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Original Article

Vaccine effectiveness to protect against moderate or severe disease in COVID cases: A prospective cohort study

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ABSTRACT

Background: This study was carried out to evaluate the effectiveness of partial and full vaccination with ChAdOx1 nCoV-19 (COVISHIELD) to prevent the development of moderate or severe illness among COVID-positive cases.

Methods: This prospective cohort study was conducted among Armed Forces personnel deployed in Northern India who were found COVID positive during the study period between January and June 2021. Information about the vaccination status, age and comorbidities was collected at the time of diagnosis. Classification of COVID cases as moderate or severe was performed as per criteria given by the Government of India. Individuals were considered partially vaccinated three weeks after one dose and fully vaccinated two weeks after the second dose. Risk ratio and vaccine effectiveness (VE) to prevent moderate or severe disease among COVID cases were calculated.

Results: A total of 2005 COVID-19 patients were included in our study. Partial vaccination and full vaccination with ChAdOx1 nCoV-19 offered 13% (95% credible interval (CI): −56.8%, 52.8%) and 66.6% (95% CI: 34.9%, 84.6%) protection against progression to moderate/severe illness among COVID-positive individuals. The risk of moderate-severe disease among COVID-positive cases occurring 4–11 weeks after the first dose was also lesser among those who had taken the second dose of vaccine than individuals who have been vaccinated with only one dose.

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Conclusion: Interval between the first and second doses of ChAdOx1 nCoV-19 vaccine should be reduced to 4–6 weeks, as partial vaccination offers lower protection against the development of moderate-severe illness after COVID infection.

Introduction

The physical, mental, psychological and economic effects of the COVID-19 pandemic have resulted in a humanitarian crisis of unprecedented levels. Several non-pharmacological interventions have been implemented to break the chain of community transmission[1]; however, these preventive methods are not sustainable for a long time. COVID-19 vaccination is now the most crucial preventive measure towards control of the COVID-19 pandemic. China and Russia were the first countries to authorise vaccines against the SARS-CoV-2 in June and August 2020, respectively.[2,3] This was followed by the emergency use authorisation of the mRNA vaccines and the adenovirus vector vaccine in the USA and UK.[4,5]

Initially, two vaccines received approval for emergency use in India: COVISHIELD, a brand of the Oxford-AstraZeneca vaccine manufactured by the Serum Institute of India, and COVAXIN, developed by Bharat Biotech.[6] Sputnik V and Moderna vaccines were added to the approved vaccines in India after clinical trial results indicated an acceptable efficacy.[7] The first phase of the vaccine rollout in India, which started on 16 Jan 2021, involved healthcare workers (HCWs) and frontline workers (FLWs), including police, paramilitary forces, sanitation workers, and disaster management volunteers.[8] Subsequently, all adults above 18 years of age were made eligible for the COVID vaccine in a phased manner. Around 435 million vaccine doses were administered in India as of 25 July 2021 against COVID-19.

Based on efficacy data from clinical trials,[9] ChAdOx1 nCoV-19 vaccine was authorised for emergency use in several countries in a regimen of two standard doses administered four to twelve weeks apart for adults over 18 years of age. Later, based on the findings of Voysey et al,[10] the United Kingdom increased the gap between two vaccine doses to 12 weeks. In India, two doses of the ChAdOx1 nCoV-19 vaccine were administered at intervals of four–six weeks for all HCWs and FLWs.[8] In March and May 2021, the duration was first increased to 6–8 and then 12–16 weeks.[11,12] The decisions were based on the evidence available from the studies carried out in the UK, though no data supporting this decision were available from India.[13]

Vaccines developed in 2020 and authorised for use in various countries were developed against the original Wuhan strain of the SARS-CoV-2. However, the virus has undergone several mutations, which fuelled the increase in cases in various countries.[14–16] Increasingly, there are reports of breakthrough infections in fully vaccinated individuals.[17–21] There was a concern that extending the duration between doses may create a pool of partially immune people who may drive virus mutations and create a vaccine-resistant strain.[22,23] These concerns prompted the United Kingdom to shorten the duration between two ChAdOx1 nCoV-19 vaccine doses to eight weeks.[24] It is now well established that the COVID 19 vaccines may not entirely prevent asymptomatic infections,[25,26] but still prevent hospitalisation[27–30] and death.[25,26,31] Moderate and severe infections tend to burden the healthcare system due to the hospitalisation required; hence the ability of a vaccine to protect against disease requiring hospital care or mortality is the most critical effectiveness endpoint.[32] Given the limited evidence regarding the protective effect of the vaccines in India, this study was planned to evaluate the effectiveness of partial and full vaccination with ChAdOx1 nCoV-19 (COVISHIELD) to protect against moderate or severe disease in COVID cases.

Materials and methods

This prospective cohort study was conducted among the Indian Armed Forces personnel deployed in Northern India who were found COVID positive during the study period between January and June 2021. These security forces personnel were among the priority group to be given ChAdOx1 nCoV-19 Corona Virus Vaccine Recombinant (COVISHIELD) during the vaccination drive of India against this pandemic, and their vaccination drive started on 16 Jan 2021. The second dose of vaccine was offered four to six weeks after the first dose to these persons throughout the study period. However, many individuals took the second dose of the vaccine after six weeks as they were away on leave in the intervening period. As per the existing policy to prevent infection in barracks, all security forces personnel coming back from leave or on new posting were tested by the rapid antigen test (RAT). In addition, anyone showing symptoms suggestive of COVID infection or high-risk contacts of confirmed COVID cases were tested by the RT-PCR test. Personnel in our area who tested positive either by the RAT or the RT-PCR test during the study period were included in this study. Information about the age, vaccination status, past COVID infection and comorbidities was collected at the time of diagnosis and verified from the records. The following definitions were used for the vaccination status of the individuals.[9,28,33,34]

Fully vaccinated: Two weeks after the second dose of ChAdOx1 nCoV-19 Corona Virus Vaccine.

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Partially vaccinated: Individuals were considered partially vaccinated three weeks after the first dose till two weeks after the second dose.

Unvaccinated: Individuals were considered unvaccinated until three weeks post the first dose or had not received any dose.

COVID-positive cases were admitted in Adhoc isolation facilities if they were asymptomatic or had mild disease only. All cases in Adhoc isolation facilities were monitored at least twice daily by a trained health team comprising doctors and paramedical staff. COVID-positive patients were transferred to hospitals for further management if they developed moderate-severe disease. All cases diagnosed were monitored until they recovered, and no case was lost to follow up. The outcome variable for our study was moderate or severe cases among study participants. Classification of cases as moderate or severe was done as per the Ministry of Health & Family Welfare (MoHFW), Government of India classification of COVID cases.[29] A case was classified as moderate if the patient had breathlessness with a respiratory rate between 24 and 30 per minute or the SpO2 levels were between 90 and 93% on room air. In case COVID patients had respiratory rates >30 with breathlessness or the SpO2 levels were below 90% on room air, they were classified as severe cases.

Sample size and sampling

The sample size was calculated assuming the risk of moderate-severe disease among non-vaccinated to be 5%[35] and a vaccine efficacy of 60%.[33] The minimum sample size required for this study with 80% power, 95% confidence level and the ratio of unvaccinated to vaccinated as two was 1245 (830 unvaccinated and 415 vaccinated individuals). To calculate vaccine effectiveness (VE) separately for partially and fully vaccinated persons, we decided to include at least 415 partially vaccinated, 415 fully vaccinated and 830 unvaccinated COVID patients in our study. We included all consecutive individuals who were COVID positive after 16 Jan 2021 until the required sample size for each group was achieved on 15 Jun 2021. We decided to exclude any case with documented lab-confirmed COVID-positive infection in the past from our study. The required sample size for the unvaccinated group was achieved on 15 Jun 2021; hence, cases included in the other two groups were more than the minimum sample size required.

Statistical analysis

Data of COVID cases were collected from Adhoc isolation facilities and hospitals daily and analysed for this study. Data are summarised by mean, standard deviation and proportions. The chi-square test is used to compare the difference in proportions in various groups. Incidence proportions and risk ratios (RRs) with 95% credible intervals (CIs) are calculated for the occurrence of moderate or severe disease among COVID cases using Bayesian regression analysis. The VE to prevent moderate or severe disease among COVID-infected persons was calculated as 100 X (1-RR). The primary analysis was performed for overall VE in partially and fully vaccinated COVID cases.

Further subgroup analysis was performed to calculate VE in different age groups. In India, the gap between two doses of COVISHIELD vaccine has been increased to 12 weeks; hence, we assessed the probability of developing moderate-severe disease among COVID infected study participants in the period of 4–11 weeks after the first dose and compared the effectiveness of only one dose and two doses of the vaccine to prevent moderate-severe disease during this period. The probability of direction (pd), which tells about the proportion of the posterior distribution of the median's sign, was also calculated. Sensitivity analysis was done using different priors and excluding cases occurring in each month at a time from the analysis. Statistical analysis was done using R software ver 3.6.3.

Ethics

Institutional Ethics Committee approval was taken for the study. Informed consent of study participants was obtained.

Results

We tested 80,529 individuals during the study period (74,655 by the RAT and 5874 by the RT-PCR test); of these, 2005 (2.49%) tested positive (1614 by the RAT and 391 by the RT-PCR test). None of these patients had documented history of previous COVID infection. Hence, we included all these 2005 COVID-positive individuals in our study. Out of these, 831 (41.45%) cases were unvaccinated, 464 (23.14%) were partially vaccinated and 710 (35.41%) were fully vaccinated. The mean (S.D.) age of study participants was 31.82 (7.36) years. Only five (0.25%) patients were females, and three (0.15%) had comorbidities. Sixty-two patients (3.09%) progressed to severe/moderate disease as per the MoHFW criteria. Out of these, 49 (2.44%) had developed a moderate disease, and 13 (0.65%) developed severe disease. As shown in Table 1, the risk of developing moderate-severe disease among COVID patients increased with age. No mortality was observed among study participants – either in the vaccinated group or in the non-vaccinated group.

Among our study participants, 4.21% (35/831) of unvaccinated cases developed moderate-severe disease as compared to 3.66% (17/464) moderate-severe cases among partially vaccinated and 1.41% (10/710) moderate-severe cases among fully vaccinated (Table 1). VE of partial vaccination against moderate or severe disease was found to be 13.0% (95% CI: −56.8%, 52.8%). However, full vaccination was found to be 66.6% effective (95% CI: 34.9%, 84.6%) against moderate/severe illness among COVID-positive individuals (Table 2). Sensitivity analysis showed similar results regarding VE of partial and full vaccination.

During stratified analysis of VE in different age groups, it was observed that partial vaccination and full vaccination had almost similar VE in individuals less than 35 years. However, among individuals above 35 years, partial vaccination was not found to be effective to prevent moderate or severe disease, while full vaccination provided 73.3% (95% CI: 36.2%, 91.5%) effectiveness against moderate or severe illness. Thus, age

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Table 1 – Distribution of moderate and severe COVID cases according to age and vaccination.

Characteristics	Total number (%) of cases (N = 2005)	Number (%) of moderate cases (N = 49)	Number (%) of severe cases (N = 13)	Number (%) of total moderate/severe cases (N = 62)	P-value
Age (in years)					
Less than 30	946 (47.18)	7 (0.74)	0 (0.00)	7 (0.74)	<0.0001[a]
30–40	731 (36.46)	27 (3.69)	6 (0.82)	33 (4.51)	
More than 40	328 (16.36)	15 (4.57)	7 (2.13)	22 (6.71)	
Vaccination Status					
Non-vaccinated	831 (41.45)	28 (3.37)	7 (0.84)	35 (4.21)	
Partially vaccinated	464 (23.14)	12 (2.59)	5 (1.08)	17 (3.66)	0.7383[b]
Fully vaccinated	710 (35.41)	9 (1.27)	1 (0.14)	10 (1.41)	0.0016[b]

[a] Chi square for trend.
[b] Chi-square test.

Table 2 – Vaccine effectiveness to prevent moderate/severe disease among partially and fully vaccinated COVID cases.

Vaccination status	Number of cases	Number (%) of moderate/severe disease	Risk ratio (95% CI)	VE (95% CI)	p.d
Overall VE (N = 2005)					
Non-vaccinated	831	35 (4.21%)	Ref.	Ref.	
Partially vaccinated	464	17 (3.66%)	0.870 (0.472, 1.568)	13.0% (−56.8%, 52.8%)	69.01%
Fully vaccinated	710	10 (1.41%)	0.334 (0.154, 0.651)	66.6% (34.9%, 84.6%)	99.97%
VE among individuals up to 35 yrs of age (N = 1326)					
Non-vaccinated	553	14 (2.53%)	Ref.	Ref.	
Partially vaccinated	311	4 (1.29%)	0.508 (0.144, 1.448)	49.2% (−44.8%, 85.6%)	90.70%
Fully vaccinated	462	5 (1.08%)	0.427 (0.134, 1.116)	57.3% (−11.6%, 86.6%)	96.18%
VE among individuals more than 35 yrs of age (N = 679)					
Non-vaccinated	278	21 (7.55%)	Ref.	Ref.	
Partially vaccinated	153	13 (8.50%)	1.125 (0.543, 2.340)	−12.5% (−134.0%, 45.7%)	63.01%
Fully vaccinated	248	5 (2.02%)	0.267 (0.085, 0.638)	73.3% (36.2%, 91.5%)	99.91%

CI: credible interval; p.d.: probability of direction.

appears to be an effect modifier for VE in our study (Table 2 and Fig. 1).

As India has increased the minimum gap between two doses of COVISHIELD from 4 weeks to 12 weeks, we calculated the effectiveness of one dose and two doses of the vaccine among COVID cases diagnosed 4–11 weeks after the first dose. It was observed that the risk of moderate or severe illness decreased significantly if a second dose has been taken during this period (VE 52.1%, 95% CI: 15.6%, 75.3%) (Table 3 and Fig. 2). In cases who had taken the second dose after a gap of four to six weeks, 1.66% (13/763) progressed to moderate/severe disease, while among those who had taken the second dose more than six weeks after the first dose, 3.08% (4/130) developed moderate/severe infection.

Discussion

In this study carried out among Armed Forces personnel to assess protection offered by COVISHIELD against moderate-severe disease, 3.09% of patients progressed to moderate/severe infection. Reports have suggested that 5% of all infected patients may develop severe disease and require critical care support.[35,36] Among hospitalised patients, the proportion of severe patients may vary from 5 to 20%.[37–39] A lower incidence of moderate/severe infection was observed in our study, even in non-vaccinated individuals, as we had a younger and healthier study population. Also, we carried out testing of a large number of individuals coming back from leave. Due to this extensive testing of serving personnel, many individuals with asymptomatic/mild infection were detected, which could have resulted in a lower proportion of moderate-severe infection in our study as compared to other studies.

We report VE of 13% (partial vaccination) and 66.6% (full vaccination) against progression to moderate-severe disease. A review of VE studies shows that VE varies depending on the type of vaccine, vaccination status (partial or complete), the outcome variable measured and the variant of the virus being studied. Most studies have reported comparable VE with two doses of the ChAdOx1 vaccine as reported by our study. These studies have also reported that partial vaccination has reduced effectiveness compared to full vaccination which corroborates the findings of our study (Table 4).[9,10,28,30,40–42,50] It is also evident that VE is higher against severe disease and death than symptomatic infection (Table 4). A study by Muthukrishnan et al from Delhi reported no significant

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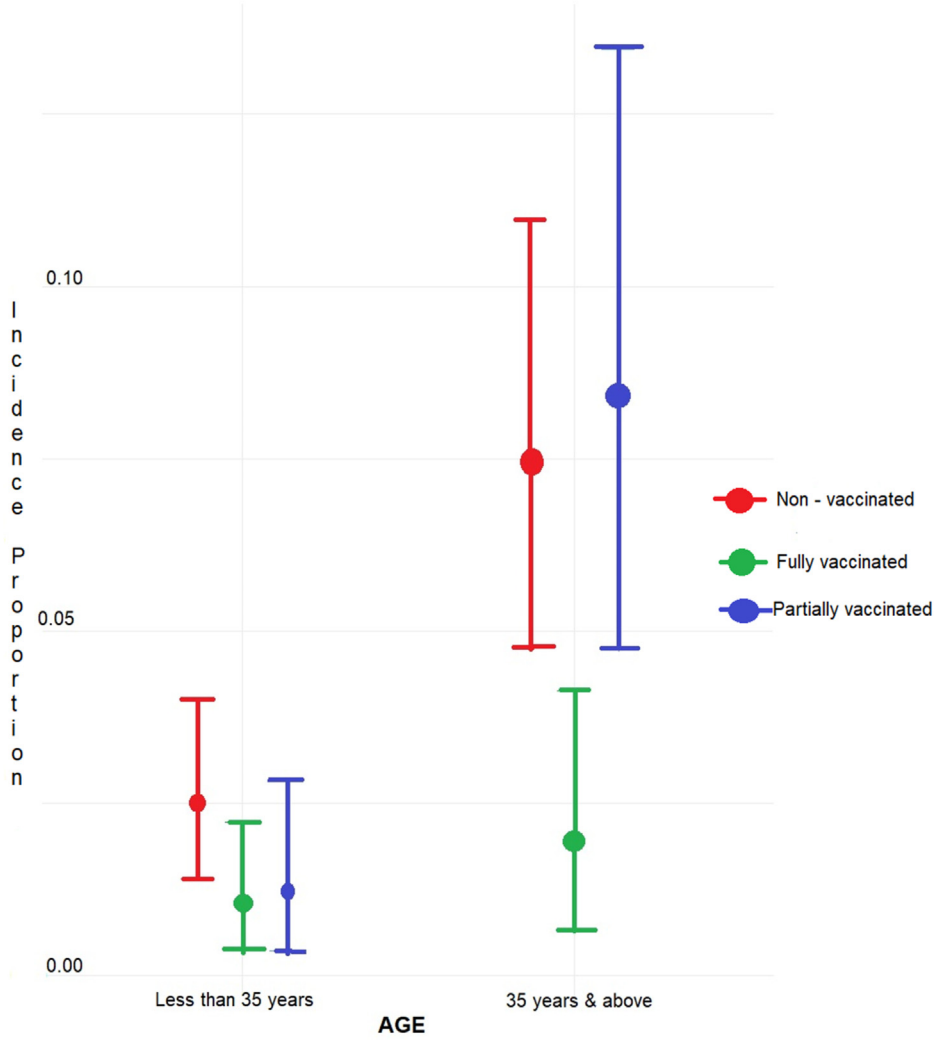

Fig. 1 – Risk of moderate/severe disease (with 95% credible interval) among non-vaccinated, partially vaccinated and fully vaccinated COVID cases stratified as per age.

Table 3 – Disease severity among COVID cases occurring between 4 and 11 weeks of the first dose.

Vaccine status	Total number	Number (%) of moderate/severe disease	Risk ratio (95% CI)	VE	p.d.
Non-vaccinated	831	35 (4.21)	Ref.	Ref.	
Only one dose	185	9 (4.86)	1.155 (0.522, 2.387)	−15.5% (−138.7%, 47.8%)	63.65%
Both doses	743	15 (2.02)	0.479 (0.247, 0.844)	52.1% (15.6%, 75.3%)	99.46%

CI: credible interval; p.d.: probability of direction.

difference in mortality between the unvaccinated and partially vaccinated patients; however, fully vaccinated patients had a significant reduction in odds of death as compared to non-vaccinated cases.[43] A recent yet unpublished study from India evaluated the VE of the ChAdOx1 vaccine against infection and moderate/severe infection. Partial vaccination offered lesser protection both against infection and moderate/severe infection than full vaccination.[44] Large population-based studies from Israel, USA, Spain and the UK reported higher VE for all outcomes with two doses of mRNA vaccines or ChAdOx1 vaccine.[28,45–49] These studies mirror our findings of higher protection with full vaccination.

Our study shows reduced VE with a single dose of the ChAdOx1 vaccine; however, few studies have shown much higher VE with even a single dose of the ChAdOx1 vaccine. A study from CMC Vellore[50] had shown high VE of partial as well as of complete vaccination in the prevention of hospitalisation (70 and 77%), oxygen requirement (92 and 94%) and ICU care (95 and 94%) in a cohort of 10,567 HCWs. However, this study did not consider different time periods of observation for each group, which could have affected the results.

A recent study on all Armed Forces personnel by Ghosh et al, had reported almost similar corrected VE of ChAdOx1 vaccine against any infection among partially vaccinated

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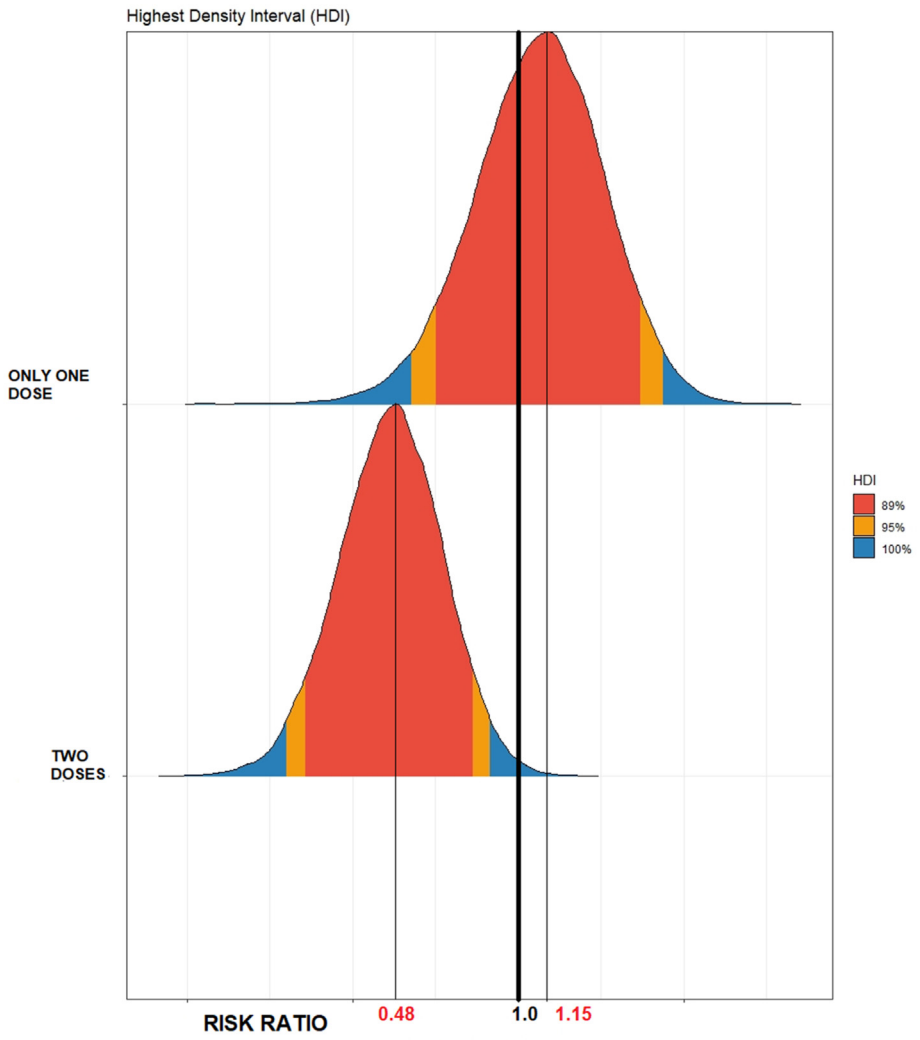

Fig. 2 – Posterior distribution of risk ratios for the development of moderate-severe disease among COVID cases, diagnosed 4–11 weeks after the first dose in comparison with non-vaccinated COVID cases.

(crude VE:75.2%, corrected VE: 94.3–95.1%) and fully vaccinated personnel (crude VE = 54.6%, corrected VE: 91.8%–94.3%).[42] In our study, we also observed similar VE in the partial and complete vaccinated individuals less than 35 years of age. However, in those above 35 years, partial vaccination did not prevent moderate or severe disease, while complete vaccination provided 73.3% (95% CI: 36.2%, 91.5%) protection against moderate or severe illness. Thus, the findings of our study suggest that the protection offered by the vaccine against moderate/severe infection may also depend on the age of the vaccine recipient. As severe infection and mortality in COVID 19 increase with age, we need to be cautious against the increased reliance on one dose, especially in older populations, to protect against severe disease in our country.

Voysey et al had reported higher VE (81.3%) when the second dose was given after 12 weeks.[10] The decision in India to prolong the duration between two doses of COVISHIELD to 12–16 weeks was based on studies carried out in the UK, though there was no supporting evidence from India. However, the duration between two doses of COVAXIN has been maintained at four to six weeks. Similarly, the duration between the mRNA vaccines has been kept at 21–28 days in the countries that authorised them for use. Hence, an increase in gap only for ChAdOx1 nCoV-19 vaccine to more than 12 weeks has raised many concerns.[51] Our study shows that individuals are at a higher risk of developing moderate-severe illness after 4–11 weeks of the first dose if they are not vaccinated with the second dose during this period. There is a need for more data from India on the protective effect of one/two doses of the ChAdOx1-S vaccine against moderate/severe infections and benefits, if any, provided by increased duration between doses. We could not find any Indian studies that have explored the variation in VE with a varying duration between vaccines. In India, the concern for the government and the healthcare system should be the prevention of moderate/severe infections which lead to hospitalisation and deaths. Given the present evidence of reduced effectiveness of one dose against the newer strains of the virus, we recommend reconsidering the present policy of a gap of 12–16 weeks between two doses of COVISHIELD.

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Table 4 – Comparison of efficacy/effectiveness of ChAdOx1 nCoV-19 (COVISHIELD) vaccine from various studies.

	Our study	Voysey et al[9] (interim analysis)	Voysey et al[10]	Bernal et al[28]	Victor PJ et al[50]	Shrorti et al[40]	Sheikh et al[30]	Bernal et al[41]	Ghosh et al[42]
Country	India	UK, Brazil, South Africa	UK, Brazil, South Africa	UK	India	UK	UK	UK	India
Study population	Confirmed COVID cases among security personnel 18–55 years old	Adults 18–55 years	Adults 18–55 years		Healthcare workers	>65 years	National healthcare data set	>70 years	Armed Forces personnel
Period of study	Jan–Jun 2021	Apr–Nov 2020	Apr–Dec 2020	Oct 20–May 21	Feb–May 2021	Dec 20–Mar21	Apr–Jun 2021	Dec 20–Feb 21	16 Jan–30 May 2021
VE dose 1	13.0%	58.3%	76%	30.7% (Delta) 48.7% (Alpha)	61%[&] 70%[@] 94%[+] 95%[#]	56%–62%	18% (Delta variant) 32% (Alpha variant)	60%–73%[&] 43%[@] 51% [+]	Crude VE: 75.2%[&] Corrected VE: 94.3%–95.1%[&] Crude VE: 7.0%[+] Corrected VE: 87%[+]
VE dose 2	66.6%	62% 53.4% (<6 weeks between doses) 65.4% (>6 weeks between doses	63.1% (overall) 81.3% (>12 weeks duration) 55.1% (<6 weeks duration)	67.0% (Delta) 74.5% (Alpha)	65%[&] 77%[@] 92%[+] 94%[#]		60% (Delta) 66% (Alpha)		Crude VE: 54.6%[&] Corrected VE: 91.8%–94.3%[&] Crude VE: 66%[+] Corrected VE: 98%[+]
Outcome	Moderate and severe COVID disease	Confirmed symptomatic COVID-19 disease	Confirmed symptomatic COVID-19 disease	PCR confirmed symptomatic cases	[&]Confirmed Cases [@]Hospitalisation [+]Oxygen requirement [#]ICU admission	PCR confirmed infection	PCR Confirmed cases	[&]Confirmed symptomatic cases [@]Emergency hospital admission [+] Death	[&]Any infection [+]Death

VE: Vaccine efficacy/effectiveness.

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The main strength of our study is that the cohort of patients was selected from the population and not only from hospitalised patients. As we have tested a large proportion of our study population, this study gives a better estimate of the proportion of moderate and severe disease among COVID cases, which is also an indicator of the proportion of COVID cases requiring hospitalisation and oxygen support. Our study participants came back from leave from different parts of the country and were representative samples of COVID cases in India. Moreover, we could monitor and follow up 100% of the study participants, and no one was lost to follow up. Most other studies have evaluated overall VE against moderate-severe disease. However, they could not differentiate whether the protection provided by the COVID vaccine was due to reduced risk of infection or due to reduction in the risk of progression of the disease to moderate-severe levels. This is one of the very few studies that have evaluated the role of the ChAdOx1 vaccine in preventing progression to moderate-severe COVID-19 infection. However, as the study population was predominantly healthy young males, the generalisability of the study findings to other populations is limited. We could not analyse VE separately for severe disease because of a smaller number of severe cases. Moreover, we did not have sufficient numbers for further subgroup analysis. However, our study provides significant evidence regarding the effectiveness of the COVID vaccine to prevent moderate/severe cases after COVID infection.

Conclusions

Full vaccination with COVISHIELD offers 66.6%, and partial vaccination offers 13% protection against the development of moderate or severe illness after COVID infection. The risk of moderate-severe disease among COVID-positive cases occurring 4–11 weeks after the first dose was greater among those who have taken only one dose of vaccine than individuals who have been vaccinated with two doses during this period. Based on our study's findings, we recommend a change in vaccination policy wherein the two doses are given at intervals of 4–6 weeks to reduce the risk of progression to moderate-severe disease among COVID cases.

Disclosure of competing interest

The authors have none to declare.

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