Efficacy and Effectiveness of SARS-CoV-2 vaccine: A systematic review and a meta-analysis.

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Systematic Review

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Abstract

Background SARS coronavirus number 2 or SARS-CoV-2 emerged as a pandemic in 2019 and affected millions of people with a large number of deaths. Since no cure for this highly spreadable virus is known till now the need for a rapid vaccine development started early and the vaccination process started in December 2020 with many types of vaccines of different techniques.

This research aimed to shed the light on different studies evaluating the efficacy, effectiveness of COVID-19 vaccines in phase III trials.

Method Online database search was performed, and all relevant randomized controlled trials and observational studies considering COVID-19 vaccination by any type of vaccine and to any age were included. A meta-analysis was conducted to measure the efficacy/ effectiveness of COVID-19 vaccines to prevent mortality and to reduce severe infection after the first & the second dose. Assessment of risk of bias, publication bias & heterogenicity were also performed.

Results From 21567 screened articles twenty-five studies were eligible for quantitative analysis. The odds ratio of mortality 7 days after full vaccination decreased significantly among vaccinated compared to the unvaccinated group OR=0.14 (95CI, 0.05-0.41), I^2=63%. In total 213 of 4807683 vaccinated people developed severe COVID-19 one week after the second dose, compared to 3298 of unvaccinated 1915476 subjects. The OR of having severe COVID-19 decreased by 0.08 (0.03-0.25), I^2 was 74%. Vaccination was also significant in reducing COVID-19 infection in either symptomatic or asymptomatic cases.

Conclusion This study showed that most vaccines have comparable efficacy and effectiveness, and it is believed that with the mass vaccination of COVID-19, it is possible to control the infection and end this global pandemic

Introduction

Three novel coronaviruses have been discovered until the moment of writing this study. The first virus caused severe acute respiratory syndrome (SARS) and was named SARS-CoV-1 based on the illness they cause. In 2002, more than 8000 infections and around 10% of fatalities were caused by the first virus in China (1). The second virus emerged in Saudi Arabia in 2012 and was called Middle East respiratory syndrome coronavirus (MERS-CoV) with more than 2500 cases and a case fatality rate of about 33%(2)(3).

Following the appearance of SARS-CoV-1 and MERS-CoV, many vaccines have been developed with live-attenuated, DNA-based, and recombinant viral vectors vaccines (4)(5)(6). However, the development of clinical trials to test these postulated vaccines have been abandoned when the outbreaks subsided due to limited numbers of patients (7)(8).

With the appearance of SARS coronavirus number 2 or SARS-CoV-2 pandemic in 2019 and with the affection of millions of people with millions of deaths, the need for a rapid vaccine development started early and the vaccination process started in December 2020 with the Pfizer-BioNTech and Moderna mRNA vaccines and the Astra Zeneca/Oxford Chad Ox vaccines, as well as the Chinese Sinovac, inactivated SAR-CoV-2 and Russian Sputnik V adenovirus vaccines, and hundreds of vaccines at different stages of development and different mechanisms, including protein subunit with adjuvant, non-replicating viral vectors, RNA, virus-like-particles (VLP), DNA, inactivated- and live-attenuated virus(9)(10).

On the 23rd of August 2021, the US Food and Drug Administration has approved the Pfizer-BioNTech vaccine to protect from COVID-19 for people above 16 years old. The vaccine's previous emergency use authorization will continue for 12- to 15-year-old (11).

The World Health Organization (WHO), 7 vaccines were approved for emergency use till the beginning of September 2021. Two of them are RNA vaccines, Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2). There were three Non-replicating viral vectors are Janssen (Johnson & Johnson) (Ad26.COV2.S), Oxford/AstraZeneca (AZD1222), and Serum Institute of India Covishield (Oxford/AstraZeneca formulation). In addition to the inactivated virus technique Sinopharm (Beijing) BBIBP-CorV (Vero Cells) and Sinovac (CoronaVac)(12). In total 42.6% of the population in the world has got at least one dose of a COVID-19 vaccine. about 6 billion doses have been provided world-wide, and about 30 million are now administered each day. While in low-income countries, only about 2% of people have received at least one dose. (13)

Characteristics of an ideal vaccine are the following: can be produced at a large scale with the lowest possible cost, safe, easy to store and distribute, induces strong, protective, long-lasting neutralizing antibody and T cell responses, and should be equally suitable for any age and sex, and with the appearance of many variants of the virus, the vaccine was also needed to be technically modifiable to deal with these emerging variants (14).

One of the major determinants of vaccine acceptance is the safety profile, which ranges from mild side effects: a sore arm from the injection, feeling tired, headache, feeling achy, feeling or being sick, high temperature, or feel hot or shivery 1 or 2 days after vaccination. Very rare side effects included allergic reactions. Also, reports of an extremely rare blood clotting problem affecting a small number of people who had the Oxford/AstraZeneca vaccine were seen. The United Kingdom National Health Services (NHS) advised patients aged 40 or over and those with other health conditions, to be vaccinated with the Oxford/AstraZeneca vaccine as the benefits outweigh any risk of clotting problems to take. For people under 40 without other health conditions, NHS prefers to have the Pfizer/BioNTech or Moderna vaccine(15).

The aim of this systematic review and meta-analysis was to shed the light on different studies evaluating the efficacy/ effectiveness of COVID-19 vaccines in phase III trials.

Methodology

Criteria for considering studies.

Types of studies

All randomized controlled trials and observational studies considering COVID-19 vaccination were included. Criteria of selections included: two arms of comparison, and excluded abstract only, letter to the editor, reviews, conference, study protocols, author response, case reports, case series, and surveillance studies with no control group, in addition to any study, that had unreliable data for extraction or duplicates.

Types of participants

All age groups patients were included, with no gender restriction, either they were unvaccinated (didn't receive any type of SARSCov-2 vaccines all over the follow-up period or control group taking placebo), partially vaccinated (received only one dose of COVID-19 vaccine) or fully vaccinated (after at least 7 days from second vaccine dose)

Types of interventions

Any type of SARS CoV2 vaccine (mRNA, inactivated, viral vector, or protein-based), while controls are unvaccinated persons, or those taking placebo.

Types of outcome measures

Primary outcomes

- Efficacy or effectiveness of the COVID-19 vaccine to prevent Covid-19 mortality.

Secondary endpoints included

- Efficacy/effectiveness of the vaccine at preventing COVID-19 any time in reducing severe covid-19 infection.
- Efficacy/effectiveness of the vaccine at preventing COVID-19 within the 1st week of the 1st dose, and 1,2, 3, or 4 weeks after the 1st dose.
- Efficacy /effectiveness of the vaccine at preventing COVID-19 any time after the 1st dose.
- Efficacy/effectiveness of the vaccine at preventing COVID-19 within the 1st week of the 2nd dose, and 1,2 weeks after the 2nd dose.
- Efficacy or effectiveness of the vaccine at preventing COVID-19 any time after the 2nd dose.

Operation cases definition

Vaccine efficacy is often measured from RCT, under ideal conditions, it is the reduction proportion in confirmed symptomatic or asymptomatic confirmed cases between intervention and control group, from which percentage reduction in cases number attributable to the vaccine can be calculated (16). (Confirmed cases are persons who had positive Nucleic Acid Amplification Test (NAAT), person with positive SARS CoV-2 RDT antigen test and fulfill probable or suspected criteria of WHO case definitions, or Positive SARS CoV-2 antigen RDT test asymptomatic patient but in close contact to probable or confirmed case (17)).

Vaccine effectiveness is often measured from an observational study, represents real situations, and can detect the efficacy of vaccination against new variants, and it calculated as attributable risk reduction in COVID-19 symptomatic and asymptomatic cases in vaccinated and unvaccinated people due to vaccine (18).

Severe COVID-19: Adult patients categorized as having severe COVID-19 if matching one of the following criteria (room air oxygen less than 90%, respiratory rate more than 30 breaths per minute, or had signs of severe respiratory distress)(19).

Critical COVID-19: Adult patients with acute respiratory distress syndrome, septic shock, or any life-threatening condition needs critical care admission or mechanical ventilation(19).

Test negative cases control design: The best study design to detect risk factors of severe COVID-19 illness. At this study type symptomatic COVID-19 patients are tested using PCR test, then categorized into cases (test positive patients) and controls (test-negative patients) (20).

Search methods for identification of studies

Electronic searches: The following databases were searched: Embase, Scopus, EBSCO, MEDLINE central/PubMed, Science Direct, Cochrane Central Register for Clinical Trials (CENTRAL), Clinical Trials.gov, WHO International Clinical Trials Registry Platform (ICTRP), COVID Trial, COVID Inato, Web of Science (WoS), ProQuest thesis, ProQuest Coronavirus database, SAGE thesis, Google scholar, research square, and Medxriv. Search terms were determined and approved after the consultation of PubMed help. The following keywords were used in our search, after adapting according to each database search strategy, ('coronavirinae'/exp OR 'coronavirinae' OR 'coronaviridae infection'/exp OR 'coronaviridae infection' OR 'coronavirus disease 2019'/exp OR 'coronavirus disease 2019' OR 'coronavirus' OR 'coronavirus'/exp OR coronavirus OR 'coronavirus infection'/exp OR 'coronavirus infection') AND (Vaccin* efficac* OR Vaccin* effectiven* OR Vaccin* immun*). We searched these databases to compile all available studies on COVID-19 vaccination till 28th June 2021, without any publication or language restriction.

Searching other resources: In addition to, searching grey literature, manual search of studies by checking references list of all accepted papers, to ensure that we didn't miss any relevant stud.

Data collection and analysis:

Two independent reviewers searched each database (SH, RMG) and a third part dissolved their disagreements (RG), then all search outputs are extracted to Endnote 20 to remove duplicates. Then converted to Excel sheet to perform title abstract screening step, that completed by (RA, AM, NH, DM, OR) and resolved by (RMG) with inter- reviewer agreement K=0.8, after which an excel sheet is performed with accepted papers eligible for full-text screening which was checked by (RMG and SH).

Measurement of treatment effect:

The number of confirmed COVID-19 cases was reported in each treatment group, to analyze it according to the intention to -treat analysis as possible. The effect size will be reported as risk ratio and 95% confidence interval level.

Assessment of risk of bias in included studies: risk of bias was assessed using 2 tools according to the type of study used. ROB2 (Cochrane risk of bias to for randomized clinical trials) (21), and National heart, lung, and blood institute quality assessment tools for cohort, cross-sectional, and case-control studies (22). DM and NH reviewed the quality of studies, and any disagreement was solved by RMG and SH.

Assessment of publication bias: thorough visual inspection of the funnel plot.

Assessment of heterogeneity:

- Visual inspection of the forest plot to analyze the consistency of intervention effects across included studies. If the same intervention effect is estimated, there should be overlap between the confidence intervals for each effect estimate on the forest plot, but if the overlap is weak, or there are outliers, then statistical heterogeneity is likely to be present.
- Statistically test for variation: heterogeneity was assessed by inspecting the forest plots to detect overlapping CIs and the I^2 statistic used to denote levels of heterogeneity as defined in the Cochrane Handbook for Systematic Reviews of Interventions (23).

Heterogeneity was classified as follow:

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

Subgroup analysis and investigation of heterogeneity: The included studies were divided into subgroups based on research design (RCT and observational), and the study outcomes were compared between these subgroups of studies.

Sensitivity analysis: In this approach, we recalculated the results of our meta-analysis K times, each time leaving out one study. This analysis also provides a classification for what's considered influential. We ordered studies in the plot via I^2. Here we identified the studies with the highest heterogeneity as well as the final heterogeneity when these studies were removed.

Meta-regression: The outcome variable is the effect estimate (COVID-19 vaccine efficacy/effectiveness). The explanatory variables are study design (RCT or observational), Type of vaccine (mRNA/ not mRNA), and country.

Results

1. Prisma Flow chart

Study selection process.

A total of 21567 articles were found after searching 9 different databases. A total of 8088 articles were excluded either they were duplicates as found by Endnote X8 or were published before 2019. Title and abstract screening of 13479 papers resulted in the exclusion of irrelevant papers (13284) and 195 manually rejected duplicates. A total of 78 articles were screened for eligibility. Finally, 25 papers were eligible, for the meta-analysis. (Fig. 1)

Table 1: Summary of included studies in the quantitative analysis.

Author, year	Country	Study design	Study population (criteria)	Key Inclusion criteria Key Exclusion Criteria	Primary outcome Secondary outcome	type of vaccine /n of doses	Time points of analysis	Adjus effica 1st d
Baden,2021 (24)	USA	RCT	Sample size:30420 • Intervention (14550) • Control (14598) Mean age 51.4 Y Sex: 47.3% F	Age ≥ 18 years, no known history of SARS-CoV-2. Presence of SARS-CoV-2–binding Ab.	Prevention Covid-19 illness ≥ 14 days after the 2nd dose. Prevention of severe Covid-19 or efficacy of the vaccine at preventing Covid-19 after a single dose or at preventing Covid-19 according to a secondary (CDC), less restrictive case	Moderna/2 doses	14 days after the 1st dose	94.10 symp infect
Polack, 2021 (25)	USA	RCT	Sample size:37706	Age ≥ 16 Y, healthy or had stable chronic medical conditions. no medical history of Covid-19. Treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.	Prevention Covid-19 illness ≥ 7 days after the 2nd dose. Efficacy in participants +/- evidence of prior infection	Pfizer–BioNTech/2 doses	≥ 7 days after the 2nd dose	
Voysey, 2021a (26)	UK, Brazil, and South Africa	RCT	Sample size (17178) • Intervention (8597) • Control (8581)	Individuals 18 years and older	Virologically confirmed symptomatic COVID-19 disease more than 14 days after the second dose. Secondary efficacy analyses included cases occurring at least 22 days after the first dose	ChAdOx1 nCoV-19/ AstraZeneca/2 doses	3 months after the first dose and 14 days after the second dose	76·0%
Shinde, 2020 (27)	SA	RCT	Sample size: 4387 • Intervention (2199) • Control (2188) Mean age 32.0 Y Sex: 57% M	Healthy aged 18–84 y, without HIV infection or a subgroup aged 18–64 y with medically stable HIV. Pregnancy, receipt of immunosuppressive therapy, autoimmune or immunodeficiency disease except for medically stable HIV infection, a history of confirmed or suspected Covid-19, and SARS-CoV-2 infection as confirmed on a nucleic acid amplification test (NAAT).	Safety and vaccine efficacy against laboratory-confirmed symptomatic Covid-19 at 7 days or more after the second dose among participants without previous SARS-CoV-2 infection.	Novavax	≥ 7 days after the 2nd dose	

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Emary, 2021 (28)	UK	RCT	Sample size: 8534 • Intervention (4244) • Control (4290) Sex: 59% F	Age ≥ 18 years who were enrolled in phase 2/3 vaccine efficacy studies in the UK, and who were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 or a meningococcal conjugate control (MenACWY) vaccine, who received 2 doses of the intervention were included. Single-dose recipients were excluded. Cases were excluded if they occurred fewer than 15 days after the second dose of vaccine or occurred in participants who were not seronegative on a SARS-CoV-2 N protein assay at baseline.	Symptomatic COVID-19 disease, defined as a positive NAAT result on an upper airway swab in a participant with at least one symptom, including cough, fever of 37·8°C or higher, shortness of breath, anosmia, or ageusia. The efficacy analysis included symptomatic COVID-19 in seronegative participants with a NAAT positive swab more than 14 days after the second dose of vaccine.	ChAdOx1 nCoV-19/ AstraZeneca/2 doses	≥ 7 days after the Second dose	
Logunov, 2021 (29)	Russia	RCT	Sample size: 19866 • Intervention (14964) • Control (4902) Mean age 45·3 Y Sex: 61·1% M	Age ≥ 18 y; negative HIV, hepatitis B and C, and syphilis test results; No known history of SARS-CoV-2; negative drug and alcohol tests at screening visit; no history of vaccine-induced reactions. pregnancy or breastfeeding; the active form of a disease caused by HIV, syphilis, or hepatitis B or C.	confirmed COVID-19 by PCR from day 21 after receiving the first dose.	Gam-COVID-Vac/ 2 doses	≥ 7 days after the 1st dose.	91·6%
kaabi, 2021 (30)	UAE & Bahrain	RCT	Sample size: 40382 13459 Received SARS-CoV-2WIV04 and 13 465 received HB02 • Control (13 458) Mean age 36.1 Y Sex: 84.4% Men	. Healthy Age ≥ 18 y, 3females with a negative urine pregnancy test, With self-ability to understand the study procedures and sign the informed consent form. Confirmed acute cases of SARS-CoV-2 infection; With a medical history of SARS, MERS virus infection or with severe chronic illness, and other circumstances judged by investigators	Symptomatic laboratory-confirmed COVID case that occurred at least 14 days after second dose.	SARS-CoV-2 WIV04/ 2 doses And HB02/ 2 doses.	≥ 7 days after the second dose	

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Frenck, 2021 (31)	Multinational	RCT	Sample size: 2260 • Intervention (1131) • Control (1129) Sex: 50.1% M	adolescents 12 to 15 Y, healthy or had stable pre-existing disease (hepatitis B, hepatitis C, or human immunodeficiency virus infection). History of SARS-CoV-2 infection, diagnosis of an immunocompromising or immunodeficiency disorder, or treatment with immunosuppressive therapy.	Safety objectives included the assessment of local or systemic reactogenicity events, Immunogenicity assessments (SARS-CoV-2 serum neutralization assay, and receptor-binding domain [RBD]. The efficacy of BNT162b2 against confirmed Covid-19 with an onset 7 or more days after dose 2.	BNT162b2/2 doses	≥ 7 days after the second dose	
Sadoff, 2021 (32)	Multinational	RCT	Sample size: 39321 • Intervention (19630) • Control (19691)	BMI < 30 kg/m2, healthy or had stable pre-existing disease (including hepatitis B, hepatitis C, or HIV infection). history of anaphylaxis or other serious ADRs to vaccines or their excipients; has an abnormal function of the immune system resulting from clinical conditions Persons with a previous clinical or virologic Covid-19 diagnosis or SARS-CoV-2 infection	Vaccine efficacy against moderate to severe–critical coronavirus disease 2019 (Covid-19) with an onset at least 14 days and at least 28 days after administration.	Ad26.COV2. S/ 1 dose.	After the 1st dose.	66.9%
Dagan, 2021 (33)	Israel	Observational study	Sample size:71152	Age ≥ 16 y, No known history of SARS-CoV-2 and a member of the health care organization during the previous year. No Clalit membership, Unmapped place of residence, Being health care workers, and Residence in a long-term care facility.	Documented SARS-CoV-2 infection, symptomatic Covid-19, hospital admission for Covid-19, and death from Covid-19.	BNT162b2/ 2 doses	days 14 through 20 (after 1 dose). 7 days after the second dose.	57% f symp infect for hospi
Martínez-Baz,2021 (34)	Spain	Prospective cohort	Sample size: 20961 801 received Comirnaty, 524 (Vaxzevria and 56 Moderna vaccine.	aged ≥ 18 years covered by the Navarre Health Service, who had been close contacts of laboratory-confirmed COVID-19 cases from January to April 2021. Close contacts with a positive test for SARS-CoV-2 before January 2021, nursing home residents and those who did not complete the testing protocol	Preventing confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, symptomatic confirmed SARS-CoV-2 infections, and COVID-19 hospitalizations in adults (≥ 18 years old) who had had close contact to a person with confirmed infection.	Comirnaty/ 2 doses, Vaxzervria/ 2 doses and Moderna/ 2 doses	After the first and second doses	35% f infect 42% f symp infect 72% for hospi

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Swift, 2021 (35)	USA	Retrospective cohort	Sample size: 71152 • Cohort (47221) • Controls (23931)	Health care workers (HCWs). Individuals with a positive molecular assay prior to 1/1/2021 or an inactive employment status were excluded.	Vaccine effectiveness in the subpopulation of HCP reached through employer vaccination programs.	BNT162b2 /2 doses and Moderna /2 doses	After the first and second doses	
Tenforde, 2021 (36)	USA	Case control	Sample size: 417 • Cases (187) • Control (230)	Aged ≥ 65 years on the date of hospital admission, received clinical testing for SARS-CoV-2 Participants with unverified COVID-19 testing status or vaccination status, or vaccination with Janssen COVID-19 vaccine.	Effectiveness of Pifzer and Moderna vaccines among adults aged > 65 years	BNT162b2 /2 doses and Moderna /2 doses	After the first and second doses	64%.
Khan, 2021 (37)	USA	Retrospective cohort	Sample size: 14697 • Cohort (7321) • Controls (7376)	Aged ≥ 18 years who had not previously been diagnosed with SARS-CoV-2 infection, who were taking an IBD medication, and who had at least 6 months of VHA outpatient visit data prior to the index date. Janssen COVID-19 vaccine given limited sample size and follow-up data.	Time to SARS-CoV-2 infection, determined by PCR testing. All-cause mortality and severe SARS-CoV-2 infection.	BNT162b2 /2 doses and Moderna /2 doses	> 7 days after the 2nd dose	
Bernal, 2021 (38)	UK	Case control	Sample size: 156930 • Cases (138869) • Controls (18061)	Adults aged 70 years and older who reported symptoms of covid-19 between 8 December 2020 and 19 February 2021 and were successfully linked to vaccination data in the National Immunization Management System. Those with a previous positive PCR or antibody test result at any time before 8 December	Confirmed symptomatic SARS-CoV-2 infections. Admissions to hospital for covid-19, and deaths with covid-19	BNT162b2 / 2 doses and ChAdOx1-S)/ 2 doses	≥ 42 days after the 1st and 14 after the 2nd dose	60–7 BNT1 And 60–7 ChAd after dose
Fabiani,2021 (39)	Italy	Retrospective cohort	Sample size: 6423 • Cohort (5333) • Control (1090)	Health care workers (HCWs). HCWs infected with COVID-19 before the vaccination campaign, HCWs working outside hospitals and district outpatient centres, support staff, and administrative staff.	Effectiveness of the vaccine.	BNT162b2 / 2 doses	14–21 days After 1st dose and ≥ 7 days after 2nd dose	84%

Author, year	Country	Study design	Study population (criteria)	Key Inclusion criteria Key Exclusion Criteria	Primary outcome Secondary outcome	type of vaccine /n of doses	Time points of analysis	Adjus effica 1st d
Gras-Valentí ,2021 (40)	Spain	Case control	Sample size: 268 • Cases (70) • Control (198)	HCP with suspected COVID-19 and HCP close contacts of COVID-19 cases were included and PCR tested for COVID-19; those with positive PCR were considered cases and those with negative PCR were considered controls.	Effectiveness of a dose of (BNT162b2) after 12 days of administration in health personnel of a department of Health	BNT162b2	12 days After the first dose	52.6% adjus vacci effica 74.6%
Hall, 2021 (41)	UK	Prospective cohort	Sample size: 1106905 • cohort (396318) • Control (710587) Median age 46·1 Y Sex: 84% F	HCWs, support staff, and administrative staff (aged ≥ 18 Y) working at hospital sites participating in SIREN who could provide written informed consent and anticipated remaining engaged in follow-up for 12 months. Participants were excluded from this analysis if they had no PCR tests after Dec 7, 2020, or had insufficient PCR and antibody to complete cohort assignment	Vaccinated participants for the vaccine coverage analysis and SARS-CoV-2 infection confirmed by a PCR test for the vaccine effectiveness analysis.	BNT162b2	After the first and second doses	70%
Haas, 2021 (42)	Israel	observational study	Sample size: 6538911 • vaccinated (4714932) • Control (1823979)	The study population consisted of residents of Israel who aged ≥ 16 Y. Cases were excluded from the analysis if they had received only one dose or had received two doses of BNT162b2 and fewer than 7 days had passed since the 2nd dose.	Covid-19 infection Hospitalization, severe infection, symptomatic infection, and death	BNT162b2 / 2 doses	> 7 days after the Second dose	
Pilishvili,2021 (43)	USA	Cases-control	Sample size: 1843 • Cases (623) • Controls (1220)	HCW with a positive SARS-CoV-2 test symptoms were enrolled as case-patients, and HCW with a negative SARS-CoV-2 PCR test result, regardless of symptoms, were eligible for enrolment as controls. Positive SARS-CoV-2 PCR or antigen-based test result > 60 days earlier.		BNT162b2 / 2 doses and Moderna/ 2 doses	14 days after the 1st dose and ≥ 7 days after the second dose	82%
Vasileiou, 2021 (44)	UK	Prospective cohort	Sample size: 4409588 • cohort (1331993) • Controls (3077595)	Received a single dose of vaccine between Dec 8, 2020, and Feb 22, 2021, with maximum follow-up time censored at Feb 22, 2021. Previously tested positive with real-time reverse transcription-PCR (rt PCR) for SARS-CoV-2 infection.	Any hospital admission with COVID-19 as the main cause, or hospital admission within 28 days of a positive rtPCR test for SARS-CoV-2 infection from Dec 8, 2020, to Feb 22, 2021.	BNT162b2 / 2 doses and ChAdOx1-S)/ 2 doses	28–34 days post the first dose vaccination.	91% f BNT1 88% f ChAd vacci

Author, year	Country	Study design	Study population (criteria)	Key Inclusion criteria Key Exclusion Criteria	Primary outcome Secondary outcome	type of vaccine /n of doses	Time points of analysis	Adjus effica 1st d
Madhi, 2021 (45)	South Africa	RCT	Sample size: 2026 • Intervention (1013) • Control (1013) Median age: 30 Y Sex: 56.5% M	HIV-negative adults aged 18 to > 65 Y. HIV- positive adults at screening, previous or current laboratory-confirmed Covid-19, a history of anaphylaxis in relation to vaccination, and morbid obesity (BMI ≥ 40).	Safety and efficacy of the vaccine against laboratory-confirmed symptomatic Covid-19 more than 14 days after the second dose.	ChAdOx1/ 2 doses	14 days after the second dose	
Britton, 2021 (46)	USA	Retrospective cohort	Sample size: 463 (304 had received 2 vaccine doses, 72 had received 1 dose and 87 had not received any doses).	Residents of skilled nursing facilities were included if they were admitted at either facility during one or more rounds of facility-wide SARS-CoV-2 testing during the week before or any time after their facility's first vaccination clinic.		BNT162b2 / 2 doses	After the first dose	63%
Menni, Klaser, 2021 (47)	UK	prospective observational study	Sample characteristics: 67 293 app users received BNT162b2 and 36329 received ChAdOx1 nCoV-19 Compared to 464 356 unvaccinated app users	Not reported	The proportion of app users reporting adverse effects within 8 days after vaccination. Infection rates in individuals after receiving a 1st dose of either the vaccines.	BNT162b2 / 2 doses and ChAdOx1-S)/ 2 doses	8 days after the first dose	64% f BNT1 52% f ChAd
Voysey, 2021b	UK, Brazil, and South Africa	RCT	Sample size COV002 (UK; LD/SD; N = 2741) COV002 (UK; SD/SD; N = 4807) COV003 (Brazil; all SD/SD; N = 4088)	Cases were eligible for inclusion in efficacy if the first symptom or first NAAT-positive result was on or before the data cutoff date (Nov 4, 2020). Seropositive participants at baseline or those who had no baseline result were excluded. Other exclusions included those with NAAT-positive swabs within 14 days after the second vaccination.	Virologically confirmed, symptomatic COVID-19asymptomatic infections, in COV002 in Uk tested weekly by self-administered nose and throat swab from 1 week after first vaccination using kits provided. Adverse events.	COV002: LD (2·2 × 10¹⁰ viral particles), SD (5 × 10¹⁰ viral particles) COV003: two doses of the vaccine at a dose of 3·5–6·5 × 10¹⁰ viral particles with administration up to 12 weeks apart (target 4 weeks),	14 days after their second dose	

2.Quality assessment:

Quality assessment for the studies included in this meta-analysis was conducted using Cochran risk assessment tool (21), and NOS checklists (22). Quality assessment for RCTs is presented in the summary of the risk of bias graph Fig. 2 Quality assessment of observational studies is uploaded as supplementary material. LINK: https://docs.google.com/document/d/1199T2CxcP3z1X_L-5ICLY25E4xNIEsbg/edit?usp=sharing&ouid=100587500715661436749&rtpof=true&sd=true)

3. Outcomes

3.1 Mortality after vaccination

- **Mortality after 7 days from dose 2**

In total 6 studies assessed mortality related to the COVID-19 vaccine 7 days after vaccination. Four studies were randomized controlled trials, and two were observational. Only two studies reported a significant decline in the OR of mortality related to COVID-19 vaccination, however, the overall effect was statically

significant. The odds ratio of mortality 7 days after full vaccination decreased significantly among vaccinated compared to the unvaccinated group OR=0.14(95CI, 0.05-0.41), I^2=63%. The study of Logonov *et al* (29) was removed after conducting sensitivity analysis, this resulted in the reduction of heterogeneity to 54%, the OR became 0.10 (95CI%, 0.04-0.27).

- **Two weeks after the second dose**

Four studies addressed mortality after two weeks of the second dose, all these studies were observational. Except for the study of Sadoff *et al* (32), the odds ratio was significantly decreased. Pooled OR was 0.34 (95CI 0.26-0.44), however, the heterogeneity was statistically high 85%. After conducting a leave-one-out sensitivity analysis, the study of Khan *et al* (37), was omitted. The observed heterogeneity dropped to 0%, and the pooled effect was still significant OR= 0.46, (95% CI 0.35-0.61).

3.2 Severity after vaccination

- **The severity of COVID 19 infection one week after the second dose**

Seven research studied the severity of COVID-19 one week after the second dose. In total 213 of 4807683 vaccinated people developed severe COVID-19 one week after the second dose, compared to 3298 of unvaccinated 1915476 subjects. The OR of having severe COVID-19 decreased by 0.08 (0.03-0.25), I^2 was 74%. After subgrouping the included studies into randomized and observational, the heterogeneity dropped to 0%. The difference between observational and interventional studies was not significant (P=0.46). The odds ratio of severe COVID-19 of RCT was 0.14 (0.03-0.75), while the OR in observational studies was 0.06 (0.02-0.24).

- **The severity of COVID-19 infection one week after the first dose**

With a heterogeneity of $I^{2=}$= 61%, OR of having severe COVID-19 one week after the first dose was 0.21 (95% CI, 0.11-0.40). After omitting the study of Khan *et al* (37), the OR of having severe COVID-19 after the first dose of vaccination among 79176 vaccinated and 78810 unvaccinated subjects in 6 studies was increased to 0.29 (0.19-0.46), I^2 was 25%. Only this study of Sadoff *et al* (32), did not show any protective effect of vaccination.

3.3 Efficacy/effectiveness of the 1st dose

- **Cases reported within the first week of vaccination after the 1st dose:**

Total (Symptomatic and asymptomatic)

Two researchers evaluated the effectiveness of the COVID-19 vaccine in reducing numbers of cases within one week after the 1st dose; Dagan *et al* (33), reported that 1965 of 596618 vaccinated subjects get COVID-19 compared to 2362 of 596618 unvaccinated individuals, OR =0.83. Hall *et al* (41), highlighted that incidence of COVID-19 was 140 of 20641 unvaccinated subjects, still lower than cases reported among unvaccinated (977/2683), OR 0.01.

Symptomatic cases

Bernal *et al* (38) reported that 346 of 864 vaccinated subjects versus 8988/24706 of unvaccinated subjects developed COVID-19, OR 1.17(95%CI 1.02-1.34) meaning that it has no protective effect. Dagan *et al* (33), mentioned that COVID-19 vaccine had a protective effect OR was 0.78 (95%CI, 0.72-0.84). Among vaccinated subjects (596618), about 1103 developed COVID-19, while among unvaccinated individuals 596618, about 1419 developed symptomatic COVID 19.

Due to significant heterogeneity, we could not pool the findings of these two outcomes.

- **Cases reported within two weeks of vaccination after the 1st dose:**

Total (Symptomatic and asymptomatic)

Four research studied effectiveness/efficacy of COVID-19 within two weeks after the first dose. In total 3909 of 637142 vaccinated people developed COVID-19 within 2 weeks after the first dose, compared to 5087 of unvaccinated 614989 subjects. The OR of having severe COVID-19 decreased by 0.17 (0.02- 1.72), I^2 was 100%. After subgrouping included studies into randomized and observational, the heterogeneity dropped to 94%. The difference between observational and interventional studies was significant (P=0.001). The odds ratio of infection with COVID-19 of RCT was 0.79 (0.48-1.3), while the OR in observational studies was 0.17(0.02-0.172).

Symptomatic cases reported within 14 days of the first dose

Bernal *et al* (38) reported 958 symptomatic cases of 1154 vaccinated subjects compared to 89 of 8988 unvaccinated subjects the OR = 488 (95CI 337-633), meaning that vaccination increases the risk. The protective effect of the COVID-19 vaccine was addressed by Dagan *et al* (33), OR was 0.82 (1967/596618 vaccinated vs 2393/596618) and Fabiani *et al* (39), OR 0.1 (47/5333 vaccinated versus 89/1090 unvaccinated). Pooling of results was achieved due to significant heterogeneity.

Asymptomatic cases reported after the first dose.

Three studies addressed the effectiveness/efficacy of vaccination in reducing the risk of having asymptomatic COVID-19. The OR was 0.23 (0.06-1.63), meaning that it has no effect. The reported heterogeneity was 97%. After conducting leave one-out sensitivity analysis, the study of Fabiani *et al* (39) was omitted. Heterogeneity dropped to 80%, vaccination still have no protective effect, OR = 0.73 (95CI, 0.35-1.53)

- **Cases reported after three weeks of vaccination with 1st dose**

Total (Symptomatic and asymptomatic)

Five researchers studied the effectiveness/efficacy of COVID-19 within three weeks after the first dose. In total 4621 of 642572 vaccinated people developed COVID-19 within 3 weeks after the first dose, compared to 6318 of unvaccinated 620356 subjects. The OR of having COVID-19 was by 0.19 (0.03- 1.17), I^2 was 100%. After subgrouping included studies into randomized and observational, the heterogeneity dropped to 0%. The difference between observational and interventional studies was insignificant (P=0.33). The odds ratio of infection with COVID-19 of RCT was 0.45 (0.31-0.65), while the OR in observational studies was 0.13 (0.01-1.49).

Symptomatic cases

For Dagan *et al* (33); the OR of having symptomatic COVID-19 after vaccination was 0.73(95CI, 0.69-0.77), Of 596618 Vaccinated individuals 2250 developed COVID-19, compared to 3079 of 596618 unvaccinated subjects. Fabiani *et al* (39) reported that 51/53333 vaccinated subjects developed COVID-19 compared to 97/1090 unvaccinated subjects, OR =0.1(95%CI 0.07-0.14). results could not be pooled due to significant heterogeneity.

Asymptomatic cases

Only the study of Fabiani *et al* (39) reported this outcome. In total 15 of 5333 vaccinated subjects developed asymptomatic COVID-19 compared to 46 of 1090, OR = 0.06 (0.04-0.12)

- **Cases reported within the first 4 weeks of vaccination with 1st dose**

The total cases either symptomatic or asymptomatic were reported in two studies; Dagan *et al* (33) documented 4405 of 596618 vaccinated individuals compared to 5775 of 596618 subjects. Hall *et al* (41), diagnosed 427 of 20641 subjects, and 977 0f 2683 unvaccinated subjects the OR were 0.76 (95CI, 0.73-0.79) and (0.04 (95CI 0.03-0.4) respectively. The research team could not pool the OR ratio due to significant heterogeneity.

All cases reported after the first dose

Among 777171 vaccinated subjects with a single dose of COVID-19 vaccine, 8246 developed COVID-19, while 58261 of 1104745 unvaccinated subjects developed COVID, OR =0.14 (0.07-0.4) I^2 =100%. After subgrouping based on the study design, the heterogeneity dropped to 0%, OR in RCT studies was 0.14 (95CI; 0.07-0.27), and in observational studies 0.15 (95CI; 0.06-0.4). The difference between subgroups was not significant, P=0.88

3.4. Efficacy/effectiveness of the second dose

- **Cases reported within 7 days of the second dose**

All cases

After the second dose, six studies reported COVID-19 cases after seven days of vaccination, two studies were RCT, and four observational studies, the odds ratio was significantly decreased by 0.06 (95%CI, 0.02-0.21) among vaccinated compared to the unvaccinated group. However, the heterogeneity was high 98%. The test for subgroup differences suggests that there is no statistically significant subgroup effect (P = 0.98), meaning that type of study did not statistically significantly modify the effectiveness/efficacy of vaccination. Vaccination decreased the number of cases regardless of the study design, although the protective effect was greater in RCT than in observational studies. There is no heterogeneity between results from the RCT, while the heterogeneity of observational studies was 99%. By conducting a meta-regression 100% of substantial heterogeneity can be explained, using type of vaccine and country as predictors, [m RNA type, B= -3.33, P-value = 0.028; country UK, B= -3.7, P-value = 0.025; country US, B= -2.03, P-value = 0.037]

Symptomatic cases within 7 days of dose 2

Two observational studies reported symptomatic SARS-COV-2 cases, the odds ratio was decreased by 0.11 (95CI, 0.01-1.98) among the vaccinated group compared to the unvaccinated group with considerable heterogeneity of 77%.

- **Cases within 14 days of second dose**

Total cases

Three studies highlighted the number of new cases reported within 14 days of dose 2, Baden *et al* (48), reported no cases among 14550 vaccinated subjects compared to 19 of 14598 unvaccinated individuals. Dagan *et al* (33), reported 332 confirmed cases of 187702 vaccinated subjects, while 949 cases were diagnosed among 186553 unvaccinated subjects. Hall *et al* (41), reported 10 cases of 1607 vaccinated subjects and 977 cases of 2683 unvaccinated individuals. The pooled OR was 0.05 (95% CI, 0.0-01.34), I^2=99 meaning that the effect of the vaccine was insignificant. After conducting leave one out sensitivity analysis, the study of Dagan *et al* (33) was omitted, the OR became 0.01(95%CI, 0.01-0.02), I^2= 0%, and still insignificant.

- **Cases reported 7 days after 2nd dose**

Overall

Among 4747653 vaccinated subjects, the number of confirmed covid-19 cases reported 7 days after the second was 6295, while 111252 confirmed cases were reported among 1854768 unvaccinated individuals. The OR was 0.03 (95%CI 0.02-0.05), meaning that vaccination is protective against COVID-19. The researchers explained 98.73% of this heterogeneity by the meta-regression of vaccine type and country predictors; where significant predictors are non m-RNA vaccine (B= 3.33, P-value =0.014), country Spain (B= 3.27, P-value =0.002), and country USA (B=1.53, P-value =0.039).

Symptomatic cases reported after 7 days of dose 2

With a heterogeneity of 0%, the effectiveness/efficacy of the COVID-19 vaccine in preventing symptomatic COVID-19 infection among 4721975 vaccinated and 1826910 unvaccinated subjects was 0.02 (95CI, 0.02-0.02). Three studies were included in the analysis one RCT and two observational studies.

Asymptomatic Cases reported after 7 days of the second dose

Two studies (recruited 4720118 vaccinated, 1825069 unvaccinated) assessed asymptomatic COVID-19 infection after 7 days of vaccination. Vaccination was protective against COVID-19.

- **Cases reported within 14 days after the second dose**

Total (Symptomatic and asymptomatic)

Regarding total cases either symptomatic or asymptomatic 14 days after second dose. There are nine studies included in this analysis. The overall effect was reported in 4080 cases from 4832289 vaccinated persons, while 119829 persons were diagnosed as COVID cases from 1940635 unvaccinated persons, OR = 0.08, 95% CI (0.02,0.34) with substantial heterogeneity I^2 = 100%. Hence, the research team performed subgroup analysis in 2 steps, first, we categorized the cases as asymptomatic or symptomatic, then sub-grouped by study type either RCT or observational, but it didn't affect the heterogeneity.

Therefore, a meta-regression was performed to understand the main predictors for this heterogeneity. Where we find that the type of vaccine and the country were responsible for 88.21% from this heterogeneity, [non mRNA vaccine B=3.519, P-value= 0.004; Country Spain B=2.6256, P-value = 0.028).

- **Cases reported 7-14 days after the second dose**

The result couldn't be pooled due to substantial heterogeneity I^2 =99%. Dagan *et al* (33) reported 51 cases from 108529 vaccinated persons and 278 cases from 107209 unvaccinated one, OR = 0.18 (0.13-0.24), while Hall *et al* (41) reported 4 cases from 1607 vaccinated to 977 from 2683 unvaccinated, OR = 0 (0 - 0.01).

- **All cases reported after the 2nd dose**

In total 377 confirmed cases of 228715 subjects were reported after the second dose, while 2435 cases of 224569 unvaccinated subjects were reported, OR 0.179 (95CI, 0.15-0.19), I^2 =98%. The test for subgroup differences suggests that there is no statistically significant subgroup effect (P = 0.98), meaning that type of study did not significantly modify the effectiveness/efficacy of vaccination. Vaccination decreased the number of cases regardless of the study design, although the protective effect was greater in RCT than in observational studies. There is no heterogeneity between results from the RCT, while the heterogeneity of observational studies was I^2=99%.

Discussion

COVID-19 is a life-threatening disease that has no effective therapy until this moment. The aim of vaccine development is to provide a weapon that protects individuals from getting infected or become a source of transmission. In 2020, several vaccines had become available for use in across the world, over 40 different vaccines were in human trials, and over 150 were in preclinical trials. An updated list of vaccine candidates under evaluation is maintained by the WHO (12). Although some of the vaccines have been approved for emergency use by the FDA in the States and the health departments in every country, the efficacy of the vaccine has not yet been widely discussed. It is worthy to note that vaccinations are still being administered worldwide; however, the vaccinated population are still a small proportion of the entire population, effectiveness and efficacy represent main concerns for many people. Therefore, in the current meta-analysis, we provide systematic and comprehensive data regarding the vaccines' efficacy and effectiveness against SARS-CoV-2. Here, we included RCTs and observational studies on the efficacy, and effectiveness of COVID-19 vaccines.

Several studies recruited different numbers of participants aimed at studying various outcomes with variable endpoints providing different doses of vaccine with variable durations. The efficacy/efficiency of several types of COVID-19 vaccines has been stressed in this study to give strong evidence to decision-makers in health policy to deal with the continuing epidemic. The research team included 25 articles to study the desired outcomes. The included studies according to their design were ten RCT, four case-control, and eleven cohort. In the systematic review section, the highest number of recruited patients in a single study was 6538911 (42), while the smallest number was 268 subjects (40).

This is the first study on the efficacy/ effectiveness of COVID-19 vaccines using RCTs and observational studies. Based on the finding of this meta-analysis, the **overall efficacy/effectiveness** of the COVID-19 vaccine was 0.18 (95CI, 0.12–0.27), I^2 = 100%. In fact, the type of vaccine (mRNA, non-mRNA) and country where the vaccine was provided explained about 38.9 % of this heterogeneity. The OR of **mortality** related to COVID-19 two weeks after vaccination was significantly decreased, OR = 0.46, (95%CI 0.35–0.61), I^2 = 0. Similarly, Mortality one week after vaccination dropped significantly OR = 0.0.1, (95%CI 0.05–

0.41), I^2 = 54. The odds ratio of **severe COVID**-19 of RCT was 0.14 (0.03–0.75) I^2 = 30%, while the OR in observational studies was 0.06(0.02–0.24), I^2 = 85%. In the same line, the OR of having severe COVID-19 after the first dose was 0.15 (0.10–0.25), I^2 was 26%.

First dose: **Within a week of the second dose**, vaccination decreased the number of cases reported regardless of the study design, although the protective effect was greater in RCT than in observational studies. The substantial heterogeneity was due to the type of vaccine and country as predictors. Similarly, in **symptomatic cases, within 7 days of the second dose, decreased significantly 0.11 (95CI, 0.01–1.98), I^2 = 77%. Cases within 14 days of the second dose; the total number of cases reported decreased significantly**, 0.01(95%CI, 0.01–0.02), I^2 = 0%. **Cases reported 7 days after 2nd dose, the total number of cases decreased significantly concurrent with vaccination**, OR 0.03(95%CI, 0.02–0.05), I^2 = 73%, 98.73% of this heterogeneity by the meta-regression of vaccine type and country. Regarding symptomatic cases, the effectiveness/efficacy of covid-19 vaccine COVID-19 infection 0.02(95CI, 0.02–0.02). Cases reported 14 d after dose 2, the OR among vaccinated versus unvaccinated subjects was 0.06 (95CI, 0.01–0.41). All **cases reported after the second dose**, vaccination decreased the number of cases regardless of the study design, although the protective effect was greater in RCT than in observational studies.

A lot of studies on the tolerance of the elderly population to the vaccine still are needed. In addition, there are currently no published results of clinical trials targeting juveniles. Only the study of Frenck et al (31) evaluated the vaccine effectiveness among adolescences. Most studies recommend double-dose vaccination, but the interval needs further study.

Efficacy

Overall, the efficacy of the vaccine varies by the dosing interval. The studies were initially planned to test only single dose. However, a review of phase III data showed a significant increase in neutralizing antibodies with a second dose of the vaccine(49). It was also advised that when vaccine supply is scarce, countries should vaccinate with a single dose. This may provide better overall protection in the population than vaccinating half the number of individuals with both doses(50).

Strength And Limitations

This systematic review has some limitations: No evidence of the long-term effectiveness of the vaccine. Due to the urgency of vaccine development, most trials only followed up to 28 days after vaccination. Second, this metanalysis cannot give solid evidence on the efficacy/effectiveness of COVID-19 on the variant strain B.1.351. This variant strain can escape neutralizing relevant antibodies. These data indicate reinfection with antigenically distinct variants and mitigates the full efficacy of spike-based COVID-19 vaccines(51). Third, A lot of studies on the tolerance of the elderly population to the vaccine still are needed. In addition, there are currently no published results of clinical trials targeting juveniles. Only the study of Frenck et al (31)evaluated the vaccine effectiveness among adolescence 12–15 years. Most studies recommend double-dose vaccination, but the interval needs further study.

Points of strength include, this systematic review did not include preprinted documents, which have not been peer-reviewed and some of the data are not available. Due to the scarcity of RCT, observational studies were included, retrospective case analysis. Animal studies were excluded, and we did not have lingual restrictions.

Conclusion

This systematic review & meta-analysis summarized the results of clinical trials related to the COVID-19 vaccine, showing that most vaccines had comparable effectiveness. It is believed that with the widespread vaccination of COVID-19, it is possible to control the global pandemic of COVID-19

Declarations

Competing interests: The authors declare no competing interests

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Figures

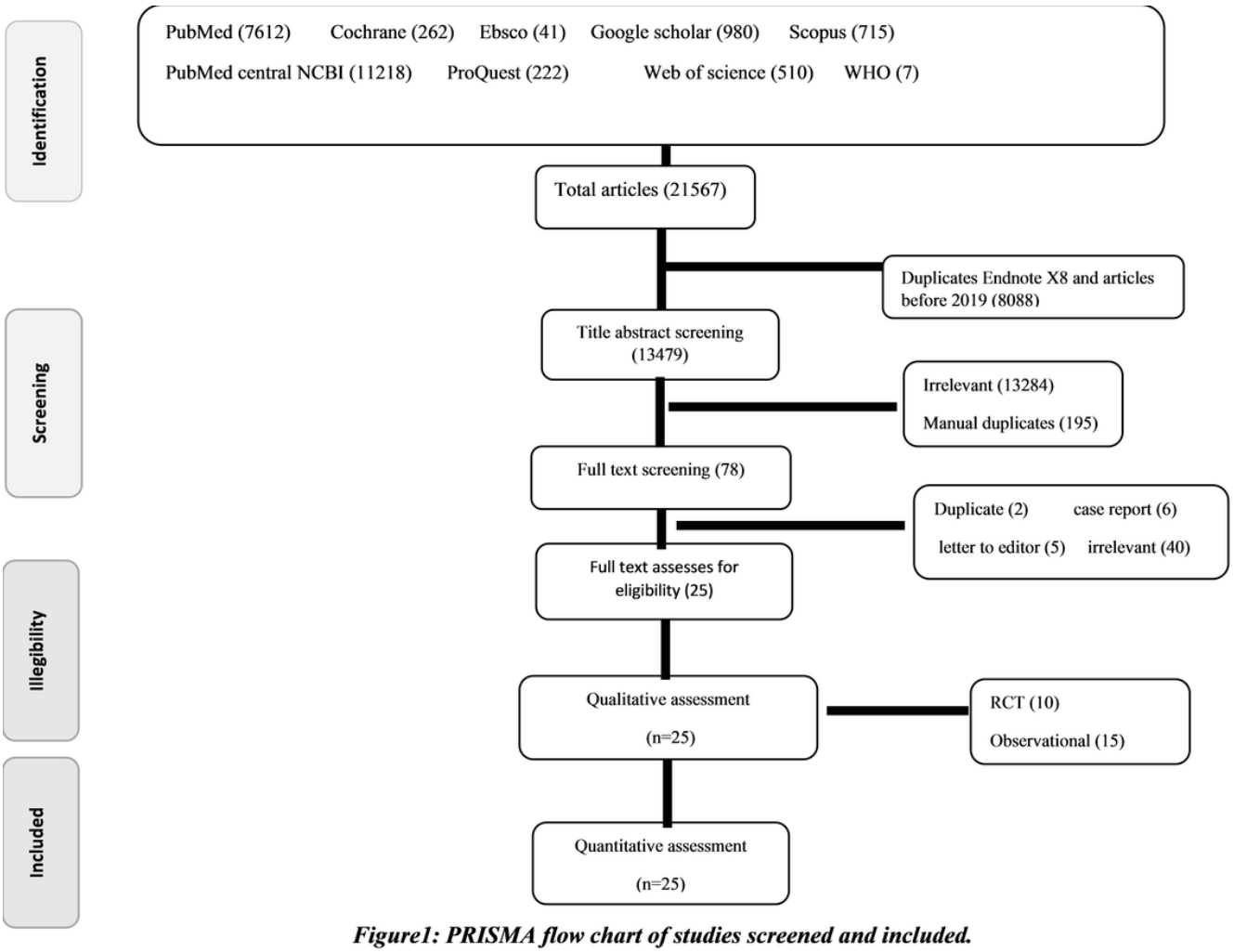

Figure1: PRISMA flow chart of studies screened and included.

Figure 1

PRISMA flow chart of studies screened and included.

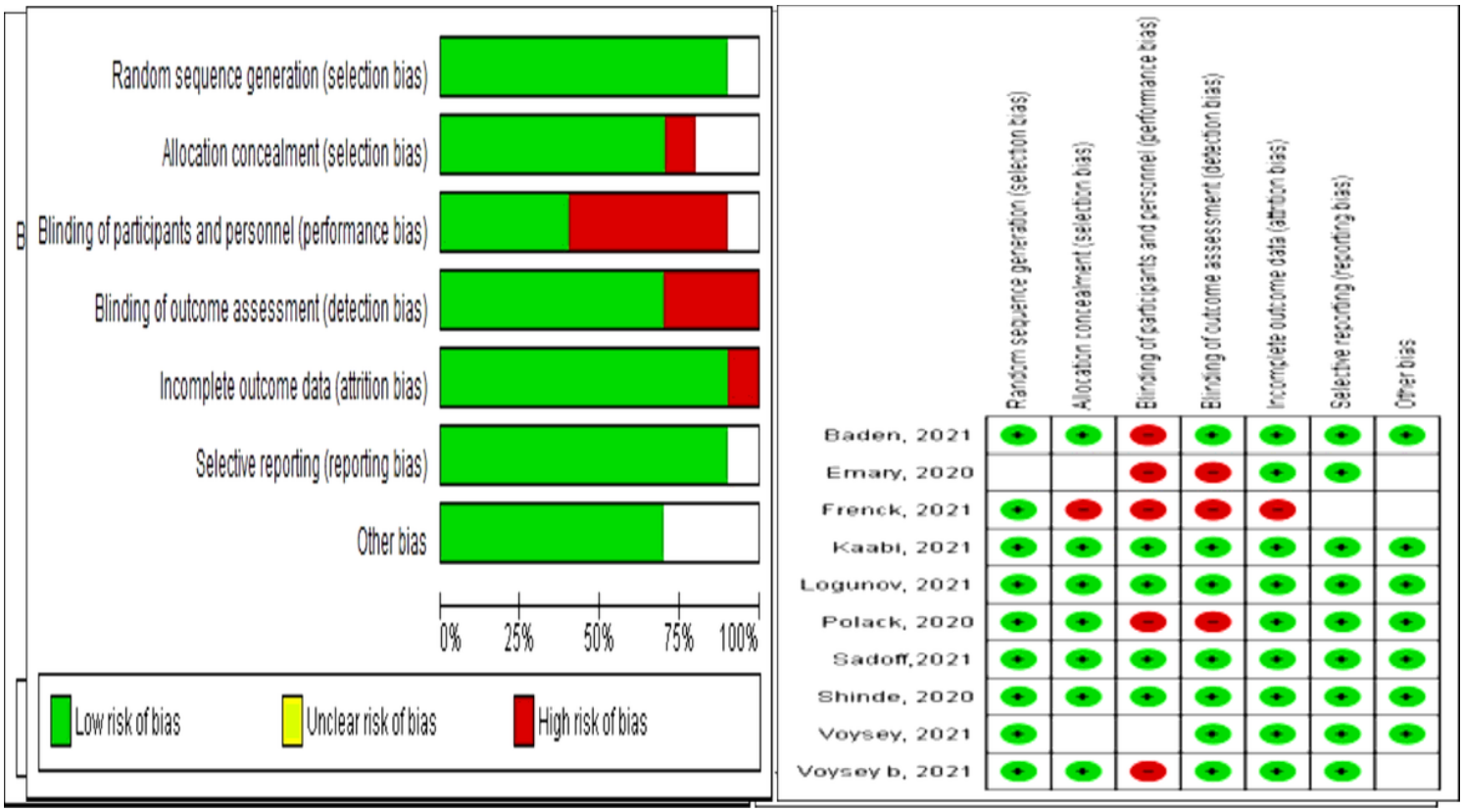

Figure 2

Quality assessment of RCT studies.

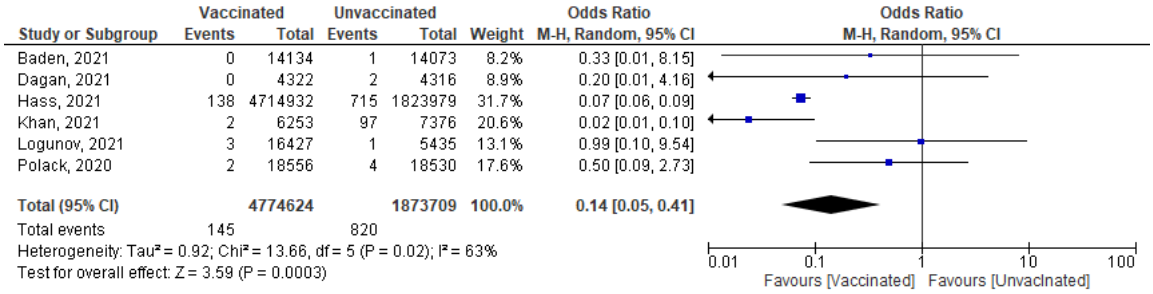

Figure 3

overall odds ratio mortality 7 days after full vaccination

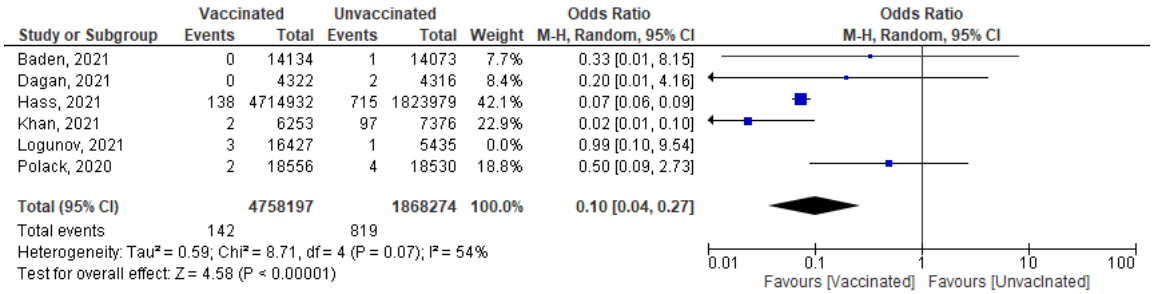

Figure 4

After leave one out sensitivity analysis

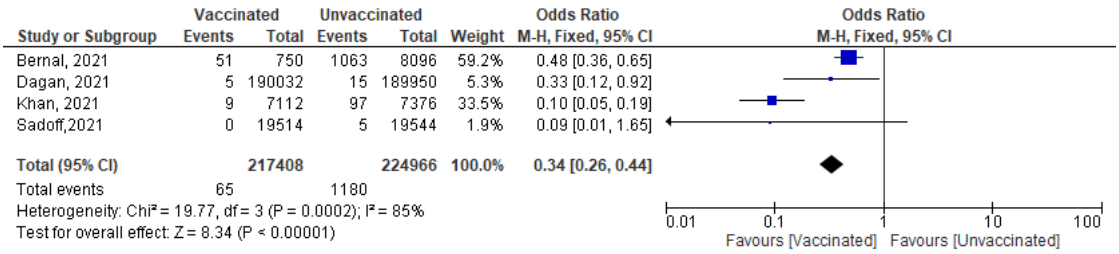

Figure 5

Mortality odds ratio after 2 weeks of 2nd dose.

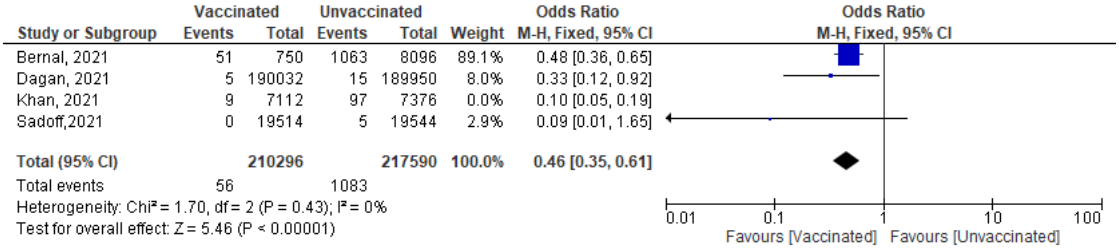

Figure 6

Mortality odds ratio after 2 weeks of 2nd dose, leave-one-out sensitivity analysis

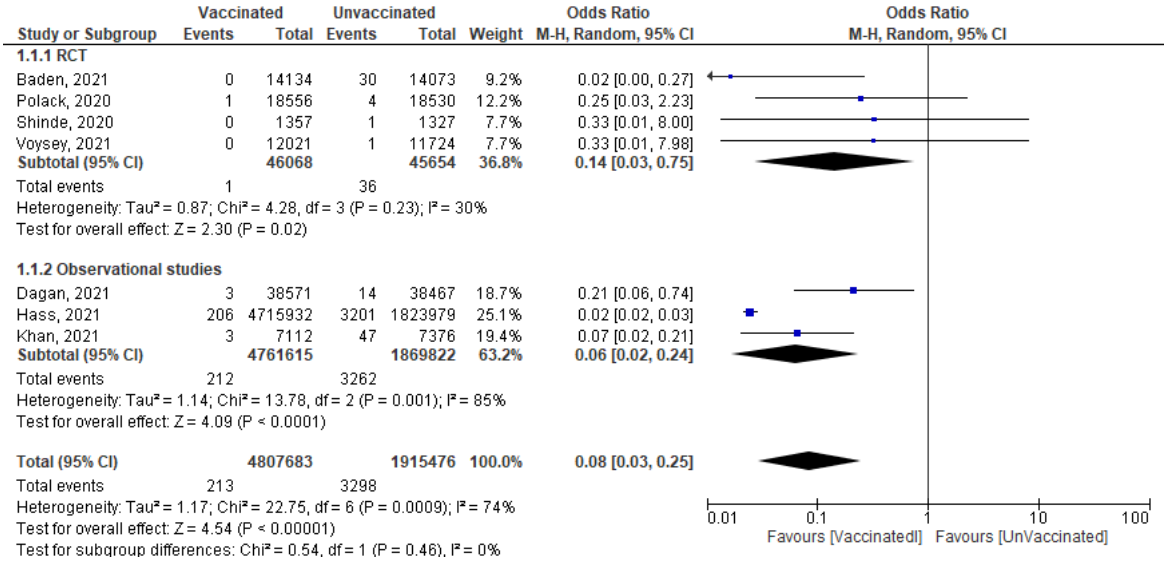

Figure 7

Subgroup analysis of odds ratio for severity of COVID-19 infection 1 week after 2nd dose.

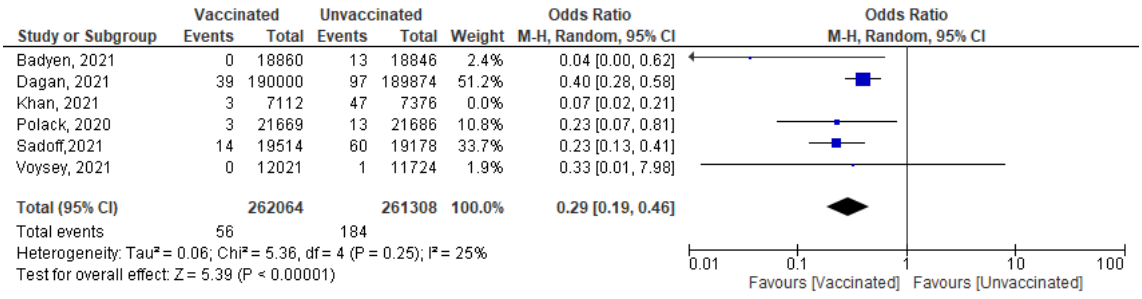

Figure 8

Odds ratio of COVID-19 severity infection one week after 1st dose, after omitting Khan et.al study.

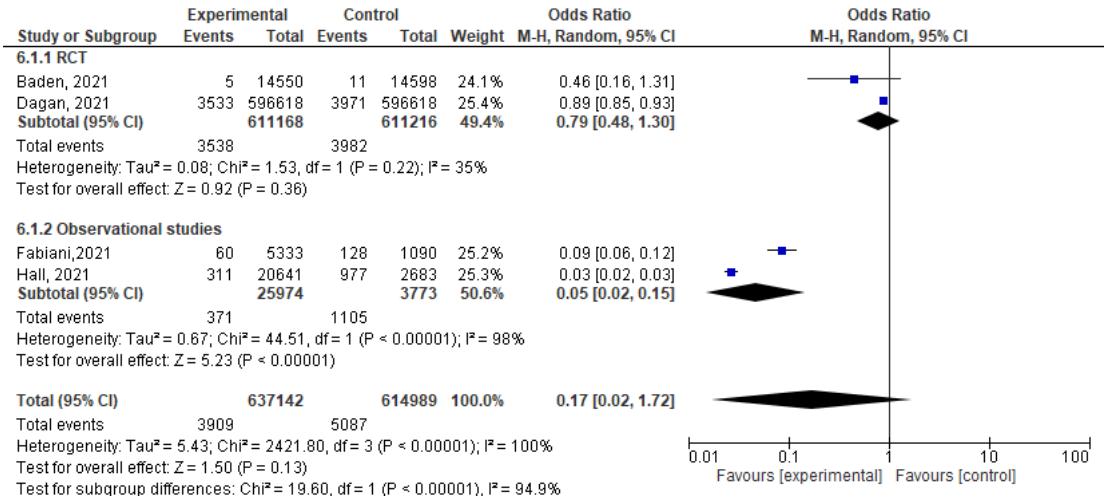

Figure 9

Odds ratio of Total COVID-19 reported cases within 2 weeks of 1st dose, sub grouped by RCT or observational studies.

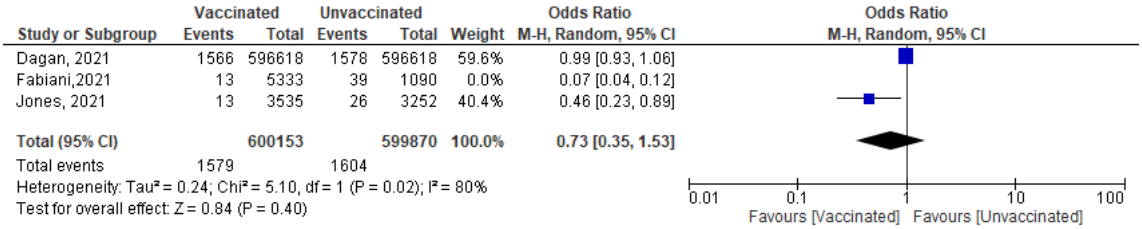

Figure 10

leave one-out sensitivity analysis for odds ratio of asymptomatic cases reported after 1st dose.

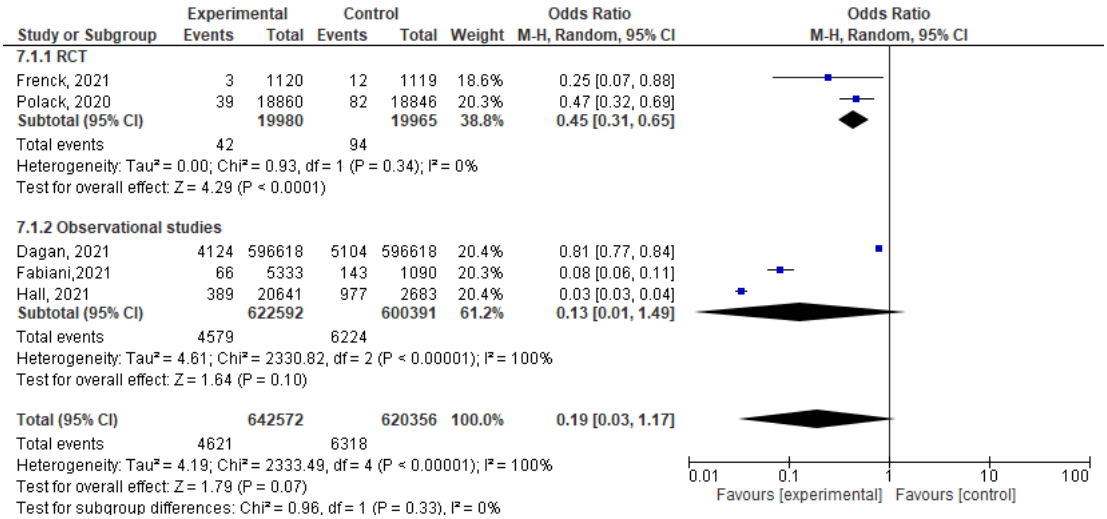

Figure 11

subgroup analysis of total case reported after 3 weeks of 1st dose odds ratio.

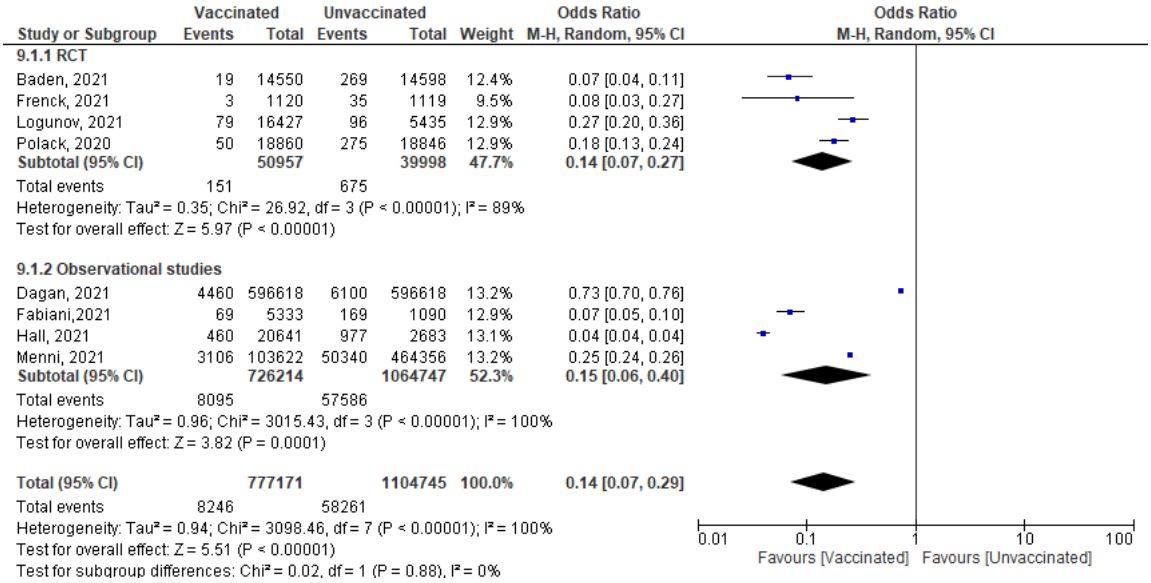

Figure 12

Subgroup analysis of all case reported after 1st dose odds ratio .

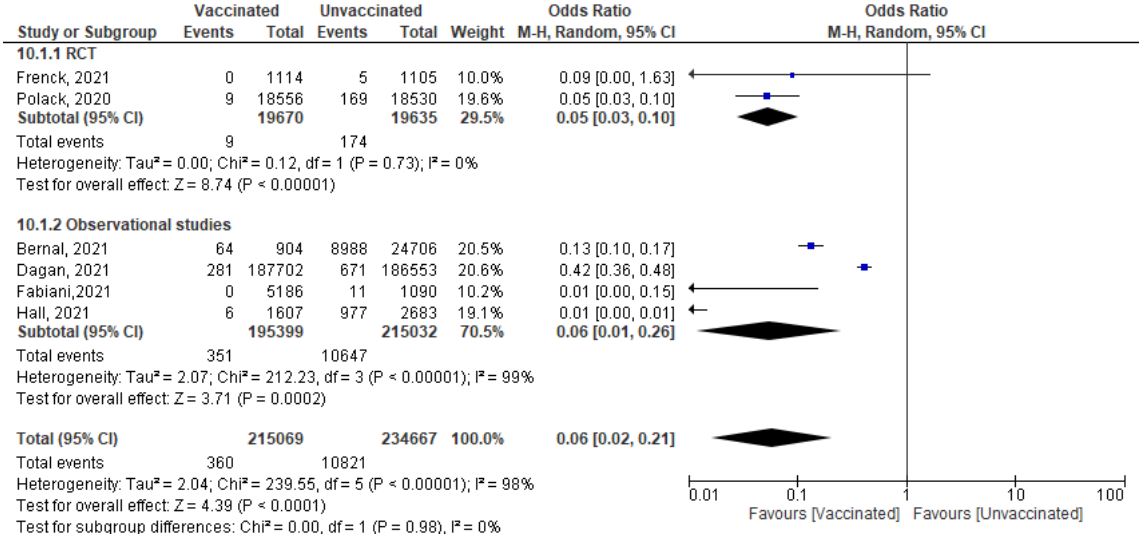

Figure 13

subgroup analysis of all reported cases within 7 days of 2nd dose odds ratio.

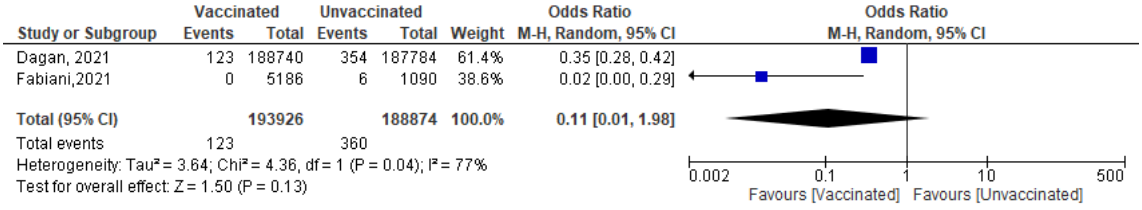

Figure 14

Overall odds ratio of symptomatic cases within 7 days of 2nd dose.

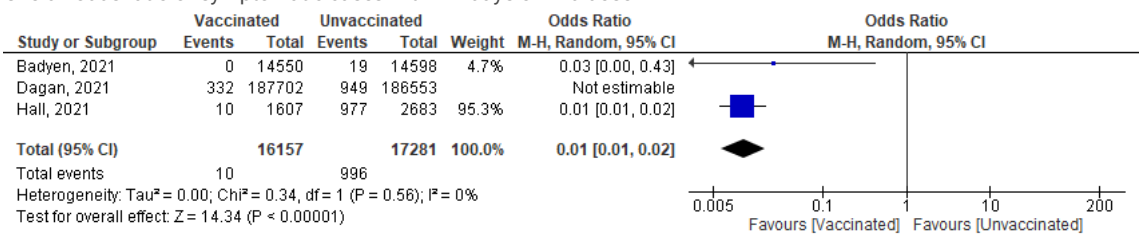

Figure 15

leave one-out sensitivity analysis of total cases within 14 days of 2nd dose.

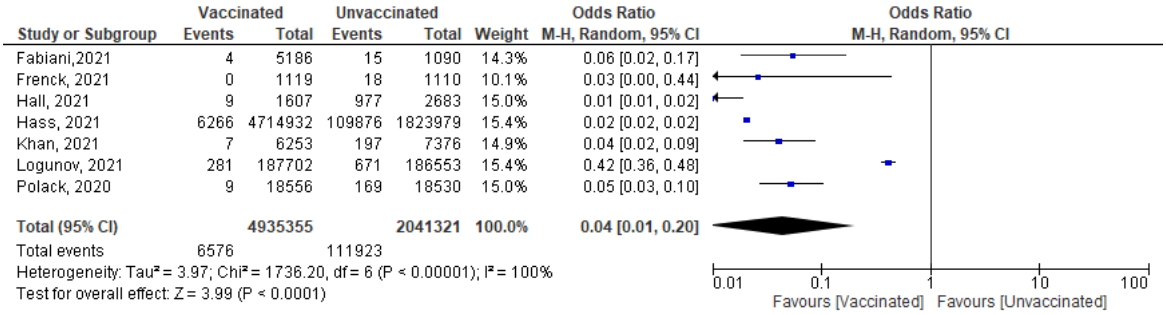

Figure 16

Odds ratio of overall cases reported 7 days after 2nd dose.

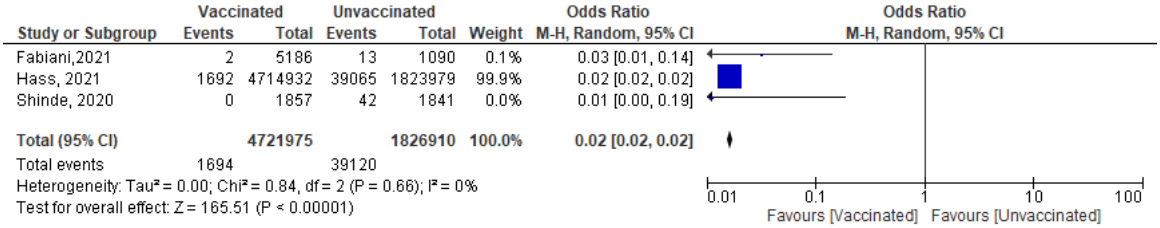

Figure 17

Pooled OR of symptomatic cases reported 7days after 2nd dose.

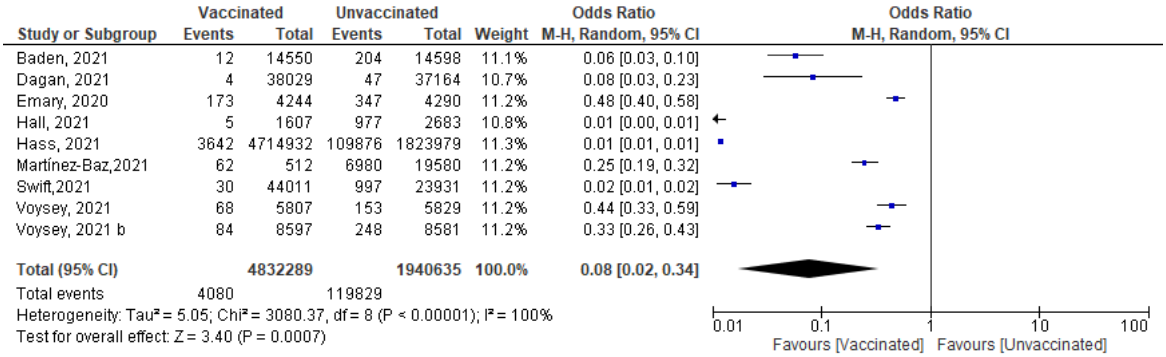

Figure 18

Odds ratio of total cases within 14 days after 2nd dose.

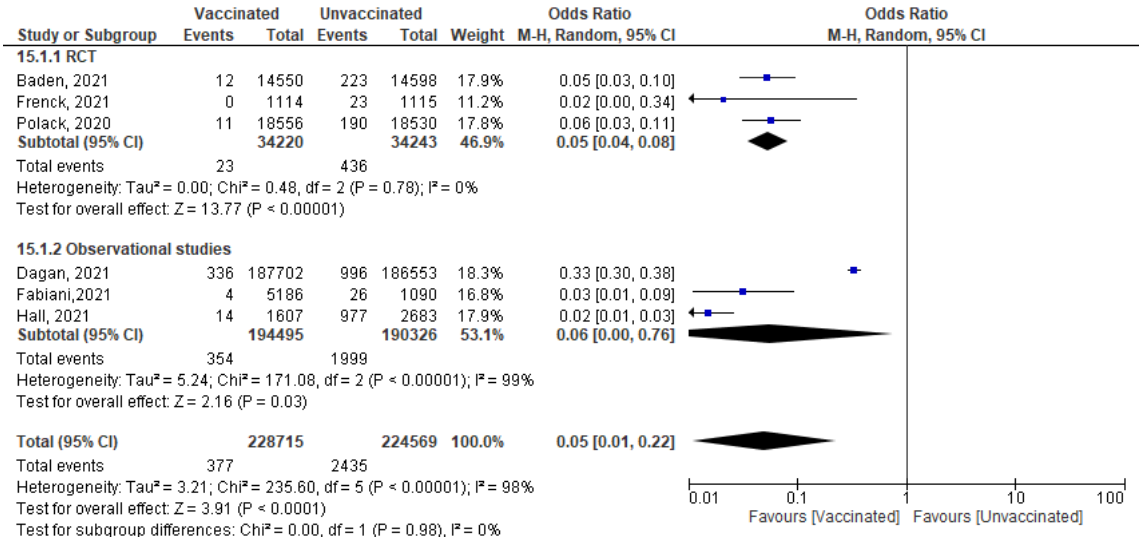

Figure 19

Odds ratio of cases reported after 2nd dose with subgroup analysis