Effectiveness of BBV152/Covaxin and AZD1222/Covishield vaccines against severe COVID-19 and Delta variant in India, 2021: A case-control study

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Abstract

Background: India introduced BBV152/Covaxin and AZD1222/Covishield vaccines from January 2021. We estimated effectiveness of these vaccines against severe Coronavirus disease 2019 (COVID-19) among individuals aged >=45 years.

Methods: We did a multi-centric, hospital-based, case–control study between May and July 2021. Cases were severe COVID-19 patients and controls were COVID-19 negative individuals from 11 hospitals. Vaccine effectiveness (VE) was estimated for full (2 doses ≥14days) and partial (1 dose ≥21 days) vaccination; duration between two vaccine doses and against the Delta variant. We used a random effects logistic regression model to calculate adjusted odds ratios (aOR) with 95% CI after adjusting for relevant known confounders.

Findings: We enrolled 1,143 cases and 2,541 controls. The VE of full vaccination was 80% (95% CI: 73%-86%) with AZD1222/Covishield and 69% (95% CI: 54%-79%) with BBV152/Covaxin. The VE was highest for a gap of 6-8 weeks between two doses of AZD1222/Covishield (92%, 95% CI: 82%-96%) and BBV152/Covaxin (92%, 95% CI: 26%-99%). The VE estimates were similar against the Delta strain and sub-lineages.

Interpretation: BBV152/Covaxin and AZD1222/Covishield were effective against severe COVID-19 among the Indian population during the period of dominance of highly transmissible Delta variant in second wave of pandemic. An escalation of two-dose coverage with COVID-19 vaccines is critical to control the pandemic in the country.

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Research in context

Evidence before this study

The effectiveness of COVID-19 vaccines is important to understand its real-world benefits, particularly from a healthcare perspective in terms of protection against severe COVID-19 and hospitalization and to validate the efficacy estimates for the regulators, policy makers and the public at large. We reviewed the evidence of effectiveness of the vaccines in use in India (BBV152/Covaxin and AZD1222/Covishield) available until 31st October 2021 from the National Library of Medicine article database and MedRxiv for pre-print publications using the terms effectiveness, BBV152, Covaxin, AZD1222, Covishield, India and COVID-19.

In India, a few studies describing the effectiveness of BBV152/Covaxin and/or AZD1222/Covishield vaccines against COVID-19 have been conducted across various geographic areas, using different sampling and recruitment strategies, as well as study design. Most studies are limited to healthcare workers and policemen in smaller sub-national areas, with small sample size, and none are population-representative. As per these studies, the vaccine effectiveness ranges from 77% to 92% with wide confidence intervals. No study provided a vaccine effectiveness estimate specifically against the Delta strain of SARS-Cov-2.

Added value of this study

India represents one of the largest populations at-risk for COVID-19 and currently reports the second highest number of individuals vaccinated with at least one dose of a COVID-19 vaccine globally. Because of its large size and population diversity, India represents logistically complex conditions for COVID-19 vaccination.

This multicentric hospital-based study across 11 cities represents vaccine effectiveness at the national level, covering India's large expanse and during the period of dominance of the Delta strain of SARS-CoV-2 in the country. The findings indicate an overall effectiveness of two doses of 80% with AZD1222/Covishield and 69% with BBV152/Covaxin against severe COVID-19. The VE was highest for a 6-8 week interval between two doses of the both the vaccines. Similar VE estimates were found against the Delta strain and its sub-lineages. Our findings indicate a substantial reduction in the risk of severe COVID-19 and particularly against the Delta strain.

Implication of all the available evidence

The robust real-world effectiveness of the two vaccines against severe COVID-19 in India several months into the second wave of the epidemic with predominant circulation of the highly transmissible Delta variant with potential for immune escape suggests that the strategy for vaccination in the country is effective particularly in the background of high seroprevalence of SARS-CoV-2 IgG antibodies in most parts of the country. Continued expansion of the two-dose vaccination coverage and stringent application of control measures remain warranted to prevent a surge in cases in the near future in the country.

Introduction

India's drugs regulator authorized emergency use for BBV152/Covaxin (Bharat Biotech Limited, India) and AZD1222/Covishield (ChAdOx1-Recombinant, Serum Institute of India Limited, India) in January 2021 and since then India rolled out vaccination beginning with healthcare and frontline workers and cascading from sextugenarians to all aged above 18 years.[1,2] By October 2021, 88% of total 10 billion vaccinees had received AZD1222/Covishield.[3]

Vaccine effectiveness (VE) might be different in specific areas or demographics, and against various disease outcomes and newly emerging SARS-CoV-2 variants. From a healthcare perspective it is imperative to know if the vaccine is effective against severe COVID-19 and eventual hospitalization. In the Indian context, real-world effectiveness of AZD1222/Covishield and BBV152/Covaxin against SARS-CoV-2 infection have been reported among healthcare workers and policemen.[4-6] However, vaccine evaluation in a larger population context will provide post-authorization confirmation of effectiveness of conditionally approved products for regulatory bodies. Hence, we conducted a multicentric study among the general population to estimate effectiveness of BBV152/Covaxin and AZD1222/Covishield vaccines against severe COVID-19 and the Delta variant.

Methods

Study design:

We conducted hospital-based, case–control study among individuals aged >=45 years recruited from 11 tertiary care hospitals across India in May-July 2021. We defined cases as severe COVID-19 [positive based on rRT-PCR/Rapid Antigen Test/GeneXpert/TrueNat test at admission or documented within 14 days prior to hospitalization] patients hospitalised with

any signs and symptoms of fever, cough, dyspnoea, fast breathing, plus respiratory rate > 30 breaths/min or SpO2 < 90% on room air anytime during hospitlization.[7] We defined controls as individuals attending COVID-19 testing facility of the same study hospital irrespective of symptom status with negative SARS-CoV-2 result by rRT-PCR.

We excluded individuals with rRT-PCR negative report but highly suggestive of COVID-19 on CT scan, unwilling to participate or known contraindication to COVID-19 vaccine.

***Sample size**:*

We needed 1300 cases and 2600 controls assuming VE of 75%, 15% controls vaccinated with two doses, 95% confidence interval (CI), 20% relative width of 95% CI and 1:2 case-control ratio.[8]

***Data collection**:*

Trained investigators screened all hospitalized COVID-19 patients and individuals attending COVID-19 testing facility for the eligibility criteria. All rRT-PCR negative individuals were telephonically contacted seven days after enrolment to confirm any change in COVID-19 test status subsequent to the initial negative report. Data was collected through face-to-face interview with participants or their family members, and review of hospital/laboratory/vaccination records using a pre-tested, pre-coded standardized paper-based form. We collected COVID-19 vaccination status based on data from India's COVID-19 vaccination portal (https://www.cowin.gov.in)/vaccination certificate/text message on mobile phone, or participant recall, if documents were unavailable. Previous SARS-CoV-2 infection was documented based on reported history and rRT-PCR/RAT report.

We collected nasal/throat swabs from cases and controls and transported to ICMR-National Institute of Virology, Pune for viral RNA screening and Next-Generation Sequencing (NGS) of

COVID-19 positive samples to determine lineages of the sequences (Supplementary appendix).

Statistical analyses:

We entered the data in Research Electronic Data Capture (REDCap) software (https://www.project-redcap.org/) after the investigators verified the filled paper forms for completeness and errors. We compared the demographics, vaccination status and risk behaviors of cases and controls using chi-square test for categorical and t-test for continuous variables.

For the primary VE analysis, we compared proportion of fully vaccinated (two dose recipients, with interval between second dose and COVID-19 testing/hospitalization >=14 days) and unvaccinated individuals (non-receipt of any COVID-19 vaccine) among cases and controls. Additionally, we estimated VE for three categories of partial vaccination: (a) one dose recipients, with interval between vaccination and COVID-19 testing/hospitalization <21 days (one dose<21 days); (b) one dose recipients, with interval between vaccination and COVID-19 testing/hospitalization >=21 days (one dose>=21 days); (c) two dose recipients with interval between vaccination and COVID-19 testing/hospitalization <14 days (two dose<14 days). Among fully vaccinated individuals, we estimated the VE by the interval between two doses (<6, 6-8, 9-11, ≥12 weeks). Additionally, we estimated VE for Delta variant and its sub-lineages as a subgroup analysis. Persons with past SARS-CoV-2 infection were included in the VE analysis as vaccination was regardless of prior infection status.

Covariates with a p-value<0.20 for crude OR were selected for multiple logistic regression.[9] After assessing for multi-collinearity, relevant covariates were identified as confounders by comparing the −2 log likelihood ratio values of the models with and without the potential

confounder(s) as per the conceptual framework based on directed acyclic graphs.[10] In order to account for the heterogeneity of effect by study sites we used a random effects multiple logistic regression model to calculate the adjusted odds ratio (aOR) with 95% CI after adjusting for relevant confounders. We calculated VE as (1-aOR) × 100%. Statistical analyses were done using Stata (version SE 17.0) software (StataCorp, Texas, USA).

Ethics statement:

We obtained written informed consent from all the participants or their legally authorized representatives. Study procedures were approved by the Institutional Human Ethics Committees of all participating institutions.

Results

We recruited 1143 cases and 2541 controls from 11 study hospitals. Cases were older [61.1 (SD: 10.5) vs 56.5 (SD: 8.7) years, p<0.001] and included significantly more females, rural residents, non-earning, poorly educated and those reporting pre-existing comorbidities than the controls (Table 1).

Overall, 326 (29%) cases and 1422 (56%) controls reported receipt of at least one dose of any vaccine (p<0.001). The vaccination history of 142 (43%) vaccinated cases and 802 (7%) vaccinated controls was verified using vaccination records. Majority of the vaccinated cases (n=256, 79%) and controls (n=1145, 81%) had received AZD1222/Covishield. Compared to controls, a significantly higher proportion of cases reported participation in social/religious event 14 days prior to testing (10% vs. 3%, p<0.001), did not always use masks (47% vs. 27%, p<0.001), and came in contact with COVID-19 individual (21% vs. 11%, p<0.001) (Table 2).

Nasal/throat swabs of 708 (62%) (non-vaccinated=521, vaccinated with single dose=127, vaccinated with two doses=60) of the 1143 cases were selected for NGS based on the Cyclic

threshold (Ct) values (11.32 to 36.1). SARS-CoV-2 sequences with a genomic coverage of >95% were obtained for 510 (72%) samples (Supplementary Table S1). Of the 510 samples (367 unvaccinated, 93 single dose and 50 two doses vaccinated individuals), 508 (99.6%) showed presence of the Delta variant and its sub-lineages including B.1.617.2 (70%; 67% unvaccinated; 63% single dose; 88% two doses), AY.26 (21%; 22% unvaccinated; 23% single dose; 10% two doses) and others (Supplementary Table S2).

The sequences having >98% SARS-CoV-2 genome coverage (n=448, including 319 non-vaccinated, 84 one dose, 48 two doses) were used for generation of phylogenetic tree along with 12 representative sequences. Four broader sub-lineages of the Delta variant were observed and majority of the AY pangolin lineages (AY.7.1, AY.25, AY.24, AY.20, AY.4 and AY.33) were grouped in the sub-lineage-I (Figure 1). We did not observe any specific differentiation in branching of phylogenetic tree between vaccinated and unvaccinated individuals. Amino acid changes by lineages are given in Supplementary Table S3. .

Vaccine effectiveness by type, dose and duration since vaccination

Overall, 94 (8%) cases and 554 (22%) controls reported full vaccination, 815 (71.3%) cases and 1116 (43.9%) controls were unvaccinated and the remaining 201 (18%) cases and 714 (22%) controls reported partial vaccination (Table 3). The effectiveness of vaccination with one dose>=21 days (64%; 95% CI: 56%-70%) and one dose<21 days (67%, 95% CI: 47%-89%) was not different (p=0.733) than the effectiveness of full vaccination (79%; 95% CI: 74%-84%) and two dose <14 days [(85%; 95% CI: 67-93), p=0.453]. Effectiveness of two doses<14 days was significantly higher than one dose>=21 days (p=0.031) (Table 3).

Of the 1073 cases and 2264 controls, 6% cases and 17% controls reported full vaccination and 16% cases, and 28% controls reported partial vaccination with AZD1222/Covishield. The effectiveness of full vaccination with AZD1222/Covishield was 80% (95% CI: 73%-86%). It

was significantly higher than vaccination with one dose>=21 days (66%; 95% CI: 58%-72%). Effectiveness of one dose vaccination>=21 days and one dose<21 days was similar (p=0.510) as was the effectiveness of full vaccination and two doses<21 days (p=0.217). Effectiveness of two doses<14 days was significantly higher than vaccination with one dose>=21 days (p=0.031) (Table 3).

Of 887 cases and 1384 controls, 3.4% cases and 5.3% controls reported full vaccination and 16% cases and 28.3% controls reported partial vaccination with BBV152/Covaxin. Effectiveness of full vaccination with BBV152/Covaxin was 69% (95% CI: 54%-79%). It was significantly (p=0.027) higher than vaccination with one dose>=21 days [40% (95% CI: 4%-62%)]. Effectiveness of one dose<21 days was significantly higher than with one dose>=21 days (p=0.045). Effectiveness of two doses<14 days was similar to vaccination with one dose>=21 days (p=0.279) as was the effectiveness of full vaccination and two doses<21 days (p=0.954). (Table 3)

Vaccine effectiveness by interval between two doses

Vaccine effectiveness was highest (92%;, 95% CI: 83%-97%) for an interval of 6-8 weeks between two doses of either vaccines and was significantly higher than <6 weeks (p=0.003) and ≥12 weeks (p=0.034). When calculated separately, the VE was highest for an interval of 6-8 weeks for AZD1222/Covishield (92%; 95% CI: 82%-96%) and BBV152/Covaxin (91%; 95% CI: 26%-99%). However, the estimation of VE for fully vaccinated individuals with an interval of >=12 weeks was under-powered (Table 3).

Vaccine effectiveness against the Delta variant and sub-lineages

Vaccine effectiveness against the Delta variant and sub-lineages was 64% (95% CI: 40%-79%) for full dose and 44% (95% CI: 0%-71%) for vaccination with one dose>=21 of

BBV152/Covaxin [p=0.261]. In terms of doses, VE was 81% (95% CI: 71%-88%) for full dose and 73% (95% CI: 64%-80%) for partial dose of AZD1222/Covishield [p=0.180]. VE of AZD1222/Covishield against the Delta variant was highest for interval of 6-8 weeks between the two doses (92%, 95% CI: 74%-98%) (Table 4).

Discussion

The results from this large multicentric study indicate that both AZD1222/Covishield and BBV152/Covaxin significantly reduce the risk of severe COVID-19 and against the Delta variant among the Indian population aged >=45 years, more so with two doses, albeit higher for AZD1222/Covishield than BBV152/Covaxin. Highest reduction in risk of severe COVID-19 was documented for 6-8 week gap between the two doses.

Our estimates of vaccine effectiveness were expectedly lower than the efficacy estimates from vaccine trials. BBV152/Covaxin was introduced based on high safety, tolerability and immune responses among the Indian participants.[11,12] Subsequently, the efficacy in the phase III trial was estimated to be 93% against severe COVID-19.[13] Real world estimates of VE should be considered in the context of programmatic issues such as storage and cold chain maintenance, and off-schedule and incomplete delivery of doses.[14] Besides, the field performance of vaccines were influenced by newly emerging SARS-CoV-2 variants. Published studies indicate that global estimates of VE of two doses of AZD1222/Covishield against severe infection with the Delta variant were reported to be 92%[15] and the estimate from United Kingdom was 67% for Oxford-ChAdOx1-S.[16] Indian studies indicated reduced neutralization capability of BBV152/Covaxin and AZD1222/Covishield vaccine against Delta variant.[17,18] Our study was conducted when B.1.617 lineages were dominating in India.[19]

Our results are consistent with the VE reports of either AZD1222/Covishield or BBV152/Covaxin against hospitalization to be 77% for full and 70% for partial vaccination among healthcare workers in South India.[4] However, our VE estimates are lower than those reported among healthcare and frontline workers of the Indian armed forces for full (92%) and partial (94%) vaccination with AZD1222/Covishield against development of infection.[6]

These studies were conducted at a time when the Delta variant was not documented to be dominant and among a relatively young men aged 40-60 years with minimal comorbidities and very high vaccination coverage as compared to the profile in the present study.

The gap between the two doses can also influence the VE in programmatic condition. We estimated a maximum effectiveness for a 6-8 week gap for both vaccines, with a gradual decline beyond 12 weeks. Unlike our observation, other published studies of Oxford-ChAdOx1-S indicated higher efficacy or immunogenicity for >12 weeks gap between two vaccine doses.[20,21] During the high transmission period, when we conducted this study, asymptomatic or known SARS-CoV-2 infection few weeks prior to the first or second dose could have boosted the vaccine-induced immunogenicity manifesting as improved vaccine performance at a shorter gap. Our finding has programmatic implications on rolling out of the vaccination to reach the maximum eligible Indian population at the earliest, where after an initially gap of four weeks for both BBV152/Covaxin and AZD1222/Covishield, the gap was increased to 12-16 weeks for AZD1222/Covishield.[22] The policy on interval between the two doses vary across countries and needs further evidence towards its standardization.[23]

Our study had several limitations. Firstly, misclassification bias could have affected the VE estimates in several ways. (1) It is possible that vaccinated individuals could have had higher risk of COVID-19 due to (a) potential transmission during travel for vaccination, (b) crowding at the vaccination centres, and (c) risky behaviors post-vaccination due to the self-perceived vaccine protection. This could have led to underestimation of the VE. (2) Low sensitivity or specificity of rRT-PCR testing and asymptomatic status of COVID-19 could have led to differential misclassification of the control status.[24] To reduce such bias, we did confirm the rRT-PCR status among negative controls after a week. However, we could not confirm all the

negative controls and hence, we could have underestimated the VE. (3) The status of IgG used as a surrogate marker for recent infection, though done, could not to differentiate the antibodies generated by the vaccine or the infection. Accordingly, we could have misclassified the infection status of those infected prior to joining the study but not tested positive at the time of enrolment and thus leading to underestimation of VE. (4) We anticipated differential misclassification about the interval between two doses of vaccine, as cases might have recalled vaccination dates better than controls- thereby causing a biased estimate of VE by dosing interval, in either direction. Secondly, prior SARS-CoV-2 infection and conferred immunity thereof, could have influenced the VE estimates.[25] Such prior infection could reduce the chance of re-infection. While being aware of a prior infection can reduce the likelihood of vaccination, unknown prior infection (e.g., asymptomatic) is unlikely to have influenced the decision to vaccinate. The bias in estimating VE due to unknown prior infection is reported to be minimal in case-control studies.[14] Thirdly, the sample size could have influenced the VE estimates. Four-fifth of the study participants had received AZD1222/Covishield and hence recruited study size was inadequate for VE estimates for BBV152/Covaxin. Nevertheless, our study had adequate power for a single vaccine, except for BBV152/Covaxin two doses (<14 days). Such power could be attributed to substantially higher vaccine coverage than the assumed coverage for sample size calculation. Estimation of VE for interval of >9 weeks was under-powered and hence needs to be interpreted cautiously. Further, it did not allow us to statistically compare VE across intervals. WHO suggets that any useful COVID-19 vaccine should have VE estimates with lower bound of the 95% CI above 50%.[14] Finally, the external validity of the VE findings beyond 45 years needs to be considered cautiously. The younger adults (18-44 years) had recently become eligible for vaccination and hence, we expect similar VE results in the younger age group as well.

Our findings highlight significant real-word protection with two vaccine doses against severe COVID-19 and specifically against the currently dominant Delta variant in India. The substantial effectiveness of only one dose, more so for AZD1222/Covishield, supports the policy decision from a public health perspective to initially maximize coverage with single - dose in the country. Vaccine effectiveness below 100% suggests the possibility of infection among vaccinated and thus further likely transmission albeit at lower efficiency, particularly if they remain asymptomatic or unaware of their infection status.[26,27] Adherence to masking and social distancing would therefore still be needed to limit transmission until a large enough population is fully vaccinated.

Our findings of high variation in the Delta lineage across the country suggests fast mutations in Delta due to its immune escape ability in host genome. The dominance of Delta variant and its sub-lineages in India with higher transmissibility and potential for immune escape makes the task of achieving a robust protection even with near universal vaccination coverage much more difficult.[28,29] Nevertheless, for an effective and timely control of the pandemic it is critical to accelerate the two-dose vaccination coverage taking into account the complex strategic and programmatic aspects of the vaccination program in India.

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Table 1: Background characteristics of cases and controls, India, May-July 2021

Characteristics	**Cases (%)**	**Controls (%)**	**p-value**
Mean age in years (SD)	**(n=1143)** 61.1 (10.5)	**(n=2541)** 56.5 (8.7)	<0.001
Gender	**(n=1143)**	**(n=2541)**	
Male	654 (57.2)	1590 (62.6)	0.007
Female	489 (42.8)	950 (37.4)	
Residence	**(n=1138)**	**(n=2520)**	
Rural	560 (49.2)	941 (37.3)	<0.001
Urban	578 (50.8)	1579 (62.7)	
Occupation	**(n=1143)**	**(n=2538)**	
Unemployed/student/Homemaker	574 (50.2)	901 (35.5)	<0.001

Retired	139 (12.2)	333 (13.1)	
Agriculture	121 (10.6)	262 (10.3)	
Professional/technical/administrative/management	89 (7.8)	374 (14.7)	
Skilled manual	85 (7.4)	272 (10.7)	
Unskilled manual	65 (5.7)	158 (6.2)	
Sales and services	53 (4.6)	167 (6.6)	
Clerical	17(1.5)	71 (2.8)	
Education	**(n=1142)**	**(n=2541)**	
Illiterate	225 (19.7)	426 (16.8)	<0.001
Primary school	195 (17.1)	248(9.8)	
Middle school	210 (18.4)	347 (13.7)	
Secondary school	185 (16.2)	528 (20.8)	

Higher secondary school (11th and 12th std)	122 (10.7)	335 (13.2)	
Graduation	152 (13.3)	467 (18.4)	
Post-graduation and above	53 (4.6)	190 (7.5)	
Smoking status	**(n=1114)**	**(n=2522)**	
Never smoked	915 (82.1)	2083 (82.6)	0.43
Former smoker	118 (10.6)	237 (9.4)	
Current smoker	81 (7.3)	202 (8.0)	
Any pre-existing comorbidity	**(n=1143)** 781 (68.3)	**(n=2541)** 1336 (52.6)	<0.001
Type of pre-existing comorbidity			
Hypertension	**(n=781)** 528 (67.6)	**(n=1335)** 678 (50.8)	<0.001

Diabetes mellitus	**(n=781)** 501 (64.1)	**(n=1333)** 651 (48.8)	<0.001
Heart disease	**(n=778)** 135 (17.3)	**(n=1335)** 195 (14.6)	0.09
Asthma	**(n=780)** 50 (6.4)	**(n=1333)** 49 (3.7)	0.004
Lung disease other than asthma	**(n=767)** 49 (6.4)	**(n=1335)** 30 (2.2)	<0.001
Any malignancy	**(n=780)** 45 (5.8)	**(n=1336)** 260 (19.5)	<0.001
Liver disease	**(n=780)** 33 (4.2)	**(n=1336)** 35 (2.6)	0.04

Any immunodeficiency disorder	**(n=779)** 29 (3.7)	**(n=1332)** 45 (3.4)	0.68
Renal disease	**(n=781)** 63 (8.1)	**(n=1334)** 69 (5.2)	0.008
Active tuberculosis	**(n=780)** 10 (1.3)	**(n=1330)** 10 (0.7)	0.23

Table 2. Vaccination and other COVID-19 related behaviours among cases and controls, India, May-July 2021

Vaccination status and COVID-19 related behaviour	**Cases (%)**	**Controls (%)**	**p-value**
Taken any COVID=19 vaccine	**(n=1143)** 326 (28.5)	**(n=2541)** 1422 (56.0)	<0.001
Vaccine type	**(n=326)**	**(n=1422)**	
BBV152/Covaxin	70 (21.5)	265 (18.6)	0.14
AZD1222/Covishield	256 (78.5)	1145 (80.5)	
Others	0	12 (0.8)	
Vaccine doses – Any vaccine	**(n=1143)**	**(n=2541)**	
Unvaccinated	815 (71.3)	1116 (43.9)	<0.001
One dose	226 (19.8)	807 (31.8)	
2 doses	102 (8.9)	618 (24.3)	

Vaccine doses – BBV152/Covaxin	**(n=887)**	**(n=1384)**	
Unvaccinated	815 (91.9)	1116 (80.6)	<0.001
One dose	31 (3.5)	92 (6.6)	
2 doses	41 (4.6)	176 (12.7)	
Vaccine doses - AZD1222/Covishield	**(n=1,073)**	**(n=2264)**	
Unvaccinated	815 (76.0)	1116 (49.3)	<0.001
One dose	196 (18.3)	715 (31.6)	
2 doses	62 (5.8)	433 (19.1)	
Source of vaccination details	**(n=328)**	**(n=1418)**	
Recall	186 (56.7)	616 (43.4)	<0.001
Text message from vaccination centre	105 (32.0)	458 (32.3)	
Vaccination certificate	26 (7.9)	282 (19.9)	

Hospital records	11 (3.3)	38 (2.7)	
CO-WIN registry	0 (0.0)	24 (1.7)	
Participated in social/religious event within 14 days of COVID-19 testing	**(n=1141)** 113 (9.9)	**(n=2539)** 80 (3.1)	<0.001
Frequency of mask use within 14 days of COVID-19 testing	**(n=1142)**	**(n=2537)**	
Never	26 (2.3)	22 (0.9)	<0.001
Sometimes	505 (44.2)	684 (27.0)	
Always	611 (53.5)	1831 (72.2)	
COVID-19 risk perception	**(n=1142)**	**(n=2540)**	
Low risk	619 (54.2)	1440 (56.7)	<0.001
Medium risk	409 (35.8)	725 (28.5)	
High risk	114 (10.0)	375 (14.8)	

Contact with COVID-19 positive individual within 14 days of COVID-19 testing	**(n=1141)**	**(n=2537)**	
No	652 (57.1)	2222 (87.6)	<0.001
Yes	234 (20.5)	270 (10.6)	
Don’t know	255 (22.3)	45 (1.8)	
Prior RT-PCR positive for COVID-19	**(n=152)** 32 (21.0)	**(n=1219)** 278 (22.8)	0.63

Table 3: Effectiveness of COVID-19 vaccines against severe SARS-CoV-2 infection in age 45+ years by dose and time since vaccination and gap between two doses, India, May – July 2021

Vaccination status	**Cases*** **(%)**	**Controls$** **(%)**	**Crude Odds Ratio (95% CI)**	**Adjusted Odds Ratio#** **(95% CI)**	**Vaccine effectiveness (%) (95% CI)**	**Power (%)**
AZD1222 (Covishield)/ BBV152 (Covaxin)	**(n=1143)**	**(n=2541)**				
Unvaccinated	815 (71.3)	1116 (43.9)	1	1		
One dose (<21 days)	25 (2.2)	99 (3.9)	0.31 (0.20-0.49)	0.33 (0.21-0.53)	67 (47-79)	99.8
One dose (>=21 days) [Partial]	201 (17.6)	714 (21.8)	0.34 (0.29-0.41)	0.36 (0.30-0.44)	64 (56-70)	100
Two dose (<14 days)	8 (0.7)	58 (2.3)	0.16 (0.8-0.34)	0.15 (0.07-0.33)	85 (67-93)	99.9
Two dose (>=14 days) [Full]	94 (8.2)	554 (21.8)	0.20 (0.16-0.26)	0.21 (0.16-0.26)	79 (74-84)	100
Gap between 2 doses (>=14 days after	**(n=909)**	**(n=1670)**				

second dose) - AZD1222(Covishield)/ BBV152 (Covaxin)						
Unvaccinated	815 (89.7)	1116 (66.8)	1	1		
<6 weeks	75 (8.2)	383 (22.9)	0.24 (0.18 – 0.31)	0.27 (0.20-0.35)	73 (65 – 80)	100
6-8 weeks	8 (0.9)	114 (6.8)	0.08 (0.04 – 0.18)	0.08 (0.03 – 0.17)	92 (83-97)	100
9-11 weeks	7 (0.8)	42 (2.5)	0.19 (0.09 – 0.44)	0.18 (0.08 – 0.42)	82 (58 – 92)	98.2
≥12 weeks	4 (0.4)	15 (0.9)	0.28 (0.09 – 0.86)	0.35 (0.11 – 1.10)	65 (0-89)	32.3
AZD1222/Covishield	**(n=1073)**	**(n=2264)**				
Unvaccinated	815 (76.0)	1116 (49.3)	1	1		
One dose (<21 days)	24 (2.4)	79 (3.5)	0.39 (0.24-0.62)	0.42 (0.25- 0.67)	58 (33-75)	96.4
One dose (>=21 days) [Partial]	172 (16.0)	641 (28.3)	0.33 (0.27-0.4)	0.34 (0.28-0.42)	66 (58-72)	100
Two dose (<14 days)	3 (0.3)	39 (1.7)	0.09 (0.03-0.30)	0.09 (0.03-0.30)	91 (70-97)	99.7

Two dose (>=14 days) [Full]	59 (5.5)	389 (17.2)	0.18 (0.13-0.24)	0.2 (0.14-0.27)	80 (73-86)	100
Gap between 2 doses (>=14 days after second dose) - AZD1222/Covishield	**(n=874)**	**(n=1,505)**				
Unvaccinated	815 (93.2))	1116 (74.1)	1	1		
<6 weeks	42 (4.8)	236 (15.8)	0.21 (0.15 – 0.30)	0.24 (0.16 – 0.34)	76 (66 – 84)	
6-8 weeks	7 (0.8)	103 (6.8)	0.08 (0.04 – 0.18)	0.08 (0.04 -0.18)	92 (82 – 96)	100
9-11 weeks	6 (0.7)	36 (2.4)	0.19 (0.08 – 0.47)	0.18 (0.07 – 0.45)	82 (55 – 93)	95.7
≥12 weeks	4 (0.5)	14 (0.9)	0.30 (0.10 – 0.93)	0.37 (0.12 – 1.18)	63 (0 – 88)	25.6
BBV152/Covaxin	**(n=887)**	**(n=1384)**				
Unvaccinated	815 (91.9)	1116 (80.6)	1	1		
One dose (<21 days)	1 (0.1)	20 (1.4)	0.06 (0.01-0.45)	0.07 (0.01-0.55)	93 (45-99)	94.6
One dose (>=21 days) [Partial]	30 (3.4)	73 (5.3)	0.57 (0.36-0.89)	0.60 (0.38-0.96)	40 (4-62)	72.9

Two dose (<14 days)	5 (0.6)	19 (1.4)	0.34 (0.13-0.93)	0.32 (0.11-0.92)	68 (8-89)	50
Two dose (>=14 days) [Full]	36 (4.1)	156 (11.3)	0.30 (0.20-0.44)	0.31 (0.21-0.46)	69 (54-79)	100
Gap between 2 doses (>=14 days after second dose) – BBV152/Covaxin	**(n=851)**	**(n=1272)**				
Unvaccinated	815 (95.8)	1116 (87.7)	1	1		
<6 weeks	34 (4.0)	137 (10.8)	0.33 (0.22-0.49)	0.35 (0.23-0.53)	65 (47-77)	100
6-8 weeks	1 (0.1)	12 (0.9)	0.11 (0.01-0.85)	0.09 (0.01-0.74)	91 (26-99)	61.4
9-11 weeks	1 (0.1)	6 (0.5)	0.20 (0.02-1.70)	0.19 (0.02-1.64)	81 (0-98)	15.4
≥12 weeks	0 (0.0)	1 (0.1)	-	-	-	-

*****Case: Laboratory confirmed COVID-19 patients hospitalized with severe COVID-19 (One of the following: fever, cough, dyspnoea, fast breathing plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air)

$Control: RT-PCR negative individuals who remained negative upto 7 days after initial RT-PCR test

Adjusted for any pre-existing comorbidity, attending social/religious event, frequency of mask use, rural/urban residence

Table 4: Effectiveness of COVID-19 vaccines against severe SARS-CoV-2 infection by Delta variant in age 45+ years by dose and time since vaccination and gap between two doses, India, May – July 2021

Vaccination status	Cases* (%)	Controls[$] (%)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[#] (95% CI)	Vaccine effectiveness (%) (95% CI)	Power (%)
AZD1222 (Covishield)/ BBV152 (Covaxin)	**(n=511)**	**(n=2541)**				
Unvaccinated	368 (72.0)	1116 (43.9)	1	1		
One dose (<21 days)	18 (3.5)	99 (3.9)	0.53 (0.31-0.89)	0.60 (0.35-1.03)	40 (0-65)	57.4
One dose (>=21 days) [Partial]	75 (14.7)	714 (21.8)	0.29 (0.22-0.38)	0.29 (0.22-0.39)	71 (61-78)	100
Two dose (<14 days)	4 (0.8)	58 (2.3)	0.19 (0.07-0.54)	0.20 (0.07-0.56)	80 (44-93)	94.6
Two dose (>=14 days) [Full]	46 (9.0)	554 (21.8)	0.23 (0.17-0.32)	0.23 (0.16-0.33)	77 (67-84)	100
Gap between 2 doses (>=14 days after	**(n=414)**	**(n=1670)**				

second dose) of AZD1222 (Covishield)/ BBV152 (Covaxin)						
Unvaccinated	368 (88.9)	1116 (66.8)	1	1		
<6 weeks	35 (8.4)	383 (22.9)	0.26 (0.18-0.39)	0.27 (0.18-0.41)	73 (59-82)	100
6-8 weeks	3 (0.7)	114 (6.8)	0.07 (0.02-0.23)	0.07 (0.02-0.23)	93 (77-98)	100
9-11 weeks	5 (1.2)	42 (2.5)	0.30 (0.12-0.77)	0.27 (0.10-0.70)	73 (30-90)	55.6
≥12 weeks	3 (0.7)	15 (0.9)	0.45 (0.13-1.62)	0.52 (0.14-1.91)	48 (0-86)	3.4
AZD1222/Covishield	**(n=476)**	**(n=2264)**				
Unvaccinated	368(77.3)	1116 (49.3)	1	1		
One dose (<21 days)	17(3.6)	79 (3.5)	0.64(0.37-1.11)	0.71(0.40- 1.26)	29(0-60)	28.5
One dose (>=21 days) [Partial]	62 (13.0)	641 (28.3)	0.26(0.19-0.35)	0.27(0.20-0.36)	73(64-80)	100
Two dose (<14 days)	3 (0.6)	39 (1.7)	0.20(0.06-0.66)	0.20(0.06-0.69)	80(31-94)	75.9

Two dose (>=14 days) [Full]	26(5.5)	389 (17.2)	0.19(0.12-0.29)	0.19(0.12-0.29)	81(71-88)	100
Gap between 2 doses(>=14 days after second dose) of AZD1222/Covishield	**(n=394)**	**(n=1505)**				
Unvaccinated	368 (93.4)	1116 (74.1)	1	1		
<6 weeks	16 (4.1)	236 (15.7)	0.20 (0.12-0.34)	0.21 (0.12-0.36)	79 (64-88)	100
6-8 weeks	3 (0.8)	103 (6.8)	0.08 (0.02-0.26)	0.08 (0.02-0.26)	92 (74-98)	100
9-11 weeks	4 (1.0)	36 (2.4)	0.28 (0.10-0.81)	0.25 (0.08-0.73)	75 (27-92)	47.3
≥12 weeks	3 (0.8)	14 (0.9)	0.49 (0.14-1.76)	0.55 (0.15-2.04)	45 (0-85)	1.3
BBV152/Covaxin	**(n=403)**	**(n=1384)**				
Unvaccinated	368 (91.3)	1116 (80.6)	1	1		
One dose (<21 days)	1 (0.2)	20 (1.4)	0.13 (0.02-0.98)	0.15 (0.02-1.20)	85 (0-98)	43
One dose (>=21 days) [Partial]	13 (3.2)	73 (5.3)	0.60 (0.32-1.13)	0.56 (0.29-1.08)	44 (0-71)	46.7

Two dose (<14 days)	1 (0.2)	19 (1.4)	0.18 (0.02-1.42)	0.18 (0.02-1.46)	82 (0-98)	37.6
Two dose (>=14 days) [Full]	20 (5.0)	156 (11.3)	0.37 (0.22-0.61)	0.36 (0.21-0.60)	64 (40-79)	99.3
Gap between 2 doses (>=14 days after second dose) of BBV152/Covaxin	**(n=388)**	**(n=1272)**				
Unvaccinated	368 (94.8)	1116 (87.7)	1	1		
<6 weeks	19 (4.9)	137 (10.8)	0.42 (0.25-0.70)	0.41 (0.24-0.71)	59 (29-76)	96.2
6-8 weeks	0 (0.0)	12 (0.9)	-	-	-	-
9-11 weeks	1 (0.3)	6 (0.5)	0.41 (0.05-3.43)	0.40 (0.05-3.40)	60 (0-95)	3.7
≥12 weeks	0 (0.0)	1 (0.1)	-	-	-	-

*****Case: Laboratory confirmed COVID-19 patients hospitalized with severe COVID-19 (One of the following: fever, cough, dyspnoea, fast breathing plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air) infected with delta variant

$Control: RT-PCR negative individuals who remained negative upto 7 days after initial RT-PCR test

Adjusted for any pre-existing comorbidity, attending social/religious event, frequency of mask use, rural/urban residence

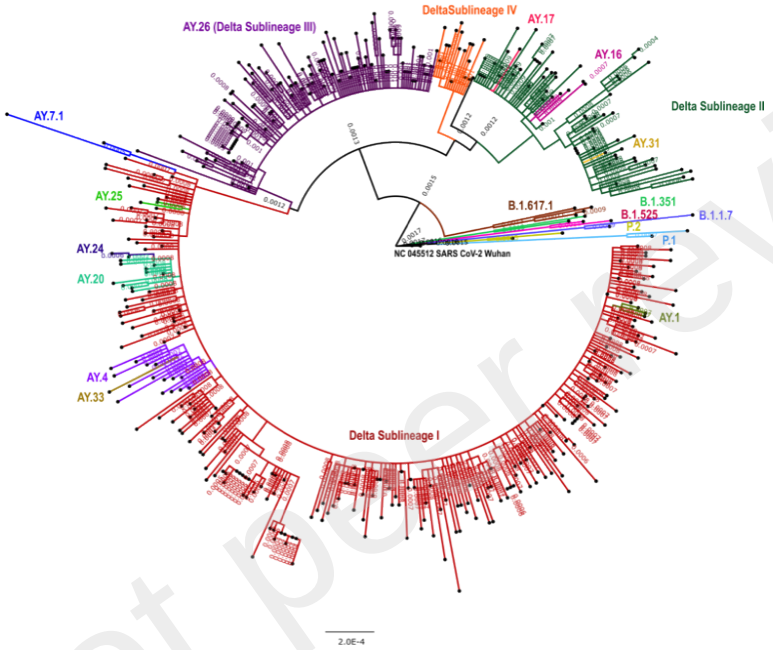

Figure 1. Maximum Likelihoodtree of the 450 SARS-CoV-2 genomes in this study: A Maximum Likelihood tree of the 448 SARS-CoV-2 sequences retrieved in this study, along with the representative SARS-Cov-2 sequences (n=12) from different clades. Tamura-Nei model with a bootstrap replication of 1000 cycles used to assess statistical robustness. Four major sub-lineages of Delta variant along with other pangolin lineageswere observed in this study are marked on branched in different colors. Sub-lineage-I-IV is marked in red, dark green, violet and orange colors on the nodes respectively. Kappa sequence is marked in brown color. The representative pangolin lineages are also marked on branches in different colors. FigTree v1.4.4 and Inkscape were used to visualize and edit the generated tree.