

# Accepted Manuscript

Assessment of the Safety and Efficacy of the COVID-19 Vaccines against Variants of Concerns: A Systematic Literature Review

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To appear in: *Journal of Neoteric Life Science*

Received Date: 06 February 2024

Accepted Date: 13 February 2024

Please cite this article as:

Singh P. Assessment of the Safety and Efficacy of the COVID-19 Vaccines against Variants of Concerns: A Systematic Literature Review. *JNL*. 2024;2(1):01-22.

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# **Assessment of the Safety and Efficacy of the COVID-19 Vaccines against Variants of Concerns: A Systematic Literature Review**

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## **Abstract**

### **Background**

During the pandemic, researchers were successful in rapidly formulating a cure for the COVID-19 disease. In this systematic review, we evaluated the safety and efficacy of three vaccines against three different variants of concern (VOCs).

### **Methods**

This systematic review was carried out as per the Preferred Reporting Project for Systematic Evaluation and Meta-Analysis (PRISMA) standards. The primary objective of the study was to evaluate the efficacy of the COVID-19 vaccine against the selected VOCs. The secondary objective of the study included the assessment of the severity of adverse events induced by the selected COVID-19 VOCs after receiving the vaccination along with reinfection rate.

### **Discussion**

A total of 22 studies were included in this systematic review with the mean age of participants ranging from 34.8 to 58.8 years. The participants affected with alpha, delta, and omicron VOCs vaccinated with either BNT162b2, mRNA1273, or ChAdOx1-S vaccine were included and assessed. The mean age of the participants from the included studies was 42 years (ranging from 34.8 to 58.8 years) while the median age of the participants was 54 years (ranging from 30 to 77 years). Among the three vaccines, mRNA1273 achieved highest efficacy of 73.1% ranging from 46.0% to 98.4% with approximately 24% adverse event reactions in participants.

### **Conclusion**

This systematic review summarized the safety and efficacy of the various research studies conducted and represented by researchers worldwide. The review's findings showed that while the

examined vaccinations are effective and safe for people, additional research is required to mitigate the adverse reactions and rates of reinfection in those who received the vaccinations.

**Keywords:** COVID-19, effective, vaccination, SARS-CoV-2, adverse events, reinfection.

## **Introduction**

The coronavirus disease of 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led the world to face one of the biggest and most challenging pandemics, even after all these technological advancements in the healthcare industry. Until now, the World Health Organization (WHO) has disclosed many COVID-19 variations and classified them according to their virulence rate and mode of transmission. As per the WHO, like other viruses, SARS-CoV-2 mutates over time and will keep changing the more it spreads into different variants.<sup>1</sup> This virus has constantly evolved ever since its emergence due to mutation, and at times these changes produce a new viral strain. Certain alterations and modifications enable the virus to proliferate more quickly, making it immune to drugs or vaccinations, producing different variants capable of immune escape.

Differentiating characteristics like enhanced transmissibility and antigenicity were observed in these variants, which were mostly caused by non-synonymous mutations in the spike protein.<sup>2</sup> These variants are also categorized into different categories, including Variants of Interests (VOI), Variants of Concerns (VOC), Variants of High Consequences (VOHC), and Variants Being Monitored (VBM).<sup>3</sup> As of now, the WHO (as well as national public health organizations) have designated five SARS-CoV-2 variations as variants of concern (VOCs), meaning that they should be closely monitored because of their significantly changed transmissibility or immune escape.<sup>2</sup> These variants include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529).<sup>4</sup>

Of these variants, Alpha, Beta, and Gamma were the first to spread in early 2021 and shared the N501Y substitution. These variations were replaced in summer 2021 by the Delta variant, which had unique changes like as the L452R substitution and was associated with increased virulence. It

was rapidly superseded by the Omicron variant by the end of 2021, which has since become more prevalent due to its staggering number of mutations. The emergence of VOCs revealed a dynamic development of SARS-CoV-2 via selection and mutation accumulation. This has not only resulted in a gradual improvement in the transmissibility of SARS-CoV-2 but has also contributed to the virus's immunological escape.<sup>5</sup> These variants may spread faster and easier than others, increasing the number of COVID-19 cases. There were around 687 million COVID-19 instances worldwide as of May 2, 2023. Approximately 660 million individuals had recovered from the virus infection, while nearly 6.87 million had died. Among the nations most severely affected by the pandemic are Brazil, India, and the United States of America (USA).<sup>6</sup> With around 375,000 fatalities, COVID-19 was the third largest cause of death in the USA in 2020, after heart disease and cancer. People of all ages are susceptible to this virus, especially people aged  $\geq 60$  years with comorbidities, who are most susceptible to the severe COVID-19 infection.<sup>7-8</sup>

To prevent the spread and virulence of these variants, healthcare organizations all around the world have developed plenty of vaccinations and guidelines. However, to date, there is no treatment available for the COVID-19 infection other than immunization. Pfizer, in collaboration with German biotech firm BioNTech, developed the first-ever nucleoside-modified mRNA vaccine encoding the nucleoside-modified mRNA named Comirnaty (BNT162b2) for emergency use.<sup>9</sup> Shortly after that, Moderna manufactured the second vaccine, the mRNA1273 vaccine for adults, which was also a nucleoside-modified mRNA vaccine.<sup>10</sup> Moreover, Oxford-AstraZeneca manufactured the ChAdOx1-S, a recombinant COVID-19 vaccine, which was also recommended by the WHO for use in people aged 18 and above.<sup>11</sup> These vaccines were listed by the WHO for emergency use during the pandemic.<sup>12</sup> Other than these vaccines, WHO has listed all the approved vaccines for immunization to prevent the spread and infection rate of the COVID-19 virus.<sup>13</sup> In this

review, we will assess the safety and efficacy of these vaccines against different VOCs of the COVID-19 virus and their associated adverse events in the general population.

## **Methods**

### ***Objectives***

The primary outcomes of the study were to evaluate the efficacy of the COVID-19 vaccine against the selected variants of concern (VOCs), including alpha (B.1.1.7), beta (B.1.351), and omicron (B.1.1.529) variants. The COVID-19 vaccines that were analyzed during this systematic review included BNT162b2 (Pfizer), mRNA-1273 (Moderna), and ChAdOx1-S (Oxford-AstraZeneca), since these vaccines were the most analyzed for their safety and efficacy rates.

The study's secondary objective included assessing the severity of adverse events induced by the selected COVID-19 VOCs after receiving the vaccination. In addition, this study also evaluated the reinfection rate in the vaccinated participants.

### ***Eligibility criteria of the studies***

This systematic review was carried out as per the Preferred Reporting Project for Systematic Evaluation and Meta-Analysis (PRISMA) standards. We included randomized-controlled trials (RCTs) or parallel individual clinical trials evaluating the safety, efficacy, and immunogenicity of the COVID-19 vaccines on different variants of concerns.

### ***The inclusion criteria of the study included:***

- Studies examining the virulence and transmission rate of the COVID-19 variants
- Randomized controlled trials on the efficacy of the COVID-19 vaccine
- Full-text articles
- English-language articles

- Articles published between 2012 and 2023
- Studies including the adverse effects linked to the COVID-19 vaccine

*The exclusion criteria of the study included:*

The following studies will be excluded:

- Systematic reviews and meta-analyses
- Editorial reviews and letters of communication
- Review articles
- News reports or commentaries
- Articles available only with abstracts
- Case reports/series
- Articles in other languages
- Conference papers

***Literature search strategy***

Studies falling under the inclusion criteria were searched in different electronic databases and journals like PubMed, Scopus, ResearchGate, Google Scholar, The Lancet, The New England Journal of Medicine (NEJM), Nature, BioMed Central (BMC), Frontiers, the Public Library of Science (PLOS), Journal of Biomedical Sciences, Cell, British Medical Journal (BMJ), MedComm, and the Journal of the American Medical Association (JAMA). Preprint repositories such as medRxiv and bioRxiv were also searched for related preprint articles. In addition, data related to vaccines and VOCs were also collected from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) websites. The publication year was restricted to 2012 to 2023.

Moreover, the search was conducted using the following keywords: “COVID-19” OR “SARS-CoV-2” AND “vaccine” OR “effective vaccination” OR “vaccine effectiveness” OR “efficacy of vaccines” OR “immunogenicity” AND “variants of concern” OR “VOC” OR “strains” AND “randomized-controlled trials” AND “side effects” OR “adverse events” AND “transmission” OR “spread” AND “virulence” AND “mechanism” AND “inflammation”. No additional filters were used during the research paper collection.

### ***Data management and analysis***

The data was stored in a Microsoft Excel sheet that included the required parts of the completed research. The data was extracted and evaluated systematically from these sheets and was analyzed with SAS software version 9.4.

## **Results**

### ***Study description and their baseline clinical characteristics***

A total of 38 papers were collected and screened, of which 22 papers were included in the study as per the inclusion and exclusion criteria for the analysis. Out of the 22 included studies, 6 were peer-reviewed publications, 4 were retrospective cohort studies, 4 were research articles, and 1 study, each not peer-reviewed, was an open-label controlled interventional study, a cross-sectional study, a placebo-controlled trial, a randomized trial, a commentary research article, and a test-negative case-control study. Among these studies, 10 were included in the efficacy analysis, and three were included in the safety analysis. Besides these studies, 5 studies were analyzed for reinfection rate in patients treated with the COVID-19 vaccines.

The participants from the included studies were not restricted to any age group. The mean age of the participants from the included studies was 42 years (ranging from 34.8 to 58.8 years),<sup>14-27, 29-30</sup>

while the median age of the participants from the included studies was 54 years (ranging from 30 to 77 years).<sup>28, 31</sup> Furthermore, only the participants affected with alpha, delta, and omicron VOCs were included in the study analysis. The studies included three vaccinations, including BNT162b2 by Pfizer, mRNA1273 by Moderna, and ChAdOx1-S by Oxford–AstraZeneca.

A few baseline clinical and demographic characteristics were not reported due to incomplete data from the included studies. The complete baseline clinical characteristics of the included studies are reported in **Table 1**.

**Table 1 Clinical and Demographic Characteristics of the Studies**

Article	Total patients (N)	Age (Mean)	Sex (n)			Race/Ethnicity				Variants			Vaccines
			Male	Female	Other <sup>a</sup>	Asian	White	Black	Other <sup>b</sup>	Alpha	Delta	Omicron	
Ward et al 2022 <sup>14</sup>	10,35,149	41.1	4,78,268	5,56,881	NA	46,034	8,85,866	39,305	63,944	NR	2,21,146	8,14,003	NR
Nyberg et al 2022 <sup>15</sup>	15,16,702	34.8	7,09,107	8,07,595	0	75,037	1,26,3101	80,921	97,643	NR	4,48,843	1,067,859	497,736 <sup>c</sup> ; 6,38,254 <sup>d,e</sup>
Zali et al 2022 <sup>16</sup>	2,70,624	48.2	1,35,931	1,34,693	NR	NR	NR	NR	NR	34,656	8,682	NR	NR
Strasser et al 2022 <sup>17</sup>	1,02,315	44	38,833	6,34,82	NR	3,882	78,133	6,720	13,580	NR	20,770	81,545	NR
Webster et al 2022 <sup>18</sup>	1,243,212	45.9	541,797	701,415	NR	112,272	978,894	40,756	63,544	NR	NR	1,243,212	NR
Canetti et al 2022 <sup>19</sup>	821	58.8	253	568	NR	NR	NR	NR	NR	NR	NR	NR	154 <sup>d</sup> , 120 <sup>e</sup>
Gram et al 2022 <sup>20</sup>	73,24,464	54.8	3,06,6307	42,58,157	NR	NR	NR	NR	NR	10,61,427	33,99,651	2,863,386	7,27,593 <sup>c</sup> ; 4,770,188 <sup>d</sup>
Kirsebom et al 2022 <sup>21</sup>	1,127,517	NR	426,669	698,771	2,077	20,519	104,522	4,979	997,497	NR	NR	511,889	NR
Lau et al 2023 <sup>22</sup>	5,242	40.3	2,548	2,680	14	NR	NR	NR	NR	NR	NR	NR	3,759 <sup>d</sup>
Bruxvoort et al 2021 <sup>23</sup>	5,186	39.6	894	1,133	NR	75	634	309	1009	1,436	2,027	NR	NR
Alqahtani et al 2022 <sup>24</sup>	958	NR	478	480	NR	NR	NR	NR	NR	NR	NR	NR	480 <sup>d</sup> ; 478 <sup>c</sup>
Guo et al 2022 <sup>25</sup>	7,17,577	NR	2,09,794	4,81,574	NR	NR	NR	NR	NR	NR	NR	NR	323,185 <sup>d</sup> ; 3,29,056 <sup>e</sup>
Hammerman et al 2022 <sup>26</sup>	1,49,032	39.3	67,870	81,162	NR	NR	NR	NR	NR	NR	NR	NR	83,356 <sup>d</sup>
Bernal et al 2021 <sup>27</sup>	19,109	41.8	9,373	9,728	8	3563	11463	390	3,693	14,837	4,272	NR	758 <sup>d</sup> ; 3,444 <sup>c</sup>
Skowronski et al 2022 <sup>28</sup>	16,993	77*	8,336	8,657	NR	NR	NR	NR	NR	509	16	NR	10,569 <sup>d</sup> ; 1,882 <sup>e</sup>
Andrews et al 2021 <sup>29</sup>	1,87,887	41.3	75,088	112,541	258	NR	1,59,622	2,037	26,228	NR	56,439	581	98,022 <sup>d</sup> ; 65,242 <sup>c</sup> ; 5,683 <sup>e</sup>
Emary et al 2021 <sup>30</sup>	8,534	36.5	3,469	5,065	NR	NR	7,863	NR	146	NR	NR	NR	4,244 <sup>c</sup>

Madhi et al 2021 <sup>31</sup>	2,021	30*	1,142	879	NR	NR	259	1,421	337	NR	NR	NR	1,011 <sup>c</sup>
Neto et al 2022 <sup>32</sup>	58,097	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	58,097 <sup>d</sup>
Rahman et al 2022 <sup>33</sup>	1,644	38.4	940	704	NR	NR	NR	NR	NR	NR	NR	NR	731 <sup>c</sup>
Polack et al 2020 <sup>34</sup>	36,523	53.2	19,075	18,631	NR	1,608	31,266	3,492	11,883	NR	NR	NR	18,860 <sup>d</sup>
Yung et al 2023 <sup>35</sup>	299,901	10.7	158,947	140,954	NR	NR	NR	NR	NR	NR	NR	3,644	135,197 <sup>d</sup>

Abbreviation: NR, not reported.

Note: N, total number of patients; n, number of subjects with observation

\*median age

<sup>a</sup>unknown, not determinable, and missing

<sup>b</sup>includes Hispanic and missing

<sup>c</sup>ChAdOx1-S vaccine

<sup>d</sup>BNT162b2/ booster vaccine

<sup>e</sup>mRNA1273 vaccine.

### *Efficacy of selected vaccines against variants of concerns*

A total of 10 studies, in which participants were immunized with any one of three vaccines (BNT162b2, mRNA1273, and ChAdOx1-S), were included for the efficacy analysis.<sup>19-23, 27-</sup>

<sup>31</sup> Pfizer's BNT162b2 vaccination had a mean effectiveness of 61.2% in 7 of 10 studies, with efficacy ranging from 33.0% to 90.0% across studies.<sup>19-22, 27-29</sup> Moderna's mRNA1273 vaccination had a mean effectiveness of 73.1% in 5 of 10 studies, with efficacy ranging from 46.0% to 98.4%,<sup>19-21, 23, 28</sup> whereas Oxford-AstraZeneca's ChAdOx1-S vaccination had a mean effectiveness of 68.7% in 5 of 10 studies, with efficacy ranging from 48.9% to 89.8%.<sup>21, 27, 29-31</sup>

These vaccinations, when investigated against the alpha, delta, and omicron VOCs to identify which was the most effective, the BNT162b2 was found to have a mean effectiveness of 58.4%,<sup>19, 27-28</sup> 73.2%,<sup>20, 27, 29</sup> and 54.3%<sup>19, 21-22, 29</sup> against alpha, delta, and omicron variants, respectively. Similarly, the mRNA1273 achieved a mean effectiveness of 73.3%,<sup>19-20, 23, 28</sup> 78.0%,<sup>20, 23</sup> and 67.9%<sup>19, 21</sup>, whereas ChAdOx1-S achieved a mean effectiveness of 66.7%,<sup>27, 30-31</sup> 48.8%,<sup>27</sup> and 81.6%<sup>21, 29</sup> against alpha, delta, and omicron variants, respectively. The complete data representing the efficacy rates of these vaccines against different VOCs is presented in **Table 2**.

**Table 2 Efficacy Rates of the Vaccines against VOCs**

Variants of Concerns (VOCs)	Article	Vaccines		
		BNT162b2 (%)	mRNA1273 (%)	ChAdOx1-S (%)
Alpha	Canetti et al 2022 <sup>19</sup>	37.0	46.0	NR
	Gram et al 2022 <sup>20</sup>	NR	81.9	NR
	Bruxvoort et al 2021 <sup>23</sup>	NR	98.4	NR
	Bernal et al 2021 <sup>27</sup>	71.2	NR	61.6
	Skowronski et al 2022 <sup>28</sup>	67.0	67.0	NR
	Emary et al 2021 <sup>30</sup>	NR	NR	64.0
	Madhi et al 2021 <sup>31</sup>	NR	NR	74.6
Delta	Gram et al 2022 <sup>20</sup>	83.7	74.5	NR
	Bruxvoort et al 2021 <sup>23</sup>	NR	81.6	NR
	Bernal et al 2021 <sup>27</sup>	59.4	NR	48.9
	Andrews et al 2021 <sup>29</sup>	76.6	NR	NR
Omicron	Canetti et al 2022 <sup>19</sup>	37.0	46	NR
	Kirsebom et al 2022 <sup>21</sup>	89.8	89.8	89.8

	Lau et al 2023 <sup>22</sup>	33.0	NR	NR
	Andrews et al 2021 <sup>29</sup>	57.3	NR	73.4

Abbreviations: NR = not reported.

Note: Data is presented in percentage.

### ***Safety results***

The adverse event reactions for BNT162b2, mRNA1273, and ChAdOx1-S vaccines ranged from 8.1% to 41.0%, 3.8% to 16.9%, and 11.9% to 45.0%, respectively, across studies (Table S1). The total number of adverse events varied largely across these studies.

For the BNT162b2 vaccine, the most common adverse events ( $\geq 10\%$  events) were systematic (41.0%), local (24.8%), myalgia (20.6%), fatigue (18.6%), fever (18.5%), headache (15.9%), and chills (10.9%). For the mRNA1273 vaccine, the most common adverse events ( $\geq 10\%$  events) were headache (16.9%) and fatigue (14.5%). For the ChAdOx1-S vaccine, the most common adverse events ( $\geq 10\%$  events) were systematic (45.0%), general system disorder NEC (31.4%), fever (27.2%), fatigue (25.1%), myalgia (20.3%), headache (15.7%), joint pain (11.9%), and infections (10.8%; Table S1). A complete description of the adverse events is reported in Supplementary Table 1.

### ***Reinfection rate in patients after receiving vaccination***

A few studies showed that even after receiving COVID-19 vaccination, some participants got reinfected with the virus. We included a total of 5 studies to evaluate the reinfection rate of participants infected with COVID-19 virus even after receiving the BNT162b2 and ChAdOx1-S vaccinations. No study was found or assessed for the reinfection rate related to the mRNA1273 vaccine. Four studies were analyzed for reinfection rate after receiving the BNT162b vaccine,<sup>26, 32, 34-35</sup> whereas only one study was found for the ChAdOx1-Sv vaccine. The reinfection rate reported in BNT162b-vaccinated participants ranged from 2.1% to 0.4%.<sup>26, 32, 34-35</sup> In case of the

ChAdOx1-S vaccine, only 5.2% participants were found to be reinfected.<sup>33</sup> The complete description of the reinfection rate in vaccinated participants is represented in **Table** .

**Table 3      Reinfection Rate in Vaccinated Participants**

Article	Vaccine	Vaccinated, (n)	Reinfections, n(%)
Hammerman et al 2022 <sup>26</sup>	BNT162b2	83,356	354 (0.42%)
Neto et al 2022 <sup>32</sup>	BNT162b2	58,097	9 (0.02%)
Rahman et al 2022 <sup>33</sup>	ChAdOx1-S	731	38 (5.19%)
Polack et al 2020 <sup>34</sup>	BNT162b2	18,860	8 (0.04%)
Yung et al 2023 <sup>35</sup>	BNT162b2	135,197	2,845 (2.10%)

Note: n, number of subjects with observation.

## Discussion

This systematic review evaluated the safety, efficacy, and reinfection rates of the three COVID-19 vaccines, including BNT162b, mRNA1273, and ChAdOx1-S against alpha, delta, and omicron VOCs. The efficacy results showed that mRNA1273 vaccine by Moderna has the highest efficacy rate among the other vaccines with a mean effectiveness of 73.1% (ranging from 46.0% to 98.4%).<sup>19-21, 23, 28</sup> A similar efficacy was reported for the mRNA1273 and ChAdOx1-S vaccines concluding the fact that all of these three vaccines were effective, protecting thousands of people against COVID-19 VOCs (alpha, delta, and omicron).

Additionally, we evaluated the safety of these vaccines with the same VOCs and analyzed the frequency of adverse event reactions in vaccinated participants. Moreover, the adverse event reactions for BNT162b2, mRNA1273, and ChAdOx1-S vaccines ranged from 8.1% to 41.0%, 3.8% to 16.9%, and 11.9% to 45.0%, respectively, across studies.<sup>24-25, 31</sup> It concluded the fact that even though the efficacy of these vaccination in their recipients is effective, the frequency of these adverse events were not less, which demands further research to improve the safety of these vaccines. Further analysis suggested that the reinfection rate of the BNT162b vaccine ranged from 2.1% to 0.4%, whereas the reinfection rate of the ChAdOx1-S vaccine was 5.2%,<sup>26, 32-35</sup> which suggested the waning efficacy of the vaccination doses in these participants.

These numbers urge the researchers to conduct further clinical trials to improve the safety and efficacy of these vaccinations for longer run in patients infected with different variants of COVID-19.

### **Conclusion**

This systematic review summarized the safety and efficacy of the various research studies conducted and represented by researchers worldwide. The review's findings showed that while the examined vaccinations are effective and safe for people, additional research is required to mitigate the adverse reactions and rates of reinfection in those who received the vaccinations.

### **Conflict of interest**

The authors whose names are listed in the paper have no confederations with or involvement in any organization or entity with any financial interest (similar to honoraria, educational grants, participation in speakers' divisions, membership, employment, consultancies, stock ownership, or other equity interest; and expert evidence or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, confederations, knowledge, or beliefs) in the subject matter or accouterments banded in this paper.

### **Data availability statement**

The data can be made available upon request from the author.

### **Acknowledgement**

Not applicable.

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