was defined as diagnosis of laboratory-confirmed SARS-CoV-2 infection after the second vaccine dose and before the cut-off date. Those who did not develop SARS-CoV-2 infection after the second vaccine dose were censored on the cut-off date.

The analysis was performed using the SPSS Version 24 statistical software.

RESULTS

Between March 24, 2020 and June 18, 2021, there were 1806 eligible employees who were included in the analysis. The baseline characteristics are shown in Table 1. There were 1015 (56.2%) males; the median age was 32 (18–64) years; 323 (17.9%) had not received any COVID-19 vaccine; 1483 (82.1%) had received at least one vaccine dose; and 1085 (60.1%) had received 2 doses. Of those who received at least one vaccine dose, the overwhelming majority

(1466, 98.9%) received the ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant), whereas a small minority (18, 1.2%) received the whole virion inactivated vaccine (BBV152).

A total of 408 (22.6%) employees developed at least one episode of SARS-CoV-2 infection, of whom 6 (1.47%) developed reinfection, 332 (18.4%) developed SARS-CoV-2 before vaccination, 25 (1.4%) after first vaccine dose and before the second vaccine dose, and 56 (3.1%) after the second dose. Of those who developed SARS-CoV-2 infection, 126 (30.9%) required hospitalization for any reason, with a median of 8 (1–35) days of hospitalization. Of those who were hospitalized, 12 (9.5%) required oxygen administration and there was 1 death due to COVID-19 (Table 1).

Overall incidence of SARS-CoV-2 infection among all employees since the beginning of pandemic

The denominator for this analysis was all employees of the institution (N=1806). At a median follow-up of 64.4 weeks, the cumulative actuarial probability of SARS-CoV-2 infection was 22.6% (95% CI, 20.73-24.59%) (Figure 1).

Incidence of SARS-CoV-2 infection before vaccination

The denominator for this analysis was all employees of the institution (N=1806). At a median follow-up of 47.4 (0-64.4) weeks, the 60-week cumulative actuarial probability of SARS-CoV-2 infection was 22.3% (95% CI, 19.95-24.95%) (Figure 2A). On the univariable analysis, there was no significant difference in the 60-week probability of infection between males and females (22.7% vs 21.9%, p=0.32) (Figure 2B) and between older (≥50 years) and younger (<50 years) employees (21.6% vs 22.4%, p=0.50) (Figure 2C). In
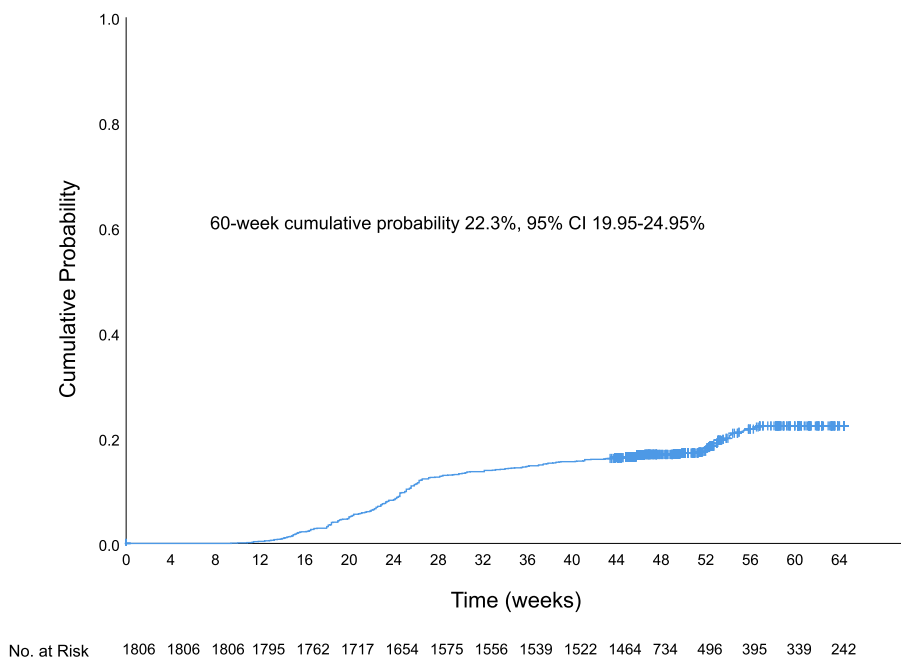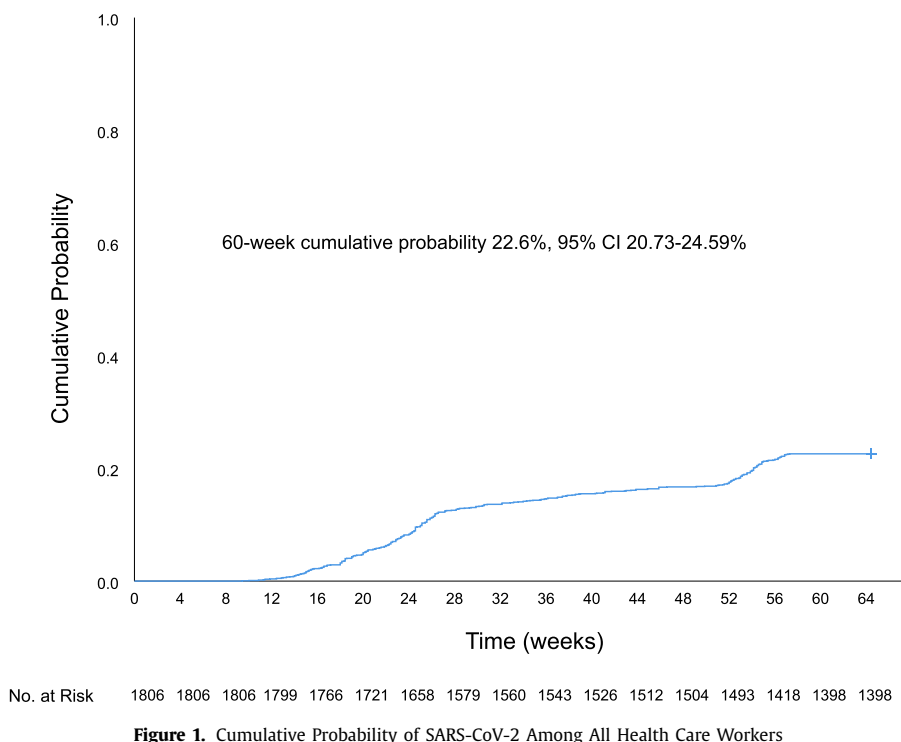
Figure 1. Cumulative Probability of SARS-CoV-2 Among All Health Care Workers

Figure 2. Cumulative Probability of SARS-CoV-2 Among Health Care Workers Prior to Vaccination
Figure 2A: All Workers
Figure 2B: By Sex
Figure 2C: By Age
Figure 2A: Cumulative Probability of SARS-CoV-2 Among All Health Care Workers Prior to Vaccination
Figure 2B: Cumulative Probability of SARS-CoV-2 Among All Health Care Workers Prior to Vaccination, by Sex
Figure 2C: Cumulative Probability of SARS-CoV-2 Among All Health Care Workers Prior to Vaccination, by Age

the multivariable Cox regression analysis including sex (male or female, self-reported), age (as a continuous variable), and their respective time-interaction terms, it was found that the proportional hazards assumption was not met for both sex and age. After adjusting for each other and their time-interaction terms, females had a significantly lower probability of SARS-CoV-2 infection before vaccination than males (HR=0.494; 95% CI, 0.274-0.892; p=0.019), whereas older employees had a significantly higher probability of this infection (HR=1.041; 95% CI, 1.008-1.075; p=0.013) (Table 2).
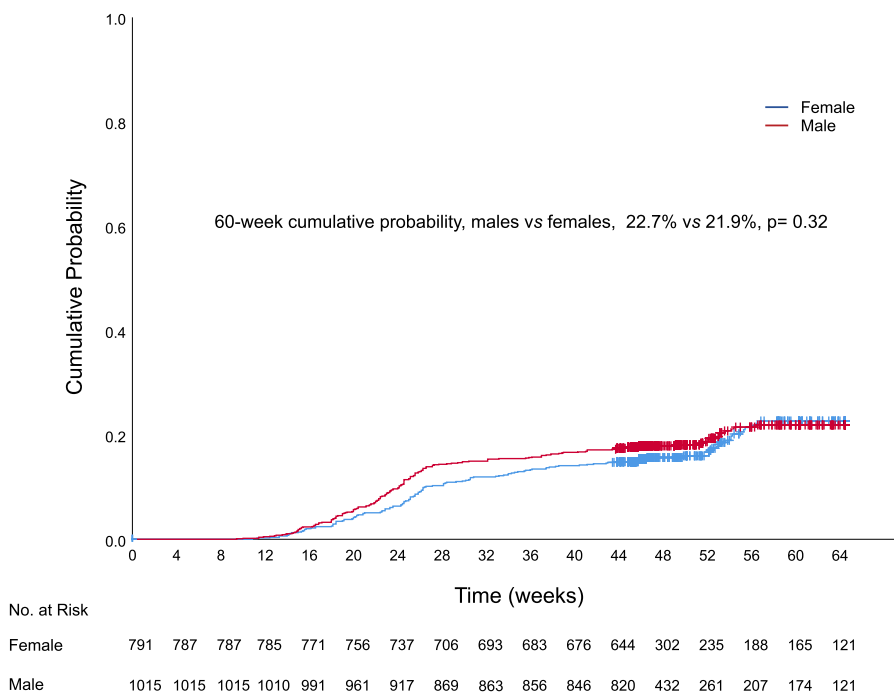
60-week cumulative probability, males vs females, 22.7% vs 21.9%, p= 0.32

No. at Risk

Female	791	787	787	785	771	756	737	706	693	683	676	644	302	235	188	165	121
Male	1015	1015	1015	1010	991	961	917	869	863	856	846	820	432	261	207	174	121

Figure 2. Continued

60-week cumulative probability, >/= 50 years vs < 50 years, 21.6% vs 22.4%, p= 0.50

No. at Risk

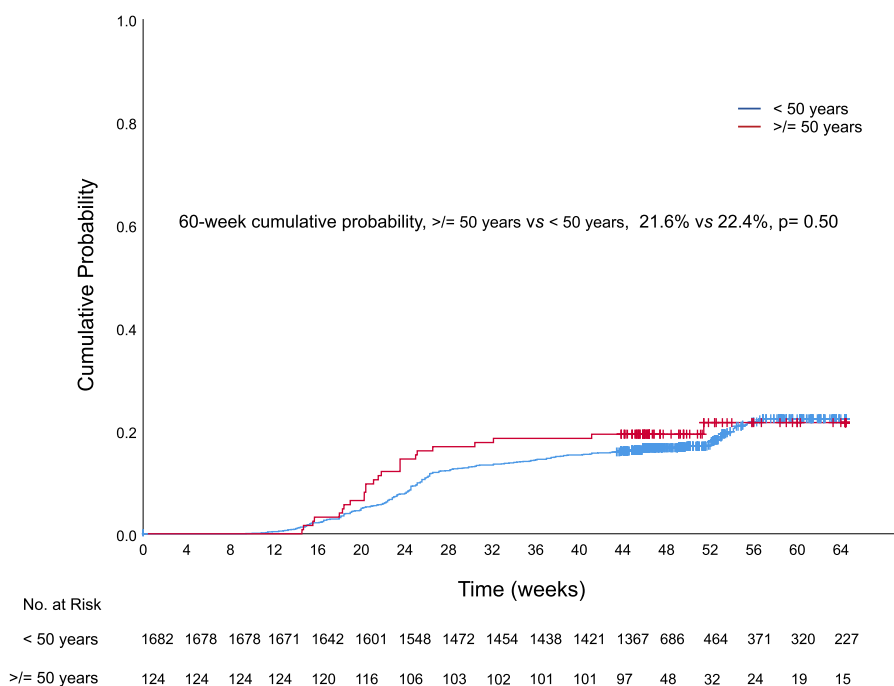|																	
< 50 years	1682	1678	1678	1671	1642	1601	1548	1472	1454	1438	1421	1367	686	464	371	320	227
>/= 50 years	124	124	124	124	120	116	106	103	102	101	101	97	48	32	24	19	15

Figure 2. Continued

Table 2
Multivariable Cox analysis of factors affecting incidence of SARS-CoV-2 Infection before Vaccination

Factor	Hazard Ratio (95% CI)	P value
Sex (females vs males)	0.494 (0.274–0.892)	0.019
Age (continuous)	1.041 (1.008–1.075)	0.013
Sex*Time	1.022 (1.002–1.043)	0.027
Age*Time	0.999 (0.998–1.000)	0.02

Incidence of SARS-CoV-2 reinfection after previous SARS-CoV-2 infection

The denominator for this analysis were all employees who developed at least one episode of laboratory-confirmed SARS-CoV-2 infection (n=408). At a median follow-up of 38.4 (7.1-55.0) weeks after first infection, the 52-week cumulative actuarial probability of SARS-CoV-2 infection was 2.2% (95% CI, 1.0-4.91%) (Figure 3).
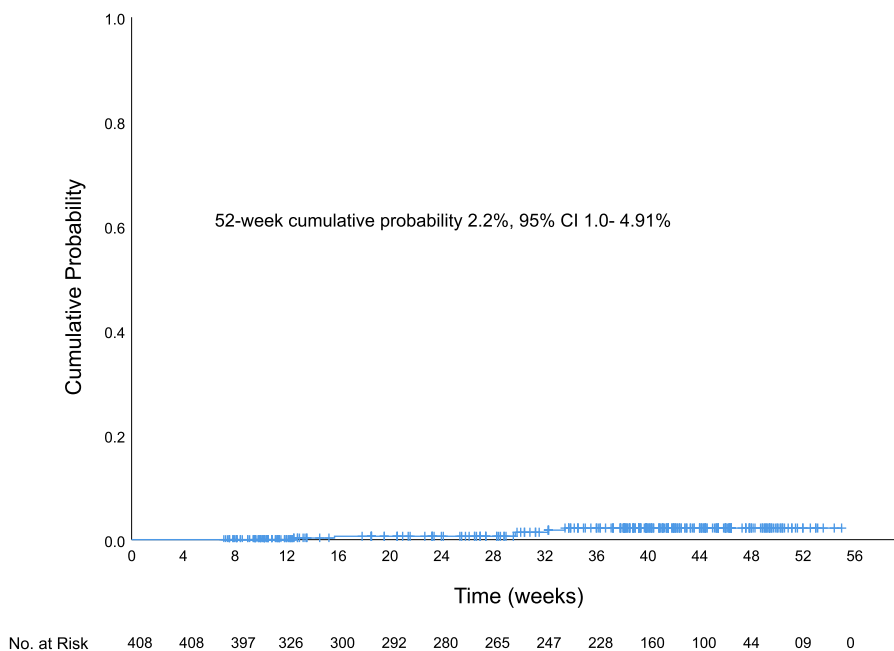
Figure 3. Cumulative Probability of SARS-CoV-2 Among Health Care Workers After Previous SARS-CoV-2 Infection

Incidence of SARS-CoV-2 infection after first and before second dose of vaccine

The denominator for this analysis were all employees who received at least one dose of recombinant ChAdOx1 nCoV-19 Corona Virus Vaccine or whole virion inactivated vaccine (BBV152) (n=1458). At a median follow-up of 5.3 (0-20.9) weeks, the 20-week cumulative actuarial probability of SARS-CoV-2 infection after first and before the second vaccine dose was 2.7% (95% CI, 1.78-4.16%) (Figure 4A). Among those who experienced the event for this analysis (n=25), the median time to SARS-CoV-2 infection after the first vaccine dose was 3.86 weeks. In the univariable analysis, the probability of infection after the first vaccine dose was not significantly different between employees who had previous SARS-
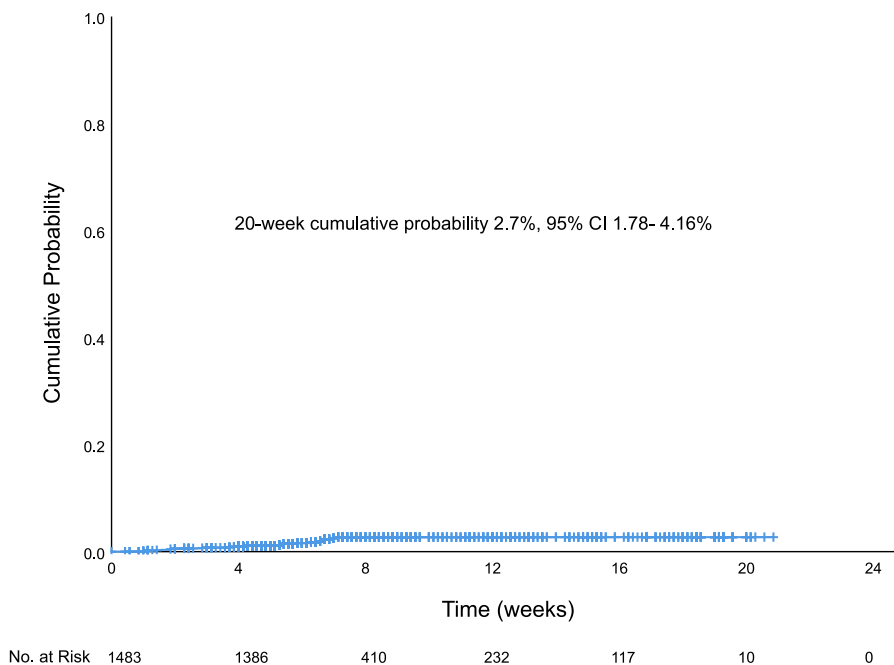

Figure 4. Cumulative Probability of SARS-CoV-2 Among Health Care Workers After One Vaccine Dose
Figure 4A: All Workers
Figure 4B: By Prior SARS-CoV-2 Infection
Figure 4A: Cumulative Probability of SARS-CoV-2 Among All Health Care Workers After One Vaccine Dose
Figure 4B: Cumulative Probability of SARS-CoV-2 Among Health Care Workers After One Vaccine Dose, by Prior SARS-CoV-2 Infection
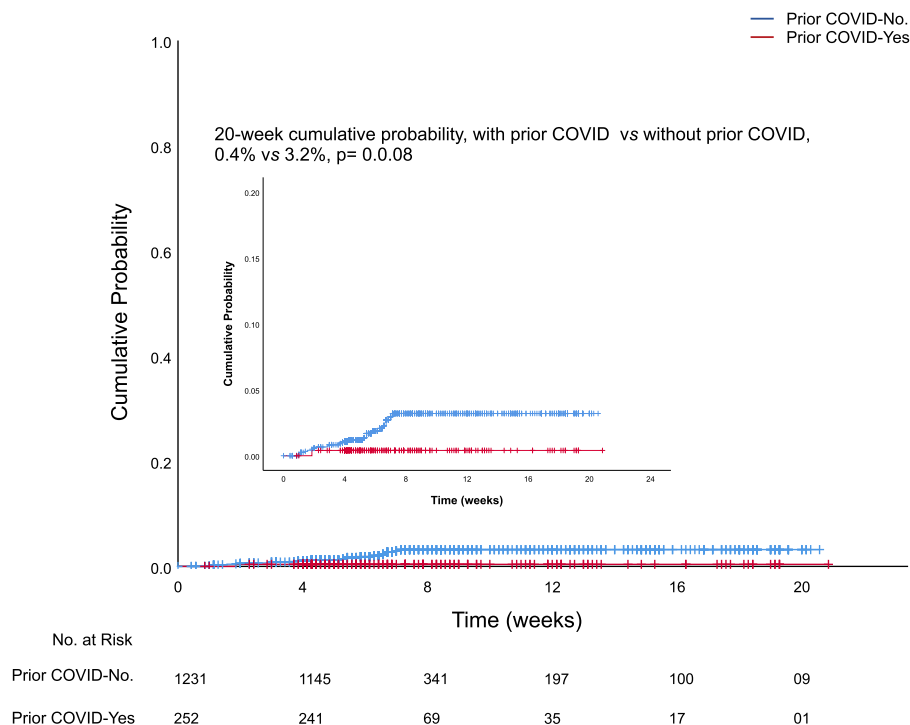
Figure 4. Continued

CoV-2 infection compared with those without previous SARS-CoV-2 infection (20-week cumulative probability 0.4% vs 3.2%, p=0.08) (Figure 4B).

Incidence of SARS-CoV-2 infection after second dose of vaccine

The denominator for this analysis were all employees who received 2 doses of recombinant ChAdOx1 nCoV-19 Corona Virus Vaccine or whole virion inactivated vaccine (BBV152) (n=1085). At a median follow-up of 13.3 (0-16.6) weeks, the 16-week cumulative actuarial probability of SARS-CoV-2 infection after the second vaccine dose was 5.6% (95% CI, 4.33-7.23%) (Figure 5A). Among those who experienced the event for this analysis (n=56), the median time to SARS-CoV-2 infection after the second vaccine dose was 4.1 weeks. In the univariable analysis, the probability of infection after the second vaccine dose was significantly lower among males than females (16-week cumulative probability 3.8% vs 7.9%, p=0.007) (Figure 5B) and in those with previous SARS-CoV-2 infection than those without previous SARS-CoV-2 infection (16-week cumulative probability 1.8% vs 6.4%, p=0.016) (Figure 5C), but there was no significant difference between older ($\geq$50 years) and younger employees (16-week cumulative probability 3.9% vs 5.7%, p=0.55) (Figure 5D). In the multivariable Cox analysis, the proportional hazards assumption was met for all covariates. In this model, female sex (HR=2.06; 95% CI, 1.19-3.56; p=0.01) and lack of previous SARS-CoV-2 infection (HR=3.49; 95% CI, 1.09-11.20; p=0.036) were associated with significantly higher probability of infection after the second vaccine dose, but there was no significant association with age (continuous variable) (HR=1.01; 95% CI, 0.98-1.04; p=0.419) (Table 3). A sensitivity analysis was performed after excluding those who developed SARS-CoV-2 infection within 14 days of receiving the second vaccine dose (n=8) and counting the period of risk after 14 days of second vaccine dose. This did not change the results and in the multivariable Cox model, female sex and lack of previous SARS-CoV-2 infection continued to be significantly associated with higher risk of infection (data not shown).

Table 3

Multivariable cox analysis of factors affecting incidence of SARS-CoV-2 infection after 2 vaccine doses

Factor	Hazard Ratio (95% CI)	P value
Sex (females vs males)	2.055 (1.187–3.557)	0.010
Age (continuous)	1.012 (0.983–1.041)	0.419
Previous SARS-CoV-2 infection (no vs yes)	3.490 (1.088–11.199)	0.036
Type of Vaccine (Covishield vs Covaxin)	0.542 (0.073–4.024)	0.549

DISCUSSION

The results of this retrospective longitudinal analysis in healthcare workers suggest that the first episode of SARS-CoV-2 infection provides strong protection against reinfection, which lasts for at least a year, including during periods of high transmission in the community. Vaccination with ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) also provides protective immunity, albeit weaker than that by natural infection, and previous infection with SARS-CoV-2 adds to the protection provided through vaccination. These results provide quantitative estimates of probabilities of reinfections and vaccine breakthrough infections, which would be useful to epidemiologists in modelling the future course of the pandemic. They would also be useful to hospital administrations, especially cancer centers, in human resource planning during the ongoing pandemic.

The period of this analysis spans the first and second waves of COVID-19 pandemic in India in a location that had high rates of transmission during both waves. Of note, the second wave in India predominantly involved the Delta (B.1.617.2) variant of SARS-CoV-2 (Thangaraj et al., 2021). The majority of SARS-CoV-2 infections in our cohort had occurred before the onset of second wave and therefore, the results suggest that infection by the genetic variants during first wave provided substantial cross-protection against the Delta (B.1.617.2) variant. In this context it is worth noting that of the 408 individuals in our study at risk of developing a reinfection, 328 (80.4%) received at least one dose of vaccine and 248 (60.8%)
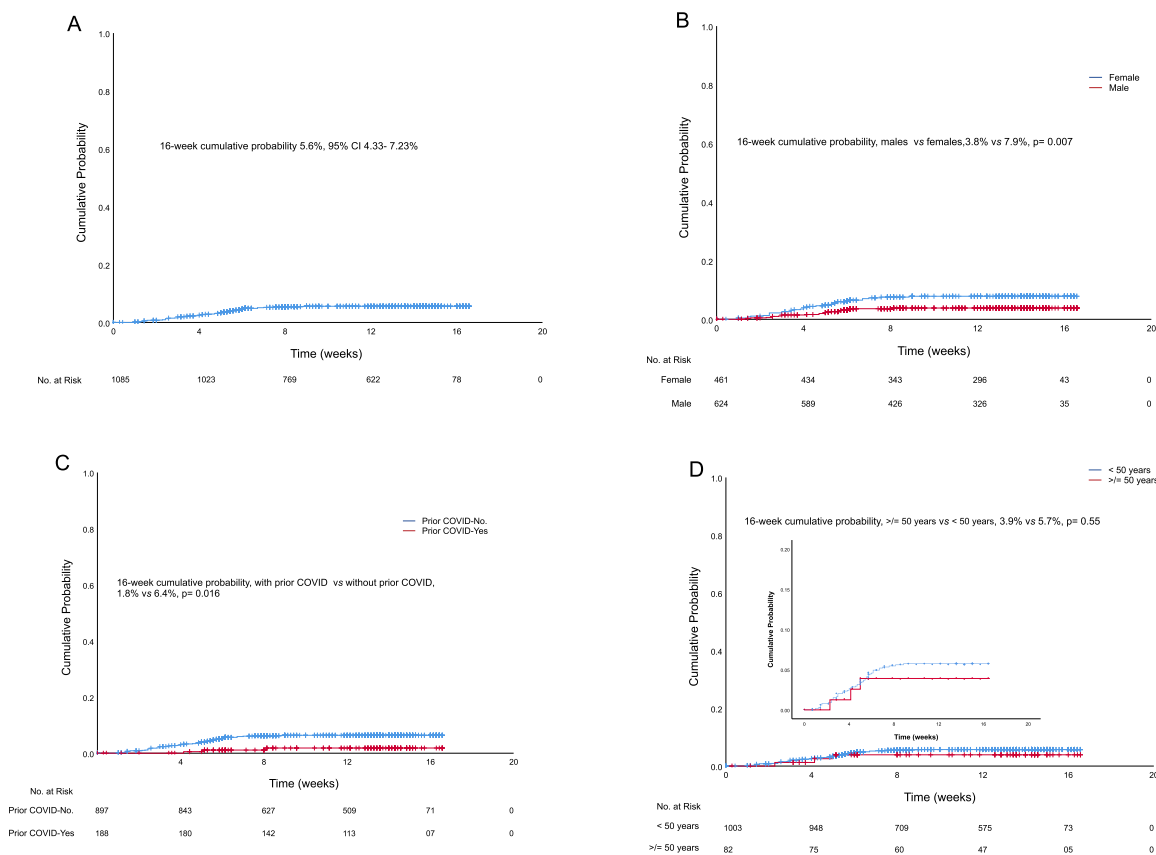
Figure 5. Cumulative Probability of SARS-CoV-2 Among Health Care Workers After Two Vaccine Doses
Figure 5A: All Workers
Figure 5B: By Sex
Figure 5C: By Prior SARS-CoV-2 Infection
Figure 5D: By Age
Figure 5A: Cumulative Probability of SARS-CoV-2 Among All Health Care Workers After Two Vaccine Doses
Figure 5B: Cumulative Probability of SARS-CoV-2 Among Health Care Workers After Two Vaccine Doses, by Sex
Figure 5C: Cumulative Probability of SARS-CoV-2 Among Health Care Workers After Two Vaccine Doses, by Prior SARS-CoV-2 Infection
Figure 5D: Cumulative Probability of SARS-CoV-2 Among Health Care Workers After Two Vaccine Doses, by Age

received 2 doses of vaccine before the data cut-off date of June 18, 2021. Therefore, the low rate of reinfection is also attributable to vaccination of individuals at risk of reinfection during the second wave of pandemic. It is likely that reinfection would have been higher if individuals had not been vaccinated after first episode of infection. Overall, our results provide evidence that previous infection and vaccination contribute to protection against SARS-CoV-2 infection.

Interestingly, Figure 1 shows a "stepwise" increase in the incidence of SARS-CoV-2 infection in essentially 2 steps. Since the data for entire cohort started on day 0, the "first step" (from week 12 to week 26) corresponds to the period between mid-June 2020 and end-September 2020 (first "wave" in India) and the "second step" (from week 51 to week 58) corresponds to the period between mid-March 2021 and early May 2021 (second "wave" in India). The second wave seems to be weaker than the first wave among our study cohort, contrary to the pattern in Indian population. In Figure 2A, week 43 (mid-January 2021) corresponds to the start of vaccination program in India and which was limited to only healthcare and other frontline workers until March 2021, after which it was rolled out for the general population. Therefore, it is likely that the attenuated second wave in our study cohort was attributable to vaccination of some of our employees before the onset of second wave in India.

The overwhelming majority of individuals in this cohort received the recombinant ChAdOx1 nCoV-19 Corona Virus Vaccine. The cumulative probabilities of SARS-CoV-2 infection after first and second vaccine doses of 2.7% and 5.6%, respectively, within relatively short follow-up durations suggest weaker protection by vaccination compared to natural infection. The incidence of vaccine breakthrough infections was significantly lower among employees who had previous SARS-CoV-2 infection, attesting to the substantial protection provided by natural infection, a result that has also been reported by others (Gazit S, et al., 2021). The incidence of SARS-CoV-2 after previous COVID-19 and one vaccine dose was 0.4%, whereas the incidence of SARS-CoV-2 infection without previous COVID-19 but after two vaccine doses was 6.4%. This suggests that individuals with previous infection likely develop similar or even higher levels of antibody and possibly nonantibody immunity than those without previous COVID-19 after 2 vaccine doses (Perkmann T, et al, 2021).

The incidence of SARS-CoV-2 infection in unvaccinated females was significantly lower than unvaccinated males, but the incidence of vaccine breakthrough infections was significantly higher in females than males for unclear reasons. Higher breakthrough infections in females have also been reported by others (Birhane M, et al., 2021; Vaishya et al., 2021), although the underlying mechanisms remain obscure. We did not collect information

about other factors such as profession, social interaction pattern, use of public versus private transport at various time periods of the pandemic, etc. that could potentially clarify this result. The genetic characterization of SARS-CoV-2, which was responsible for vaccine breakthrough infections in this cohort is being reported in a separate report, but the large majority were due to the Delta (B.1.617.2) variant.

This analysis has several strengths. There was complete follow-up information on the entire study population with no loss of longitudinal information. The analysis period spanned both waves of the pandemic in India with results that are contemporaneous and relevant. The diagnosis of SARS-CoV-2 infection was performed by reliable, within-institution testing by the reverse transcriptase-polymerase chain reaction (RT-PCR) method. We used the time-to-event Kaplan-Meier method for estimating the risk of reinfection and vaccine breakthrough infection, which does not discard any data.

The analysis also has some weaknesses. The predisposition to SARS-CoV-2 infection involves many variables, including COVID-19-appropriate behavior, which were uncontrolled in this analysis. The period of follow-up, especially after vaccination, is short and therefore, the estimates of breakthrough infections might change with further follow-up. Systematically collected data on immunological variables, including serum neutralizing antibodies, were not available.

We chose not to set a time-limit of 14 days after the second vaccine dose for characterizing breakthrough infections because our primary aim was to report the incidence of such infections in a real-world setting rather than correlate them with immunological status of the subjects.

In conclusion, this analysis suggests that previous natural SARS-CoV-2 infection provides substantial protection against reinfection. Previous infection adds to the protection offered by vaccination and females experience higher incidence of vaccine breakthrough infections.

Ethical Approval Statement

This study was approved by the Institutional Ethics Committee of Tata Memorial Centre and registered in the Clinical Trials Registry of India (CTRI/2021/08/035655) before being initiated.

Author Contributions

Concept and design: Sudeep Gupta. Data Acquisition: Sachin Dhumal, Amar Patil, Navin Khattry, and Sudeep Gupta. Interpretation of data and Manuscript drafting, including revisions: Sachin Dhumal, Amar Patil, Ashwini More, Sujeet Kamtalwar, Amit Joshi, Anant Gokarn, Sumeet Mirgh, Puneeth Thatikonda, Prashant Bhat, Vedang Murthy, Preeti Chavan, Amey Oak, Suvarna Gore, Atanu Bhattacharjee, Nikhil Patkar, Sadhana Kannan, Nitin Shetty, Anjali Rawat, Meera Achrekar, Bhakti Trivedi, Siddhartha Laskar, Pankaj Chaturvedi, Rajendra Badwe, Navin Khattry, and Sudeep Gupta. Statistical analysis: Sudeep Gupta, Sadhana Kannan, and Atanu Bhattacharjee. Administrative, technical, or material support: Navin Khattry, and Sudeep Gupta. Supervision: Sudeep Gupta.

Declaration of Competing Interest

The authors report no conflict of interest.

References

Altawalah H. Antibody Responses to Natural SARS-CoV-2 Infection or after COVID-19 Vaccination. Vaccines (Basel) 2021;9(8).

Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403–16.

Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. N Engl J Med 2021;385(16):1474–84.

Birhane M, Bressler S, Chang G, Clark T, Dorough L, Fischer M, et al. COVID-19 Vaccine Breakthrough Infections Reported to CDC — United States, January 1–April 30, 2021. MMWR Morb Mortal Wkly Rep 2021;70:792–3 http://dx.doi.org/10.15585/mmwr.mm7021e3.

Ella R, Reddy S, Jogdand H, Sarangi V, Ganneru B, Prasad S, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. Lancet Infect Dis 2021;21(7):950–61.

Gazit S SR, Perez G, et al. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections. bioRxiv 2021.

Huang AT, Garcia-Carreras B, Hitchings MDT, Yang B, Katzelnick LC, Rattigan SM, et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. Nat Commun 2020;11(1):4704.

Kellam P, Barclay W. The dynamics of humoral immune responses following SARS–CoV-2 infection and the potential for reinfection. J Gen Virol 2020;101(8):791–7.

Kim DS, Rowland-Jones S, Gea-Mallorqui E. Will SARS-CoV-2 Infection Elicit Long-Lasting Protective or Sterilising Immunity? Implications for Vaccine Strategies (2020). Front Immunol 2020;11.

Li J, Hui A, Zhang X, Yang Y, Tang R, Ye H, et al. Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study. Nat Med 2021;27(6):1062–70.

Perkmann T, Perkmann-Nagele N, Koller T, Mucher P, Radakovics A, Wolzt M, et al. Serum antibody response to BNT162b2 after natural SARS-CoV-2 infection. Eur J Clin Invest 2021;51(11):e13632.

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603–15.

Tareq AM, Emran TB, Dhama K, Dhawan M, Tallei TE. Impact of SARS-CoV-2 delta variant (B.1.617.2) in surging second wave of COVID-19 and efficacy of vaccines in tackling the ongoing pandemic. Hum Vaccin Immunother 2021 1-2.

Thangaraj JWV, Yadav P, Kumar CPG, Shete A, Nyayanit DA, Rani DS, et al. Predominance of delta variant among the COVID-19 vaccinated and unvaccinated individuals, India, May 2021. J Infect 2021. doi:10.1016/j.jinf.2021.08.006.

Vaishya R, Sibal A, Malani A, Prasad KH. SARS-CoV-2 infection after COVID-19 immunization in healthcare workers: A retrospective, pilot study. Indian J Med Res 2021;153(5&6):550–4.

Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet 2021;397(10277):881–91.