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Effectiveness of COVID-19 vaccines: A systematic review

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ABSTRACT

COVID-19 vaccine effectiveness has been the subject of numerous investigations conducted globally. The public's and health-care professionals' acceptance of vaccines looks to be crucial to the pandemic's effective management. This review's objective was to present an up-to-date evaluation of COVID-19 vaccine acceptance rates across the globe. The current systematic evaluation of the literature seeks to identify the many global outcomes of the COVID-19 vaccine's efficacy. The study was carried out following preferred reporting items for systematic reviews and meta-analysis recommendations for systematic reviews. The MEDLINE and EMBASE database were used the retrieve the articles. A detailed descriptive analysis was done on the various outcomes of vaccine efficacy, viral load, transmission rate, hospitalization rate, death rate, and infectivity rate on age group. The present systematic review has identified that vaccines effectively reduced infection transmission. It not only provides fewer hospital stays but reduced the death rate. However, the Ct values were similar in unvaccinated and vaccinated. Breakthrough infections were most reported in the vaccinated group.

Key words: Systematic review; COVID-19 vaccine; Viral load; Outcomes; Viral transmission

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel species of coronavirus, has set out the coronavirus disease 2019 (COVID-19) pandemic from December 2020.[1] The COVID-19 pandemic is not only a primary health menace for all mankind but also strikes the world's economy. Elderly, healthcare workers, patients with underlying comorbidities, and those living in areas with high community transmission were vulnerable to infection.[2-4] Even the younger age group is also susceptible to infection. The risk of the pandemic has been alleviated due to the diverse global efforts. Adequate preventive actions including vaccination camps are one of the most significant preventive measures to contain infectious diseases.[5] Immunization against COVID-19 will not only prevent the spread of the virus but will also limit the serious health consequences of the pandemic.[5,6] Several vaccine candidates have been tested and found to be effective and safe against COVID-19. Two messenger RNA (mRNA) vaccines, three adenovirus vector vaccines, four inactivated vaccines, and two protein subunit vaccines have been approved for use against COVID-19 at the national and international levels.[6-8] The safety and efficacy of these vaccine candidates were evaluated in laboratory studies, randomized clinical trials, and observational studies before they were approved for emergency or full use.[5,6]

In the United States (US), SARS-CoV-2 vaccines include two mRNA vaccines BNT162b2[9] and mRNA-1273,[10] and one adenovirus vector vaccine Ad26.COV2.S.[11] As of November 21, 2021, 59% of the United States and 42% of the world's population were fully vaccinated against SARS-CoV-2.[12] In randomized, placebo-controlled, and Phase III trials, the BNT162b2, mRNA-1273, and Ad26.

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COV2.S vaccines showed 95%, 94%, and 67% efficacy against symptomatic disease due to SARS-CoV-2.[12] However, the temporal evolution of vaccine protection against future SARS-CoV-2 infection, symptomatic, and severe COVID-19 remains poorly understood. As countries around the world face surges of COVID-19 cases, the question of waning immunity and its contribution to new outbreaks must be urgently addressed. In this systematic review, our objective was to evaluate the overall, age- and vaccine-specific efficacy/effectiveness (VE) of BNT162b2, mRNA-1273, Ad26.COV2.S, CoviShield, and covaxin vaccines against SARS-CoV-2 infection, symptomatic, and severe COVID-19 disease over time. The main aim of this study was to investigate the published literature to evaluate the efficacy, immunogenicity, and safety of the COVID-19 vaccines.

MATERIALS AND METHODS

A systematic review was done to assess the incidence of COVID-19 among individuals vaccinated with available vaccines and non-vaccinated. A study was conducted on the incidence of COVID-19 infection at various parameters such as different age groups, healthcare workers, viral load, rate of infectivity, and Indian scenario. The study was conducted based on preferred reporting items for systematic reviews and meta-analysis guidelines for systematic reviews.[13]

Inclusion criteria

The following criteria were included in the study:

(1) Those studies included the evaluation of COVID-19 vaccination. (2) All cross-sectional, clinical trials, case–control studies, cohort studies, and qualitative studies. (3) Studies conducted between December 2020 and June 2022. (4) Studies that assessed the incidence of COVID-19 among vaccinated individuals and non-vaccinated. (5) Studies that evaluated the incidence of CoVID-19 infection at various parameters like different age groups, health care workers, viral load, rate of infectivity, and Indian scenario. (6) All cross-sectional and qualitative studies. 6. Full-length published articles in English.

Exclusion criteria

In general, those articles not matching the inclusion criteria were excluded from the study. Case reports and letters to the editor were excluded from the study.

Search methods

The MEDLINE database was used to retrieve the articles. The MeSH terms used were (COVID-19) AND (Vaccinated and Novaccinated individuals) AND (healthcare workers) AND (viral load and rate of infectivity) AND (age) AND (INDIA). The PubMed advanced search was used. Boolean operator "AND" was used in between the MeSH terms in the advanced search. For EMBASE search, Emtree thesaurus was used to retrieve the articles from EMBASE.

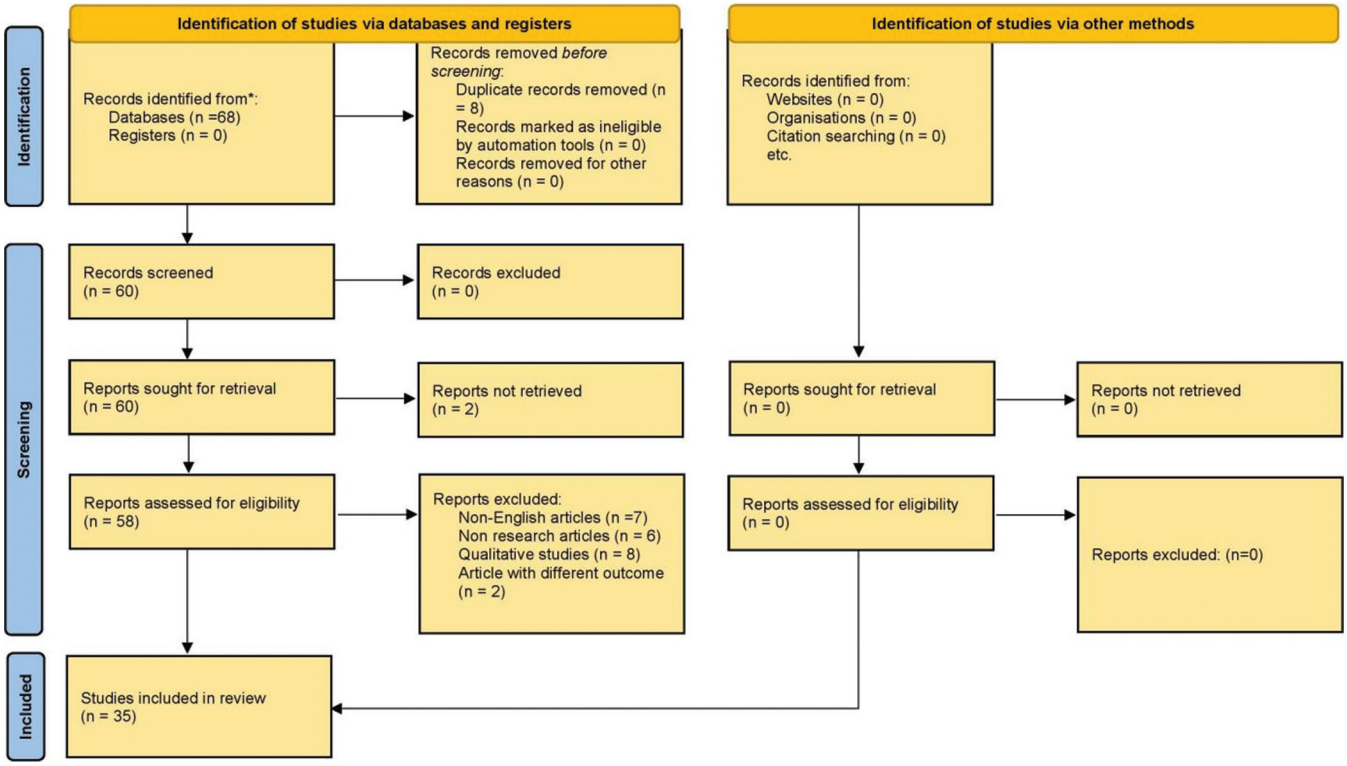

Figure 1: PRISMA flowchart showing the selection of articles for the study

Selection of articles

The articles were analyzed and authors selected those articles based on the inclusion and exclusion criteria. The suitability of the articles was reviewed and those articles with inadequate data were excluded from the study (Figure 1).

Synthesis of results

A descriptive analysis was done on the data available in the articles. All the data were organized in the form of a table and were narrated descriptively. As the data were highly heterogeneous, metanalysis was not conducted.

Table 1: Incidence of COVID-19 in vaccinated and unvaccinated individuals

Author	Year	Country	Study tool	Sample size	Results
Haas et al.[14]	2021	Israel	Observational study	232268	The incidence of SARS-CoV-2 outcomes declined due to increased vaccination coverage. 97.5% efficacy was noted against severe or critical COVID-19-related hospitalization, and 96.7% against COVID-19-related death. The estimated prevalence of the B.1.1.7 variant was 94.5% among SARS-CoV-2 infections.
Menni et al.[15]	2021	UK	Prospective observational study	627383	3106 of 103622 vaccinated individuals and 50340 of 464356 unvaccinated controls tested positive for SARS-CoV-2 infection. The risk of infection was significantly reduced starting at 12 days after the first dose.
Kustin et al.[16]	2021	Israel	Cohort study		B.1.351 variant was found in individuals fully vaccinated with BNT162b2 as compared to the unvaccinated controls. Furthermore, an increased proportion of B.1.1.7 was found in partially vaccinated individuals. The study could not relate the reason for increased breakthrough rates of B.1.1.7.
Hall et al.[17]	2021	England	Prospective multicentric, cohort study	23324	977 new infections were recorded in the unvaccinated cohort. The vaccinated cohort had 71 new infections. In the unvaccinated cohort, 56% of participants had typical COVID-19 symptoms. A single dose of the BNT162b2 vaccine showed vaccine effectiveness of 70%, 21 days after the first dose, and 85%, 7 days after two doses in the study population.
Brown et al.[18]	2021	Massachusetts	Observational Study	469	Delta variant in 119 from 133 (89%) cases and the Delta AY.3 sublineage in one (1%) case. Vaccine products received by persons experiencing breakthrough infections were Pfizer-BioNTech (159), Moderna (131), and Janssen (56). Among persons with breakthrough infection, 79% reported signs or symptoms, four were hospitalized, and no deaths were reported. Real-time RT-PCR Ct values in specimens from 127 fully vaccinated patients were similar to those among 84 patients who were unvaccinated, not fully vaccinated, or whose vaccination status was unknown.
Polack et al.[9]	2020	Multinational	Multinational, placebo-controlled observer-blinded pivotal efficacy trial	43,548	BNT162b2 was 95% effective in preventing COVID-19. Among 10 cases of severe COVID-19 with onset after the first dose, nine occurred in placebo recipients and one in a BNT162b2 recipient.
Pawlowski *et al.*[19]	2021	Arizona, Florida, Iowa, Minnesota, and Wisconsin	Retrospective study	136,532	BNT162b2 and mRNA-1273 were 86.1% effective in preventing PCR – confirmed SARS-CoV-2 infection.

(Contd...)

Table 1: *(Continued)*

Author	Year	Country	Study tool	Sample size	Results
Chung et al.[20]	2021	Canada	Prospective study	324033	Vaccine effectiveness against symptomatic infection observed ≥14 days after one dose was 60%. Vaccine effectiveness observed ≥7 days after two doses was 91%. Vaccine effectiveness against hospital admission or death observed ≥14 days after one dose was 70% and after two doses the efficacy of vaccine was 98%. For adults aged ≥70 years, vaccine effectiveness was observed to be lower when compared to those for younger people.
Emary et al. [21]	2021	England, Wales, Scotland	Single Blind multicentrerandomized trial	8534	Vaccine efficacy of ChAdO×1 nCoV-19 was 70·4% against symptomatic COVID-19 caused by the B.1.1.7 variant and 81·5% against symptomatic COVID-19 caused by non-B.1.1.7 variants. For asymptomatic cases, the vaccine efficacy was higher for non-B.1.1.7 infections than for B.1.1.7.
Self et al.[22]	2021	USA	Multicentre Case-Control Study	1210	Vaccine effectiveness was similar for both Pfizer BioNTech and Moderna. Among VOC the effectiveness was 92.8%. The efficacy was slightly reduced in patients with underlying comorbidities and among 45 patients with vaccine-breakthrough COVID hospitalizations, 44 were ≥50 years old and 20 had immunosuppression.
Puranik et al.[23]	2021	USA	Retrospective study	119,463+60,083	The effectiveness of mRNA-1273 and BNT162b2 in preventing SARS-CoV-2 infection after the second dose was 86% and 76%, respectively, in the study. Full vaccination was also highly effective against COVID-19-associated hospitalization. Individuals vaccinated with mRNA-1273 had reported fewer breakthrough infections and also conferred a two-fold risk reduction against breakthrough infection compared to BNT162b2.
Accorsi and Britton[24]	2022	USA	Retrospective test-negative case-control analysis	70 155	Three doses of mRNA vaccine, concerning unvaccinated and receipt of two doses, were associated with protection against both the Omicron and Delta variants. The Ct values were generally higher among those with three vaccine doses compared with unvaccinated or to two doses for delta and omicron variant cases and were statistically significant.
Moreira et al.[25]	2022	US, Brazil, South Africa	Randomized controlled trial	5081 participants received a third BNT162b2 dose and 5044 with a placebo	A booster dose of the BNT162b2 vaccine administered provided 95.3% efficacy against COVID-19.

RESULTS

A total of 68 articles were retrieved from the database out of which 35 articles were chosen based on the inclusion and exclusion criteria. The systematic review was conducted to analyze the various outcomes and incidence of COVID-19 in vaccinated and unvaccinated individuals.

On analyzes of the incidence of COVID-19 among vaccinated and non-vaccinated individuals (Table 1), it was observed that the incidence of COVID-19 infections, hospitalization and death rate was significantly reduced due to vaccines.[14] However, breakthrough infections were reported in vaccinated individuals and the Ct values of RTPCR were similar in vaccinated and

Table 2: Incidence of COVID-19 in vaccinated and unvaccinated individuals in correlation with age

Author	Year	Country	Study tool	Sample size	Results
Bernal et al.[26]	2021	England	Test negative case-control study	156930	Participants aged 80 years and above vaccinated with BNT162b2 had higher odds of testing positive for COVID-19. The efficacy was noted to reach 70%withBNT162b2 and ChAdO×1-S.The risk of hospitalization was reduced to 43% and 37% with BNT162b2 and with the ChAdO×1-S vaccine, respectively.
Emary et al.[21]	2021	England, Wales, Scotland	Single Blind multicenter randomized trial	8534	Of 8534 participants in the primary efficacy cohort, 6636 were aged 18–55 years. Vaccine efficacy of ChAdO×1 nCoV-19 was 70·4% against B.1.1.7 variant and 81·5% against non-B.1.1.7 variants. For asymptomatic cases, the vaccine efficacy was higher for non-B.1.1.7 infections than for B.1.1.7.
Haas et al.[27]	2021	Israel	Observational Study (National surveillance data)	4714932	66·6% of the infections were noted in people aged 16 and older. 4481 severe or critical COVID-19 hospitalizations and 1113 COVID-19 deaths occurred in people aged 16 years or older. Severe COVID-19 infection requiring hospitalization and COVID-19-related death were more significant in the age group above 65. Deaths recorded In age 65 and older 554 deaths were recorded among unvaccinated and it was 124 in vaccinated individuals.
Brown et al.[18]	2021	Massachusetts	Observational study	469	Among the 469 cases, 346 persons were fully vaccinated; of these, 301 (87%) were male, with a median age of 42 years.
Tenforde et al.[28]	2021	USA	Observational study	1210	Vaccine efficacy for full vaccination using Pfizer-BioNTech or Moderna vaccine was 86.9% and adjusted. Both of the vaccines exhibited similar efficacy and were highest in adults aged 18–49 years. Immunosuppressed patients had lower vaccine efficacy.
Thomas et al.[29]	2021	USA	Multinational placebo-controlled observer-blinded trial	44165	Vaccine efficacy against COVID-19 was 91.3% through 6 months of follow-up among the participants without evidence of previous SARS-CoV-2 infection. Vaccine efficacy against severe disease was 96.7%. In South Africa, where the SARS-CoV-2 variant of concern B.1.351 was predominant, a vaccine efficacy of 100% was observed
Thangaraj et al.[30]	2021	India	Prospective Study	539	The median age of the unvaccinated individuals, who received 1 and 2 doses were 47 years, 53 years, and 54 years, respectively.
Ghosh et al.[31]	2021	India	VIN-WIN cohort study	1,595,630	The mean age of patients with breakthrough infections was 33.16 (SD 8.46) years.
Shamier et al.[32]	2021	Netherlands	Retrospective study	24,706	The mean age of the HCWs with a breakthrough infection was 25.5 years.
Kang et al.[33]	2021	Guangdong, China	Retrospective study	167	Of 167 patients, 41.3% were male. The median age was 47.0 years with 22 (13.2%) cases aged under 15 years and 44 (26.3%) over 65 years.
Elliott et al.[34]	2021	England	REACT-1 study	Around 100,000	The Delta variant overtook the alpha variant during the second wave. High prevalence in younger, especially among those aged 13–17 years.

REACT-1: Real-time assessment of community transmission-1

unvaccinated patients.[18,24] B.1.1.7 and B1.351 variants were more reported in vaccinated patients.[14,16] In adults aged ≥70 years, the vaccine effectiveness was observed to be lower when compared to those for younger people.[20]

Table 2 shows the systematic review of COVID-19 in relation with age. Old age patients (80 years and above) vaccinated with BNT162b2 had higher odds of testing positive for COVID-19.[26] However, BNT162b2 and the ChAdOx1-S vaccines reduced the risk of hospitalization.[26] Severe COVID-19 infection requiring hospitalization and COVID-19-related death were more significant in the age group above 65 and immunosuppressed patients.[27,28] Higher prevalence of delta variant was reported in younger age group.[34]

Table 3: Indian scenario of incidence of COVID-19 in vaccinated and unvaccinated individuals

Author	Year	Country	Study tool	Sample size	Results
Victor et al.[35]	2021	India	Prospective Study	8991	1350/8991 HCWs tested positive for SARS CoV2. Among 7080 fully vaccinated HCWs, 679 had the infection. The protective effect of vaccination in preventing infection, hospitalization, need for oxygen, and intensive care unit admission was 65%, 77%, 92%, and 96%, respectively.
Thangaraj et al.[30]	2021	India	Prospective study	539	Median RT-PCR cycle threshold values were similar in the unvaccinated, partially, and fully vaccinated groups. B.1.617.2 (Delta variant) was the predominant VOC. The prevalence was 72.4% in unvaccinated, 68.1% in partially, and 74.3% in fully vaccinated groups. Five participants were positive for AY.1 (Delta plus variant). Of the five patients with AY.1 infection, one required hospitalization for oxygen support and the rest had mild disease. The prevalence of B.1.617.2 was not different between the vaccinated and unvaccinated groups. However, the proportion of patients progressing to severe illness and mortality was lower in the vaccinated group.
Bhattacharya et al.[36]	2021	India	Single center prospective cross-sectional study	638	110/164 participants who were not vaccinated were RTPCR positive. 62/240 fully vaccinated individuals were infected. The association between the vaccination status and the severity of COVID-19 was statistically significant (P<0.001). Two deaths were recorded in fully vaccinated.
Ghosh et al.[31]	2021	India	VIN-WIN Cohort Study	1,595,630	Median time to infection after the first dose was 21 days and after the second dose was 31 days. Vaccines had protective effects against COVID-19.

Table 4: Incidence of COVID-19 in vaccinated and unvaccinated healthcare workers

Author	Year	Country	Study tool	Sample size	Results
Angel et al.[37]	2021	Tel Aviv, Israel	Retrospective cohort study	6710 healthcare workers	8 fully vaccinated healthcare workers and 38 unvaccinated healthcare workers had symptomatic SARS-CoV-2 infection. Asymptomatic SARS-CoV-2 infection occurred in 19 fully vaccinated healthcare workers and 17 unvaccinated healthcare workers.
Ioannou et al.[38]	2021	Greece	Prospective cohort	55 HCWs	Most cases (54/55) were due to variant B.1.1.7. 23 of 24 vaccinated HCWs were infected with B.1.1.7 and one was with B.1.177. Similar viral load in vaccinated and non-vaccinated HCWs infected by SARS-CoV-2 variant B.1.1.7, suggesting potentially reduced efficacy of BNT162b2.
Thompson et al.[39]	2021	England	Prospective cohort study	3975 HCWs and frontline workers	204 participants were infected with SARS CoV2 of whom five were fully vaccinated, 11 partially vaccinated, and 156 unvaccinated. There were 10 genetically sequenced viruses detected in partially or fully vaccinated participants; three of these 10 viruses (30%) were variants of concern (all the B.1.429 variant [epsilon]), as compared with seven of the 70 viruses detected in unvaccinated participants.

The Indian scenario of incidence of COVID-19 among vaccinated and non-vaccinated individuals is shown in Table 3. The protective effect of vaccination in preventing infection, hospitalization, need for oxygen, and intensive care unit admission was significant.[35] The prevalence of B.1.617.2 was not different between the vaccinated and unvaccinated groups. However, the severity of infection and mortality rate was lower in the vaccinated group.[30,35] B.1.617.2 (Delta variant) was the predominant VOC.[30] Two deaths were recorded in fully vaccinated.[36]

Systematic review analyses of COVID-19 among vaccinated and unvaccinated healthcare workers (Table 4) also underline the protective effect of vaccines. Asymptomatic SARS-CoV-2 infection was reported in vaccinated healthcare workers.[37] Vaccinated HCWs were infected with B.1.1.7 and with B.1.177. Similar viral load in vaccinated and non-vaccinated HCWs infected by SARS-CoV-2 variant B.1.1.7.[38]

Impact of COVID-19 vaccination on SARS COV2 infectivity rate, viral load, and transmission rate is shown

Table 5: Impact of COVID-19 vaccines on viral load, transmission, and infectivity

Author	Year	Country	Study tool	Sample size	Results
Elliott et al.[34]	2021	England	REACT-1 study	Around 100,000	Prevalence among unvaccinated individuals was greater than for those who reported having had two doses of vaccine. 44% of infections occurred in doubly vaccinated individuals, reflecting imperfect VE against infection. Among participants aged 18–64 years, based on self-reported vaccination status, VE against infection was estimated as 49%.
Shamier et al.[32]	2021	Netherlands	Retrospective study	24,706	161 fully vaccinated HCWs were diagnosed with COVID-19 by PCR. In 126 samples a SARS-CoV-2 lineage could be identified, 90.5% of these were delta variants. The mean age of the HCWs with a breakthrough infection was 25.5 years. All of the HCWs had mild and did not require hospital admission.
Salazar et al.[40]	2021	Catalonia, Spain	Retrospective Study	58,000	Vaccines prevented 75% of documented infections and 74% of deaths. The study also analyzed that 2 weeks after 70% of residents were fully vaccinated, the detected transmission was reduced by 69% (90% CI), 54%, 50%, 69%, and 90% for each subsequent epidemiological week.
Kang et al.[33]	2021	Guangdong, China	Retrospective study	167	4.8% had asymptomatic, mild, normal, and severe or critical 17.4%, 66.5%, and 11.4%, respectively. Deaths were not reported. High viral load (0–7 days after onset) and the median Ct values were 23.0 (IQR: 19.3–28.6) for the N gene of the Delta variant, significantly lower than the values of the wild-type N gene (median: 36.5, IQR: 33.0–40.0).

REACT-1: Real-time assessment of community transmission–1, VE: Vaccine effectiveness

in Table 5. The prevalence among SARS COV 2 infection in unvaccinated individuals was greater.[34] Breakthrough infection was reported in vaccinated individuals. However, the severity of infection and mortality rate was less.[32] Transmission rate also was reduced with mass vaccination.[40]

DISCUSSION

There was a significant reduction in the incidence and hospitalization of COVID-19 cases after vaccination. Even a single vaccine dose reduces the risk of infection. All the studies also stated that ICU admission was less in vaccinated individuals. Vaccine breakthrough infections were reported in vaccinated individuals. VOCs B.1.351 was reported in BNT 162b2 vaccinated and B.1.17 in partially vaccinated.[16] Some studies state that the mRNA 1273 vaccine was effective against breakthrough infection.[23] RTPCR Ct values were similar in both groups.[18] However, death rates were lower in vaccinated people. Vaccine efficacy was less in people with underlying comorbidities. Vaccine effectiveness was lower in old age when compared with young people. Patients 65 years and above had a higher risk for hospitalization and death.[27] The mean age for vaccine breakthrough infection was 33.16, SD±8.46.[31]

Indian studies also go in hand with other studies from around the world. A significant decrease in infection prevention, hospitalization, need for oxygen, and ICU admission was observed in vaccinated individuals.[35] However, VOC B.1.617.2 was isolated from vaccinated people. Although the Ct values were similar in both vaccinated and non-vaccinated, the severity of infection was less in vaccinated cases.[30] Two deaths were reported in vaccinated individuals.[36]

A systematic review was done to see the efficacy of vaccines in healthcare workers also. Similar to the above groups, the Ct values showed no significant difference between vaccinated and non-vaccinated HCWs. Most of the vaccinated HCWs had asymptomatic infection.[37] VOC (B.1.1.7) was isolated from vaccinated HCW.[38]

Reviews regarding viral load and infectiousness revealed that 25 was the mean age for breakthrough infections.[32] Vaccination reduced the transmission rate.[40]

CONCLUSION

The present systematic review has identified that COVID-19 vaccination has reduced the incidence of COVID-19, hospitalizations, and death rate. The COVID-19 vaccination is a safer and better way to protect themselves and community from the COVID-19. However, vaccine breakthrough infections were seen in the vaccinated group.

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PS- Conceptualized and designed the study, literature search, prepared the first draft of manuscript, and critical revision of the manuscript; **IK-** Conceptualized the study, interpretation, and critical revision of the manuscript; and **PRT-** Concept of the study, literature search, and review of study.

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