

**Effectiveness of COVID-19 vaccines against B.1.617.2 (Delta) variant: A systematic review**

by

**Joseph White**

Biological Sciences, University of Pittsburgh, 2019

Submitted to the Graduate Faculty of the

*Department of Epidemiology*

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2021

UNIVERSITY OF PITTSBURGH  
GRADUATE SCHOOL OF PUBLIC HEALTH

This essay is submitted

by

**Joseph White**

on

*December 17, 2021*

and approved by

**Essay Advisor:** Nancy W. Glynn, PhD, Director, Master's Degree Programs, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

Essay Reader: Graham M. Snyder, MD, MS, Associate Professor, Department of Medicine, School of Medicine, University of Pittsburgh

Essay Reader: Mary Patricia Nowalk, PhD, RD, Professor, Department of Family Medicine, University of Pittsburgh

Copyright © by Joseph White

2021

# COVID-19 vaccine effectiveness against SARS-CoV-2 Delta variant: A systematic review

Joseph White, MPH

University of Pittsburgh, 2021

## Abstract

**Introduction:** The coronavirus disease 2019 (COVID-19) pandemic continues to inflict significant morbidity and mortality globally. The asymmetric distribution of vaccines continues to foment the emergence of more transmissible SARS-CoV-2 variants of concern (VOC). Research has shown a reduction in vaccine effectiveness (VE) against these variants, with the most recent being the B.1.617.2 (Delta) variant. The aim of this systematic review is to synthesize COVID-19 VE estimates and their 95% confidence intervals (95% CI) against SARS-CoV-2 Delta variant infection, symptomatic disease, and hospitalization. An updated synthesis of VE estimates against Delta variant is necessary to inform clinical decision-making, policy decisions, and promote vaccine development to protect against future variants.

**Methods:** A comprehensive literature search was conducted using the Ovid-MEDLINE database on October 16, 2021. Observational studies examining VE of WHO-approved COVID-19 vaccines were included. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the non-randomized observational studies included in this review.

**Results:** Eleven studies met eligibility criteria to be included in the review. Overall VE estimates against SARS-CoV-2 Delta variant infection for WHO-approved vaccines reported in this review ranged from 59% [95% CI: 16, 81.6] to 75% [95% CI: 71, 78]. VE against symptomatic Delta variant infection was reported as 79.6 [76.7, 82.1]. Overall VE against Delta variant

hospitalization ranged from 86% [95% CI: 82, 89] to 93% [95% CI: 84, 96]. VE against specific vaccines was also reported.

**Conclusions:** Studies included in this review provide evidence that VE against the Delta variant of SARS-CoV-2 is less than VE against previous VOC and wild type SARS-CoV-2 for preventing infection, symptomatic disease and hospitalization. This review demonstrates the vital need for continuous surveillance of VE so that vaccine programs are dynamic and adaptable to the epidemiology of COVID-19. Subsequent research is necessary to examine if the primary reason for reduced VE is VOC immune evasion or waning immunity due to time. This review is relevant to public health practice because it can inform how vaccine programs should adapt to the dynamic nature SARS-CoV-2, in measures such recommending booster doses for certain populations.

## Table of Contents

|                                                                                |           |
|--------------------------------------------------------------------------------|-----------|
| <b>Preface.....</b>                                                            | <b>x</b>  |
| <b>1.0 Introduction.....</b>                                                   | <b>1</b>  |
| <b>1.1 Background.....</b>                                                     | <b>1</b>  |
| <b>1.2 Gaps in Knowledge.....</b>                                              | <b>3</b>  |
| <b>1.3 Public Health Significance.....</b>                                     | <b>3</b>  |
| <b>2.0 Objective .....</b>                                                     | <b>4</b>  |
| <b>3.0 Methods.....</b>                                                        | <b>5</b>  |
| <b>3.1 Search Strategy .....</b>                                               | <b>5</b>  |
| <b>3.2 Eligibility Criteria .....</b>                                          | <b>6</b>  |
| <b>3.3 Data Abstraction.....</b>                                               | <b>7</b>  |
| <b>3.4 Study Assessment.....</b>                                               | <b>7</b>  |
| <b>3.5 Vaccine Effectiveness Measurement.....</b>                              | <b>8</b>  |
| <b>3.6 Outcomes .....</b>                                                      | <b>9</b>  |
| <b>3.7 Study Characteristics .....</b>                                         | <b>10</b> |
| <b>4.0 Results .....</b>                                                       | <b>11</b> |
| <b>4.1 Study Characteristics .....</b>                                         | <b>11</b> |
| <b>4.2 Newcastle-Ottawa Scale Risk of Bias Assessment .....</b>                | <b>13</b> |
| <b>4.3 Primary Outcomes.....</b>                                               | <b>14</b> |
| <b>4.4 Vaccine Effectiveness against Delta by Vaccine Type.....</b>            | <b>18</b> |
| <b>4.5 Effect of Time on Vaccine Effectiveness against Delta Variant .....</b> | <b>20</b> |
| <b>5.0 Discussion.....</b>                                                     | <b>21</b> |

|                                                                          |           |
|--------------------------------------------------------------------------|-----------|
| <b>Appendix A Newcastle-Ottawa Risk of Bias Assessment Results .....</b> | <b>25</b> |
| <b>Bibliography .....</b>                                                | <b>27</b> |

## **List of Tables**

|                                                                                                                                                                                               |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>Table 1. Search terms used in the Ovid-MEDLINE database to retrieve articles assessing vaccine effectiveness (VE) against SARS-CoV-2 Delta variant.....</b>                                | <b>5</b>  |
| <b>Table 2. Characteristics of studies evaluating COVID-19 Vaccine Effectiveness (VE) against SARS-CoV-2 Delta variant infection and during Delta variant predominance .....</b>              | <b>11</b> |
| <b>Table 3. COVID-19 Vaccine Effectiveness (VE) against infection, symptomatic disease, and hospitalization from the SARS-CoV-2 Delta variant and during Delta variant predominance .....</b> | <b>14</b> |
| <b>Table 4. Vaccine-specific vaccine effectiveness (VE) against SARS-CoV-2 Delta variant or during high Delta variant circulation .....</b>                                                   | <b>18</b> |
| <b>Table 5. Newcastle-Ottawa risk of bias assessment for test-negative case control studies included in the review .....</b>                                                                  | <b>25</b> |
| <b>Table 6. Newcastle-Ottawa risk of bias assessment for cohort studies included in the review .....</b>                                                                                      | <b>26</b> |

## **List of Figures**

|                                                                                                                                                      |           |
|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>Figure 1. Flowchart for articles assessing COVID-19 vaccine effectiveness against Delta variant obtained from the Ovid-MEDLINE database .....</b> | <b>10</b> |
| <b>Figure 2. Overall vaccine effectiveness (VE) against SARS-CoV-2 Delta variant infection by study and population .....</b>                         | <b>16</b> |
| <b>Figure 3. Overall vaccine effectiveness (VE) against SARS-CoV-2 Delta variant hospitalization by study and population .....</b>                   | <b>17</b> |

## **Preface**

I would like to thank my essay mentors Dr. Glynn, Dr. Snyder, and Dr. Nowalk for their support and guidance during my essay-writing process. I would also like to thank my fellow students in Pitt Epidemiology for their encouragement and friendship.

## **1.0 Introduction**

### **1.1 Background**

COVID-19 was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020.<sup>1</sup> The causative agent of COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped  $\beta$ -coronavirus that emerged in late 2019.<sup>2</sup> As of October 2021, over 230 million infections and over 4.8 million deaths have occurred globally.<sup>3</sup> To prevent further catastrophic human and economic costs associated with the pandemic, a paradigm shift in vaccine approval was critical. Prior to emergence of SARS-CoV-2, the vaccine development process generally took years from initial development to approval and widespread use.<sup>4</sup> The spread of COVID-19 necessitated the rapid development of vaccines that built on the foundation of previous work creating vaccines to prevent SARS (severe acute respiratory syndrome) and MERS (Middle east respiratory syndrome).<sup>4</sup>

Evidence from clinical trials of several COVID-19 vaccine candidates demonstrated the safety and immunogenicity of these vaccines in the prevention of symptomatic laboratory-confirmed disease, severe disease, and death.<sup>5–10</sup> As of October 16, 2021, seven efficacious COVID-19 vaccines have been approved for use by the WHO: mRNA-1273 (Moderna), BNT162b2 (Pfizer), Ad26.COV2.S (Janssen/Johnson & Johnson), AZD1222 (Oxford/AstraZeneca), Covishield (Oxford/AstraZeneca formulation; Serum Institute of India), BIBP-CorV (Sinopharm), and CoronaVac (Sinovac).<sup>11</sup> As of October 2021, 6.7 billion vaccine doses have been administered across the world.<sup>3</sup>

Observational studies (e.g., retrospective cohort, test-negative case control) of vaccine effectiveness (VE) for COVID-19 have shown sustained protection against the wild type virus under real-world conditions against symptomatic and severe disease.<sup>12–14</sup> As SARS-CoV-2 rapidly spread through the global population, variants emerged that demonstrated a change in antigenicity of the spike protein.<sup>15</sup> Reports have shown WHO-classified variants of concern (VOC), including the B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) variants, have superior immune evasion (i.e., escaping detection by SARS-CoV-2 antibodies) and viral load relative to SARS-CoV-2 parent lineages due to mutations in the spike protein of the virus, ultimately leading to increased transmissibility.<sup>16–18</sup> These mutations are significant because the antigen target for licensed COVID-19 vaccines is the SARS-CoV-2 spike protein, thus, significant mutations in the variant spike proteins may attenuate vaccine-induced neutralizing antibody response.<sup>15</sup> There is a demonstrated decrease in effectiveness against each successive VOC compared to wild type.<sup>20</sup> In a meta-analysis of VE against VOC, Liu and colleagues reported that the pooled VE against Alpha variant infection was 85% [95% CI: 80, 91], 75% [95% CI: 71, 79] for the Beta variant, and 54% [95% CI: 35, 74] for the Gamma variant.<sup>19</sup> VE against SARS-CoV-2 Delta variant and during times of high Delta spread in the population has not been well-studied.

Currently, Delta is the dominant variant in circulation as of October 2021.<sup>21</sup> Delta emerged in India in December 2020 and made up the highest proportion of cases between June and July 2021 across the globe.<sup>21</sup> Despite some reports of attenuated VE against variants, the BNT162b2 has shown robust neutralizing antibody response against all VOC to date in sera that were drawn from vaccinated individuals two weeks post-vaccination.<sup>22</sup> The exact immune correlates of protection have not been established for SARS-CoV-2,<sup>23</sup> however, there is evidence that antibodies generated by the BNT162b2 vaccine are effective against the Delta variant.<sup>22</sup> More research is

needed to assess vaccine impact on COVID-19 incidence and prevalence for all WHO-approved vaccine platforms.

## **1.2 Gaps in Knowledge**

As time since vaccination passes, neutralizing antibodies against SARS-CoV-2 have been shown to decrease, leading to reduced protection against COVID-19.<sup>24</sup> Further investigation is needed to discern whether attenuated VE is due to waning immunity or immune evasion of the Delta variant. Observational, test-negative designs are commonly used to establish VE post-vaccine licensure when the use of randomized controlled trials (RCTs) would face ethical challenges.<sup>25</sup> This systematic review will describe current VE estimates of WHO-approved vaccines against the Delta variant from observational studies.

## **1.3 Public Health Significance**

Better understanding of waning vaccine-induced immunity to COVID-19 and potential vaccine-escape of SARS-CoV-2 VOC is necessary to develop a dynamic vaccine program to control COVID-19. VE data are used to make decisions about booster doses and which vaccines should be indicated for those who are immunocompromised. Due to the dynamic nature of the Delta variant and the expedited pace of publications investigating VE, an updated synthesis of the literature is necessary. This information can inform clinical decision-making, policy decisions, and promote vaccine development to protect against future variants.

## **2.0 Objective**

The aim of this systematic review was to synthesize COVID-19 vaccine effectiveness (VE) estimates against SARS-CoV-2 Delta variant infection, symptomatic disease, and hospitalization and to provide insight into current vaccine protection and examine how VE was affected by Delta variant immune evasion and waning effectiveness over time.

### 3.0 Methods

#### 3.1 Search Strategy

A comprehensive literature search was conducted using the Ovid-MEDLINE database on October 16, 2021. Institutional access was granted through the University of Pittsburgh Health Sciences Library System (HSLs), and a HSLs librarian with expertise in systematic reviews assisted in the search. Search queries included terms related to SARS-CoV-2, COVID-19, WHO-approved COVID-19 vaccines, and the Delta variant. Articles were restricted to the English language. The specific search terms (Table 1) must have appeared in the title or the abstract. EndNote X9 and Sciwheel software were used for reference management. HSLs-developed systematic review spreadsheets were used for all screening activities.<sup>26</sup>

**Table 1. Search terms used in the Ovid-MEDLINE database to retrieve articles assessing vaccine effectiveness (VE) against SARS-CoV-2 Delta variant**

| Line # | Search terms                                                                         |
|--------|--------------------------------------------------------------------------------------|
| 1.     | (Moderna or "mRNA-1273" or mRNA1273).ti,ab,kf,rn.                                    |
| 2.     | ("Pfizer/BioNTech" or PfizerBioNTech or Pfizer or BioNTech or BNT162b2).ti,ab,kf,rn. |
| 3.     | (Janssen or Johnson or "Ad26.COV2.S" or Ad26COV2S).ti,ab,kf,rn.                      |
| 4.     | ("Oxford/AstraZeneca" or OxfordAstraZeneca or AstraZeneca or AZD1222).ti,ab,kf,rn.   |
| 5.     | ((serum adj1 Institute adj2 India) or Covishield).ti,ab,kf,rn.                       |
| 6.     | (Sinopharm or "BBIBP-CorV" or BBIBPCorV or (Vero adj1 Cells)).ti,ab,kf,rn.           |
| 7.     | (Sinovac or CoronaVac).ti,ab,kf,rn.                                                  |
| 8.     | 1 or 2 or 3 or 4 or 5 or 6 or 7                                                      |
| 9.     | COVID-19 Vaccines/                                                                   |
| 10.    | COVID-19/                                                                            |
| 11.    | (covid or (sars adj1 cov) or coronavirus).ti,ab,kf,rn.                               |
| 12.    | 10 or 11                                                                             |

|     |                                                    |
|-----|----------------------------------------------------|
| 13. | vaccination/ or mass vaccination/                  |
| 14. | (vaccine* or vaccination*).ti,ab,kf.               |
| 15. | 13 or 14                                           |
| 16. | 12 and 15                                          |
| 17. | 9 or 16                                            |
| 18. | 8 or 17                                            |
| 19. | (delta or "B.1.617.2" or "B-1-617-2").ti,ab,kf,rn. |
| 20. | 18 and 19                                          |
| 21. | limit 20 to English language                       |

### 3.2 Eligibility Criteria

Articles were included in the review if they were primary research studies (i.e., not a review or meta-analysis) assessing VE against the SARS-CoV-2 Delta variant specifically or during times of predominant Delta variant circulation using one of the WHO-approved COVID-19 vaccines at the time of literature search. Inclusion was restricted to peer-reviewed observational studies indexed as of October 16, 2021. Studies that used non-human participants, did not control for confounding in their VE estimates (e.g., by age), and did not verify vaccination status using a reliable record (e.g., medical record, government surveillance database, etc.) were excluded. Further, studies were excluded if they reported VE of partial vaccination only (e.g., one dose of a two-dose series), Studies that did not report a Delta variant-specific VE measure (e.g., against infection, symptomatic disease, or hospitalization) were also excluded. Conference presentations, abstracts, and preprints were not included in this review to ensure articles underwent a full peer-review process. While the speed of the pandemic necessitates quick sharing of information, this review did not include pre-prints due to the uncertainty in the quality of the data being reported. Peer-review increases the quality of the methods and data provided by the researchers.

### **3.3 Data Abstraction**

Data abstracted from the selected articles included: name of vaccine(s) evaluated, observational study type (e.g., case control or cohort study), country of the study, population type, age of participants, demographic information, sample size, length of follow-up, number of cases and controls, VE outcomes (e.g., against symptomatic disease, infection, hospitalization) and whether the VE estimate was adjusted and by which covariates. For studies that investigated VE stratified by time since vaccination, median time from vaccination to outcome was recorded. VE directly against Delta as confirmed by genomic testing and VE assessed during times of majority Delta variant circulation (derived from the study or genomic surveillance reports) were included and directly compared. Data were visualized using Excel and R version 4.0.3 (2020-10-10).

### **3.4 Study Assessment**

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the non-randomized observational studies included in this review.<sup>27</sup> The assessment consists of a point system in which each category has a certain number of points to be earned, with slightly different criteria for case control and cohort studies.

For case control studies, the evaluation categories included Selection (0-4 points), Comparability (0-1 point), and Exposure (0-2 points). In the Selection category, the reviewer assessed the adequacy of the case definition, the representativeness of the cases, and selection and definition of controls. The comparability category was assessed on the comparability of cases and controls based on the design or analysis. Ascertainment of exposure and non-response rate were

evaluated in the Exposure Category. Non-response rate is not relevant to the test-negative design; therefore, it was dropped from the assessment for this systematic review.

For cohort studies, the evaluation categories included Selection (0-4), Comparability (0-1), and Exposure (0-3). Selection was assessed by the representativeness of the exposed cohort, the selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study. Comparability was assessed similarly to case control studies through considering the comparability of cohorts based on the design or analysis. The Outcome category was evaluated on the assessment of the outcome, follow-up being long enough for outcomes to occur, and the adequacy of cohort follow-up.

### **3.5 Vaccine Effectiveness Measurement**

Vaccine effectiveness is a relative measure assessing how well a vaccine performs in “real-world” conditions, unlike the controlled environment of an RCT where vaccine efficacy can be derived.<sup>28</sup> In cohort studies, VE is determined by examining risk of disease outcome between vaccinated and unvaccinated groups; it is interpreted as the proportionate reduction in disease among the vaccinated group. It is reported as a percentage and is calculated as one minus the relative rate ratio of association, multiplied by 100% ( $1 - \text{the incidence rate ratio (IRR)} \times 100$ ). Hazard ratios calculated from Cox proportional hazard models can also be used to calculate VE and be used to control for confounding factors through inclusion of relevant terms in the model.

Case control studies that use a test-negative approach compare the frequency of vaccination in care-seeking symptomatic test-positive (case) and test-negative (control) individuals.<sup>29</sup> VE is calculated using  $(1 - \text{the odds of vaccination}) \times 100$  between the cases and control groups.

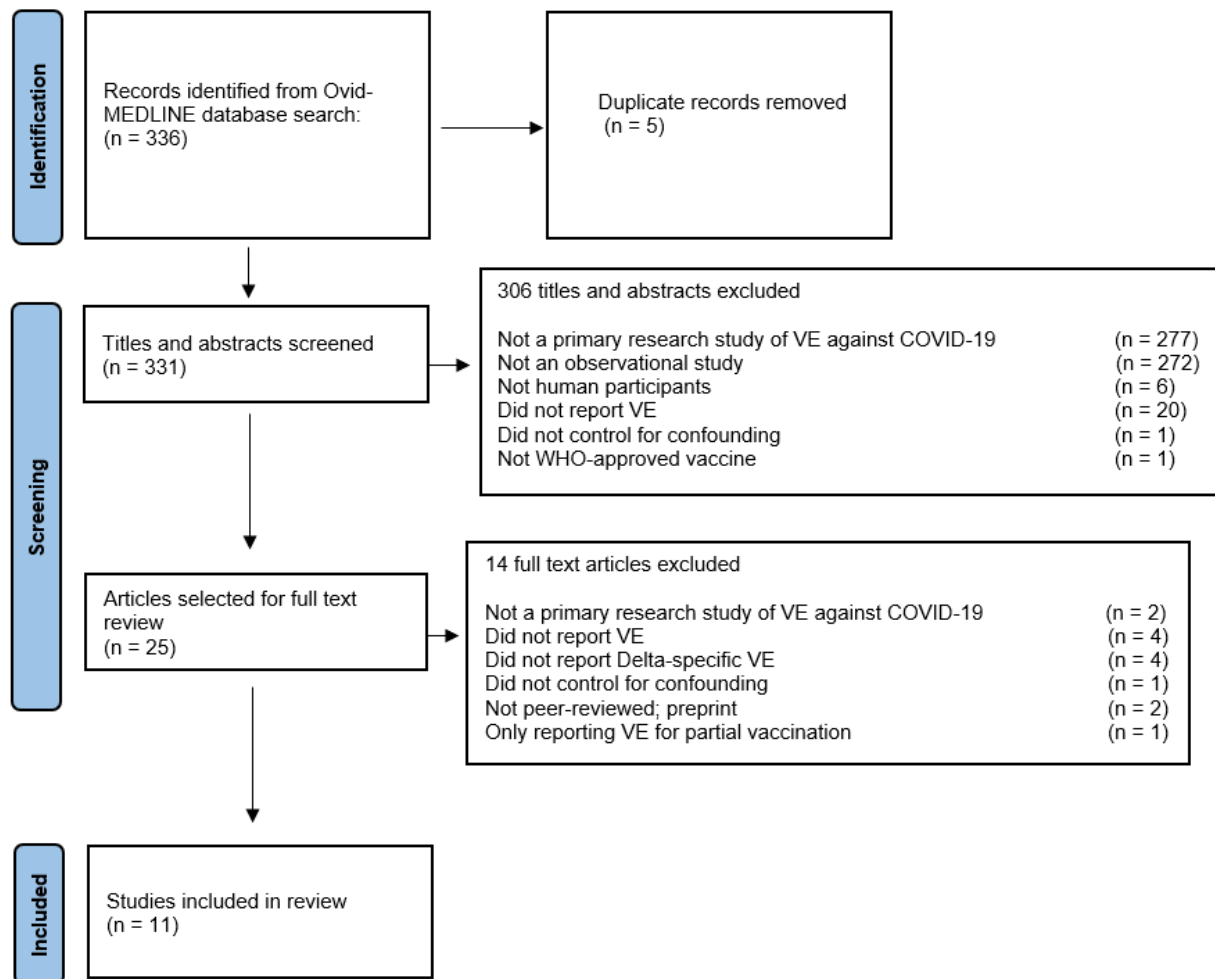
Logistic regression can be used to estimate the odds while adjusting for additional covariates that may be confounding factors of the exposure, such as age or gender. Heterogeneity in population composition, vaccine schedules (who was eligible for vaccination at what time), community prevalence, behaviors (i.e. increased social interactions), follow-up period, and predominant variants may influence VE estimates.<sup>30,31</sup>

### **3.6 Outcomes**

Studies were included in the review if they reported Delta variant-specific VE or VE measured during times of Delta variant predominance. The primary outcomes examined were VE against symptomatic or asymptomatic Delta variant infection (test positive only), symptomatic disease (test positive with clinical signs and symptoms), and hospitalization (test positive and admitted to hospital due to complications of COVID-19 infection). VE against death was not examined in this review due to low COVID-19 mortality amongst vaccinated individuals against the preceding VOC.<sup>19</sup> The VE estimates and their 95% confidence intervals for each study were tabulated. A subgroup analysis examined VE stratified by vaccine type in the studies that provided vaccine-specific estimates. In studies that reported the VE as an aggregate of data, these estimates were classified as overall VE and reported separately from vaccine-specific VE. The VE estimates were visualized with their confidence intervals using forest plots.

### 3.7 Study Characteristics

The search query returned 336 articles from the Ovid-MEDLINE database. Five duplicate articles were removed prior to title and abstract screening; therefore 331 records underwent title and abstract screening against the eligibility criteria. Of the 331 abstracts screened, twenty-five articles fulfilled the eligibility criteria and were selected for full-text review. Following full-text review, eleven studies satisfied criteria for selection into the systematic review (Figure 1).<sup>32–42</sup>



**Figure 1. Flowchart for articles assessing COVID-19 vaccine effectiveness against Delta variant obtained from the Ovid-MEDLINE database**

## 4.0 Results

### 4.1 Study Characteristics

Of the 11 studies that satisfied the selection criteria, five studies were conducted in the United States,<sup>32,33,35,37,40</sup> one in China,<sup>36</sup> one in Israel,<sup>34</sup> two in the United Kingdom,<sup>41,42</sup> one in Scotland,<sup>39</sup> and one in Norway. (Table 1)<sup>38</sup> Five studies were analyzed as test-negative case control studies,<sup>32,35,36,39,42</sup> five were analyzed as cohort studies,<sup>33,34,37,38,40</sup> and one was a population-level survey.<sup>41</sup> Study populations examining VE included the general population of adults 18 years and older in the US, general population of those 16 years and older in the UK and Scotland, those in the Kaiser Permanente Southern California health system (KSPC) ages 12 and older, the general population of adults ages 18 and older in Norway, adolescents 12-15 years in Israel, a cohort of healthcare workers, essential workers, hospitalized veterans, and first responders in the US, and adults in an outbreak of Delta variant in China. (Table 2)

**Table 2. Characteristics of studies evaluating COVID-19 Vaccine Effectiveness (VE) against SARS-CoV-2**

#### Delta variant infection and during Delta variant predominance

| Study                                | Country | Population                                         | Study Type                 | Vaccine(s) evaluated             | Follow-up interval                   |
|--------------------------------------|---------|----------------------------------------------------|----------------------------|----------------------------------|--------------------------------------|
| <b>Fowlkes et al 2021</b>            | US      | Adult Frontline Workers ( $\geq 18$ years)         | Prospective cohort         | BNT162b2, mRNA-1273, Ad26.COV2.S | December 14, 2020 to August 14, 2021 |
| <b>Robilotti et al 2021</b>          | US      | Healthcare personnel ( $\geq 18$ years)            | Retrospective cohort       | BNT162b2                         | November 1, 2020 to August 31, 2021  |
| <b>Tartof et al 2021<sup>2</sup></b> | US      | Population in KSPC <sup>3</sup> ( $\geq 12$ years) | Retrospective cohort       | BNT162b2                         | December 14, 2020 to Aug 8, 2021     |
| <b>Bajema et al 2021</b>             | US      | Veterans ( $\geq 18$ years)                        | Test-negative case control | mRNA-1273, BNT162b2              | February 1–August 6, 2021            |

|                                                |          |                               |                            |                                                            |                               |
|------------------------------------------------|----------|-------------------------------|----------------------------|------------------------------------------------------------|-------------------------------|
| <b>Grannis et al 2021<sup>1</sup></b>          | US       | Adults ( $\geq 18$ years)     | Test-negative case control | mRNA-1273, BNT162b2, Ad26.COV2.S                           | June–August 2021              |
| <b>Glatman-Freedman et al 2021<sup>2</sup></b> | Israel   | Adolescents (12-15 years)     | Retrospective cohort       | BNT162b2                                                   | July 1 to August 26, 2020     |
| <b>Li et al 2021</b>                           | China    | Adults ( $\geq 18$ years)     | Test-negative case control | BBIBP-CorV/CoronaVac                                       | --                            |
| <b>Seppala et al 2021</b>                      | Norway   | Population ( $\geq 18$ years) | Retrospective cohort       | BNT162b2, mRNA-1273, ChAdOx1, ChAdOx1 and mRNA, combo mRNA | April 15, to August 15, 2021  |
| <b>Sheikh et al<sup>1</sup></b>                | Scotland | Population ( $\geq 18$ years) | Test-negative case control | BNT162b2, ChAdOx1                                          | April 1, 2021 to June 6, 2021 |
| <b>Lopez Bernal et al<sup>1</sup></b>          | UK       | Population ( $\geq 16$ years) | Test-negative case control | BNT162b2, ChAdOx1                                          | April 12 to May 30 2021       |
| <b>Pouwels et al 2021<sup>1</sup></b>          | UK       | Population ( $\geq 16$ years) | Population survey          | BNT162b2, ChAdOx1                                          | May 17 to August 1 2021       |

1=Stratified VE against Delta by vaccine type; 2=Stratified VE against Delta by time since vaccination; 3=Kaiser Permanente Southern California; '--'=Not reported; BNT162b2=Pfizer; mRNA-1273=Moderna; Ad26.COV2.S=Johnson & Johnson/Janssen; ChAdOx1=AstraZeneca/Oxford; BBIBP-CorV=Sinovac

The most common VE outcome measured among all studies was SARS-CoV-2 test-positive infection in nine of the 11 studies.<sup>33,34,36–41</sup> For all the test-negative case control studies, logistic regression models were used to calculate OR in the VE calculation (1-OR). VE models were most commonly adjusted by age, sex, calendar week (week during pandemic), geographic region (location of cases), race (White/Caucasian, Black/African American, Asian/Pacific Islander, American Indian or Alaska native) and ethnicity (Hispanic/Latino). Spline terms (to address temporal confounding) and interactions (to assess effect modification) were included by

some researchers in their models for variables dealing with age, calendar day, and number of prior COVID tests.

Three of the five retrospective cohort studies used hazard ratios (HR) for VE calculation (1-HR) derived from Cox proportional hazards models.<sup>33,38,40</sup> The other cohort studies used incidence rate ratios for VE calculation (1-IRR).<sup>34,37</sup> In the Cox models, the studies were adjusted for age, sex, race/ethnicity, underlying comorbidities (diabetes, cancer etc.), occupation, epidemiologic week (week of COVID-19 pandemic), and other sociodemographic characteristics.

Three of the 11 studies reported VE against COVID-19 hospitalization,<sup>32,35,40</sup> two studies reported VE against symptomatic COVID-19 infection,<sup>39,42</sup> and one study assessed VE against emergency department or urgent care (ED/UC) visits that were not admitted to the hospital.<sup>35</sup> All studies defined full vaccination as >14 days after second dose of the vaccine for those that require two doses or 14 days after a single-dose vaccine.

#### **4.2 Newcastle-Ottawa Scale Risk of Bias Assessment**

The NOS assessment results for the test-negative case controls studies ranged from 6 to 7 out of a maximum 7 (Appendix A). The most frequent point loss was in studies that used hospital controls.<sup>32,35</sup> Li and colleagues were deducted a point in the Exposure section because cases and controls were not identified using the same method; controls were drawn from close contacts identified through case investigation.<sup>36</sup>

The NOS results for cohort studies also ranged from 6 to 7 out of a maximum 8. Points were most commonly lost in the Outcome section because of inadequate follow-up. The WHO recommends that VE studies have 12 months of follow up for sound interpretation,<sup>43</sup> and none of

the cohort studies satisfied this criterion to examine VE against Delta. A study of health care personnel also lost a point for weak comparability between exposed and unexposed cohorts where those who were vaccinated were much more likely to be tested compared to the unvaccinated cohort. Overall, NOS assessment indicated that the test-negative case control and cohort studies included in this review were of high quality (Appendix A).

### 4.3 Primary Outcomes

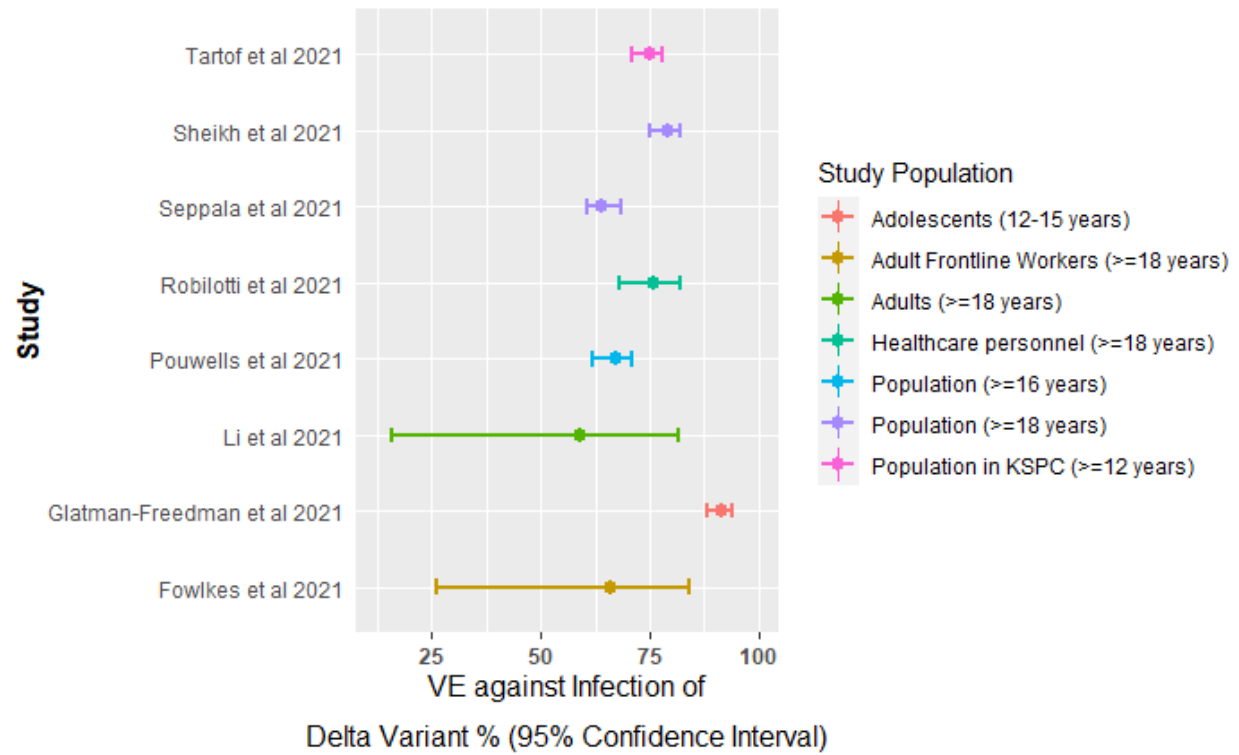
Overall VE (non-vaccine specific VE) estimates against SARS-CoV-2 Delta variant infection (test-positive) for WHO-approved vaccines reported in this review ranged from 59% [95% CI: 16, 81.6]<sup>36</sup> to 75% [95% CI: 71, 78]. (Figure 2)<sup>40</sup> Additionally, VE against symptomatic Delta variant infection was reported as 79.6 [76.7, 82.1]. (Table 3)<sup>42</sup> Overall VE against Delta variant hospitalization ranged from 86% [95% CI: 82, 89]<sup>35</sup> to 93% [95% CI: 84, 96]. (Figure 3)<sup>40</sup>

**Table 3. COVID-19 Vaccine Effectiveness (VE) against infection, symptomatic disease, and hospitalization from the SARS-CoV-2 Delta variant and during Delta variant predominance**

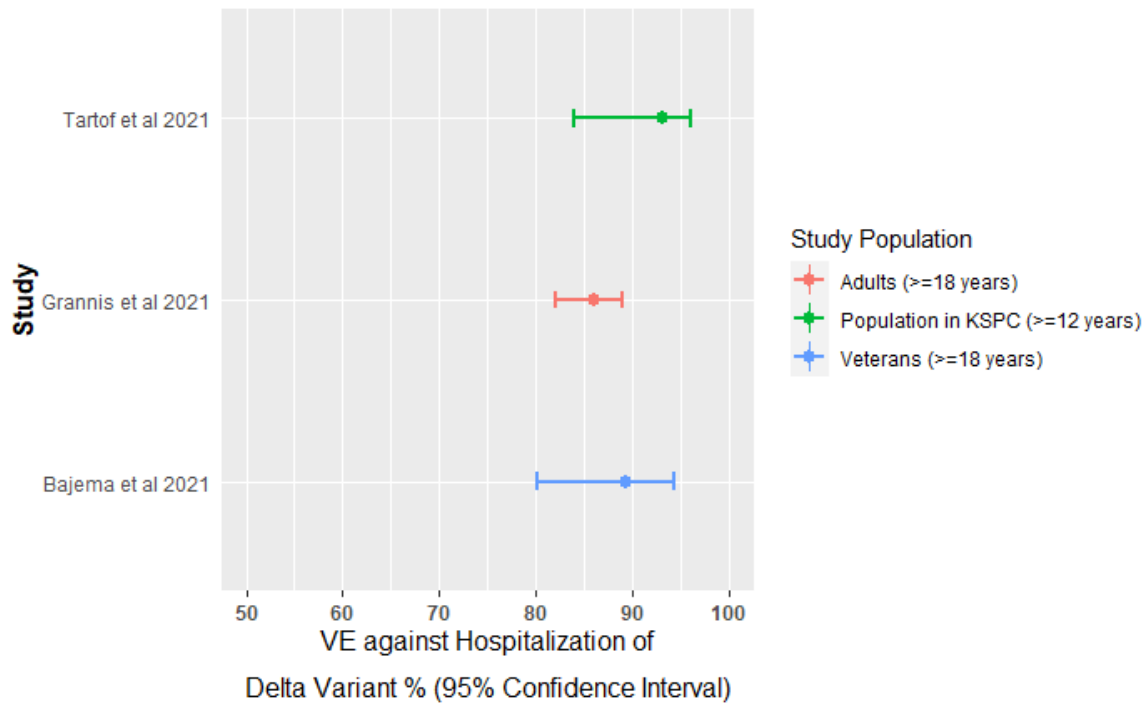
| Study                       | Vaccine(s) evaluated             | Population                                  | Overall VE % reported [95% CI] |                              |                                |                        |
|-----------------------------|----------------------------------|---------------------------------------------|--------------------------------|------------------------------|--------------------------------|------------------------|
|                             |                                  |                                             | <i>Infection</i>               | <i>Symptomatic infection</i> | <i>ED/UC visit<sup>1</sup></i> | <i>Hospitalization</i> |
| <b>Fowlkes et al 2021</b>   | BNT162b2, mRNA-1273, Ad26.COV2.S | Adult Frontline Workers (≥18 years)         | 66 [26, 84]                    | --                           | --                             | --                     |
| <b>Robilotti et al 2021</b> | BNT162b2                         | Healthcare personnel (≥18 years)            | 75.6 [68.2, 81]                | --                           | --                             | --                     |
| <b>Tartof et al 2021</b>    | BNT162b2                         | Population in KSPC <sup>2</sup> (≥12 years) | 75 [71, 78]                    | --                           | --                             | 93 [84, 96]            |

|                                    |                                                            |                               |                                               |                                               |             |                   |
|------------------------------------|------------------------------------------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|-------------|-------------------|
| <b>Bajema et al 2021</b>           | mRNA-1273, BNT162b2                                        | Veterans ( $\geq 18$ years)   | --                                            | --                                            | --          | 89.3 [80.1, 94.3] |
| <b>Grannis et al 2021</b>          | mRNA-1273, BNT162b2, Ad26.COV2.S                           | Adults ( $\geq 18$ years)     | --                                            | --                                            | 82 [81, 84] | 86 [82, 89]       |
| <b>Glatman-Freedman et al 2021</b> | BNT162b2                                                   | Adolescents (12-15 years)     | 91.5 [88.2, 93.9]                             | --                                            | --          | --                |
| <b>Li et al 2021</b>               | BBIBP-CorV/CoronaVac                                       | Adults ( $\geq 18$ years)     | 59.0 [16.0, 81.6]                             | --                                            | --          | --                |
| <b>Seppala et al 2021</b>          | BNT162b2, mRNA-1273, ChAdOx1, ChAdOx1 and mRNA, combo mRNA | Population ( $\geq 18$ years) | 64 [60.6, 68.2]                               | --                                            | --          | --                |
| <b>Sheikh et al 2021</b>           | BNT162b2, ChAdOx1                                          | Population ( $\geq 18$ years) | BNT162b2: 79 [75, 82]<br>ChAdOx1: 60 [53, 66] | BNT162b2: 83 [78, 87]<br>ChAdOx1: 61 [51, 70] | --          | --                |
| <b>Lopez Bernal et al 2021</b>     | BNT162b2, ChAdOx1                                          | Population ( $\geq 16$ years) | --                                            | 79.6 [76.7, 82.1]                             | --          | --                |
| <b>Pouwells et al 2021</b>         | BNT162b2, ChAdOx1                                          | Population ( $\geq 16$ years) | BNT162b2: 82 [79, 85]<br>ChAdOx1: 67 [62, 71] | --                                            | --          | --                |

‘--’=Not reported; 1=Emergency Department/Urgent Care visit; 2=Kaiser Permanente Southern California



**Figure 2. Overall vaccine effectiveness (VE) against SARS-CoV-2 Delta variant infection by study and population**



**Figure 3. Overall vaccine effectiveness (VE) against SARS-CoV-2 Delta variant hospitalization by study and population**

#### 4.4 Vaccine Effectiveness against Delta by Vaccine Type

Six of the articles stratified by vaccine type in their reports of VE against Delta (Table 4). Vaccines against Delta variant included in the search results were the mRNA-1273 (Moderna, one study), BNT162b2 (Pfizer/BioNTech, six studies), ChAdOx1-S/nCoV-19 (AstraZeneca/Oxford, three studies), Ad26.COV2.S (Janssen, one study), BIBP-CorV (Sinopharm, one study), and CoronaVac (Sinovac, one study). The literature search produced articles examining all of the WHO-approved vaccines except for Covishield, an AstraZeneca/Oxford formulation produced in India.

Overall VE against infection against the SARS-CoV-2 Delta variant in the general adult population for the BNT162b2 vaccine ranged from 75% [95% CI: 71, 78]<sup>40</sup> to 82% [95% CI: 79, 85].<sup>41</sup> Against symptomatic disease, VE ranged from 83% [95% CI: 78, 87]<sup>39</sup> to 88% [95% CI: 85.3, 90.1].<sup>13</sup> COVID-19-related hospitalization VE was a range of 80% [95% CI: 73, 85]<sup>35</sup> to 93% [95% CI: 84, 96].<sup>40</sup> (Table 4)

**Table 4. Vaccine-specific vaccine effectiveness (VE) against SARS-CoV-2 Delta variant or during high Delta variant circulation**

| <b>Study</b>             | <b>VE<br/>infection<br/>[95% CI]</b> | <b>VE symptomatic<br/>[95% CI]</b> | <b>VE ED/UC<br/>encounter<br/>[95% CI]</b> | <b>VE<br/>hospitalization<br/>[95% CI]</b> |
|--------------------------|--------------------------------------|------------------------------------|--------------------------------------------|--------------------------------------------|
| <b>mRNA-1273</b>         |                                      |                                    |                                            |                                            |
| Grannis<br>et al<br>2021 | --                                   | --                                 | 92 [89, 93]                                | 95 [92, 97]                                |
| <b>BNT162b2</b>          |                                      |                                    |                                            |                                            |
| Grannis<br>et al<br>2021 | --                                   | --                                 | 77 [74, 80]                                | 80 [73, 85]                                |

|                    |                         |                 |                   |             |             |
|--------------------|-------------------------|-----------------|-------------------|-------------|-------------|
|                    | Lopez Bernal et al 2021 | --              | 88.0 [85.3, 90.1] | --          | --          |
|                    | Robilotti et al 2021    | 75.6 [68.1, 82] | --                | --          | --          |
|                    | Sheikh et al 2021       | 79 [75, 82]     | 83 [78, 87]       | --          | --          |
|                    | Tartof et al 2021       | 75 [71, 78]     | --                | --          | 93 [84, 96] |
|                    | Pouwels et al 2021      | 80 [77, 83]     | --                | --          | --          |
| <b>ChAdOx1</b>     | Lopez Bernal et al 2021 | --              | 67.0 [61.3, 71.8] | --          | --          |
|                    | Sheikh et al 2021       | 60 [53, 66]     | 61 [51, 70]       | --          | --          |
|                    | Pouwels et al 2021      | 67 [62, 71]     | --                | --          | --          |
| <b>Ad26.COV2.S</b> | Grannis et al 2021      | --              | --                | 65 [56, 72] | 60 [31, 77] |

‘--’=Not reported

VE specific to the mRNA-1273 vaccine was only available against hospitalization. In the general population, VE of mRNA-1273 vaccine was shown to be 95% [95% CI: 92, 97]. (Table 4)<sup>35</sup> No other vaccine-specific data were available on VE against infection or symptomatic infection.

There were three studies from Europe detailing VE for AstraZeneca/Oxford ChAdOx1 vaccine. Vaccine-specific VE was available for the ChAdOx1 vaccine for protection against infection and symptomatic infection during Delta circulation predominance. Overall VE against

infection was found to range from 60% [95% CI: 53, 66]<sup>39</sup> to 67% [95% CI: 62, 71].<sup>41</sup> VE against symptomatic disease was found to range from 61% [95% CI: 51, 70]<sup>39</sup> to 67% [95% CI: 61.3, 71.8]. (Table 4)<sup>13</sup>

The BIBP and CoronaVac VE data were from an aggregate of the two vaccines – it was not stratified by individual vaccine but rather for both in an outbreak of Delta variant in Guangzhou, China. VE against infection for these inactivated vaccines was 59.0% [95% CI: 16, 81]. (Table 4)<sup>36</sup> This was the only study that reported on VE from these vaccines.

Grannis and colleagues reported vaccine-specific VE during high Delta circulation for hospitalization and ED/UC visits, which was found to be 60% [95% CI: 31, 77]<sup>35</sup> and 65% [95% CI: 56, 72],<sup>35</sup> respectively. (Table 4) The other studies that included the vaccine were pooled VE estimates for all available vaccines in the US.

#### **4.5 Effect of Time on Vaccine Effectiveness against Delta Variant**

Two studies stratified VE against Delta variant by time since vaccination. Glatman-Freedman and colleagues examined VE in Israel among adolescents ages 12 to 15 during high Delta-variant circulation. Two to four weeks post-vaccination, VE against infection in this population was shown to be 91.5% [95% CI: 88.2, 93.9].<sup>34</sup> Tartof and colleagues conducted a retrospective cohort study of individuals in the Kaiser Permanente healthcare system and stratified BNT162b2 VE by time (months) since vaccinated. VE against Delta variant infections one month after full vaccination was reported to be 93% [95% CI 85, 97] and declined to 53% [95% CI 39, 65] after four months.<sup>40</sup> There was no significant difference in VE decline between Delta and other variants.

## 5.0 Discussion

This systematic review characterized current vaccine effectiveness (VE) estimates for WHO-approved vaccines against SARS-CoV-2 Delta variant infection, symptomatic infection, and hospitalization in 11 studies. Overall VE against SARS-CoV-2 Delta variant ranged from 59% to 75% against infection, was reported to be 79.6% against symptomatic infection, and ranged from 86% to 93% against hospitalization. Vaccine-specific VE against Delta variant was reported in six studies, with most data available for the BNT162b2 vaccine. VE for the BNT162b2 vaccine ranged from 60% to 80% against Delta variant infection, 83% to 88% for symptomatic infection, and 80% to 93% for hospitalization. The vaccine with the second most available data was the ChAdOx1 vaccine, with reported VE against Delta variant infection ranging from 60% to 67% and 61 to 67% for symptomatic infection.

Studies included in this review provide evidence that SARS-CoV-2 vaccines have demonstrated decreased effectiveness against COVID-19-related hospitalization, symptomatic disease, and infection of the Delta variant compared to previous VOC and wild type SARS-CoV-2.<sup>15,44</sup> A previous meta-analysis of all SARS-CoV-2 vaccines reported that VE against Alpha variant infection was 85%, 75% for the Beta variant, and 54% for the Gamma variant.<sup>19</sup> This phenomenon of lower VE against VOC is consistent with the results of this review examining the Delta variant. Vaccine protection remains high against hospitalizations according to studies included in the review, but there was a documented decrease in VE against the Delta variant infection and symptomatic disease.<sup>40</sup>

The decline in VE may be explained by the Delta variant achieving a higher viral load compared to previous VOC, which was demonstrated by Pouwels and colleagues, who found that

Delta variant reduced VE and attenuated peak viral burden.<sup>41,45</sup> However, recent literature has demonstrated that vaccine-induced antibodies retain high neutralizing capacity against the Delta variant in sera drawn within a month after vaccination.<sup>22</sup> Tartof and colleagues reported a VE of 93% against Delta variant infection one month after vaccination, but demonstrated a reduction in VE down to 53% after 4 months.<sup>40</sup> These results suggest that attenuated VE and breakthrough infections may be driven by waning effectiveness of vaccines over time. A recent study in Israel (published outside the database search range) demonstrated that SARS-CoV-2 infections during July 11 to 31 (a time of high Delta circulation) were higher among those fully vaccinated in January 2021 compared to those fully vaccinated two months later in March.<sup>24</sup> Further analytic studies are necessary to examine if VOC immune evasion or waning immunity is the primary reason for reduced VE.

The findings from this review demonstrate that COVID-19 vaccine VE has decreased following the emergence of SARS-CoV-2 Delta variant – mainly against infection and symptomatic disease. Vaccine protection against hospitalization remains high, particularly for the BNT162b2 and mRNA-1273 vaccines. Reported VE remained consistent between both test-negative case control studies and cohort studies. Overall, the BNT162b2 vaccine was shown to have the most data and the highest effectiveness against SARS-CoV-2 Delta variant infection among the WHO-approved vaccines. These findings have implications for vaccination programs, as data support the need for a booster dose to compensate for diminished SARS-CoV-2 VE. However, certainty about which vaccine product is superior cannot be determined based on this review alone, due to the limited number of studies examining each WHO-approved vaccine.

A weakness of the literature is that context of the VE estimates can be highly variable, be it in case definition, study design, vaccine schedule, or population composition. Further, the small

sample size of articles meeting eligibility criteria for this review may reflect a broader lack of peer-reviewed literature examining VE against the Delta variant. Only one study met eligibility criteria for the inactivated CoronaVac and BBIBP vaccines,<sup>36</sup> and only one examined mRNA-1273.<sup>35</sup> Further research should assess how these individual vaccines perform against the Delta variant and future VOC.

The NOS assessment revealed low possibility of bias in the studies included in this review, but observational data should still be interpreted carefully. While test-negative designs have advantages in alleviating selection bias like test-seeking behavior, there may be bias due to unmeasured confounding due to the lack of randomization. Additionally, fluctuation in sensitivity or specificity of PCR testing could potentially bias the results through misclassification of outcome status.

Strengths of this review include the synthesis of information on a rapidly developing public health issue. Other reviews of VE against the Delta variant were identified but have not undergone the peer-review process, indicating the need for a synthesis of available data and critical appraisal. The NOS risk of bias assessment conducted is a strength of this study, as it established that these studies were methodologically sound in reporting on VE against Delta.

There are several limitations to this review. First, a limited number of articles met eligibility criteria to be included in the review. This implies that regulators and public health authorities may be lacking crucial data to aid in pandemic response, such as data supporting the roll-out of booster doses. This review did not specifically examine VE after a single dose of a two-dose series. Information about VE after single doses could inform vaccination strategies in the context of vaccine scarcity or where circumstances necessitate distributing single doses across an unvaccinated population. Another limitation in this review is the omission of neutralization studies

in contextualizing VE estimates against Delta. While research has shown there to be immediate robust neutralizing activity against Delta and other VOC, sera should be examined from those who have been vaccinated longer to assess immune protection.<sup>22</sup>

Heterogeneity in populations and vaccine programs among countries and regions presents potential challenges in comparing VE estimates across studies. Also, some of the studies examined VE during periods of Delta predominance, but not directly against Delta as verified through genetic typing. This may lead to some bias in the measurement of VE against the SARS-CoV-2 Delta variant, as misclassification may have occurred. This could bias the estimate either towards or against the null; for instance, test-positive cases during times of Delta predominance may be infected by another variant. This variant may or may not have comparable fitness to the Delta variant. Additionally, many of these studies lacked follow-up data, which prevented collection of more data on VE against severe outcomes like ICU admission and death from being adequately calculated.

The results of this review have demonstrated that VE against the Delta variant remains high against hospitalization but has shown decline against infection and symptomatic infection – especially as time from vaccination increases. This demonstrates the vital need for continuous research and surveillance of VE so that vaccine programs are dynamic and adaptable to the epidemiology of the COVID-19 pandemic. The findings of this review are of public health significance as they inform clinical decision-making, policy decisions, and further vaccine development necessary for safeguarding the population against SARS-CoV-2 variant.

## Appendix A Newcastle-Ottawa Risk of Bias Assessment Results

Table 5. Newcastle-Ottawa risk of bias assessment for test-negative case control studies included in the review

| Study              | Selection                |                             |                       | Comparability          |                                     | Exposure                  |                                    | Overall Score |
|--------------------|--------------------------|-----------------------------|-----------------------|------------------------|-------------------------------------|---------------------------|------------------------------------|---------------|
|                    | Case Definition Adequate | Representativeness of cases | Selection of controls | Definition of controls | Comparability of cases and controls | Ascertainment of exposure | Same method for cases and controls |               |
| Bajema et al 2021  | ★                        | ★                           | 0                     | ★                      | ★                                   | ★                         | ★                                  | 6             |
| Grannis et al 2021 | ★                        | ★                           | 0                     | ★                      | ★                                   | ★                         | ★                                  | 6             |
| Li et al 2021      | ★                        | ★                           | ★                     | ★                      | ★                                   | ★                         | 0                                  | 6             |
| Lopez et al 2021   | ★                        | ★                           | ★                     | ★                      | ★                                   | ★                         | ★                                  | 7             |
| Sheikh et al 2021  | ★                        | ★                           | ★                     | ★                      | ★                                   | ★                         | ★                                  | 7             |

★=1 point

**Table 6. Newcastle-Ottawa risk of bias assessment for cohort studies included in the review**

| Study                                | Selection                            |                                 |                           |                                                       | Comparability                                        |                       | Outcome                                    |                                  | Overall Score |
|--------------------------------------|--------------------------------------|---------------------------------|---------------------------|-------------------------------------------------------|------------------------------------------------------|-----------------------|--------------------------------------------|----------------------------------|---------------|
|                                      | Representativeness of Exposed Cohort | Selection of non-exposed cohort | Ascertainment of exposure | Outcome of interest was not present at start of study | Comparability of cohorts based on design or analysis | Assessment of Outcome | Follow-up long enough for outcome to occur | Adequacy of follow-up of cohorts |               |
| <b>Fowlkes et al 2021</b>            | ★                                    | ★                               | ★                         | ★                                                     | ★                                                    | ★                     | 0                                          | ★                                | 7             |
| <b>Glatman - Freedman et al 2021</b> | ★                                    | ★                               | ★                         | ★                                                     | ★                                                    | ★                     | 0                                          | ★                                | 7             |
| <b>Robilotti et al 2021</b>          | ★                                    | ★                               | ★                         | ★                                                     | 0                                                    | ★                     | 0                                          | ★                                | 6             |
| <b>Seppala et al 2021</b>            | ★                                    | ★                               | ★                         | ★                                                     | ★                                                    | ★                     | 0                                          | ★                                | 7             |
| <b>Tartof et al 2021</b>             | ★                                    | ★                               | ★                         | ★                                                     | ★                                                    | ★                     | 0                                          | ★                                | 7             |

★=1 point

## Bibliography

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Accessed October 22, 2021. <https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>
2. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ*. 2020;371:m3862. doi:10.1136/bmj.m3862
3. COVID-19 Map - Johns Hopkins Coronavirus Resource Center. Accessed October 22, 2021. <https://coronavirus.jhu.edu/map.html>
4. Ball P. The lightning-fast quest for COVID vaccines - and what it means for other diseases. *Nature*. 2021;589(7840):16-18. doi:10.1038/d41586-020-03626-1
5. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med*. 2021;384(23):2187-2201. doi:10.1056/NEJMoa2101544
6. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577
7. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389
8. Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *N Engl J Med*. Published online September 29, 2021. doi:10.1056/NEJMoa2105290
9. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis*. 2021;21(1):39-51. doi:10.1016/S1473-3099(20)30831-8
10. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet*. 2021;398(10296):213-222. doi:10.1016/S0140-6736(21)01429-X
11. WHO – COVID19 Vaccine Tracker. Accessed October 25, 2021. <https://covid19.trackvaccines.org/agency/who/>

12. Thompson MG, Burgess JL, Naleway AL, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70(13):495-500. doi:10.15585/mmwr.mm7013e3
13. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ.* 2021;373:n1088. doi:10.1136/bmj.n1088
14. Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings. *N Engl J Med.* 2021;385(15):1355-1371. doi:10.1056/NEJMoA2110362
15. Harvey WT, Carabelli AM, Jackson B, et al. SARS-CoV-2 variants, spike mutations and immune escape. *Nat Rev Microbiol.* 2021;19(7):409-424. doi:10.1038/s41579-021-00573-0
16. Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *Nat Med.* 2021;27(4):622-625. doi:10.1038/s41591-021-01285-x
17. Abdool Karim SS, de Oliveira T. New SARS-CoV-2 Variants - Clinical, Public Health, and Vaccine Implications. *N Engl J Med.* 2021;384(19):1866-1868. doi:10.1056/NEJMc2100362
18. Tracking SARS-CoV-2 variants. Accessed October 28, 2021. <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>
19. Liu Q, Qin C, Liu M, Liu J. Effectiveness and safety of SARS-CoV-2 vaccine in real-world studies: a systematic review and meta-analysis. *Infect Dis Poverty.* 2021;10(1):132. doi:10.1186/s40249-021-00915-3
20. Rubin R. COVID-19 Vaccines vs Variants-Determining How Much Immunity Is Enough. *JAMA.* 2021;325(13):1241-1243. doi:10.1001/jama.2021.3370
21. CDC COVID Data Tracker. Accessed October 28, 2021. <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>
22. Liu J, Liu Y, Xia H, et al. BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants. *Nature.* 2021;596(7871):273-275. doi:10.1038/s41586-021-03693-y
23. Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med.* 2021;27(11):2032-2040. doi:10.1038/s41591-021-01540-1

24. Goldberg Y, Mandel M, Bar-On YM, et al. Waning Immunity after the BNT162b2 Vaccine in Israel. *N Engl J Med*. Published online October 27, 2021. doi:10.1056/NEJMoa2114228
25. Lipsitch M, Jha A, Simonsen L. Observational studies and the difficult quest for causality: lessons from vaccine effectiveness and impact studies. *Int J Epidemiol*. 2016;45(6):2060-2074. doi:10.1093/ije/dyw124
26. Helena VonVille, MLS, MPH | HSLS. Accessed November 3, 2021. <https://www.hslls.pitt.edu/staff/helena-vonville>
27. Ottawa Hospital Research Institute. Accessed October 28, 2021. [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
28. Sullivan SG, Tchetgen EJ, Cowling BJ. Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. *Am J Epidemiol*. 2016;184(5):345-353. doi:10.1093/aje/kww064
29. Fukushima W, Hirota Y. Basic principles of test-negative design in evaluating influenza vaccine effectiveness. *Vaccine*. 2017;35(36):4796-4800. doi:10.1016/j.vaccine.2017.07.003
30. World Health Organization. Regional Office for Europe. Cohort study to measure COVID-19 vaccine effectiveness among health workers in the WHO European Region: guidance document. Published online 2021.
31. Lewnard JA, Patel MM, Jewell NP, et al. Theoretical Framework for Retrospective Studies of the Effectiveness of SARS-CoV-2 Vaccines. *Epidemiology*. 2021;32(4):508-517. doi:10.1097/EDE.0000000000001366
32. Bajema KL, Dahl RM, Prill MM, et al. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19-Associated Hospitalization - Five Veterans Affairs Medical Centers, United States, February 1-August 6, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(37):1294-1299. doi:10.15585/mmwr.mm7037e3
33. Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(34):1167-1169. doi:10.15585/mmwr.mm7034e4
34. Glatman-Freedman A, Hershkovitz Y, Kaufman Z, Dichtiar R, Keinan-Boker L, Bromberg M. Effectiveness of BNT162b2 Vaccine in Adolescents during Outbreak of SARS-CoV-2 Delta Variant Infection, Israel, 2021. *Emerging Infect Dis*. 2021;27(11):2919-2922. doi:10.3201/eid2711.211886
35. Grannis SJ, Rowley EA, Ong TC, et al. Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19-Associated Emergency Department or Urgent Care

- Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.617.2 (Delta) Variant Predominance - Nine States, June-August 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70(37):1291-1293. doi:10.15585/mmwr.mm7037e2
36. Li X-N, Huang Y, Wang W, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. *Emerg Microbes Infect.* 2021;10(1):1751-1759. doi:10.1080/22221751.2021.1969291
  37. Robilotti EV, Whiting K, Lucca A, et al. Clinical and Genomic Characterization of SARS CoV-2 infections in mRNA Vaccinated Health Care Personnel in New York City. *Clin Infect Dis.* Published online October 13, 2021. doi:10.1093/cid/ciab886
  38. Seppälä E, Veneti L, Starrfelt J, et al. Vaccine effectiveness against infection with the Delta (B.1.617.2) variant, Norway, April to August 2021. *Euro Surveill.* 2021;26(35). doi:10.2807/1560-7917.ES.2021.26.35.2100793
  39. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet.* 2021;397(10293):2461-2462. doi:10.1016/S0140-6736(21)01358-1
  40. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet.* 2021;398(10309):1407-1416. doi:10.1016/S0140-6736(21)02183-8
  41. Pouwels KB, Pritchard E, Matthews PC, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nat Med.* Published online October 14, 2021. doi:10.1038/s41591-021-01548-7
  42. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med.* 2021;385(7):585-594. doi:10.1056/NEJMoA2108891
  43. Evaluation of COVID-19 vaccine effectiveness. Accessed November 1, 2021. [https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine\\_effectiveness-measurement-2021.1](https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1)
  44. Kow CS, Hasan SS. Real-world effectiveness of BNT162b2 mRNA vaccine: a meta-analysis of large observational studies. *Inflammopharmacology.* 2021;29(4):1075-1090. doi:10.1007/s10787-021-00839-2
  45. Teyssou E, Delagrèverie H, Visseaux B, et al. The Delta SARS-CoV-2 variant has a higher viral load than the Beta and the historical variants in nasopharyngeal samples from newly diagnosed COVID-19 patients. *J Infect.* 2021;83(4):e1-e3. doi:10.1016/j.jinf.2021.08.027