COVID VACCINES ANALYSIS

ABSTRACT:

Objective

To estimate the coronavirus disease 2019 (COVID-19) vaccine effectiveness (VE) against concerned outcomes in real-world settings.

Methods

Studies reporting COVID-19 VE from August 6, 2020 to October 6, 2021 were included. The summary VE (with 95% confidence intervals (95% CI)) against disease related to COVID-19 was estimated. The results were presented in forest plots. Predefined subgroup analyses and sensitivity analyses were also performed.

Introduction

Globally, as of October 15, 2021, there had been more than 239.4 million confirmed cases of coronavirus disease 2019 (COVID-19), including over 4.8 million deaths (WHO, 2021b). Since the outbreak of COVID-19, several vaccines have been tested and granted emergency use authorization.

Phase III trials reported high vaccine effectiveness (VE) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with these vaccines, such as 70.4% effectiveness of the ChAdOx1 nCoV-19 vaccine (AZD1222; Oxford-AstraZeneca) (Voysey et al., 2021), 95% effectiveness of the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) (Skowronski and De Serres, 2021), 94.1% effectiveness of the mRNA-1273 vaccine (Moderna) (Baden et al., 2021), and 50.7% effectiveness of an absorbed COVID-19 (inactivated) vaccine (CoronaVac) (Palacios et al., 2020).

Given that the outcomes of clinical trials may be influenced by the various study settings, it is necessary to estimate the effectiveness of vaccines rolled out to the public in real-world settings.

Recently, a series of studies have reported real-world VE from all over the world. A nationwide mass vaccination setting in Israel showed 92% effectiveness

for documented infections after the second dose of the BNT162b2 vaccine (Dagan et al., 2021).
The UK government adopted a strategy of delaying the second dose to increase the vaccine coverage, and a study suggested VE of 51.4% against SARS-CoV-2 infection after one dose of the BNT162b2 vaccine (Chodick et al., 2021).

In another study, 73% effectiveness against COVID-19 cases was observed among the elderly after vaccination with one dose of the ChAdOx1 vaccine in England (Lopez Bernal et al., 2021). In Chile, the Sinovac vaccine rolled out to the general population aged ≥16 years showed an effectiveness of 16.13% after the first dose and 66.96% after the second dose (Ministerio de Salud, 2021).

The World Health Organization (WHO) has stated that there is an urgent need to evaluate COVID-19 VE against several major outcomes, including symptomatic COVID-19, severe diseases, and death related to COVID-19 (Patel et al., 2021).

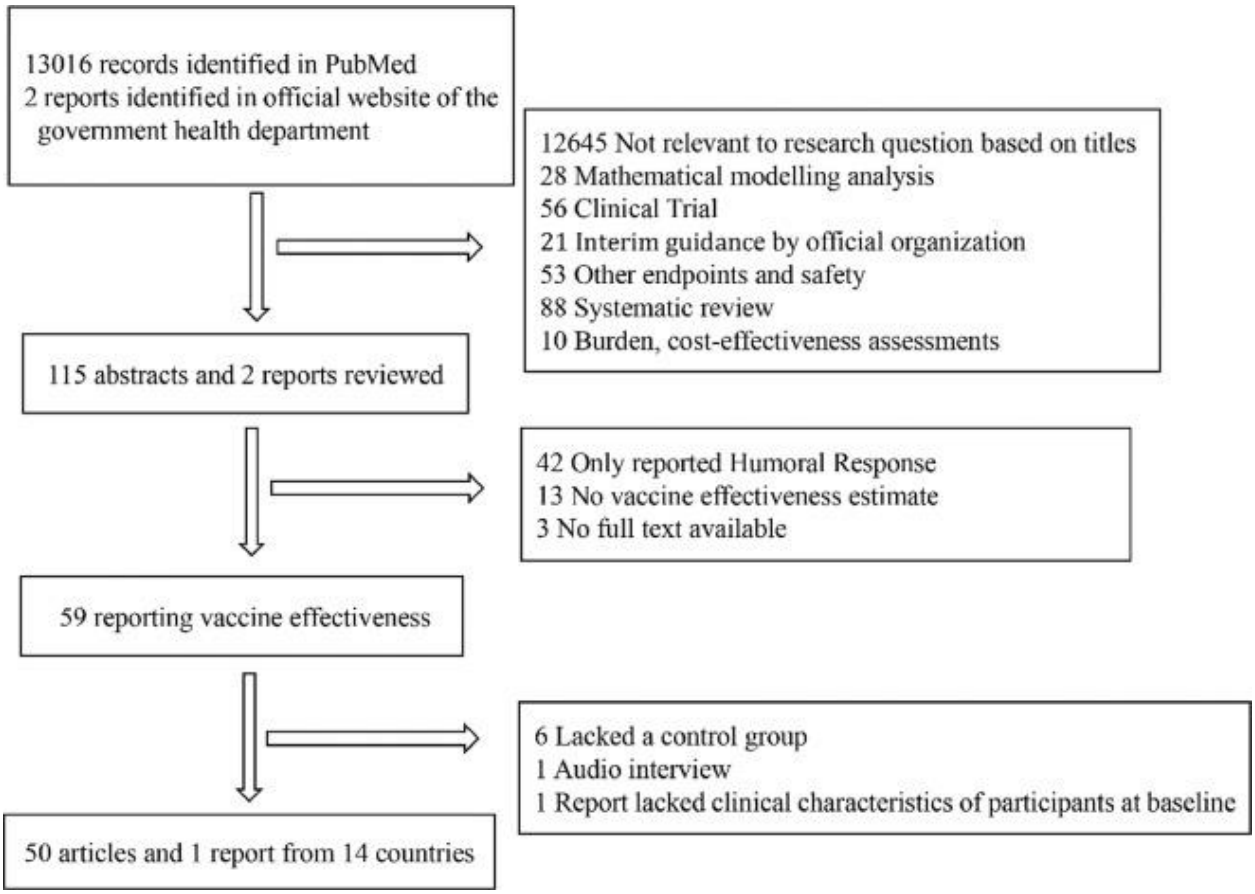
Therefore, this review and meta-analysis was conducted to estimate the COVID-19 VE against concerned outcomes in real-world settings based on the latest evidence.

Methods

Search and inclusion criteria

For this literature review and meta-analysis, a systematic search of PubMed was performed using the terms “COVID-19” or “SARS-CoV-2” and “vacc*” and “eff*” to identify articles published between August 6, 2020 (Deplanque and Launay, 2021) and October 6, 2021, from any country, reporting VE in a vaccinated population.

In addition, major news media platforms were searched to track reports from governments and health authorities around the world evaluating the effectiveness of the COVID-19 vaccine.



Observational studies (cohort, case–control, test-negative case–control) were included. Studies reporting exclusively on the immunogenicity of COVID-19 vaccine, review articles, data only in abstract form, ecological studies, and mathematical modeling analysis studies were excluded.

If two or more articles and reports presented results from the same dataset, all articles that included unique data points for the vaccine, study population, or vaccination status were included. In situations where the findings in one article were a subset of findings in another article (e.g., study sites and population), only the most comprehensive article was included in the overall analysis, but the subset was included in subgroup analyses.

At least two reviewers examined articles to confirm that the inclusion criteria were satisfied and to reach a consensus when necessary.

Data were extracted by two independent authors in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) (Page et al., 2021); the checklist is presented in **Supplementary Material** Table S1.

The following information was abstracted: the summary VE; the stratified VE estimates by COVID-19 vaccine against a range of SARS-CoV-2 outcomes, including confirmed SARS-CoV-2 infection by reverse transcription PCR (RT-PCR), and COVID-19-related hospitalization, admission to the intensive care unit (ICU)/severe or critical hospitalization, and death; vaccination status, either partially or fully vaccinated vaccine brand; study population; and study characteristics, such as the study design, study population, and sample size.

These were recorded in a Microsoft Excel database.

. Data analysis

Descriptive statistics and percentages were calculated for the article attributes. The real-world effectiveness of COVID-19 vaccines against a range of SARS-CoV-2 outcomes and according to vaccination status (partial and full vaccination), vaccinated population, and vaccine brand were estimated.

Estimates of VE expressed as a percentage (%) with their 95% confidence intervals (95% CI) were derived from the effect measures (odds ratio, relative risk, hazard ratio, and incidence rate ratio) using the following equation:
VE = [1 − effect measure] × 100. A VE estimate >0% suggests a protective effect. The results were presented in forest plots.

The heterogeneity of outcomes across studies was assessed with the I^2 statistic and was quantified as low (≤25%), moderate (25–50%), or high (>50%). A random-effects model was used if the I^2 statistic for the data was >25%. Otherwise, a fixed-effects model was chosen. Stratified meta-analyses were conducted to explore potential sources of study heterogeneity.

The Newcastle–Ottawa scale (NOS) (range from 0 to 9 points) was used to assess the quality of the included observational studies; a higher total NOS score suggests better quality (Wells et al., 2011). The influence of the inclusion of a study on the results of the meta-analyses was assessed by sensitivity analysis. Additionally, Egger's test and a funnel plot of the standard error were used to

evaluate publication bias in analyses with 10 or more included articles. Analyses were conducted in R software (version 4.1.0; R Foundation) using the metafor package for meta-analyses

. Characteristics of the studies

A total of 13 018 records were identified and screened in the literature review; 13 016 were identified in PubMed and two reports were from the official website of a government health department.

As shown in Figure 1, 13 018 records were identified. In the preliminary review, 12901 were excluded because 12 645 were not relevant to research question based on titles, 28 were mathematical modelling analysis, 56 were clinical trial, 21 were interim guidance by official organization, 53 were other enpoints and safety, 88 were systematic review, and 10 were costeffectiveness assessments.

Therefore, 115 abstracts and 2 reports remained to be reviewed. Fifty-nine articles were then read in full, of which seven were excluded because they did not meet the methodological inclusion criteria.

One report did not provide information on the time span of vaccination or the age and health status of the vaccinated persons, and was therefore also excluded. In total, 50 articles and one report were included from 14 countries, involving 38 821 141 individuals.

All of the included articles were published in 2021 and reported studies of high quality (NOS score ranging from 5 to 8) (, eight were test-negative case–control studies, and four were case–control studies.

The included studies investigated five brands of COVID-19 vaccine: Pfizer-BioNTech (46 articles), Moderna (19 articles), Oxford-AstraZeneca (10 articles), CoronaVac (5 articles), and Janssen (Johnson & Johnson) (1 article).

Most articles presented VE estimation for fully vaccinated and partially vaccinated individuals (34 articles, 66.7%); 11 articles (21.6%) only presented effectiveness in partially vaccinated individuals.

Vaccine effectiveness for full vaccination

The effectiveness of COVID-19 vaccines against a range of SARS-CoV-2 outcomes was estimated. A total of 35 articles reported VE against SARS-CoV-2 infection among fully vaccinated people, and the summary VE was 89.1% (95% CI 85.6–92.6%) for the prevention of SARS-CoV-2 infection

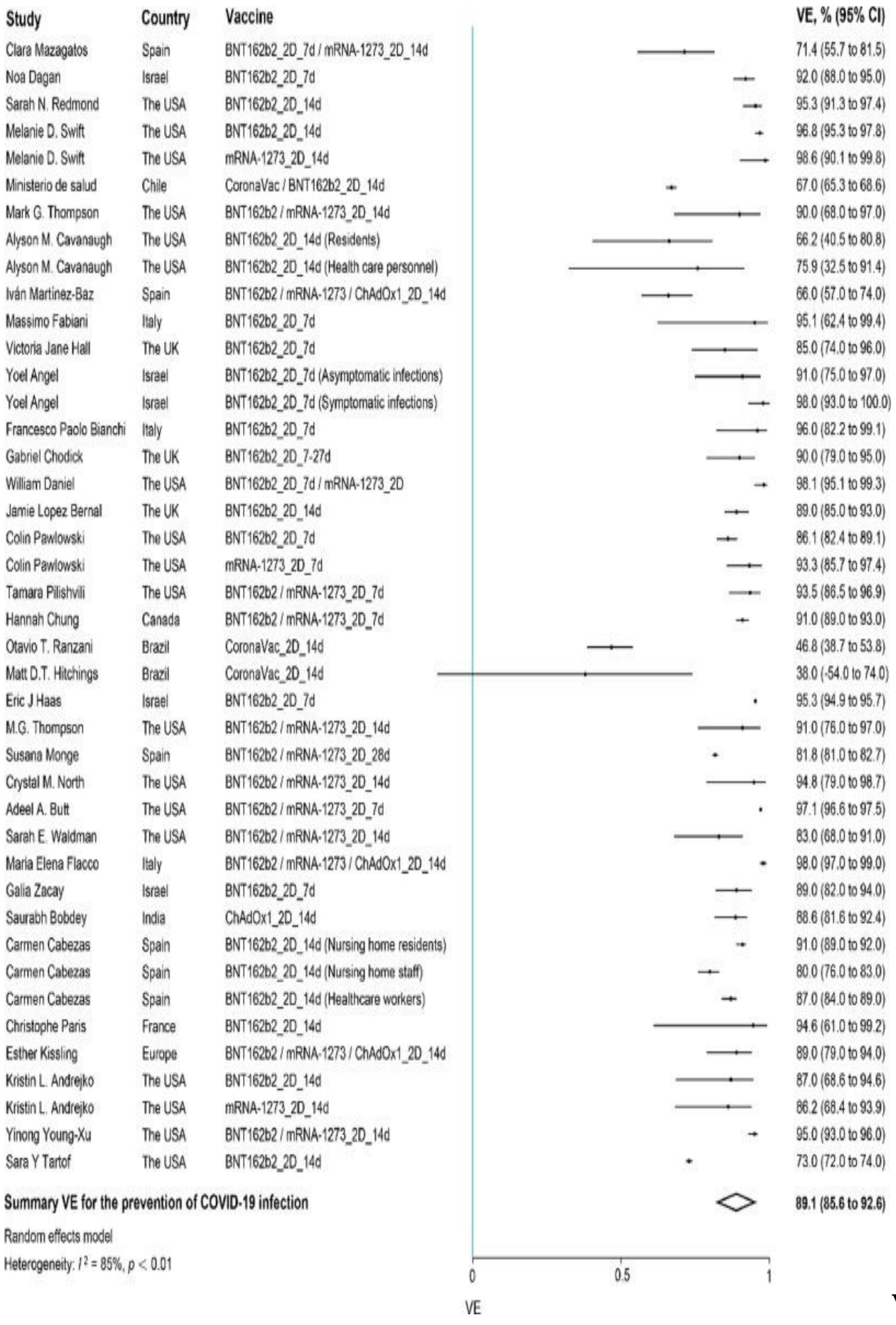
In addition, 15 of the included studies estimated VE against COVID-19-related hospitalization, four studies estimated VE against COVID-19-related ICU admission or severe disease, and eight studies estimated VE against COVID-19-related death.

The results showed 97.2% VE (95% CI 96.1–98.3%) for the prevention of hospitalization, 97.4% VE (95% CI 96.0–98.8%) for the prevention of ICU admission or severe disease, and 99.0% VE (95% CI 98.5–99.6%) for the prevention of COVID-19-related death

The Egger's test and funnel plots showed no publication bias for the VE against SARS-CoV-2 infection (*t*-value of Egger's test = −2.91, *P* = 0.0988) among fully vaccinated individuals, while there was publication bias of the VE against COVID-19-related hospitalization .

After correcting for publication bias with trim and fill methods, the summary VE against COVID-19-related hospitalization among fully vaccinated individuals was 97.2% (95% CI 94.4–100.0%) .

The sensitivity analysis suggested lower VE against COVID-19-related hospitalization (93.0%, 95% CI 91.0–96.0%) and ICU admission and severe disease (89.0%, 95% CI 76.0–100.0%) when deleting the results of the study conducted by Haas et al.


Study
Country
Vaccine
VE, % (95% CI)
Clara Mazagatos
Spain
BNT162b2_2D_7d / mRNA-1273_2D_14d
71.4 (55.7 to 81.5)
Noa Dagan
Israel
BNT162b2_2D_7d
92.0 (88.0 to 95.0)
Sarah N. Redmond
The USA
BNT162b2_2D_14d
95.3 (91.3 to 97.4)
Melanie D. Swift
The USA
BNT162b2_2D_14d
96.8 (95.3 to 97.8)
Melanie D. Swift
The USA
mRNA-1273_2D_14d
98.6 (90.1 to 99.8)
Ministerio de salud
Chile
CoronaVac / BNT162b2_2D_14d
67.0 (65.3 to 68.6)
Mark G. Thompson
The USA
BNT162b2 / mRNA-1273_2D_14d
90.0 (68.0 to 97.0)
Alyson M. Cavanaugh
The USA
BNT162b2_2D_14d (Residents)
66.2 (40.5 to 80.8)
Alyson M. Cavanaugh
The USA
BNT162b2_2D_14d (Health care personnel)
75.9 (32.5 to 91.4)
Iván Martínez-Baz
Spain
BNT162b2 / mRNA-1273 / ChAdOx1_2D_14d
66.0 (57.0 to 74.0)
Massimo Fabiani
Italy
BNT162b2_2D_7d
95.1 (62.4 to 99.4)
Victoria Jane Hall
The UK
BNT162b2_2D_7d
85.0 (74.0 to 96.0)
Yoel Angel
Israel
BNT162b2_2D_7d (Asymptomatic infections)
91.0 (75.0 to 97.0)
Yoel Angel
Israel
BNT162b2_2D_7d (Symptomatic infections)
98.0 (93.0 to 100.0)
Francesco Paolo Bianchi
Italy
BNT162b2_2D_7d
96.0 (82.2 to 99.1)
Gabriel Chodick
The UK
BNT162b2_2D_7-27d
90.0 (79.0 to 95.0)
William Daniel
The USA
BNT162b2_2D_7d / mRNA-1273_2D
98.1 (95.1 to 99.3)
Jamie Lopez Bernal
The UK
BNT162b2_2D_14d
89.0 (85.0 to 93.0)
Colin Pawlowski
The USA
BNT162b2_2D_7d
86.1 (82.4 to 89.1)
Colin Pawlowski
The USA
mRNA-1273_2D_7d
93.3 (85.7 to 97.4)
Tamara Pilishvili
The USA
BNT162b2 / mRNA-1273_2D_7d
93.5 (86.5 to 96.9)
Hannah Chung
Canada
BNT162b2 / mRNA-1273_2D_7d
91.0 (89.0 to 93.0)
Otavio T. Ranzani
Brazil
CoronaVac_2D_14d
46.8 (38.7 to 53.8)
Matt D.T. Hitchings
Brazil
CoronaVac_2D_14d
38.0 (-54.0 to 74.0)
Eric J Haas
Israel
BNT162b2_2D_7d
95.3 (94.9 to 95.7)
M.G. Thompson
The USA
BNT162b2 / mRNA-1273_2D_14d
91.0 (76.0 to 97.0)
Susana Monge
Spain
BNT162b2 / mRNA-1273_2D_28d
81.8 (81.0 to 82.7)
Crystal M. North
The USA
BNT162b2 / mRNA-1273_2D_14d
94.8 (79.0 to 98.7)
Adeel A. Butt
The USA
BNT162b2 / mRNA-1273_2D_7d
97.1 (96.6 to 97.5)
Sarah E. Waldman
The USA
BNT162b2 / mRNA-1273_2D_14d
83.0 (68.0 to 91.0)
Maria Elena Flacco
Italy
BNT162b2 / mRNA-1273 / ChAdOx1_2D_14d
98.0 (97.0 to 99.0)
Galia Zacay
Israel
BNT162b2_2D_7d
89.0 (82.0 to 94.0)
Saurabh Bobdey
India
ChAdOx1_2D_14d
88.6 (81.6 to 92.4)
Carmen Cabezas
Spain
BNT162b2_2D_14d (Nursing home residents)
91.0 (89.0 to 92.0)
Carmen Cabezas
Spain
BNT162b2_2D_14d (Nursing home staff)
80.0 (76.0 to 83.0)
Carmen Cabezas
Spain
BNT162b2_2D_14d (Healthcare workers)
87.0 (84.0 to 89.0)
Christophe Paris
France
BNT162b2_2D_14d
94.6 (61.0 to 99.2)
Esther Kissling
Europe
BNT162b2 / mRNA-1273 / ChAdOx1_2D_14d
89.0 (79.0 to 94.0)
Kristin L. Andrejko
The USA
BNT162b2_2D_14d
87.0 (68.6 to 94.6)
Kristin L. Andrejko
The USA
mRNA-1273_2D_14d
86.2 (68.4 to 93.9)
Yinong Young-Xu
The USA
BNT162b2 / mRNA-1273_2D_14d
95.0 (93.0 to 96.0)
Sara Y Tartof
The USA
BNT162b2_2D_14d
73.0 (72.0 to 74.0)
Summary VE for the prevention of COVID-19 infection
89.1 (85.6 to 92.6)
Random effects model
Heterogeneity: I^2 = 85%, p < 0.01
0
0.5
1
VE
Vaccine

Effectiveness for partial vaccination

Regarding individuals with a partial immunization status, 38 included studies reported VE against SARS-CoV-2 infection, 12 reported VE against COVID-19-related hospitalization, three reported VE against COVID-19-related ICU admission or severe disease, and eight reported VE against COVID-19-related death.

The summary VE was 68.8% (95% CI 60.1–77.5%) for the prevention of SARS-CoV-2 infection and 67.8% (95% CI 51.6–83.9%) for the prevention of hospitalization, 66.4% (95% CI 25.9–100.0%) for the prevention of admission to the ICU and severe disease, and 58.4% (95% CI 28.0–88.7%) for the prevention of COVID-19-related death .

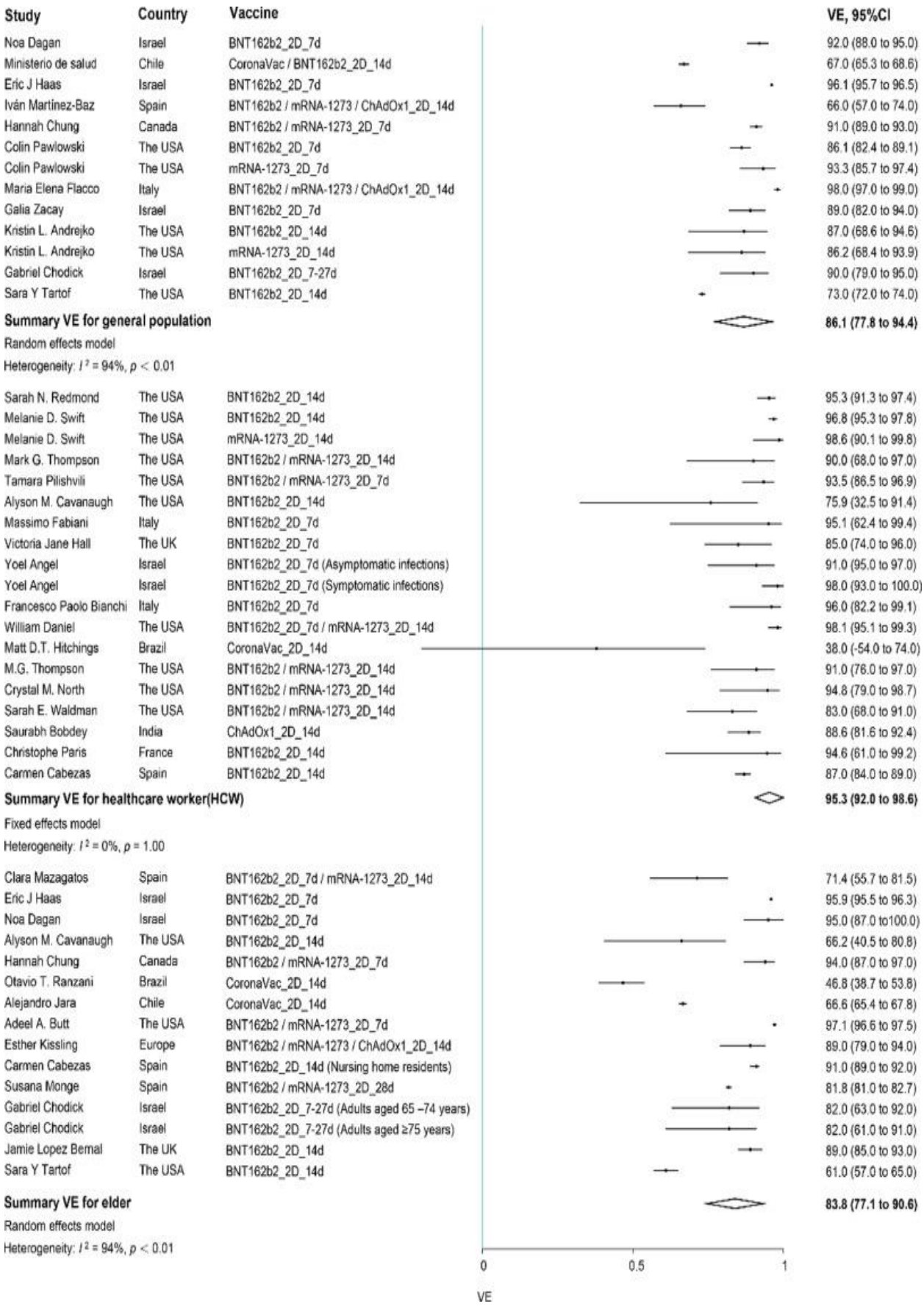
The Egger's test and funnel plots suggested no publication bias of the VE against SARS-CoV-2 infection (*t*-value of Egger's test = −1.31, *P* = 0.1956) or hospitalization (*t*-value of Egger's test = −0.28, *P* = 0.7839) for partially vaccinated individuals .

The sensitivity analysis suggested higher VE against SARS-CoV-2 infection (75.0%, 95% CI 71.0–80.0%) among the partially vaccinated individuals when deleting the results of the CoronaVac vaccine study from Chile reported by the Ministerio de Salud (Ministerio de Salud, 2021)

Subgroup analyses

The COVID-19 VE for the prevention of SARS-CoV-2 infection confirmed by RT-PCR was estimated in fully vaccinated individuals in different populations.

An analysis in the predefined subgroups of the elderly (age ≥60 years), healthcare workers (HCWs), and the general population (adults ≥16 years) was conducted.


Study
Country
Vaccine
VE, 95%CI
Noa Dagan Israel BNT162b2_2D_7d 92.0 (88.0 to 95.0)
Ministerio de salud Chile CoronaVac / BNT162b2_2D_14d 67.0 (65.3 to 68.6)
Eric J Haas Israel BNT162b2_2D_7d 96.1 (95.7 to 96.5)
Iván Martínez-Baz Spain BNT162b2 / mRNA-1273 / ChAdOx1_2D_14d 66.0 (57.0 to 74.0)
Hannah Chung Canada BNT162b2 / mRNA-1273_2D_7d 91.0 (89.0 to 93.0)
Colin Pawlowski The USA BNT162b2_2D_7d 86.1 (82.4 to 89.1)
Colin Pawlowski The USA mRNA-1273_2D_7d 93.3 (85.7 to 97.4)
Maria Elena Flacco Italy BNT162b2 / mRNA-1273 / ChAdOx1_2D_14d 98.0 (97.0 to 99.0)
Galia Zacay Israel BNT162b2_2D_7d 89.0 (82.0 to 94.0)
Kristin L. Andrejko The USA BNT162b2_2D_14d 87.0 (68.6 to 94.6)
Kristin L. Andrejko The USA mRNA-1273_2D_14d 86.2 (68.4 to 93.9)
Gabriel Chodick Israel BNT162b2_2D_7-27d 90.0 (79.0 to 95.0)
Sara Y Tartof The USA BNT162b2_2D_14d 73.0 (72.0 to 74.0)
Summary VE for general population 86.1 (77.8 to 94.4)
Random effects model
Heterogeneity: I^2 = 94%, p < 0.01
Sarah N. Redmond The USA BNT162b2_2D_14d 95.3 (91.3 to 97.4)
Melanie D. Swift The USA BNT162b2_2D_14d 96.8 (95.3 to 97.8)
Melanie D. Swift The USA mRNA-1273_2D_14d 98.6 (90.1 to 99.8)
Mark G. Thompson The USA BNT162b2 / mRNA-1273_2D_14d 90.0 (68.0 to 97.0)
Tamara Pilishvili The USA BNT162b2 / mRNA-1273_2D_7d 93.5 (86.5 to 96.9)
Alyson M. Cavanaugh The USA BNT162b2_2D_14d 75.9 (32.5 to 91.4)
Massimo Fabiani Italy BNT162b2_2D_7d 95.1 (62.4 to 99.4)
Victoria Jane Hall The UK BNT162b2_2D_7d 85.0 (74.0 to 96.0)
Yoel Angel Israel BNT162b2_2D_7d (Asymptomatic infections) 91.0 (95.0 to 97.0)
Yoel Angel Israel BNT162b2_2D_7d (Symptomatic infections) 98.0 (93.0 to 100.0)
Francesco Paolo Bianchi Italy BNT162b2_2D_7d 96.0 (82.2 to 99.1)
William Daniel The USA BNT162b2_2D_7d / mRNA-1273_2D_14d 98.1 (95.1 to 99.3)
Matt D.T. Hitchings Brazil CoronaVac_2D_14d 38.0 (-54.0 to 74.0)
M.G. Thompson The USA BNT162b2 / mRNA-1273_2D_14d 91.0 (76.0 to 97.0)
Crystal M. North The USA BNT162b2 / mRNA-1273_2D_14d 94.8 (79.0 to 98.7)
Sarah E. Waldman The USA BNT162b2 / mRNA-1273_2D_14d 83.0 (68.0 to 91.0)
Saurabh Bobdey India ChAdOx1_2D_14d 88.6 (81.6 to 92.4)
Christophe Paris France BNT162b2_2D_14d 94.6 (61.0 to 99.2)
Carmen Cabezas Spain BNT162b2_2D_14d 87.0 (84.0 to 89.0)
Summary VE for healthcare worker(HCW) 95.3 (92.0 to 98.6)
Fixed effects model
Heterogeneity: I^2 = 0%, p = 1.00
Clara Mazagatos Spain BNT162b2_2D_7d / mRNA-1273_2D_14d 71.4 (55.7 to 81.5)
Eric J Haas Israel BNT162b2_2D_7d 95.9 (95.5 to 96.3)
Noa Dagan Israel BNT162b2_2D_7d 95.0 (87.0 to100.0)
Alyson M. Cavanaugh The USA BNT162b2_2D_14d 66.2 (40.5 to 80.8)
Hannah Chung Canada BNT162b2 / mRNA-1273_2D_7d 94.0 (87.0 to 97.0)
Otavio T. Ranzani Brazil CoronaVac_2D_14d 46.8 (38.7 to 53.8)
Alejandro Jara Chile CoronaVac_2D_14d 66.6 (65.4 to 67.8)
Adeel A. Butt The USA BNT162b2 / mRNA-1273_2D_7d 97.1 (96.6 to 97.5)
Esther Kissling Europe BNT162b2 / mRNA-1273 / ChAdOx1_2D_14d 89.0 (79.0 to 94.0)
Carmen Cabezas Spain BNT162b2_2D_14d (Nursing home residents) 91.0 (89.0 to 92.0)
Susana Monge Spain BNT162b2 / mRNA-1273_2D_28d 81.8 (81.0 to 82.7)
Gabriel Chodick Israel BNT162b2_2D_7-27d (Adults aged 65 –74 years) 82.0 (63.0 to 92.0)
Gabriel Chodick Israel BNT162b2_2D_7-27d (Adults aged ≥75 years) 82.0 (61.0 to 91.0)
Jamie Lopez Bernal The UK BNT162b2_2D_14d 89.0 (85.0 to 93.0)
Sara Y Tartof The USA BNT162b2_2D_14d 61.0 (57.0 to 65.0)
Summary VE for elder 83.8 (77.1 to 90.6)
Random effects model
Heterogeneity: I^2 = 94%, p < 0.01
0
0.5
1
VE

Discussion

This review, including 51 up-to-date studies from 14 countries, reporting on the effectiveness of COVID-19 vaccines, provides estimates of the VE against disease with laboratory-confirmed SARS-CoV-2 infection, and COVID-19-related hospitalization, admission to the ICU, and death.

Estimates of VE against infection in subgroup analyses for vaccine brand, vaccinated population, and vaccination status are presented. The results suggest that the vaccines currently approved for use have a good protective effect against the major outcomes related to COVID-19, especially for critical outcomes.

It was noted that there was high heterogeneity for the summary VE against SARS-CoV-2 infection among fully vaccinated individuals. In addition to the actual effectiveness of the different vaccines, the evaluation of population effectiveness depends on a series of factors, such as the vaccinated population, the severity of the epidemic, the completeness and validity of the data sources, study design, and potential methodological biases (Patel et al., 2021).

Therefore, subgroup and sensitivity analyses were performed to explore the potential heterogeneity. Consistent with the results of phase III clinical trials, the effectiveness of different vaccines against confirmed infection in real-world conditions varied.

Synthesized evidence from different study settings showed 91.2%, 98.1%, and 65.7% effectiveness of the Pfizer-BioNTech vaccine, Moderna vaccine, and CoronaVac vaccine, respectively. For full vaccination, lower VE against COVID-19-related hospitalization and severe disease were observed when deleting the results of the study conducted by Haas et al. (Haas et al., 2021).

This study, with a high quality score, revealed that two doses of BNT162b2 were highly effective across all age groups in Israel, based on nationwide surveillance data. The sensitivity analysis showed higher VE after omitting the results of the CoronaVac vaccine.

The VE of CoronaVac, an inactivated whole virus vaccine, may be influenced in the setting of high SARS-CoV-2 Gamma variant transmission, whether in Brazil or Chile .

Similarly, VE is closely related to vaccination status. Subgroup analysis by vaccination status revealed 66.8%, 67.8%, 66.4%, and 58.4% effectiveness of

partial vaccination against disease with confirmed SARS-CoV-2 infection, COVID-19-related hospitalization, ICU admission/severe disease, and death, respectively, despite being less effective than full vaccination.

Moreover, several studies have shown higher VE for longer periods of time since vaccination, whether for partial or full Given the highest mortality observed in the elderly in long-term care facilities and higher exposure risk for HCWs many countries have prioritized both of these high-risk groups for vaccination

However, elderly patients have been less represented in clinical trials, which have mainly enrolled young populations .

In this study, we synthesized real-world evidence by vaccinated population. The most protective effect was seen in the HCWs (VE = 95.3%), while less VE was observed in the elderly (VE = 83.8%). Due to immunosenescence and comorbidities, the elderly are more susceptible to infections and have poorer responses to vaccination

Ciabattini et al., 2018; Frasca et al., 2010; McElhaney et al., 2013). Therefore, beyond vaccination, more measures for the elderly need to be implemented to reduce the severe outcomes related to infections and control the transmission in care facilities.

There are some limitations to this meta-analysis. Firstly, it was not possible to estimate the long-term effectiveness of vaccines due to the limited length of follow-up.

In the Mayo Clinic health system, the effectiveness after the second dose of the Pfizer-BioNTech vaccine or the Moderna vaccine increased from 53.6% (95% CI 40.9–63.8%) in the first week to 92.5% (95% CI 70.2–99.1%) in the sixth week (Pawlowski et al., 2021). Based on available evidence, there is increased VE within 6 weeks after full vaccination, but it is difficult to reveal the peak effectiveness and actual duration of immunization protection.

Secondly, the VE against infectiousness to others was not estimated. A retrospective cohort study in the USA suggested 80.0% (95% CI 91.0–56.0%)

effectiveness against infectiousness to others after the second dose of the Pfizer-BioNTech vaccine .

In addition, a single dose of the Moderna vaccine was estimated to reduce the potential transmission to others by 61.0% (95% CI 31.0–79.0%) (Lipsitch and Kahn, 2021).

The vaccine could reduce the risk of transmission, but further studies are needed to assess the actual VE for every vaccine.

Thirdly, the emergence of SARS-CoV-2 variants has resulted in an increase in severe infections (Gomez et al., 2021). Four dominant variants of concern (VOCs) are B.1.1.7 (Alpha, UK, Sep-2020), B.1.351 (Beta, South Africa, May-2020), P.1 (Gamma, Brazil, Nov-2020), and B.1.617.2 (Delta, India, Oct-2020) (WHO, 2021a). Several clinical trials have reported the vaccine effectiveness against variants (Haas et al., 2021).

There was no effectiveness against mild-to-moderate COVID-19 due to the B.1.351 variant (VE = 21.9%, 95% CI −49.9% to 59.8%) after two doses of the ChAdOx1 nCoV-19 vaccine (Madhi et al., 2021). Nevertheless, two doses of the Pfizer-BioNTech vaccine showed 87.0% (95% CI 81.8–90.7%) effectiveness against the B.1.1.7 variant and 72.1% (95% CI 66.4–76.8%) against the B.1.351 variant (Abu-Raddad et al., 2021).

Moreover, the VE for two doses of CoronaVac vaccine was 59.0% (95% CI 16.0–81.6%) against the B.1.617.2 variant (Li et al., 2021). A single dose of the Ad26.COV2.S also showed 68.1% (95% CI 48.8–80.7%) effectiveness against the P.1 variant to prevent moderate-to-severe COVID-19 (Sadoff et al., 2021). The estimates of VE against SARS-CoV-2 variants in real-world settings are scarce, so it was not possible to evaluate VE with the variants. This needs to examined in future studies.

Studies in the real-world setting around the world have shown that the approved vaccines are highly protective against SARS-CoV-2; therefore, the aim should be full vaccination according to the standard schedule to achieve maximum VE. It is worth noting that vaccination cannot eliminate the risk of infection (Brosh-Nissimov et al., 2021), and preventive and control measures should be taken seriously, especially for high-risk groups.

In conclusion, consistent with the results of phase III clinical trials, the authorized vaccines are highly protective against SARS-CoV-2 in real-world settings. Furthermore, the actual VE depends not only on the effectiveness of the vaccine itself but also on the vaccinated population and status. Preventive measures remain essential.

Acknowledgements

The authors are very thankful to everyone who participated in this study.

Declarations

Funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Ethical approval: This study did not require ethical approval because the meta-analysis is based on published research, and the original data are anonymous.

Statistical Analysis

Descriptive statistics including mean, SD, median, and IQR are used to describe baseline characteristics and questionnaire responses. For baseline characteristics and survey responses, differences in characteristics were examined with a *t* test or Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables.

A multivariable logistic regression model was constructed to identify factors associated with any adverse effects

Given that vaccination and adverse effects were queried monthly, participants could report 2 doses of vaccine in 1 survey. When participants reported 2 doses of vaccine in a monthly survey, the reported adverse effects were associated with the second vaccine dose.

Candidate factors in the multivariable models included age (as a continuous variable, per 10 years), sex assigned at birth (female or all others), race (Asian, Black or African American, multiracial,

White, or other), Hispanic ethnicity, subjective social status, medical conditions influenza shot in the past year, current tobacco use, current marijuana use, COVID-19 prior to vaccination, vaccine dose, and vaccine brand (BNT162b2, mRNA-1273, or JNJ-78436735).

A separate multivariable logistic regression model was constructed to identify factors associated with severe or very severe adverse effects (vs no, very mild, mild, or moderate adverse effects) using the same candidate factors. We conducted an exploratory analysis of adverse effects in participants with asthma with and without use of inhaled corticosteroids.

Statistical significance was considered to be $P < .05$, and all tests were 2-tailed. All analyses were conducted with SAS version 9.4 .

limitations

This study has limitations. Although the digital cohort study did include people from diverse groups, some groups, such as men, older adults, people belonging to minoritized racial and ethnic groups, rural residents, people reporting lower subjective social status, and non-US residents, are underrepresented, which may limit generalizability to all groups or populations outside of the United States.

Given the online nature of the study, not all participants responded to all surveys.

This may contribute to both measurement bias through undermeasurement of vaccine receipt or COVID-19 diagnosis and selection bias if participants from different groups or participants with adverse effects responded differentially to surveys.

In previous studies, we found that self-reported COVID-19 test results appeared to accurately reflect COVID-19 diagnosis.

Additionally, administration of surveys on a monthly basis could lead to measurement bias through inaccurate reporting of vaccine-related adverse effects.

Because this study included data until May 19, 2021, this reflects the early experience with vaccination, and results could differ in later time periods or with other vaccines.

Code:

```
from cowin_api import CoWinAPI

from pprint import pprint

cowin = CoWinAPI()

states = cowin.get_states()

print("All States List : ")

print(states)
```

Output:

```
All States List :
{'states': [{'state_id': 1, 'state_name': 'Andaman and Nicobar Islands'},
            {'state_id': 2, 'state_name': 'Andhra Pradesh'},
            {'state_id': 3, 'state_name': 'Arunachal Pradesh'},
            {'state_id': 4, 'state_name': 'Assam'},
            {'state_id': 5, 'state_name': 'Bihar'},
            {'state_id': 6, 'state_name': 'Chandigarh'},
            {'state_id': 7, 'state_name': 'Chhattisgarh'},
            {'state_id': 8, 'state_name': 'Dadra and Nagar Haveli'},
            {'state_id': 37, 'state_name': 'Daman and Diu'},
            {'state_id': 9, 'state_name': 'Delhi'},
            {'state_id': 10, 'state_name': 'Goa'},
            {'state_id': 11, 'state_name': 'Gujarat'},
            {'state_id': 12, 'state_name': 'Haryana'},
            {'state_id': 13, 'state_name': 'Himachal Pradesh'},
            {'state_id': 14, 'state_name': 'Jammu and Kashmir'},
            {'state_id': 15, 'state_name': 'Jharkhand'},
            {'state_id': 16, 'state_name': 'Karnataka'},
            {'state_id': 17, 'state_name': 'Kerala'},
            {'state_id': 18, 'state_name': 'Ladakh'},
            {'state_id': 19, 'state_name': 'Lakshadweep'},
            {'state_id': 20, 'state_name': 'Madhya Pradesh'},
            {'state_id': 21, 'state_name': 'Maharashtra'},
            {'state_id': 22, 'state_name': 'Manipur'},
            {'state_id': 23, 'state_name': 'Meghalaya'},
            {'state_id': 24, 'state_name': 'Mizoram'},
            {'state_id': 25, 'state_name': 'Nagaland'},
            {'state_id': 26, 'state_name': 'Odisha'},
            {'state_id': 27, 'state_name': 'Puducherry'},
            {'state_id': 28, 'state_name': 'Punjab'},
            {'state_id': 29, 'state_name': 'Rajasthan'},
            {'state_id': 30, 'state_name': 'Sikkim'},
            {'state_id': 31, 'state_name': 'Tamil Nadu'},
            {'state_id': 32, 'state_name': 'Telangana'},
            {'state_id': 33, 'state_name': 'Tripura'},
            {'state_id': 34, 'state_name': 'Uttar Pradesh'},
            {'state_id': 35, 'state_name': 'Uttarakhand'},
            {'state_id': 36, 'state_name': 'West Bengal'}],
 'ttl': 24}
```

Getting all districts in a State

Here we will use get_districts(), which return the district name, pass the integer into the get_districts(). get_districts(state_id) takes state id returned from above API, as param and returns all districts with their IDs.

Code:

```
from cowin_api import CoWinAPI

from pprint import pprint


Cowin = CoWinAPI()

state_id = '24'


districts = cowin.get_districts(state_id

)


print("Districts by State Id : ")
```

Output :

```
Districts by State Id :
{'districts': [{'district_id': 425, 'district_name': 'Aizawl East'},
               {'district_id': 426, 'district_name': 'Aizawl West'},
               {'district_id': 429, 'district_name': 'Champhai'},
               {'district_id': 428, 'district_name': 'Kolasib'},
               {'district_id': 432, 'district_name': 'Lawngtlai'},
               {'district_id': 431, 'district_name': 'Lunglei'},
               {'district_id': 427, 'district_name': 'Mamit'},
               {'district_id': 430, 'district_name': 'Serchhip'},
               {'district_id': 433, 'district_name': 'Siaha'}],
 'ttl': 24}
```

Getting all centers with Availability Information in District

Here we will get the center information in the district, get_availability_by_district() methods are able to return all the center information within the district.

Syntax:

get_availability_by_district(district_id, date, min_age_limit)

Parameters :

district_id : ID obtained using above API.

date(optional) : Date in dd-mm-YYYY format. Defaults totoday.

min_age_limit(optional) : Minimum age to be queried, sinceslots get open in different age group brackets. If not given

ages are used as filter.

Code:

```
from cowin_api import CoWinAPI

from pprint import pprint

cowin = CoWinAPI()

district_id = '425'

date = '14-05-2021'

available_centers = cowin.get_availability_by_district(district_id, date)

print("All Available Centers [ By district ] : ")

pprint(available_centers)
```

Output:

```
All Available Centers [ By district ] :
{'centers': [{'address': 'BawngkawnAizawl',
              'block_name': 'Tlangnuam RD Block',
              'center_id': 597224,
              'district_name': 'Aizawl East',
              'fee_type': 'Free',
              'from': '10:00:00',
              'lat': 23,
              'long': 92,
              'name': 'Bawngkawn South YMA Hall',
              'pincode': 796014,
              'sessions': [{'available_capacity': 0,
                            'date': '14-05-2021',
                            'min_age_limit': 45,
                            'session_id': '0b6273aa-363c-4aba-8e0a-77d6c637a1da',
                            'slots': ['10:00AM-12:00PM',
                                      '12:00PM-02:00PM',
                                      '02:00PM-04:00PM',
                                      '04:00PM-05:00PM'],
                            'vaccine': 'COVISHIELD'}],
              'state_name': 'Mizoram',
              'to': '17:00:00'},
             {'address': 'Dawrpui',
              'block_name': 'Tlangnuam RD Block',
              'center_id': 591640,
              'district_name': 'Aizawl East',
              'fee_type': 'Free',
              'from': '10:00:00',
              'lat': 23,
              'long': 92,
              'name': 'Dawrpui Multipurpose Hall 1',
              'pincode': 796001,
              'sessions': [{'available_capacity': 0,
                            'date': '14-05-2021',
                            'min_age_limit': 45,
                            'session_id': 'a30a73e4-c9fb-407e-bdc9-70d432d7e484',
                            'slots': ['10:00AM-12:00PM',
                                      '12:00PM-02:00PM',
                                      '02:00PM-04:00PM',
                                      '04:00PM-05:00PM'],
                            'vaccine': 'COVISHIELD'}],
              'state_name': 'Mizoram',
              'to': '17:00:00'}]}
```

Getting all centers with Availability Information by Pincode

Here we will get all the center availability info according to Pincode, get_availability_by_pincode are able to return the center information byPincode.

Syntax:

get_availability_by_pincode(pin_code, date, min_age_limit)

Parameter:

- *pin_code : Pincode of area to find centers.*
- *date(optional) : Date in dd-mm-YYYY format. Defaults to today.*
- *min_age_limit(optional) : Minimum age to be queried, since slots get open in different age group brackets. If not given, all ages are used asfilter.*

Code:

```
from cowin_api import CoWinAPI

from pprint import pprint

cowin = CoWinAPI()

pin_code = "796014"

date = '14-05-2021'

min_age_limit = 18

available_centers = cowin.get_availability_by_pinco+de(pin_code, date)
```

```
print("All Available Centers [ By Pincode ] : ")

pprint(available_centers)
```

Output:

```
All Available Centers [ By Pincode ] :
{'centers': [{'address': 'BawngkawnAizawl',
              'block_name': 'Tlangnuam RD Block',
              'center_id': 597224,
              'district_name': 'Aizawl East',
              'fee_type': 'Free',
              'from': '10:00:00',
              'lat': 23,
              'long': 92,
              'name': 'Bawngkawn South YMA Hall',
              'pincode': 796014,
              'sessions': [{'available_capacity': 0,
                            'date': '14-05-2021',
                            'min_age_limit': 45,
                            'session_id': '0b6273aa-363c-4aba-8e0a-77d6c637a1da',
                            'slots': ['10:00AM-12:00PM',
                                      '12:00PM-02:00PM',
                                      '02:00PM-04:00PM',
                                      '04:00PM-05:00PM'],
                            'vaccine': 'COVISHIELD'}],
              'state_name': 'Mizoram',
              'to': '17:00:00'}]}
```

Code:

```
plt.figure(figsize=(16,10))
ax = sns.barplot(x=fully_vaccinated, y=fully_vaccinated.index)
plt.xlabel("Fully Vaccinated")
plt.ylabel("Country");
plt.title('Which country has most number of fully vaccinated people?');

for patch  in ax.patches: width
    = patch.get_width() height =
    patch.get_height()x =
    patch.get_x()
    y = patch.get_y()
    plt.text(width + x, height + y, '{:.1f} '.format (width))
```

Results

The 19 586 participants had a median (IQR) age of 54 (38-66) years, and 13 420 (68.8%) were women.

Allergic reaction or anaphylaxis was reported in 26 of 8680 participants (0.3%) after 1 dose of the BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) vaccine, 27 of 11 141 (0.2%) after 2 doses of the BNT162b2 or mRNA-1273 vaccine or 1 dose of the JNJ-78436735 (Johnson & Johnson) vaccine.

The strongest factors associated with adverse effects were vaccine dose (2 doses of BNT162b2 or mRNA-1273 or 1 dose of JNJ-78436735 vs 1 dose of BNT162b2 or mRNA-1273; odds ratio [OR], 3.10; 95% CI, 2.89-3.34; $P < .001$),

vaccine brand (mRNA-1273 vs BNT162b2, OR, 2.00; 95% CI, 1.86-2.15; $P < .001$; JNJ-78436735 vs BNT162b2: OR, 0.64; 95% CI, 0.52-0.79; $P < .001$), age (per 10 years: OR, 0.74; 95% CI, 0.72-0.76; $P < .001$), female sex (OR, 1.65; 95% CI, 1.53-1.78; $P < .001$), and having had COVID-19 before vaccination (OR, 2.17; 95% CI, 1.77-2.66; $P < .001$).

Outcomes

After reporting vaccination, participants were asked to report vaccine adverse effects, with response options including fever, chills, fatigue, sore/scratchy throat, muscle pain, joint pain, headache, other pain, redness/swelling at the injection site, rash other than at the injection site, allergic reaction/anaphylaxis, other, and none of the above.

These response options were chosen because these adverse effects had been reported in vaccine clinical trials. Participants could provide free-text responses to the option of other.

Following branching logic, participants reporting adverse effects were also asked the duration of adverse effects and self-rated adverse effect severity

If participants reported receiving 2 doses of vaccine on the same survey, they were not asked to report adverse effects by dose separately.

Conclusions

In this real-world cohort, serious COVID-19 vaccine adverse effects were rare, and overall adverse effects were similar to industry and government reports.

This independent evaluation enabled the comparison of adverse effects between vaccine manufacturers, noting that adverse effects were more common with mRNA-1273 compared with BNT162b2.

Large digital cohort studies may provide a mechanism for independent postmarket surveillance of drugs and devices.