Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Are COVID-19 vaccines efficacious in preventing COVID-19 infections caused by the B.1.617.2 (Delta) Variant?

Review by: Issa Tang, MD, Mary Anne Castor, MD, Dr. Marie Carmela Lapitan, MD

RECOMMENDATIONS

1. **In areas where the Delta variant is the predominant circulating variant, we recommend for the use of the following vaccine to prevent symptomatic and severe COVID-19**:
   a. 2 doses of BBV152 (Covaxin/Bharat)
      (Moderate certainty of evidence; Strong recommendation)
   b. 2 doses of BNT162b2 (Pfizer)
      (Low certainty of evidence; Strong recommendation)
   c. 2 doses of mRNA-1273 (Moderna)
      (Low certainty of evidence; Strong recommendation)
   d. 2 doses of ChAdOx1 (Astra Zeneca)
      (Low certainty of evidence; Strong recommendation)
   e. 2 doses of CoronaVac (Sinovac)
      (Very low certainty of evidence; Strong recommendation)

2. **In areas where the Delta variant is the predominant circulating variant, we suggest the use of the following vaccines to prevent symptomatic and severe COVID-19**:
   a. Ad26.CoV2 (Janssen)
      (Low certainty of evidence; Weak recommendation)
   b. Gam-COVID-Vac (Sputnik V)
      (Low certainty of evidence; Weak recommendation

Consensus Issues

The panel agreed that all vaccines may be used in for protection against the infections caused by the Delta variant, despite some reduction in vaccine effectiveness. The panel's decisions on the strength of recommendation were based mainly on the certainty of evidence supporting the effectiveness. Vaccines with clinical evidence of effectiveness were given strong recommendations for use, whereas vaccines with only immunologic evidence of effectiveness were given weak recommendations.

Introduction

Earliest detection of the B.1.617.2 (Delta) variant was in October 2020 in India. As of writing, the Delta variant has already caused COVID-19 surges in several countries including the US, India, and Indonesia. It is the fourth variant of concern (VOC) identified by the WHO.[1] The Delta variant is characterized by the spike protein mutations T19R, Δ157-158, L452R, T478K, D614G, P681R,

and D950N.1. Current literature suggests that the Delta variant may have increased transmission and replication.[2] As with previous VOC's, there are concerns surrounding the ability of available vaccines to protect against infection with the Delta variant. Findings on the ability of vaccines to protect against COVID-19 caused by the Delta variant will have implications on vaccine procurement, distribution, and administration policies.

Review Methods

Two types of studies on vaccine protection against the Delta variant were considered for this review. First were studies that provided clinical outcomes of efficacy or effectiveness. These included randomized controlled trials on COVID-19 vaccination efficacy or cohort studies comparing infection rates among vaccinated and unvaccinated populations that were conducted during a period where the Delta strain was known to be the prevalent strain or where genomic sequencing of the cases were confirmed as caused by the Delta variant. Test negative case control studies were also included. The second type of studies considered were immunologic studies wherein the capacity of sera from vaccinated persons to neutralize B.1.617.2 and a reference strain was compared. Both antibody and T-cell responses were considered.

In the overall assessment of vaccine performance, this review utilized the rating system by the WHO in its epidemiological update reports. In terms of vaccine efficacy/effectiveness, <10% decline in VE values (compared to non-Delta) or VE of at least 90% is assessed as no significant change (symbolized by ↔); a 10-20% decline is symbolized by ↓ and >20% decline is symbolized by ↓↓. In terms of reduction in immunologic response, less than 2-fold reduction is symbolized by ↔, a 2 to <5-fold reduction by ↓ and a 5 to <10-fold reduction by ↓↓.

No pooling of results was planned for this review.

Search Results

As of October 5, 2021, 28 studies were included in the review. Three (3) studies reported on both clinical and immunologic outcomes,[3,4,5] 11 studies reported only clinical outcomes [2,6-15] and 13 studies were immunogenicity studies.[16-28] One systematic review was included.[29]

Of the studies reporting clinical outcomes, only one (1) was a randomized controlled trial [12] and the rest were observational studies. Most of the observational studies were of the test negative case control design and three (3) were retrospective cohort studies.

Six (6) vaccines were investigated, with six (6) studies reporting results of more than one vaccine: BNT162b2 (7 studies), mRNA-1273 (3 studies), ChAdOx1 (9 studies), Ad26.CoV2.S (2 studies), CoronaVac (4 studies), BBV152 (1 study) and Gam-COVID-Vac (1 study). One (1) study reported the results of mRNA-type vaccines without providing separate results for BNT162b2 and mRNA-1273.

The search failed to identify studies that reported on the performance of NVX-CoV2373 or BBIBP-CorV on the Delta variant.

The characteristics of the included studies are presented in Appendix 2.

Risk of Bias Assessment

Only the studies reporting clinical outcomes were assessed for risk of bias. The lone RCT was assessed as low risk of bias with only the domains of complete follow-up and selective reporting assessed as uncertain.[12] The rest of the studies, being observational, were assessed to be at high risk of bias providing low certainty evidence. Two (2) studies controlled for all three confounders [2,6] and another two (2) studies controlled for two confounders.[5,7]

Appendix 3 details the risk of bias assessment for the clinical studies.

Results

mRNA Vaccines (mRNA-1273 and BNT162b2)

The mRNA vaccines will be discussed together in this review because most of the studies included both types of mRNA vaccines in their investigation. Both studies on measurement of neutralization ability from sera and vaccine effectiveness were available for review. A total of eleven studies (11) were included in this review.

A systematic review by Noori, et al., included five (5) immunologic studies investigating the neutralization of vaccinated sera by mRNA vaccines against the Delta variant. All the studies included in the systematic review were already included in the search of this review and detailed in the succeeding paragraphs.[29]

Studies measuring antibody reactivity of sera from mRNA vaccinees against the Delta variant show reduced levels (minimal to mild reductions) when compared to the reference strains. For example, in a study by Edara, et al., the GMT among the mRNA-1237 samples (n = 15, 35 to 51 days after second dose) against the Delta variant was 350 (95% CI 229-535) compared with 1062 (95% CI 773-1460) against WA1/2020. The GMT of BNT162b2 (n = 10, 7 to 27 days after second dose) against the Delta variant was 235 (95% CI 164-338), as compared with 776 (95% CI 571-1056) against WA1/2020. The Delta variant was also shown to be 2.9x less susceptible to neutralization (compared to neutralization of WA1/2020) by sera from mRNA vaccine recipients and recovered patients. However, the study pointed out that all samples from vaccinated participants have detectable neutralizing activity.[19] Likewise, the study by Choi, et al., noted that sera from fully vaccinated recipients of mRNA-1273 resulted in 2.1-fold to 8.4-fold reduced neutralization against VOCs (including the Delta variant) but all remained susceptible to mRNA-1273-elicited neutralization.[21] One study investigated neutralization ability of sera from vaccinated individuals with mRNA-1273 at 209 days after administration.[22] At 2 weeks after the second dose, all antibody reactivity of sera across age groups neutralized all pseudoviruses; however, this ability was noted to wane over time. At day 209 (6 months), all sera neutralized D614G and B.1.429 variants. However, using a pseudovirus assay, only 96% of sera were able to neutralize the Delta variant. There was a trend towards lower titers against SARS-CoV-2 spike variants in the oldest individuals at day 209. However, the authors concluded that although mRNA-1273-elicited antibody activity against variants decreased (compared to WA1 and D614G), they persisted at 6 months after the second dose.

Studies on vaccine effectiveness of mRNA vaccines against the Delta variant were also reviewed. Compared to the VEs found in the clinical trials, four (4) studies demonstrated that protection provided by the mRNA vaccines is maintained with only minimal reductions in the VEs (<20% difference). Data from one study demonstrated that protection against severe disease did not change.

The study by Lopez Bernal also investigated how BNT162b2 vaccines protected against the Delta variant. The calculated vaccine effectiveness of BNT162b2 against symptomatic disease from the Delta variant is 88% (95% CI 85.3-90.1) after completion of 2 doses of the vaccine. The authors concluded that there were only modest differences in vaccine effectiveness with the Delta variant as compared to the Alpha variant.[2] Nasreen, et al., also concluded that full vaccination with BNT162b2 increased protection against the Delta variant to levels comparable to the Alpha and Beta/Gamma variants. Their study showed that the calculated vaccine effectiveness of BNT162b2 (at least 7 days after second dose) against symptomatic disease was 87% for the Delta variant. Effectiveness against severe outcomes for those fully vaccinated (with BNT162b2, mRNA-1273, and ChAdOx1) could not be reliably elicited for the Delta variant due to low numbers or absence of fully vaccinated test positive cases.[6] Test negative case control studies by Buxvoort, et al., and Tang, et al., showed a 97.6% (95% CI 92.8-99.2) and 100% efficacy against severe infection for the mRNA-1273 vaccine.[9,10]

ChAdOx1 (Astra Zeneca)

Ten (10) studies investigated protection by ChAdOx1 (AstraZeneca and Covishield) against the Delta variant. Five (5) studies assessed vaccine effectiveness through mostly test-negative case control design studies, while the other five (5) studies assessed the neutralization ability of vaccinated sera against the Delta variant.

The study by Davis, et al., measured neutralizing antibody titers from sera in recipients of BNT162b2 and ChAdOx1. A total of 18 participants in this study received two doses of AstraZeneca. Results showed that the sera from these recipients showed 1.48-fold lower neutralization ability versus the Delta variant as compared to that of the Wuhan-Hu-1 strain. The study also noted that sera from recipients of 2 doses of the BNT162b2 vaccine showed higher neutralizing ability compared to that of ChAdOx1. However, the authors noted that those vaccinated with ChAdOx1 were among older age groups than those vaccinated with BNT162b2.[16] Other studies that measured antibody response or neutralization ability showed reduced antibody titers in sera vaccinated with ChAdOx1 as compared to the antibody response to earlier variants, particularly the Alpha and wild type virus. Data from Sapkal et. al., showed that 16.1% of sera (5/31) from recipients of ChAdOx1 vaccine (4 weeks after second dose) were negative for neutralizing antibody titers against the Delta variant. This percentage increased to 58.1% in participants who only received 1 dose of the vaccine. Furthermore, neutralizing antibody titers of patients against B.1.617.2 relative to B.1 were also noted to be decreased to 69% in those who received 2 doses of the vaccine.[23]

Several studies investigating vaccine effectiveness against the Delta variant were also found. A study by Lopez Bernal et al., calculated the vaccine effectiveness of 2 doses of ChAdOx1 for symptomatic disease at 74.5% for the Alpha variant (95% CI 68.4-79.4) and 67% against the Delta variant (95% CI 61.3-71.8). The authors concluded that there are only modest differences in vaccines effectiveness noted with the Delta variant as compared to the Alpha variant.[2]

Another study conducted in Canada among 421,073 individuals (40,828 of which were positive for variants of concern, with more than 14,000 hospitalizations or deaths) showed that ChAdOx1 was 67% effective at preventing symptomatic disease at least 14 days after one dose. This was comparable to effectiveness against the Alpha variant after partial vaccination (64%). However, the effectiveness of ChAdOx1 could not be estimated for those already fully vaccinated since there were no individuals who were fully vaccinated with this vaccine that presented with Delta symptomatic disease. Against severe outcomes, partial vaccination with ChAdOx1 had a vaccine effectiveness of 88% (95% CI 60-96) and again couldn't be estimated for full vaccination because of very low numbers or absence of vaccinated test positive cases.[6] Another study in India involving 2,766 confirmed COVID-19 cases calculated vaccine effectiveness at 63.1% against symptomatic disease by the Delta variant, and a VE of 81.5% against moderate to severe disease.[4]

Despite findings from studies measuring neutralizing antibodies from sera of ChAdOx1 vaccinees showing reduced titers against Delta as compared with other variants, vaccine effectiveness studies still show that ChAdOx1 protects against symptomatic disease from the Delta variant, with the authors concluding only modest differences compared to previous variants.

Ad26.CoV2 (Janssen)

Two (2) studies specifically on Janssen vaccines are included in the review. The study by Jongeleen, et al., used sera from 8 participants 47 to 91 years old. Sera was collected 71 days after receiving the single-dose vaccine. Using a recombinant lentivirus-based pseudotyped virus neutralization assay, they determined antibody neutralization of the Delta variant compared to the Wuhan-Hu-1 strain. Results showed a 1.6-fold reduction in neutralization against Delta (3.6-fold reduction against Beta and 3.4-fold reduction against Gamma). The authors noted that the geometric mean neutralization titers (GMT) were observed to be decreased against all variants.[24]

Another study involving 60 Ad26.COV2.s vaccine recipients showed that the degree of antibody response to the variants of concern depended on the history of previous infection. It demonstrated reduction in the neutralizing antibody titers against the Delta variant compared to the ancestral strain (D614G), from 2.6- to 6.3-fold, with greater reductions in those previously infected during the Beta-predominant wave.[27]

CoronaVac (Sinovac)

Four (4) studies investigating CoronaVac protection against the Delta variant were found during the search. Two (2) studies were immunologic studies, while the other two (2) provided clinical outcomes.

The study by Jie Hu et al., included sera from 20 individuals who had received their second CoronaVac dose 7 to 14 days prior. In this study, 19 out of the 20 sera had substantial serum neutralizing activity against D614G spiked pseudotyped viruses. Compared with activity against D614G, 65% (13/20) of sera from the CoronaVac recipients was decreased below the threshold of serum neutralizing ability for the B.1.617 variant. The average neutralization potency of CoronaVac recipients was also decreased 2.5-fold (GMT 36) as compared to D614G (GMT 89).[25] Another immunologic study conducted in Thailand by Vacharathit et al., investigated the

effect of SARS-CoV-2 variants of concerns to vaccine and infection-induced antibodies.[26] In this study, sera from 60 vaccinated (2 doses of CoronaVac) healthcare workers were used. Neutralizing antibodies against the wild type, Alpha, Beta, and Delta variants were measured. The study found out that relatively low neutralizing antibody titers were elicited by CoronaVac compared to natural infection. Results also showed that quantifiable antibody titers against Delta were present in only 69.17% of vaccinated sera as compared to 99.17% against the wild type. Furthermore, only 48.33% of vaccinated participants had neutralizing antibody titers of at least 20 (the cutoff for neutralizing antibody positivity) against the Delta variant, as compared to 98.33% against the wild type. It was noted in the study that natural infection consistently produced a greater percentage of antibody positivity as compared to CoronaVac recipients across all the tested variants. The authors stated that despite a robust S1-RBD-binding IgG and 100% seropositivity sera from CoronaVac and previously infected recipients, they had significantly reduced neutralizing capacities against all the three VOCs tested. The authors concluded that relatively low neutralizing antibody titers were elicited by CoronaVac compared to natural infection. They further recommended the use of booster doses, heterologous or otherwise, to maintain long-term anamnestic response.

Observational studies providing clinical effectiveness data were conducted in China. [13,14] Both studies showed no change in the vaccine effectiveness of CoronaVac against the Delta variant, although breaching the cutoff of 30% for the lower border of the 95% CI was noted in one study. The study by Li et al., which included participants 18 to 59 years old, showed 59% (95% CI 16-81.6) vaccine efficacy against mild COVID-19 infection from the Delta variant and 70.2% (95% CI 29.6-89.3) against moderate infection. No severe infection was noted among the vaccinees. The study by Kang et al., which involved close contacts of Delta variant cases in China, showed a 69.5% vaccine efficacy (95% CI 42.8-96.3) against pneumonia. No severe COVID-19 infection from the Delta variant was noted in the vaccinees.

BBV152 (Covaxin/Bharat)

The only RCT included in this review is the Phase 3 trial of the BBV152 (Covaxin/Bharat) COVID-19 vaccine. The trial, which involved more than 25,000 participants, had 50 cases of COVID-19 infection due to the Delta variant. The study calculated that the vaccine efficacy against Delta infection is 65.2% (95% CI 33.1-83.1) as compared to the overall vaccine efficacy of 77.8%.[12]

Gam-COVID-Vac (Sputnik V)

Only one (1) immunologic study investigating antibody neutralization of the Delta variant involving the Gam-COVID-Vac was found. Data from sera of 27 participants showed a 2.5-fold reduction of neutralizing antibody titers compared to the B.1.1.1.[28]

Appendix 4 presents the summary results on the clinical (4A) and immunologic outcomes (4B).

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Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 12)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (12)					
Benefits	Large (5)	Moderate (7)	Small	Uncertain			• 4 studies demonstrated that protection provided by the mRNA vaccines is maintained with only minimal reductions in the VEs (<20% difference).
Harm	Large (2)	Small (3)	Uncertain (7)				• Studies measuring antibody reactivity of sera from mRNA vaccinees against the Delta variant show reduced levels (minimal to mild reductions) when compared to the reference strains
Certainty of evidence	High	Moderate (2)	Low (9)	Very low (1)			• Low to very low
Balance of effects	Favors vaccine (11)	Does not favor vaccine	Uncertain (1)				
Values	Important uncertainty or variability	Possibly important uncertainty or variability (10)	Possibly no important uncertainty or variability (2)	No important uncertainty or variability			
Resources required	Uncertain (3)	Large cost (4)	Moderate cost (5)	Negligible cost or savings	Moderate savings	Large savings	• Differs per vaccine combination used
Certainty of evidence of resources required	No included studies (4)	Very low (4)	Low (3)	Moderate (1)	High		• Differs per vaccine brand
Cost effectiveness	No included studies (9)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (2)			

Equity	Uncertain (3)	Reduced (2)	Probably no impact (1)	Increased (6)			• Varies per vaccine • Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; while only 28.3% in BARMM.
Acceptability	Uncertain	No	Yes (12)				• Vaccines mentioned have been approved for EUA by the Philippine FDA on varying dates.
Feasibility	Uncertain (1)	No	Yes (11)				• Varies per vaccine

Appendix 2. Characteristics of Included Studies

A. Clinical Studies

STUDY ID	STUDY SITE/PERIOD	STUDY DESIGN	STUDY POPULATION	INTERVENTION / EXPOSURE	CONTROL	FOLLOW-UP	OUTCOMES
BNT162b2 (Pfizer)							
Lopez Bernal 2021	England Infections from October 2020 to March 21 2021, extracted May 2021 (Immunologic testing from April 5, 2021 onwards)	Test-negative case control Case = PCR positive and with symptoms Control = with symptoms but PCR negative Vaccination status at time of infection defn: D1: symptom onset 21 days or more from D1 to day before D2 D2: symptom onset 14 days or more after D2 Covariates: age, sex, index of multiple deprivation, ethnicity, care home status, history of foreign travel, region, period, health and social care worker status, history of infection Logistic regression used	Persons >/=16 years old as of March 21, 2021 reporting symptoms and tested within 10 days of symptom onset vaccinated with either BNT or AZ N = 14,837 N sequenced = 12, 675 Delta = 1,054	Vaccinated			Vaccine effectiveness (at D1 and D2) (Table 2) Proportion of Delta in the vaccinated and unvaccinated cases (Odds of a Delta infection vs B.11.7 between vaccinated and unvaccinated)
Nasreen 2021	Canada	Test-negative case control	Community dwelling, >/= 16-year-old with	Measurement of Delta based on predicted	Control: RT-PCR negative		Vaccine effectiveness against symptomatic

	Dec 14 2020 to May 30 2021 (April 2021 for Delta)	Linked databases including centralized COVID-19 vaccine information system, laboratory information system and Public Health case and contact management system Covariates: age, sex, no. of tests (proxy for risk of exposure), comorbidities, influenza vaccination status, household income of neighborhood Multiple logistic regression	symptoms or severe outcome attributable to COVID-19 tested for SARS-COv-2 N = 421,073 infections Cases / positive for non-VOC = 28,705 Cases / positive for VOC = 40,828 Delta = 991 - Symptomatic infection = 991 - Severe = 165	probability (not direct genome sequencing) of those with N501-/E484K- Case = symptomatic and positive forSARS-Cov-2 in OLIS (Delta = 991) BNT D1: 50 BNT D2: <5 Mod D1: <5 Mod D2: <5 AZ D1: <5 AZ D2 :0 Severe case = hospitalized or dead with positive SARS-Cov-2, regardless of symptoms at time of testing) (Delta = 165)	for SARS-CoV-2 Symptomatic Severe N = 351,540 BNT D1: 34,747 BNT D2: 6,910 Mod D1: 7,806 Mod D2: 1,520 AZ D1: 5,916 AZ D2: 25		disease at least 7 days after 2nd dose (Table 3) VE for severe COVID (hospitalization and death) (Table 3) VE at >/=14 and at 21 days after first dose for partially vaccinated VE at >/= 7 and at 14 days for those fully vaccinated Subgroup: By vaccine By age By timing
Sheikh 2021	Scotland April 1 to June 6, 2021	Test-negative case control S-gene positive considered Delta variant Adjustment made for age, temporal trend when the swabs done, no. of previous tests, sex, deprivation	EAVEII surveillance database All hospitalized patients 19,543 positives 377 hospitalized	BNT; AZ	Unvaccinated = 117,263		D1 0-27, D1 28+, D2 0-13, D2 14+ VE for COVID infection (positive test, regardless of symptoms) VE for symptomatic COVID infection (Appendix 4)

Stowe 2021	England April 12 – June 4, 2021	Test-negative case control Linked databases	Hospitalized patients within 14 days of a positive COVID test 14,019 symptomatic cases with Delta 166 hospitalized	BNT AZ	Unvaccinated		VE for hospitalization after D1 and D2
Mlcochova 2021	India	Cross-sectional Comparing proportion of Delta vs. non-Delta Confounders: age, sex, hospital Calendar time not used as a confounder because of short duration of the study Multivariable logistic regression	Healthcare workers who developed COVID-19 infection in April and May 2021	Delta infection	Non-Delta infection		Breakthrough infection rate CT values at diagnosis Proportion of Delta vs non-Delta infection (Odds ratio of testing positive with Delta vs non-Delta in vaccinated relative to unvaccinated)
mRNA-1273 (Moderna)							
Nasreen 2021	Canada Dec 14 2020 to May 30 2021 (April 2021 for Delta)	Test-negative case control Linked databases including centralized COVID-19 vaccine information system, laboratory information system and Public Health case and contact management system Covariates: age, sex, no. of tests (proxy for risk of exposure),	Community dwelling, >/= 16-year-old with symptoms or severe outcome attributable to COVID-19 tested for SARS-COv-2 N = 421,073 infections Cases / positive for non-VOC = 28, 705	Measurement of Delta based on predicted probability (not direct genome sequencing) of those with N501-/E484K- Case = symptomatic and positive forSARS-Cov-2 in OLIS (Delta = 991) BNT D1: 50	Control: RT-PCR negative for SARS-CoV-2 Symptomatic Severe N = 351,540 BNT D1: 34,747 BNT D2: 6,910 Mod D1: 7,806 Mod D2: 1,520 AZ D1: 5,916 AZ D2: 25		Vaccine effectiveness against symptomatic disease at least 7 days after 2nd dose (Table 3) VE for severe COVID (hospitalization and death) (Table 3) VE at >/=14 and at 21 days after first dose for partially vaccinated VE at >/= 7 and at 14 days for those fully vaccinated

		comorbidities, influenza vaccination status, household income of neighborhood Multiple logistic regression	Cases / positive for VOC = 40, 828 Delta = 991 - Symptomatic infection = 991 - Severe = 165	BNT D2: <5 Mod D1: <5 Mod D2: <5 AZ D1: <5 AZ D2 :0 Severe case = hospitalized or dead with positive SARS-Cov-2, regardless of symptoms at time of testing) (Delta = 165)			Subgroup: By vaccine By age By timing
ChAdOx1 (Astra Zeneca)							
Lopez Bernal 2021	England Infections from October 2020 to March 21 2021, extracted May 2021 (Immunologic testing from April 5, 2021 onwards)	Test-negative case control Case = PCR positive and with symptoms Control = with symptoms but PCR negative Vaccination status at time of infection defn : D1: symptom onset 21 days or more from D1 to day before D2 D2: symptom onset 14 days or more after D2 Covariates: age, sex, index of multiple deprivation, ethnicity, care home status, history of foreign travel, region, period, health and social care	Persons >/=16 years old as of March 21, 2021 reporting symptoms and tested within 10 days of symptom onset vaccinated with either BNT or AZ N = 14, 837 N sequenced = 12, 675 Delta = 1,054	Vaccinated			Vaccine effectiveness (at D1 and D2) (Table 2) Proportion of Delta in the vaccinated and unvaccinated cases (Odds of a Delta infection vs B.11.7 between vaccinated and unvaccinated)

		worker status, history of infection Logistic regression used					
Nasreen 2021	Canada Dec 14 2020 to May 30 2021 (April 2021 for Delta)	Test-negative case control Linked databases including centralized COVID-19 vaccine information system, laboratory information system and Public Health case and contact management system Covariates: age, sex, no. of tests (proxy for risk of exposure), comorbidities, influenza vaccination status, household income of neighborhood Multiple logistic regression	Community dwelling, >/= 16-year-old with symptoms or severe outcome attributable to COVID-19 tested for SARS-COv-2 N = 421,073 infections Cases / positive for non-VOC = 28, 705 Cases / positive for VOC = 40, 828 Delta = 991 - Symptomatic infection = 991 - Severe = 165	Measurement of Delta based on predicted probability (not direct genome sequencing) of those with N501-/E484K- Case = symptomatic and positive forSARS-Cov-2 in OLIS (Delta = 991) BNT D1: 50 BNT D2: <5 Mod D1: <5 Mod D2: <5 AZ D1: <5 AZ D2 :0 Severe case = hospitalized or dead with positive SARS-Cov-2, regardless of symptoms at time of testing) (Delta = 165)	Control: RT-PCR negative for SARS-CoV-2 Symptomatic Severe N = 351,540 BNT D1: 34,747 BNT D2: 6,910 Mod D1: 7,806 Mod D2: 1,520 AZ D1: 5,916 AZ D2: 25		Vaccine effectiveness against symptomatic disease at least 7 days after 2nd dose (table 3) VE for severe COVID (hospitalization and death) (Table 3) VE at >/=14 and at 21 days after first dose for partially vaccinated VE at >/= 7 and at 14 days for those fully vaccinated Subgroup: By vaccine By age By timing
Sheik 2021	Scotland April 1 to June 6, 2021	Test-negative case control S-gene positive considered Delta variant	EAVEII surveillance database All hospitalized patients 19,543 positives 377 hospitalized	BNT; AZ	Unvaccinated = 117,263		D1 0-27, D1 28+, D2 0-13, D2 14+ VE for COVID infection (positive test,

		Adjustment for age, temporal trend when the swabs done, no. of previous tests, sex, deprivation by generalized additive logistic regression model					regardless of symptoms) VE for symptomatic COVID infection (appendix 4)
Stowe 2021	England April 12 – June 4, 2021	Test-negative case control Linked databases	Hospitalized patients within 14 days of a positive COVID test 14,019 symptomatic cases with Delta 166 hospitalized	BNT AZ	Unvaccinated		VE for hospitalization after D1, and D2
Thiruvengadem 2021	India April 1- May 31, 2021	Test negative case control Adjustment for age, sex, risk of exposure to COVID-19 positive individuals (balanced)	Those who tested positive for RT-PCR SARS-CoV-2 2766 confirmed cases 3.1% fully vaccinated	Case = RT-PCR positive for SARS-Cov-2 infection (2,776) Not all genome sequenced, sample of 150 done with 90% with Delta	Control = randomly selected from a computer program from individuals who tested negative, matched for each calendar week of testing during study period 2,377 individuals who tested negative during the same week		VE for COVID-19 infection (table 2) VE for moderate to severe disease (Table 3) After full and single dose vaccination
Ad26-Cov-2 (Janssen)							
(None)							
Coronavac (Sinovac)							

Li	China Guangzhou	Test negative case control	628 participants including 475 close contacts of Delta cases	Inactivated vaccine (CoronaVac or CNBG)		14 to 21 days	VE for mild, moderate, severe infection
Kang	China Guangdong	Retrospective cohort	12,501 close contacts of Delta cases	Inactivated vaccine (Sinovac, Sinopharm, BICV)			VE against pneumonia and severe/critical illness
Gam-COVID-Vac (Sputnik V)							
(None)							

BNT = BNT162b2; AZ = ChAdOx1; Mod = mRNA-1273; D1 = first dose; D2 = second dose; VOC = variant of concern

B. Immunologic Studies

STUDY ID	STUDY SITE/PERIOD	STUDY POPULATION	TIMING OF EXTRACTION	CONTROL STRAIN	OUTCOMES (Test Used)
BNT162b2 (Pfizer)					
Davis 2021	UK	Healthy individuals who have received: BNT D1 = 37 BNT D2 = 50 Note: outcomes assessed compared with ChAdOx	Not specified	WT	Reactivity by ELISA - anti S1, - anti RBD - anti N Neutralizing antibody titers Table S1 (HIV-pseudotype-based system) Reductions in mean titers / fold reduction Table S1
Mlcochova 2021	India	Live virus assay BNT = 10 Pseudovirus assay BNT = 32	Not mentioned	WT	Fold reduction (Live virus neutralization assay) Fold reduction (vs. WT) Pseudovirus assay (Figure 1e, Table e1) GMT (vs. WT vs. other vaccine) Pseudovirus assay (Figure 1e, Table e1)
Lustig 2021	Israel	Healthy HCWs N = 19	1 month after D2 (Delta-S1 and S2 substrains tested separately)	B.1	Neutralising antibody activity (micro-neutralisation assay TCID50): 1. GMT 2. fold-reduction
Planas 2021	France	Randomly selected 59 vaccinees Pfizer = 16 AZ 1 dose = 23 AZ 2 doses = 20	Pfizer: W3, W8 W16 after vaccination (W13 after D2) AZ D1: W10 AZ D2: W16	D614G	Fold reduction in neutralization titers (p279) % positivity (Fig 7)

Chia 2021	Singapore April 1- June 14, 2021	Retrospective cohort Vaccinated with serology (N = 69) Unvaccinated with serology (N = 45)	Week 1, 2 from diagnosis *Not all sequenced, for those not sequenced, lineage inferred based on epidemiologic investigations and likely B.1.617.2 included For sVNT inhibition % against WT, median day of sample collection from infection onset 6 days (IQD 3-7)	WT (Comparison available for 36 vaccinated individuals)	Vaccinated vs unvaccinated: Seropositivity for - anti N (CLIA) - anti-spike protein (CLIA) Inhibition rate (week 1, week 2) - Nab anti RBD (surrogate virologic neutralization test) WT vs. B.1.617.2 % inhibition of NaB relative to WT using multiplex-sVNT assay using Luminex platform
Edara 2021	USA	Serum samples from infected/convalescent and vaccinated persons N = 10 (post BNT)	7 to 27 days after 2nd dose	WA1/2020	Neutralizing antibody response (live virus focus reduction neutralization test on a Vero E6 cell line): 1. GMT 2. Fold reduction (Fig 1)
Liu C 2021	UK	Serum from vaccinated individuals BNT = 25 Dosing interval = 3 weeks	4 to 14 days post D2 Also studied after D1 only at D28 and D70	Victoria (VIC01/2020)	GMT (Fig 7) (Focus Reduction neutralization test) Fold reduction (Fig 7) GMT, fold reduction, % neutralization after D1 at D28 and D70 (Fig 7)

mRNA-1273 (Moderna)					
Choi 2021	USA	Participants immunized with mRNA-1273 (prime-boost) N = 8	7 days post boost	Wildtype (Wuhan-Hu-1 with D614G)	Neutralization antibody titer (VSV-Based pseudotype assay % neutralization Fold reduction in neutralization titers relative to control Relative decline in GMTs
Pegu 2021	USA	Random samples of sera from 24 volunteers	4 time points: 4 weeks after D1, 2 wks, 3 mo, 6 mo after D2	Wuhan-Hu-1 D614G	Fold reduction by pseudovirus neutralization assay and cell-surface spike binding (Fig 2G) % positivity (number with detectable antibody titers) using pseudovirus neutralization assay and cell surface spike binding (Fig 3) at the 4 time points
Edara 2021	USA	Serum samples from infected/convalescent and vaccinated persons N = 15 (post mRNA-1273)	35 to 51 days after 2nd dose	WA1/2020	Neutralizing antibody response (live virus focus reduction neutralization test (FRNT) live virus assay on a Vero E6 cell line): 1. GMT difference 2. Mean Fold reduction (Fig 1)
ChAdOx1 (Astra Zeneca)					
Sapkal 2021	India	Covishield vaccinated individuals D1 only (31) D2 (31) Covid-recovered + D1 (15) Cvoid-recovered +D2 (19) Breakthrough COVID 19 (20)	Not mentioned	B.1	% positivity Neutralizing antibodies (plaque reduction neutralization assay) Fold - reduction in Nab titers relative to B.1 GMT NaB titers
Davis 2021	UK	Healthy individuals who have received:	Not specified	WT	Reactivity by ELISA - anti S1,

		ChAdox D1 = 50 ChAdOx D2 = 18 Note: outcomes assessed compared with BNT162b			- anti RBD - anti N GMT Neutralizing antibody titers Table S1 (HIV pseudotype-based system) Reductions in mean titers Table S1
Mlcochova 2021	India	Live virus assay ChAd – 10 Pseudovirus assay Chad- 33	Not mentioned	WT	Fold reduction (live virus neutralization assay) Fold reduction (vs WT) Pseudovirus assay (Figure 1e, Table e1) GMT (vs. WT, vs other vaccine) Pseudovirus assay (Figure 1e, Table e1)
Thiruvengadem	India	Plasma from 49 fully vaccinated healthy participants	Median 61 days after D2	WT	GMT for IgG RBD (live virus neutralization) Fold reduction in neutralization – Table S3 *(but supplement not available)* Mean IFN-gamma secretion (Fig 2) % IFN responders Antigen specific CD8+ T cell (cellular granzyme B and perforin expression)
Liu 2021	UK	Serum from vaccinated individuals ChAdOx1 = 25, dosing interval 8-14 weeks	14-28 days after D2	Victoria (VIC01/2020)	GMT (Fig 7) (Focus Reduction neutralization test) Fold reduction (Fig 7)

Ad26.Cov2.S (Janssen)					
Jongeleen 2021	Brazil, USA, RSA	Sera from ph 3 ENSEMBLE trial participants		Wuhan-Hu-1 (B.1)	Anti-S Nab titers (GMT) (HIV-based lentivirus neutralization assay) fold reduction vs B.1 (Fig 3)
Keeton	South Africa	Sera from 60 healthcare workers		D614G	For infection naïve - Neutralization rate = 78% (GMT = 29) For previously infected (by D614G) - neutralization of Delta maintained but lower titers (606 to 443) = 2.7-fold reduction For previously infected with Beta - 6-fold lower neutralization of Delta (GMT = 200)
Coronavac (Sinovac)					
Hu 2021	China (timing of study not mentioned)	Sera from 20 vaccinated patients	7-14 dyas post D2	D614G	Neutralizing antibody response(pseudovirus-based neutralization assay) : 1. Neutralizing activity (positivity?) - % above threshold 2. X-fold decline in neutralization potency compared to control
Vacharathit 2021	Thailand March 2020-May 2020 April 2021 – May 2021	Healthworkers who received 2 doses of Coronavac (n=60)	Not mentioned	WT Sera from unvaccinated and naturally infected COVID-19 patients (Mar –May 2020 and Apr-May 2021)	Live virus neutralization: GMT for Nab (Table 1) % NaB positivity (table 2) GMT IgG (s-1-RBD binding IgG (table 3)
Gam-COVID-Vac (Sputnik V)					
Guschin	Russia	Sera from 16 samples	Not mentioned	B.1.1.1	VNT using live virus and spike-pseudotyped lentivirus 2.5 fold decline with Delta
BBV-152 (Covaxin)					

(none)					
NVX-CoV2373 (Novavax)					
(none)					

Appendix 3. Risk of Bias Assessment of Clinical Studies

STUDY ID	STUDY DESIGN	RANDOMIZA-TION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES / FOLLOW UP	SELECTIVE REPORTING	ASSESSMENT OF CONFOUNDING FACTORS									
									AGE			EXPOSURE RISK			COMORBIDITIES			OVERALL for CONTROL OF COUNFOUNDERS
									A	B	C	A	B	C	A	B	C	
Chia	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	Y	N	NA	NA	Y	N	Y	LOW
Lopez Bernal	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	Y	U	Y	Y	U	Y	LOW
Mlcochova	Crosssectional?	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	N	NA	NA	N	NA	NA	HIGH
Nasreen	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	Y	Y	N	Y	Y	N	Y	LOW
Sheikh	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	Y	N	Y	N	NA	NA	LOW
Stowe	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	U	U	U	U	U	U	U	U	U	HIGH
Thiruvengadem	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	Y	Y	Y	Y	N	U	N	LOW
Li	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	U	U	U	U	U	U	U	U	U	HIGH
Kang	retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	U	U	U	U	U	U	U	U	U	HIGH
Nanduri		HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	U	U	U	Y	Y	Y	U	U	U	HIGH
Buxvoort	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	Y	U	U	U	Y	Y	Y	LOW
Tang	test negative case control	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	Y	U	U	U	Y	Y	Y	LOW
Tartoff	retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	Y	N	N	N	Y	Y	Y	LOW
Ella	RCT	LOW	LOW	LOW	LOW	LOW	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	LOW
			LOW	UNCLEAR	HIGH	NOT APPLICABLE			Y	YES	N	NO	U	UNCLEAR		NA	NOT APPLICABLE	

Appendix 4. Summary of COVID-19 vaccines performance against COVID-19 infection due to the Delta Variant

A. Clinical Outcomes

	BNT162b2 (Comirnaty/ Pfizer)	**mRNA-1273** (Moderna/ USNIH)	**ChAdOx1** (Vaxzevria/ AstraZeneca)	**Ad26.COV2.S** (J&J)	**CoronaVac** (Vero Cell / Sinovac)	**Gam-COVID-Vac**	**Bharat**
B.1.617.2							
VE against symptomatic COVID-19 infection	↔ 88% (95% CI 85.3-90.1%) after 2 doses (Lopez Bernal) VE 87% after 2 doses (Nasreen)		↔ 67% (61.3-71.8%) after 2 doses (Lopez Bernal)		↔ 69.5% (95% CI 42.8-96.3) against pneumonia (calculated with sinopharm) (Kang) 59% (16-81.6) mild, Li 70.2% (29.6-89.3) moderate, Li		↓ 65.2 (33.1, 83.1) (Ella)
VE against severe COVID-19 infection	↔ 96% (CI 86-99%) after 2 doses (Stowe) 97.3 (84.4-99.5) (Tang) 93% (84-96) hospitalization (Tartof)	97.6% (92.8, 99.2) Buxvoort 100% Tang	↔ To ↓ 92% (75-97%) after 2 doses (Stowe) Full vaccination prevented moderate to severe COVID in 81.5% (95% CI 9.9, 99) (Thiruvengadem)		↔ 100% (Li, Kang)		
VE against any COVID-19 infection	↓ 79% (95% CI 75-82%) at least 14	50.6% (95% CI 45-55.7)	↓ 60% (95% CI 52-66%) at least 14				

	days after 2nd dose (Skeih) 52.4% (95% CI 48.0-56.4) including asymptomatic (Naduri) 59.6 (50.7-66.9) (Tang) 75% (71-78) (Tartoff)	including asymptomatic (Naduri) 86.1 (78.0-91.3) (Tang) 86.7% (84.3-88.7) Buxvoort	days after 2nd dose (Skeih) aOR of 3.81 (95% CI 1.11-13) 63.1% (51.5, 72.1) Thirivengadem				

B. Immunologic Outcomes

B.1. Fold reductions per vaccine

	Pfizer	Moderna	AstraZeneca	Janssen	Sinovac	Gam-COVID-Vac
Antibody neutralization	↓ to ↓↓	↓	↓ to ↓↓	↓	↓	↓
	11.3, 8.4 fold reduction vs WT (Davis, Mlchova) 2.1 fold reduction vs B.1 (Lustig) 3.3 fold reduction vs WA1 Edara) 2.5 fold reduction vs Victoria (Liu, C) 3.6 fold reduction (Tada)	2.1, 0.7-2.4 fold reduction vs Wuhan-Hu-1 with D614G (Choi, Pegu) 3-fold reduction vs WA1/2020 (edara) 4.0 fold reduction (Tada)	4.01, 6.8, 9-fold reduction vs WT (Davis, Thiruvegadem, Mlchova) 3.2 fold reduction vs B.1 (Sapkal) 4.3 fold reduction vs Victoria (Liu) 2.5 fold reduction (Wall)	1.6 fold reduction in neutralization (Jongoleen) 7.4 fold reduction (Tada)	Neutralization potency decreased 2.5-fold (Hu) Quantifiable antibody titers present in 69% with 48% having titers above the threshold (Vacharathit)	2.5 fold reduction (Guschin)

B.2. Fold Reduction in Neutralizing Capacity of COVID-19 vaccines against B.1.617.2 (Delta Variant)

Study ID	n	Test Used	Timing of Extraction	Reference Strain	Fold-reduction	Comments
BNT162b2						
Davis	D1 = 37 D2 = 50	HIV pseudotype-based system	not specified	WT	1.92 11.2	excluding seropositive at baseline
Mlcochova	10	live virus neutralization assay	not specified	WT	8.4	
Lustig	19	micro-netrualization assay	1 month after D2	B.1	2.1	
Planas	16	not described	week 13 after D2	D614G	3	
Edara	10	live virus focus reduction neutralization	7-27 days after D2	WA1/2020	3.3	
Liu C	25	Focus reduction neutralization test	4-14, 28d and 70d after D2	Victoria	2.5	
Liu J	20	plaque reduction neutralization test	2-4 weeks after D2	USA/WA1/2020	not available	
Tada	9	lentivirus pseudovirus-based neutralization	90 days	D614G	3.6	
mRNA-1273						
Choi	8	VSV-based pseurotype assay	7 days after D2	Wuhan-Hu-1 with D614G	2.1	
Pegu	24	pseudovirus neutralization assay	4 wks after D1, 2 weeks,3 mos,6 mos after D2	Wuhan-Hu-1 D614G	0.7 2.4	
Edara	15	live virus focse reduction neutralization	35 to 51 days after D2	WA1/2020	3	
Tada	8	lentivirus pseudovirus-based neutralization	80 days	D614G	4	
ChAdOx1						
Sapkal	D1 - 31 D2 - 31	plaque reduction neutralization test	not specified	B.1	3.2	
Davis	D1 - 50 D2 - 18	HIV-pseudotype-based system	not specified	WT	4.01 3.14	excluding seropositive at baseline
Mlcochova`	10 33	live virus neutralization assay pseudovirus neutralization assay	not specified	WT	9	
Thiruvengadem	49	live virus neutralization	median 61 days after D2	WT	6.8	
Liu	25	focus reduction neutralization test	14-28 days after D2	Victoria	4.3	
Wall	D1 - 60 D2 - 63	live virus neutralization assay	D1 : median 41d (IQR 30-51) D2 : median 31d (IQR 19.5-46)	D614G (after 2 doses BNT162b2)	2.5	relative to 2 doses of BNT162b2
Ad26.CoV.2						
Jongeleen	8	HIV-based lentivirus neutralization assay	not mentioned	Wuhan-Hu-1 (B.1)	1.6	
Tada	10	lentivirus pseudovirus-based neutralization	82 days after vaccination	D614G	7.4	
Coronavac						
Hu	20	pseudovirus-based neutralization assay	71-4 days after D2	D614G	2.5	
Vacharathit	60	live virus neutralization assya	not mentioned	WT	3	
Gam-COVID-Vac						
Gushchin	27	live virus neutralization assay spike-pseudotyped lentivirus	one month after D2	B.1.1.1	2.5	