Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2022;376:e068632 http://dx.doi.org/10.1136/bmj-2021-068632

Accepted: 24 January 2022

ABSTRACT

OBJECTIVE

To compare the efficacy of covid-19 vaccines between immunocompromised and immunocompetent people.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

PubMed, Embase, Central Register of Controlled Trials, COVID-19 Open Research Dataset Challenge (CORD-19), and WHO covid-19 databases for studies published between 1 December 2020 and 5 November 2021. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched in November 2021 to identify registered but as yet unpublished or ongoing studies.

STUDY SELECTION

Prospective observational studies comparing the efficacy of covid-19 vaccination in immunocompromised and immunocompetent participants.

METHODS

A frequentist random effects meta-analysis was used to separately pool relative and absolute risks of seroconversion after the first and second doses of a covid-19 vaccine. Systematic review without meta-analysis of SARS-CoV-2 antibody titre levels was performed after first, second, and third vaccine doses and the seroconversion rate after a third dose. Risk of bias and certainty of evidence were assessed.

RESULTS

82 studies were included in the meta-analysis. Of these studies, 77 (94%) used mRNA vaccines, 16 (20%) viral vector vaccines, and 4 (5%) inactivated whole virus vaccines. 63 studies were assessed to be at low risk of bias and 19 at moderate risk of bias. After one vaccine dose, seroconversion was about half as likely in patients with haematological cancers (risk ratio 0.40, 95% confidence interval 0.32 to 0.50, I^2=80%; absolute risk 0.29, 95% confidence interval 0.20 to 0.40, I^2=89%), immune mediated inflammatory disorders (0.53, 0.39 to 0.71, I^2=89%; 0.29, 0.11 to 0.58, I^2=97%), and solid cancers (0.55, 0.46 to 0.65, I^2=78%; 0.44, 0.36 to 0.53, I^2=84%) compared with immunocompetent controls, whereas organ transplant recipients were 16 times less likely to seroconvert (0.06, 0.04 to 0.09, I^2=0%; 0.06, 0.04 to 0.08, I^2=0%). After a second dose, seroconversion remained least likely in transplant recipients (0.39, 0.32 to 0.46, I^2=92%; 0.35, 0.26 to 0.46), with only a third achieving seroconversion. Seroconversion was increasingly likely in patients with haematological cancers (0.63, 0.57 to 0.69, I^2=88%; 0.62, 0.54 to 0.70, I^2=90%), immune mediated inflammatory disorders (0.75, 0.69 to 0.82, I^2=92%; 0.77, 0.66 to 0.85, I^2=93%), and solid cancers (0.90, 0.88 to 0.93, I^2=51%; 0.89, 0.86 to 0.91, I^2=49%). Seroconversion was similar between people with HIV and immunocompetent controls (1.00, 0.98 to 1.01, I^2=0%; 0.97, 0.83 to 1.00, I^2=89%). Systematic review of 11 studies showed that a third dose of a covid-19 mRNA vaccine was associated with seroconversion among vaccine non-responders with solid cancers, haematological cancers, and immune mediated inflammatory disorders, although response was variable in transplant recipients and inadequately studied in people with HIV and those receiving non-mRNA vaccines.

CONCLUSION

Seroconversion rates after covid-19 vaccination were significantly lower in immunocompromised patients, especially organ transplant recipients. A second dose was associated with consistently improved seroconversion across all patient groups, albeit at a lower magnitude for organ transplant recipients. Targeted interventions for immunocompromised patients, including a third (booster) dose, should be performed.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42021272088.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Immunocompromised patients show lower seroconversion rates than immunocompetent people after vaccination, such as with the influenza vaccine

Less is known about the response to covid-19 vaccines, particularly mRNA based vaccines

WHAT THIS STUDY ADDS

Seroconversion rates after covid-19 vaccination were found to be reduced among all immunocompromised groups, except people with HIV, but significantly increased after the second dose; in organ transplant recipients seroconversion remained severely reduced even after a second dose

Among the immunocompromised groups studied, antibody titres were lower than in immunocompetent controls

These findings suggest that a third dose of covid-19 vaccine would be efficacious in immunocompromised patients

Introduction

Transmission of SARS-CoV-2 has led to the ongoing global covid-19 pandemic. By November 2021, more than 250 million have had confirmed covid-19 and more than four million have died worldwide.

The morbidity and mortality from covid-19 and its complications and large scale economic disruption have prompted an unprecedented pace in vaccine development.[1 2] Vaccines that have been approved for use to date include new technology mRNA vaccines such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), non-replicating viral vector vaccines such as Janssen's Ad26.COV2.S (Johnson & Johnson), and traditional inactivated whole virus vaccines such as CoronaVac (Sinovac Biotech).[3] Trials and ongoing studies have sought to evaluate the efficacy and safety of these vaccines. High vaccine efficacy against symptomatic laboratory confirmed SARS-CoV-2 infection has been reported, with more than 50% efficacy after the first dose of BNT162b2 and 90% after the second dose,[4] whereas Oxford-AstraZeneca reported an efficacy of 70% after the second dose of its viral vector vaccine, AZD1222 (ChAdOx1 nCoV-19).[5] High seroconversion rates were shown regardless of class of vaccine used or previous infection status.[6]

Vaccine trials, however, have excluded immunocompromised groups, such as patients with cancer, organ transplant recipients, and those with rheumatological disorders, leading to a paucity of data on the efficacy and safety of vaccines in these groups. These patients, who comprise about 3% of the adult population,[7] are of particular interest because of possible suppression or over-activation of the immune system attributable to the primary disease or concurrent treatment. Data are urgently needed on immunocompromised patients, as infection and viral shedding have been reported to be more severe and persistent in this group.[8 9] Patients with active cancer are known to be at increased risk of severe covid-19 and death.[10 11] Transplant recipients require prolonged immunosuppression to reduce the risk of graft rejection, and past studies have shown increased risk of severe covid-19 and poor outcomes.[12] Patients requiring immunosuppressive treatment for autoimmune and inflammatory rheumatic diseases have worse outcomes from covid-19 than age and sex comparable patients without such conditions.[13] People with HIV are also at higher risk of hospital admission for severe covid-19, and in-hospital mortality.[14]

Studies have shown variable efficacy of other vaccines, such as influenza and pneumococcal vaccines, among immunocompromised groups depending on factors such as vaccine type, underlying disease, and concurrent drugs. In a meta-analysis on the immunogenicity of influenza vaccination in organ transplant recipients, the risk factors for lower seroconversion included transplantation within six months, receiving antimetabolites, and lung transplantation.[15] Other studies have shown reduced antibody response after the influenza vaccine among patients with cancer, organ transplant recipients, and those receiving other anti-CD20 based immunosuppressive drugs, such as rituximab in those with rheumatic conditions.[16 17]

To date, no systematic reviews have been performed on the immunogenicity of covid-19 vaccines in immunocompromised cohorts. In this review we compared seroconversion rates and antibody titre levels for different covid-19 vaccines between immunocompromised patients and immunocompetent controls.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Search strategy

In November 2021 and according to the study protocol, we searched several databases: Medline via PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), CORD-19, WHO COVID-19 Research Database, ClinicalTrials.gov, and WHO international clinical trials registry platform for articles published from 1 December 2020 to 5 November 2021 (see supplementary table 1 for search strategy). No restrictions on language of publication were applied. To improve validity of data, we excluded non-peer reviewed articles in preprint databases.

Study selection

We used a two stage approach for screening: first by title and abstract and then by full text article. Two researchers (ARYBL and SYW) independently screened each title, abstract, and full text, with discrepancies resolved by consensus with a third researcher. Studies were limited to human participants and of any follow-up duration and timepoints.

We performed meta-analysis of prospective observational studies that met several criteria: included human participants who received a covid-19 vaccine of any brand and type; included patients with active cancer of solid organs; patients with active haematological cancers; organ transplant recipients; patients with active immune mediated inflammatory disorders[19] except asthma or receiving immunosuppressive or immunomodulatory drugs; people with HIV/AIDS; studies that included and reported data on a control group comprising immunocompetent people or comparator groups of people who were not immunocompromised, defined as not having cancer, immune mediated inflammatory disorders, organ transplant conditions, or HIV; and studies that reported at least one of seroconversion after covid-19 vaccination or serological titres after covid-19 vaccination.

We excluded studies that included but did not report outcomes of an immunocompetent control group; reported seroconversion data in a form that prevented the calculation of proportions, risk of seroconversion, or number of seroconverted participants; and reported serological titres in a form from which neither mean nor median titres could be derived.

When studies did not have available data, we emailed the corresponding authors for information. We excluded studies only if data were not provided at the time of meta-analysis.

Given the emergence of clinical studies of a third dose of covid-19 vaccine in immunocompromised patients, we made a post hoc amendment to include studies reporting these data, for qualitative analysis: prospective observational or experimental studies that involved human participants, all of whom should be receiving a covid-19 vaccine of any brand and type; studies that involved patients with solid organ cancer, haematological cancer, immune mediated inflammatory disorders, HIV/AIDS, and organ transplant recipients; and studies that reported seroconversion rates among immunocompromised patients, with or without the inclusion of an immunocompetent control group.

Data extraction

Two researchers (ARYBL and SYW) extracted data according to a predetermined proforma in Microsoft Excel Version 16.45. All key extracted data were reviewed and quality checked at the end of the data extraction phase by the same two researchers.

Data on study characteristics comprised setting, primary and secondary outcomes, study design, sample size, dropout and non-response rates, and inclusion and exclusion criteria. Participant data comprised age, sex, and disease and treatment history, including immunosuppressive regimen. Intervention related data included vaccine type and brand, dosing schedule, number of participants receiving each type and brand of vaccine, and median or mean interval between doses. Outcome related data comprised assay type, antibody measured, method of measurement, intervals of sample collection, and number of measurements.

Risk of bias assessment

The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to rate risk of bias for non-randomised included studies. This tool assesses seven domains: risk of bias from confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results.[20] Two reviewers (ARYBL and SYW) independently judged these domains as having low, moderate, serious, or critical risk of bias, or no information. All discrepancies were resolved by the independent opinion of a third reviewer. A study would be judged as having an overall low risk of bias if all the domains were judged as low risk. A study would be considered as having critical risk of bias if one domain was judged as high risk of bias.

The Cochrane Risk of Bias 2.0 tool was to be used for randomised trials. During our search, however, no eligible randomised studies were found.[21]

Outcomes of interest

The primary outcomes of interest were seroconversion after a first and second dose of covid-19 vaccine. As brand and type of assay, type of immunoglobulin, and definition of seroconversion differed across studies, supplementary table 2 reports the respective data from each study. We sought direct evidence of vaccine protection, including asymptomatic and symptomatic covid-19 infection, need for oxygen supplementation, and hospital or intensive care unit stay in both immunocompromised patients and immunocompetent controls. No studies met our inclusion criteria for these outcomes.

Secondary outcomes of interest were mean or median serological titres and cumulative incidence of seroconversion after a first and second dose of covid-19 vaccines. As the type of antibodies measured and reported differed across studies, supplementary tables 3 and 4 show the titres after a first and second vaccine dose, respectively. Supplementary table 2 shows the timepoints of serological assessment after covid-19 vaccination and the different brands of serological kits.

Data analysis

We used the DerSimonian and Laird random effects model to estimate the pooled risk ratios and corresponding 95% confidence intervals for the primary outcomes of interest. A risk ratio <1 indicates that the immunocompromised participants had a lower risk of achieving seroconversion after covid-19 vaccination compared with immunocompetent controls. Statistical heterogeneity of the results in the included studies was assessed by χ^2 test and I^2 statistic. We considered heterogeneity to be significant when the P value by χ^2 test was <0.10, or the I^2 statistic was ≥50%.[22]

Assessment for publication bias was both qualitative, through visual inspection for funnel plot asymmetry, and quantitative, using Egger's test. We performed subgroup analyses to determine if results were influenced by the type of haematological cancers, solid cancers, immune mediated diseases, organ transplants, and covid-19 vaccines. Interaction tests were used to compare the differences between estimates from different subgroups.

As we did not expect the covid-19 antibody titre levels to be amenable to statistical pooling because of different methods and assays used, secondary outcomes were assessed using the synthesis without meta-analysis approach.

We performed separate meta-analyses for the relative risk of seroconversion (measured as risk ratios compared with immunocompetent controls) and the absolute risk of seroconversion (measured as a proportion from 0-100%) after each vaccine dose. Generalised linear mixed effects models were used to pool the logit transformed proportions of immunocompromised patients who achieved seroconversion after a first and second covid-19 vaccine dose. Between study heterogeneity was considered significant if the P value of Cochran's Q test was <0.10, or if the I^2 statistic was ≥50%.[22]

Small study effects were assessed both qualitatively, through visual inspection for funnel plot asymmetry, and quantitatively, using Egger's test. We conducted all analyses on R (version 4.0.3) using the *meta* and *metafor* packages. Unless specified otherwise, we considered a two sided P value of <0.05 to be statistically significant.

When publication bias was suspected based on either the Egger's regression-intercept test of bias or visual inspection for funnel plot asymmetry, we conducted a sensitivity analysis using the trim-and-fill method (R0 estimator, fixed random effects models) to re-estimate the pooled effect size after imputing potentially missing studies.[23 24] The trim-and-fill method shows a normal distribution of effect sizes around the centre of the funnel plot if publication bias is absent.[25]

Certainty of evidence

We assessed the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[26] Certainty of the overall evidence was rated as high, moderate, low, or very low based on the assessment of the domains for risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence, and imprecision.

Patient and public involvement

No patients or members of the public were directly involved in this research study.

Results

Figure 1 shows the selection of studies. Overall, 82 studies were included for meta-analysis (table 1, supplementary table 2).[27-108] Supplementary tables 3 and 4 present the serological antibody titres after a first and second dose of covid-19 vaccines, respectively. Five studies were included for qualitative analysis of titres but not for meta-analysis of seroconversion rates.[109-113] In addition, 11 studies reporting seroconversion data of a third vaccine dose were included for qualitative analysis (see supplementary table 5).[43 114-123] One study was included in both meta-analysis and qualitative analysis of a third vaccine dose.[43] Five studies that met the inclusion criteria for meta-analysis were excluded because missing data could not be obtained in time from the corresponding authors. Four studies did not report seroconversion rates among immunocompetent controls. One study included patients with cancer and organ transplant recipients, but did not provide seroconversion data for each group separately.

Of the 82 included studies, 77 (94%) used mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), with 66 (80%) studies involving only mRNA vaccines, 16 (20%) viral vector vaccines, and four (5%) inactivated vaccines (CoronaVac, Sinovac, Biotech). Among the viral vector vaccines, AZD1222 (ChAdOx1 nCoV-19; Oxford-AstraZeneca) featured more prominently, being used in 16 (20%) studies but as the sole vaccine in only one (1%). Ad26.COV2.S (Janssen/Johnson & Johnson) was used in only one study (in 3/289 immunocompetent controls and no immunocompromised patients).[29]

Trials primarily included immunocompromised groups of organ transplant recipients and patients with cancers and immune mediated inflammatory disorders. Eighteen (22%) studies included patients with solid cancers, 21 (26%) included patients with haematological cancer, 17 (20.7%) included patients with immune mediated inflammatory disorders, 26 (32%) included organ transplant recipients, and four (5%) included people with HIV.

First vaccine dose

Figure 2 presents the risk ratios for seroconversion among immunocompromised patients compared with immunocompetent controls after a first dose of covid-19 vaccine.

Thirty five studies reported seroconversion after a first vaccine dose in immunocompromised patients (n=4052) compared with immunocompetent controls (n=3856). See supplementary tables 2 and 3 for details of the studies.

Among the immunocompromised groups, risk ratios were lowest for organ transplant recipients, with minimal heterogeneity (risk ratio 0.06, 95% confidence interval 0.04 to 0.09, I^2=0%) (moderate certainty of evidence), followed by patients with haematological cancers (0.40, 0.32 to 0.50, I^2=80%) (moderate certainty of evidence), immune mediated inflammatory disorders (0.53, 0.39 to 0.71, I^2=89%) (moderate certainty of evidence), and solid cancers (0.55, 0.46 to 0.65, I^2=78%) (moderate certainty of evidence). Only one study reported the seroconversion rate in people with HIV and found no difference compared with immunocompetent controls (1.06, 0.74 to 1.54) (low certainty of evidence).[10]3

Second vaccine dose

Figure 3 and figure 4 show the risk ratios for seroconversion among immunocompromised patients compared with immunocompetent controls after a second dose of covid-19 vaccine. See supplementary tables 2 and 4 for details of the studies.

A total of 73 studies including 77 immunocompromised cohorts reported seroconversion in 9974 immunocompromised patients compared with 6215 immunocompetent controls after a second vaccine dose.

Among the immunocompromised groups, the lowest pooled risk ratio after a second vaccine dose was observed in organ transplant recipients (0.39, 0.32 to 0.46, I^2=92%) (moderate certainty evidence), followed by patients with haematological cancers (0.63, 0.57 to 0.69, I^2=88%) (low certainty evidence), immune mediated inflammatory disorders (0.75, 0.69 to 0.82, I^2=92%) (low certainty evidence), and solid cancers (0.90, 0.88 to 0.93, I^2=51%) (low certainty of evidence), and people with HIV (1.00, 0.98 to 1.01, I^2=0%) (low certainty of evidence).

Vaccine response

Patients with solid cancers: first dose

Eleven studies including 827 patients with solid cancers and 1653 immunocompetent controls showed a pooled risk ratio of 0.55 (0.46 to 0.65) for seroconversion after a first dose of covid-19 vaccine (fig 2). See supplementary tables 2 and 3 for details of the studies.

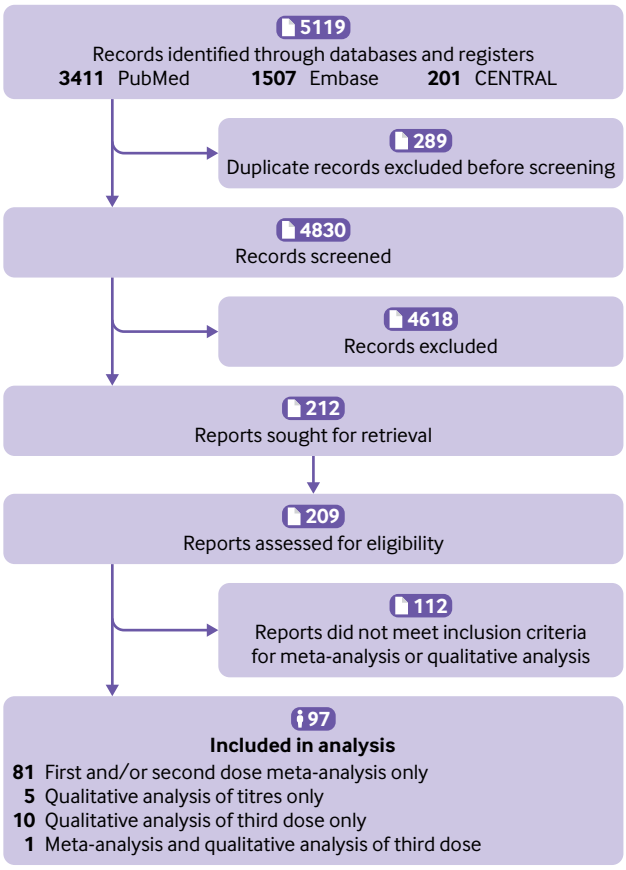

Fig 1 | Flowchart of study selection

Barriere et al[108] showed the most significant reduction in antibody titres, of 41.5-fold, among 122 immunocompromised patients (median 0.52 UI/mL, range 0-1962 UI/mL) compared with 13 immunocompetent controls (21.6 UI/mL, range 3.26-723.2 UI/mL), whereas Zagouri et al[44] showed the least significant reduction, of 1.08-fold, among 18 immunocompromised patients (median 39.5%) compared with 160 immunocompetent controls (median 42.83%). Liontos et al found lower antibody titres among immunocompetent controls compared with immunocompromised patients. The difference was not statistically significant (P=0.26).[38]

Patients with solid cancers: second dose

Fourteen studies including 1488 patients with solid cancers and 1607 immunocompetent controls showed a pooled risk ratio of 0.90 (0.88 to 0.93) for seroconversion after a second vaccine dose (fig 3). See supplementary tables 2 and 4 for details of the studies.

Barriere et al found the most significant reduction in antibody titres, of 10.3-fold, among 42 immunocompromised patients (median 245.2 UI/mL, range 0-5467 UI/mL) compared with 24 immunocompetent controls (median 2517 UI/mL, range 157.6-6318.0 UI/mL).[108] Liontos et al, however, found comparable neutralising antibody titres among patients with breast and prostate cancer compared with immunocompetent controls.[37 38]

A reduction in seroconversion rates was found in patients with solid cancer after both vaccine doses, with a significant increase of 1.64 times between the first and second dose (pooled risk ratio 0.55, 0.46 to 0.65 and 0.90, 0.88 to 0.93, respectively).

Patients with haematological cancers: first dose

Eleven studies including 1123 patients with haematological cancers and 1346 immunocompetent controls showed a pooled risk ratio of 0.40 (0.32 to 0.50) for seroconversion after a first dose of covid-19 vaccine (fig 2). See supplementary tables 2 and 3 for details of the studies.

Lim et al reported the most significant reduction in antibody titres, of 935.6-fold and 79.6-fold among immunocompromised patients (geometric mean titre 2.5 binding antibody units (BAU)/mL, 95% confidence interval 1.1 to 5.8 BAU/mL) compared with 65 and 20 immunocompetent controls who received BNT162b2 (2339 BAU/mL, 40 to 111 BAU/mL) and AZD1222 (199 BAU/mL, 140 to 282 BAU/mL).[59] Pimpinelli et al, however, reported less of a reduction in antibody titres, of 2.28-fold (median 7.5 arbitrary units (AU)/mL, 95% confidence interval 5.6 to 10.4 AU/mL) among patients with multiple myeloma and of 1.06-fold (median 16.2 AU/mL, 11.7 to 22.3 AU/mL) among patients with myeloproliferative neoplasm.[46]

Patients with haematological cancers: second dose

Nineteen studies including 2436 patients with haematological cancers and 1896 immunocompetent controls showed a pooled risk ratio of 0.63 (95% confidence interval 0.57 to 0.69) for seroconversion after a second dose of covid-19 vaccine (fig 3). See supplementary tables 2 and 4 for details of the studies.

Herishanu et al[45] found the most significant reduction, of 1315.5-fold, among 52 patients with chronic lymphocytic leukaemia (median 0.824 U/mL, interquartile range 0.4-167.3 U/mL) compared with 52 immunocompetent controls (median 1084 U/mL, interquartile range 128.9-1879 U/mL) after the second vaccine dose. The smallest reduction was reported in the study by Gavriatopoulou et al, of 1.85-fold among 90 patients with haematological cancers (mean 52%, interquartile range 47.7-56.3%) compared with 108 immunocompetent controls (mean 87.4%, interquartile range 86.1-88.7%).[52]

Seroconversion rates in patients with haematological cancers were reduced after both vaccine doses, with a significant increase of 1.58-fold between the first and second dose (pooled risk ratio 0.40, 95% confidence interval 0.32 to 0.50 and 0.63, 0.57 to 0.69, respectively).

Patients with immune mediated inflammatory disorders: first dose

Seven studies reported seroconversion rates among patients with immune mediated inflammatory disorders after a first dose of covid-19 vaccine (fig 2). Data from 1526 patients compared with 602 immunocompetent controls showed that the patients

Table 1 | Characteristics of studies included in meta-analysis

Characteristics	No (%) (n=82)
Morbidity*	
Solid cancers	18 (22)
Haematological cancers	21 (26)
Immune mediated inflammatory disorders	17 (21)
Organ transplants	26 (32)
HIV/AIDS	4 (5)
Vaccine dose	
First	35 (43)
Second	73 (89)
Country	
Israel	18 (22)
Germany	12 (15)
USA	11 (13)
Greece	9 (11)
UK	7 (9)
France	7 (9)
Italy	5 (6)
Belgium	2 (2)
Brazil	2 (2)
Switzerland	2 (2)
South Africa	1 (1)
Netherlands	1 (1)
Austria	1 (1)
Spain	1 (1)
Thailand	1 (1)
Turkey	1 (1)
Poland	1 (1)
Vaccine types	
mRNA:	
BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)	77 (94); only mRNA vaccines in 66 (80)
Non-replicating viral vector:	
AZD1222 (ChAdOx1 nCoV-19; Oxford-AstraZeneca)	16 (20); sole vaccine in 1 (1)
Ad26.COV2.S (Janssen/Johnson & Johnson)†	1 (1)
Inactivated:	
CoronaVac (Sinovac Biotech)	4 (5)

At the time of the studies, recommended vaccine regimens included two vaccine doses, except for Ad26.COV2.S (Janssen/Johnson & Johnson), which only required one dose. The current meta-analysis further stratified results according to seroconversion and antibody titres after a first dose and second dose.
*Study by Rahav et al[27] included patients with solid cancers, haematological cancers, immune mediated inflammatory disorders, organ transplants, and HIV/AIDS. Study by Monin et al[28] included patients with solid cancers and haematological cancers.
†Vaccine used in only 3/289 (1%) immunocompetent controls in study by Boekel et al[29]

had a pooled risk ratio of 0.53 (95% confidence interval 0.39 to 0.71). See supplementary tables 2 and 3 for details of the studies.

Lower antibody titres were seen after a first vaccine dose among patients with immune mediated inflammatory disorders. Rubbert-Roth et al found that the antibody titres of 51 patients with rheumatoid arthritis (median 0.4 U/mL, interquartile range 0.4-2.13 U/mL) were much lower than those of 20 immunocompetent controls (99.2 U/mL, 24.8-172 U/mL), of 248-fold.[89] Medeiros-Ribeiro et al showed a less significant decrease in 859 patients with immune mediated inflammatory disorders (median 5.1 AU/mL, interquartile range 4.7-5.5 AU/mL) compared with 179 immunocompetent controls (10.3 AU/mL, 8.5-12.5 AU/mL), of 2.02-fold.[93]

Patients with immune mediated inflammatory disorders: second dose

Seventeen studies also reported seroconversion rates among patients with immune mediated inflammatory disorders after a second dose of covid-19 vaccine (fig 4). Data from 2668 patients compared with 1296 immunocompetent controls showed that the patients had a pooled risk ratio of 0.75 (95% confidence interval 0.69 to 0.82). See supplementary tables 2 and 4 for details of the studies.

Achiron et al reported the greatest and smallest reduction in antibody titres among patients with immune mediated inflammatory disorders, which provided insights into the impact of individual immunosuppressive agents on antibody titres in patients with multiple sclerosis within a median range of 2.3-6.3 months after a second vaccine dose.[99] The greatest reductions in antibody titres were seen at 23.7-fold, 35.5-fold, and 8.88-fold for the 42 patients taking fingolimod (median 0.3, 95% confidence interval 0.3 to 0.7), 114 patients taking ocrelizumab (0.2, 0.6 to 1.2), and six patients taking rituximab (0.8, 0.7 to 5.2) compared with 89 immunocompetent controls (7.1, 6.2 to 7.1). The smallest reductions were 1.01-fold among 22 patients taking alemtuzumab (7.0, 5.7 to 8.3), 1.08-fold among 48 patients taking cladribine (6.6, 5.7 to 6.8), 0.93-fold among 35 patients taking dimethyl fumarate (7.6, 7.1 to 7.9), 0.97-fold among 32 patients taking natalizumab (7.3, 6.6 to 7.8), and 1.04-fold among 39 patients taking teriflunomide (6.8, 6.1 to 7.2) compared with the same 89 immunocompetent controls.

Seroconversion rates in patients with immune mediated inflammatory disorders were reduced after both doses, with a significant increase of 1.42 times between the first and second dose (pooled risk ratio 0.53, 95% confidence interval 0.39 to 0.71 and 0.75, 0.69 to 0.82, respectively).

Organ transplant recipients: first dose

Six studies reported seroconversion in 540 organ transplant recipients compared with 266 immunocompetent controls after a first dose of covid-19 vaccine (fig 2). The reduction in seroconversion rates was significant (pooled risk ratio 0.06, 0.04 to 0.09) and largely homogenous between studies (I^2=0%). See supplementary tables 2 and 3 for details of the studies.

Canti et al reported the most significant reduction in antibody titres, of 64.2-fold among 37 transplant recipients (median 6 IU/mL, interquartile range 2.5-77.5 IU/mL) compared with 40 immunocompetent controls (median 385.4 IU/mL, interquartile range 148.2-554.7 IU/mL) after the first dose.

Organ transplant recipients: second dose

Across 24 studies, when data were pooled for 3051 transplant organ recipients and 1679 immunocompetent controls, a strong risk for non-seroconversion was observed, with the lowest pooled risk ratio being 0.39 (0.32 to 0.46). See supplementary tables 2 and 4 for details of the studies.

Narasimhan et al reported the greatest difference in antibody titres between organ transplant recipients and immunocompetent controls: 1.7 AU/mL (95% confidence interval 0.6 to 7.5 AU/mL) and 14209 AU/mL (11261 to 18836 AU/mL), respectively, with

Study or subgroup	No of events/total: Immunocompromised patients	No of events/total: Healthy controls	Risk ratio, inverse variance, random (95% CI)
Haematological cancers			
Canti	20/37	40/40	0.55 (0.41 to 0.73)
Chowdhury	30/52	224/232	0.60 (0.47 to 0.76)
Gavriatopoulou[51]	8/58	114/213	0.26 (0.13 to 0.50)
Gavriatopoulou[52]	36/106	138/212	0.52 (0.39 to 0.69)
Lim	9/31	65/65	0.30 (0.18 to 0.51)
Marasco	131/263	166/167	0.50 (0.44 to 0.57)
Monin	8/44	32/34	0.19 (0.10 to 0.36)
Parry	63/267	66/93	0.33 (0.26 to 0.43)
Peeters	2/41	40/40	0.06 (0.02 to 0.20)
Pimpinelli	35/92	19/36	0.72 (0.48 to 1.08)
Terpos[55]	29/132	152/214	0.31 (0.22 to 0.43)
Total (95% CI)	1123	1346	0.40 (0.32 to 0.50)
Test for heterogeneity: τ^2=0.09; χ^2=48.95, df=10, P<0.01; I^2=80%			
Solid cancers			
Barriere	58/122	13/13	0.48 (0.40 to 0.57)
Di Noia	126/206	204/219	0.66 (0.59 to 0.74)
Goshen-Lago	25/86	220/261	0.34 (0.25 to 0.48)
Liontos[37]	10/36	119/160	0.37 (0.22 to 0.64)
Liontos[38]	13/25	43/100	1.21 (0.78 to 1.88)
Monin	21/56	32/34	0.40 (0.28 to 0.56)
Palich[31]	52/95	25/25	0.55 (0.46 to 0.66)
Shmueli	23/71	208/348	0.54 (0.38 to 0.77)
Shroff	36/53	49/50	0.69 (0.57 to 0.84)
Terpos[30]	15/59	186/283	0.39 (0.25 to 0.60)
Zagouri	10/18	115/160	0.77 (0.51 to 1.18)
Total (95% CI)	827	1653	0.55 (0.46 to 0.65)
Test for heterogeneity: τ^2=0.05; χ^2=44.67, df=10, P<0.01; I^2=78%			
Immune mediated inflammatory disorders			
Boekel	158/355	154/210	0.61 (0.53 to 0.70)
Mahil	60/77	17/17	0.78 (0.69 to 0.88)
Medeiros-Ribeiro	161/859	62/179	0.54 (0.42 to 0.69)
Prendecki[80]	34/119	68/70	0.29 (0.22 to 0.39)
Reuken	20/28	23/27	0.84 (0.63 to 1.11)
Rubbert-Roth	1/51	9/20	0.04 (0.01 to 0.32)
Shinjo	3/37	27/79	0.24 (0.08 to 0.73)
Total (95% CI)	1526	602	0.53 (0.39 to 0.71)
Test for heterogeneity: τ^2=0.11; χ^2=54.83, df=6, P<0.01; I^2=89%			
Organ transplant			
Mazzola	9/125	25/25	0.08 (0.04 to 0.14)
Rincon-Arevalo	1/40	35/35	0.04 (0.01 to 0.18)
Schmidt	2/38	56/70	0.07 (0.02 to 0.25)
Schramm	2/48	49/50	0.04 (0.01 to 0.17)
Stephanie	9/145	27/31	0.07 (0.04 to 0.14)
Stumpf	7/144	53/55	0.05 (0.02 to 0.10)
Total (95% CI)	540	266	0.06 (0.04 to 0.09)
Test for heterogeneity: τ^2=0; χ^2=1.61, df=5, P=0.90; I^2=0%			
HIV			
Shabir	25/36	15/23	1.06 (0.74 to 1.54)
Total (95% CI)	36	23	1.06 (0.74 to 1.54)
Test for heterogeneity: not applicable			

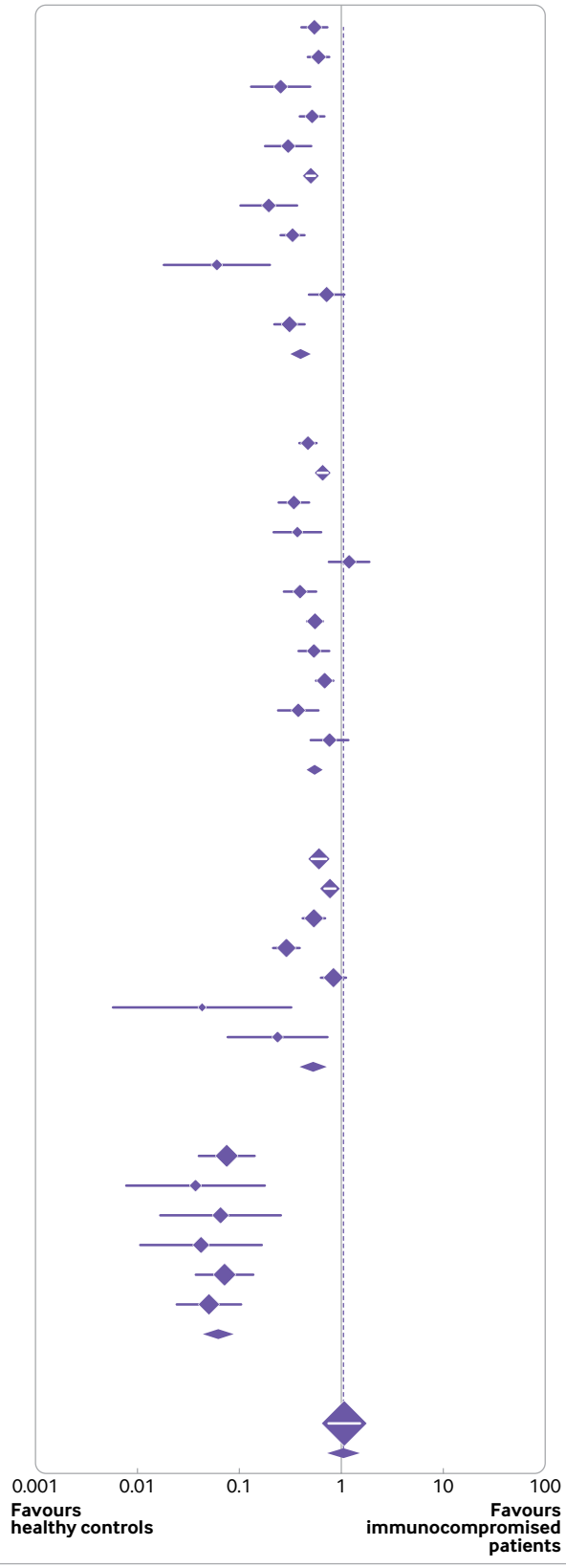

Fig 2 | Risk ratios for seroconversion among immunocompromised patients compared with immunocompetent controls after a first dose of covid-19 vaccine

Study or subgroup	No of events/total: Immunocompromised patients	No of events/total: Healthy controls	Risk ratio, inverse variance, random (95% CI)
Haematological cancers			
Bitoun	20/27	27/28	0.77 (0.61 to 0.97)
Canti	32/37	40/40	0.87 (0.76 to 0.98)
Gavriatopoulou[52]	45/74	196/212	0.66 (0.55 to 0.79)
Ghione	36/86	197/201	0.43 (0.33 to 0.55)
Herishanu	66/167	52/52	0.40 (0.33 to 0.48)
Lim	13/33	85/85	0.40 (0.27 to 0.61)
Lindemann	80/117	35/35	0.69 (0.61 to 0.77)
Malard	91/195	26/30	0.54 (0.44 to 0.66)
Marasco	170/263	166/167	0.65 (0.59 to 0.71)
Monin	3/5	12/12	0.64 (0.34 to 1.20)
Parry	39/55	36/37	0.73 (0.61 to 0.87)
Peeters	12/41	40/40	0.30 (0.19 to 0.48)
Pimpinelli	77/92	36/36	0.84 (0.77 to 0.92)
Rahav	354/529	269/272	0.68 (0.64 to 0.72)
Shem-Tov	118/152	269/272	0.78 (0.72 to 0.86)
Sherman	16/20	24/24	0.80 (0.65 to 1.00)
Stampfer	43/96	31/31	0.45 (0.36 to 0.56)
Terpos[55]	67/132	210/214	0.52 (0.44 to 0.61)
Tzarfati	235/315	107/108	0.75 (0.70 to 0.81)
Total (95% CI)	2436	1896	0.63 (0.57 to 0.69)
Test for heterogeneity: τ^2=0.03; χ^2=148.66, df=18, P<0.01; I^2=88%			
Solid cancers			
Agbarya	120/140	212/215	0.87 (0.81 to 0.93)
Barriere	40/42	24/24	0.95 (0.89 to 1.02)
Di Noia	181/194	204/204	0.93 (0.90 to 0.97)
Eliakim-Raz	83/95	66/66	0.87 (0.81 to 0.94)
Grinshpun	150/172	30/30	0.87 (0.82 to 0.92)
Linardou	171/189	98/99	0.91 (0.87 to 0.96)
Liontos[37]	30/36	150/160	0.89 (0.76 to 1.03)
Liontos[38]	18/20	72/87	1.09 (0.91 to 1.30)
Massarweh	92/102	78/78	0.90 (0.85 to 0.96)
Monin	18/19	12/12	0.95 (0.86 to 1.05)
Palich[32]	210/223	49/49	0.94 (0.91 to 0.97)
Rahav	75/90	269/272	0.84 (0.77 to 0.92)
Shmueli	95/113	258/261	0.85 (0.78 to 0.92)
Shroff	42/53	50/50	0.79 (0.69 to 0.91)
Total (95% CI)	1488	1607	0.90 (0.88 to 0.93)
Test for heterogeneity: τ^2=0.001; χ^2=26.36, df=13, P=0.02; I^2=51%			

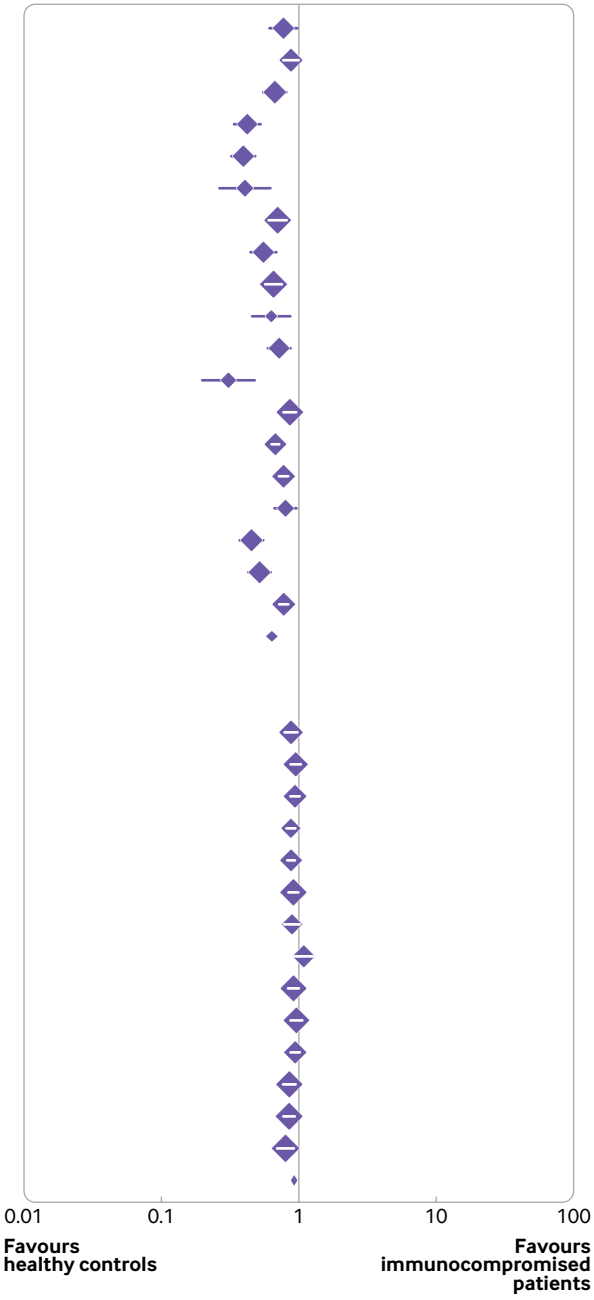

Fig 3 | Risk ratios for seroconversion among immunocompromised patients with haematological cancers and solid cancers compared with immunocompetent controls after a second dose of covid-19 vaccine

a difference of 8358.24 AU/mL.[73] Rabinowich et al reported the smallest reduction in antibody titres, of 2.10-fold (mean 95.41 (standard deviation 92.4) AU/mL *v* 200.5 (65.1) AU/mL).[66]

Seroconversion rates in organ transplant recipients were reduced after both vaccine doses, with a significant increase of 6.5-fold between the first and second dose (pooled risk ratio 0.06, 0.04 to 0.09 and 0.39, 0.32 to 0.46, respectively).

These results suggest that a second dose of covid-19 vaccine is imperative in improving seroconversion rates in organ transplant recipients. Seroconversion rates remained reduced compared with immunocompetent controls, however, necessitating future study for third (booster) doses for such patients. Non-vaccine protective measures would also be vital in protecting this vulnerable patient group.

Study or subgroup	No of events/total: Immunocompromised patients	No of events/total: Healthy controls	Risk ratio, inverse variance, random (95% CI)
Immune mediated inflammatory disorders			
Achiron[91]	34/93	46/47	0.37 (0.28 to 0.49)
Achiron[99]	205/338	87/89	0.62 (0.57 to 0.68)
Ali	14/28	7/7	0.51 (0.35 to 0.73)
Boekel	74/80	38/40	0.97 (0.89 to 1.07)
Deepak	118/133	53/53	0.89 (0.84 to 0.94)
Furer	590/686	121/121	0.86 (0.83 to 0.89)
Haberman	18/25	25/26	0.75 (0.58 to 0.97)
Medeiros-Ribeiro	605/859	171/179	0.74 (0.70 to 0.78)
Mrak	29/74	10/10	0.40 (0.30 to 0.52)
Prendecki[80]	54/91	70/70	0.60 (0.50 to 0.71)
Reuken	11/12	12/12	0.92 (0.78 to 1.08)
Rubbert-Roth	42/51	20/20	0.82 (0.73 to 0.94)
Seyahi	64/75	345/347	0.86 (0.78 to 0.94)
Shinjo	24/37	72/79	0.71 (0.56 to 0.91)
Simon	54/60	181/182	0.90 (0.83 to 0.99)
Wong	26/26	14/14	1.00 (0.90 to 1.12)
Total (95% CI)	2668	1296	0.75 (0.69 to 0.82)
Test for heterogeneity: τ^2=0.02; χ^2=179.61, df=15, P<0.01; I^2=92%			
Organ transplant			
Bruminhent	4/35	38/38	0.13 (0.05 to 0.30)
Crespo	57/90	32/32	0.64 (0.54 to 0.74)
D'Offizi	47/61	51/51	0.77 (0.67 to 0.88)
Danthu	3/74	7/7	0.05 (0.02 to 0.13)
Debska-Slizien	73/142	36/36	0.52 (0.44 to 0.60)
Grupper[64]	51/136	25/25	0.38 (0.30 to 0.47)
Grupper[65]	49/109	39/39	0.45 (0.37 to 0.56)
Hod	52/120	199/202	0.44 (0.36 to 0.54)
Kantauskaite	56/225	165/176	0.27 (0.21 to 0.33)
Korth	5/23	23/23	0.23 (0.11 to 0.49)
Marinaki	20/34	116/116	0.59 (0.45 to 0.78)
Mazzola	38/133	25/25	0.29 (0.22 to 0.38)
Miele	6/16	23/23	0.39 (0.22 to 0.72)
Narasimhan	18/73	49/49	0.25 (0.17 to 0.37)
Peled	14/77	134/136	0.18 (0.11 to 0.30)
Prendecki[105]	425/768	27/40	0.82 (0.66 to 1.03)
Rabinowich	38/80	25/25	0.48 (0.38 to 0.60)
Rahav	90/226	269/272	0.40 (0.34 to 0.47)
Rashidi-Alavijeh	34/43	20/20	0.79 (0.68 to 0.92)
Ruether	84/135	51/51	0.62 (0.55 to 0.71)
Sattler	1/39	39/39	0.04 (0.01 to 0.18)
Schmidt	12/34	70/70	0.36 (0.23 to 0.56)
Schramm	5/45	50/50	0.12 (0.06 to 0.26)
Stumpf	3051	132/134	0.34 (0.29 to 0.40)
Total (95% CI)		1679	0.39 (0.32 to 0.46)
Test for heterogeneity: τ^2=0.15; χ^2=289.46, df=23, P<0.01; I^2=92%			
HIV	139/141	258/261	
Itzchak	154/156	269/272	1.00 (0.97 to 1.02)
Rahav	15/22	10/15	1.00 (0.98 to 1.02)
Shabir	12/12	17/17	1.02 (0.65 to 1.62)
Woldemeskel	331	565	1.00 (0.87 to 1.15)
Total (95% CI)			1.00 (0.98 to 1.01)
Test for heterogeneity: τ^2=0; χ^2=0.02, df=3, P=1.00; I^2=0%			

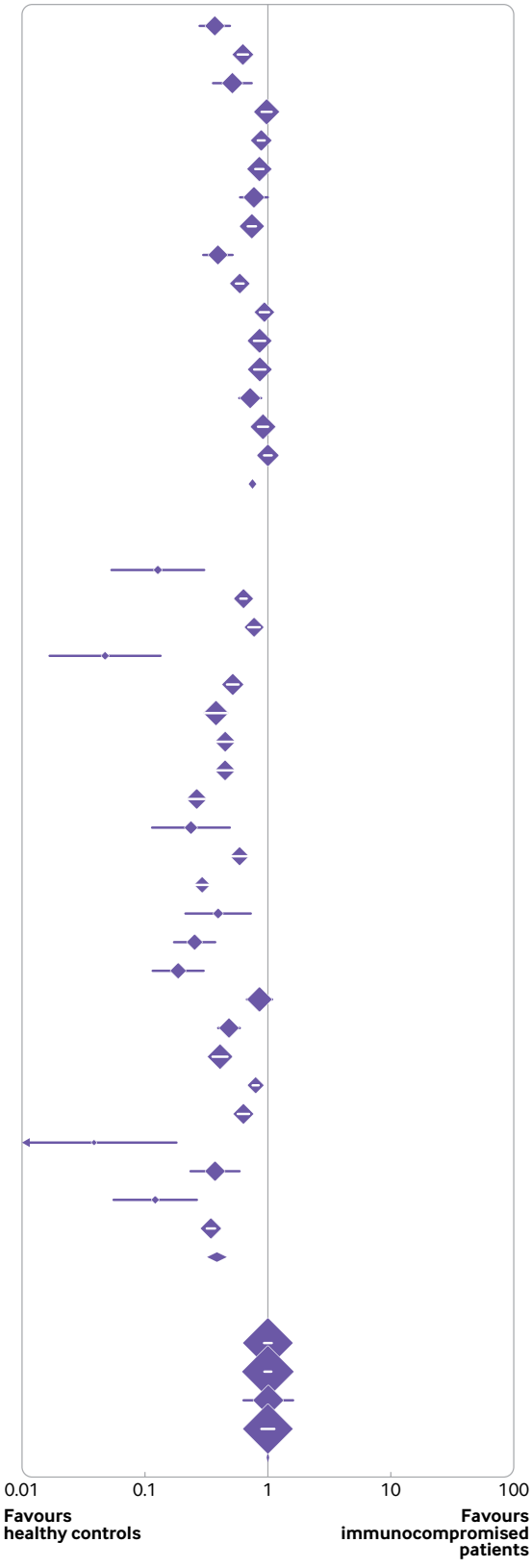

Fig 4 | Risk ratios for seroconversion among immunocompromised patients with immune mediated inflammatory disorders, organ transplant recipients, and people with HIV compared with immunocompetent controls after a second dose of covid-19 vaccine

People with HIV: first and second doses

In one study with 36 people with HIV and 23 immunocompetent controls, seroconversion rates were comparable among the two populations (risk ratio 1.06, 0.74 to 1.54) after the first dose of covid-19 vaccine. See supplementary table 2 for details of the study.

In four studies, with a total of 331 people with HIV and 565 immunocompetent controls, seroconversion rates were high among the people with HIV (pooled risk ratio 1.00, 0.98 to 1.01) after a second dose of covid-19 vaccine (fig 4). See supplementary tables 2 and 4 for details of the studies.

Antibody titres did not seem to be significantly affected or reduced among participants after a second vaccine dose, with Rahav et al[27] reporting 1.16-fold reduction among 88 people with HIV (median 18.7 relative units (RU)/mL, interquartile range 0-42 RU/mL) compared with 41 immunocompetent controls (median 20 RU/mL, interquartile range 12-27 RU/mL) and Jedicke et al[112] reporting a 0.74-fold reduction among 26 controls (median 26 RU/mL, interquartile range 18-37 RU/mL) compared with 52 people with HIV (median 35 RU/mL, interquartile range 1-128 RU/mL).

Heterogeneity in immunocompromised patients after two doses

Subgroup analysis was performed according to study and patient level categorical characteristics to account for heterogeneity in seroconversion observed after the first and second doses of covid-19 vaccine (see supplementary tables 6-11). Among studies of patients with haematological cancer, subgroup analysis was performed of studies that included only patients with one type of haematological cancer (see supplementary figure 1 and supplementary table 9). This analysis was performed in patients with multiple myeloma (n=2 studies; risk ratio 0.59, 95% confidence interval 0.35 to 0.99), recipients of haematopoietic stem cell transplant (n=5; 0.75, 0.68 to 0.83), and patients with chronic lymphocytic leukaemia (n=2; 0.54, 0.30 to 0.98). In the subgroup analyses among patients with haematological cancer, a significant subgroup effect was found according to type of cancer (P=0.01 for test of subgroup effect).

A similar subgroup analysis was performed among studies of patients with immune mediated inflammatory disorders (see supplementary figure 2 and supplementary table 10). This analysis included patients with inflammatory bowel diseases (n=2 studies; risk ratio 0.97, 0.89 to 1.07), multiple sclerosis (n=3; 0.50, 0.35 to 0.70), and rheumatoid arthritis (n=1; 0.83, 0.73 to 0.94). In subgroup analyses among patients with immune mediated inflammatory disorders, a significant subgroup effect was found according to type of disease (P<0.001 for test of subgroup effect).

Subgroup analysis of organ transplant recipients showed that seroconversion differed depending on the organ transplanted (see supplementary figure 3 and supplementary table 11). In increasing order of risk ratios, these were heart (n=2 studies; 0.16, 0.11 to 0.25), lung (n=1; 0.25, 0.17 to 0.37), kidney (n=11; 0.34, 0.26 to 0.45), and liver (n=4; 0.66, 0.55 to 0.80). The remaining six studies involving patients with various solid organ transplants (n=6; 0.41, 0.34 to 0.50) showed significantly reduced heterogeneity. Overall, the subgroup effect was significant (P<0.001 for test of subgroup effect).

Subgroup analysis was performed for studies involving only mRNA vaccines and only non-mRNA vaccines (see supplementary figure 4). Owing to the limited number of studies of only non-mRNA vaccines, subgroup analysis was only possible for patients with immune mediated inflammatory disorders after the second dose (see supplementary table 10). No significant differences (P=0.65 for test of subgroup effect) were found in effects on seroconversion between mRNA vaccines (risk ratio 0.72, 0.64 to 0.81) and non-mRNA vaccines (0.78, 0.69 to 0.88).

In subgroup analysis, the brand of serology kit and country of study were of inconsistent significance across immunocompromised groups, and hence are unlikely to be a major confounder overall (see supplementary tables 6-11). Significant subgroup differences for brand of serology kit were observed in patients with immune mediated inflammatory disorders and organ transplant recipients after the second vaccine dose and patients with haematological cancer after both the first and the second dose. Similarly, subgroups by country of study yielded significant differences only in patients with immune mediated inflammatory disorders and organ transplant recipients after the second dose and patients with solid cancer after both the first and the second dose.

Mixed effects metaregression of seroconversion against potential effect moderators (continuous and categorical study level characteristics), including average age of patients, brand of serology kit for assays, timepoints for assays after covid-19 vaccination, and risk of bias of study, did not show any consistent effect moderation across immunocompromised populations after both the first or the second dose (see supplementary tables 12-13 and supplementary tables 14-17, respectively).

All studies included in this meta-analysis involved immunocompetent controls to improve comparability of data. Responses in immunocompetent controls were homogenous across studies. Heterogeneity in meta-analysis of seroconversion risk in immunocompromised patients was largely in accordance with that of seroconversion risk ratios (see supplementary tables 18-19 and supplementary figures 5-13).

Risk of bias assessment

Sixty three studies were assessed to be at low risk of bias and 19 at moderate risk of bias (see supplementary table 20). No studies were considered at severe or critical risk of bias. Risk of bias was mainly related to confounding effects, with controls not being age matched, or missing data, with recruited patients lacking available data at predetermined endpoints.

Publication bias and trim-and-fill analysis for patients with cancer: first and second dose

Supplementary figures 14 to 21 show the funnel plot with trim-and-fill imputation of potentially missing studies for organ transplant recipients and patients with solid cancer, haematological cancer, and immune mediated inflammatory disorders after first and second doses. Publication bias was absent for most analyses, except for some concern in those involving organ transplant recipients and patients with haematological cancer after the second dose.

Immunogenicity of a third covid-19 vaccine dose

Ten prospective observational studies and one randomised controlled trial reported data after a third dose of covid-19 vaccine. Most of the studies (8/11 studies) were on organ transplant recipients,[115-122] with one study each on patients with immune mediated inflammatory disorders,[123] haematological cancers,[114] and solid cancers.[43] Nine studies utilised only mRNA vaccines (mRNA-1273 or BNT162b2), whereas two studies[114 121] administered either BNT162b2 or AZD1222 as a third dose after two doses of BNT162b2.

Most studies did not report data for controls and hence did not meet the inclusion criteria for the meta-analysis. Given that the efficacy of the third dose is an emerging area of global interest, data are summarised in supplementary table 5.

Systematic review without meta-analysis showed that a third dose of a covid-19 mRNA vaccine dose might improve seroconversion, with rates in organ transplant recipients mostly between 36.0% and 66.7%. Only one study, by Chavarot et al, reported significantly impaired seroconversion, at the lowest rate of 6.5%. Response was highly variable in organ transplant recipients.[115] No published evidence was available on the efficacy of a third dose in people with HIV.

Discussion

In this systematic review and meta-analysis of 82 studies, we found that immunocompromised groups of organ transplant recipients and patients with solid cancers, haematological cancers, and immune mediated inflammatory disorders had depressed seroconversion after a first and second dose of covid-19 vaccine compared with immunocompetent controls. Compared with immunocompetent controls, the pooled risk ratios for seroconversion after the first vaccine dose were lower among organ transplant recipients (risk ratio 0.06) and patients with haematological cancers (0.40), immune mediated inflammatory disorders (0.53), and solid cancers (0.55). Antibody response improved significantly after the second dose. The pooled risk ratios after the second dose increased to 0.39 among organ transplant recipients, 0.63 among patients with haematological cancers, 0.75 among patients with immune mediated inflammatory disorders, and 0.90 among patients with solid cancers. Although the number of studies were insufficient for meta-analysis of seroconversion after the first dose among people with HIV, the immune response to covid-19 vaccines was shown to be preserved after the second dose (risk ratio 1.00). Organ transplant recipients showed sustained low seroconversion rates after both vaccine doses.

Our findings highlight the importance of the second dose of covid-19 vaccines and subsequent third vaccine (booster) doses. The benefits of additional doses and boosters of vaccines are well established, both for covid-19[124-126] and for pre-existing vaccines, such as the inactivated polio vaccine.[127] This review similarly highlights the importance of a second dose of covid-19 vaccine, especially for immunocompromised patients. Across the included studies, a second dose of vaccine was associated with greatly improved seroconversion and antibody titre levels. In particular, a second dose was associated with increasing immunogenicity and protection in organ transplant recipients and patients with haematological cancers.

Benefits of a third dose of covid-19 vaccine

In organ transplant recipients and patients with haematological cancers, our results showed a less than ideal seroconversion rate, even after a second vaccine dose, prompting the need for additional measures. Particularly, seroconversion rates were severely reduced in organ transplant recipients across all studies.

Del Bello et al showed increasing seroconversion with each dose (from one to three) of the BNT162b2 vaccine (Pfizer-BioNTech) in organ transplant recipients.[117]

In August 2021, the US Food and Drug Administration authorised the use of a third dose of Pfizer-BioNTech and Moderna vaccines for immunocompromised populations, including organ transplant recipients,[128] with other countries following suit.[129]

Our meta-analyses suggest significant heterogeneity in immunogenicity between different immunocompromised groups, after both the first and the second dose of covid-19 vaccines. The response noticeably varied in organ transplant recipients after the second dose. This might be attributed to changes in immunosuppressive regimens in the transplant populations after emergence of data on poor responses to a first vaccine dose, or the release of a multi-society joint statement advocating vaccination for all organ transplant recipients midway through several of the reported studies.[10 130] Vaccine regimes may need to be tailored according to the cause and degree of immunocompromise. One of the included studies, by Achiron et al, also found significantly different seroconversion rates for patients receiving different treatments.[99] This finding is orthogonally supported by a study from Kennedy et al, which underscored the fact that immunosuppression caused by different biological agents could be substantial; 20 patients receiving infliximab had significantly lowered titres compared with seven patients receiving vedolizumab (mean 158 (SD 7.0) U/mL *v* 562 (SD 11.5) U/mL).[131] Ligumsky et al[132] further found that different

anticancer treatments are also associated with varying seroconversion rates and antibody titres, with patients who receive chemotherapy showing a lower median IgG titre and seroconversion rate than those receiving immune checkpoint inhibitors and targeted treatment.

Surrogate measures of immunogenicity and efficacy

Currently, no international consensus exists on measures to determine immunogenicity. Trials reported surrogate measures, including seroconversion rates and geometric mean titres. These surrogate measures involved parameters related to anti-SARS-COV-2 recombinant spike, receptor binding domain, or neutralising IgG or total antibodies. The use of immunological markers in predicting protection against covid-19 has been the subject of much debate.[133-136] Although the neutralising antibody level has more recently been established as a reliable predictor of protection against symptomatic covid-19, the measures used in many studies varied.

In this review, only studies that compared measures of effect between immunocompromised patients and immunocompetent controls were included.

Understudied populations

Minimal published data are currently available that compare the immunogenicity of covid-19 vaccines between people with HIV/AIDS and immunocompetent people. Studies have established lower rates of response to hepatitis B and influenza vaccines in people with HIV/AIDS, making study of covid-19 vaccines in this immunocompromised population pertinent.[17 137-139]

Our meta-analysis shows that the seroconversion rate in people with HIV was comparable to that in immunocompetent controls. Given the HIV/AIDS spectrum, the effect of level of depletion of CD4 counts on immune response remains to be established.

Data are also lacking in patients with primary immunodeficiencies.[140] However, even patients with primary antibody deficiencies such as combined variable immunodeficiency have been shown to develop anti-spike antibodies after covid-19 vaccination.[141] All patients with primary immunodeficiencies therefore should be vaccinated against covid-19.

Efficacy of mRNA vaccines versus non-mRNA vaccines

The covid-19 mRNA vaccines represent a new class of vaccine products. It is difficult to directly compare the seroconversion rates of the covid-19 mRNA vaccines with more traditional, frequently used vaccines. In our study, we found no significant differences in a subgroup analysis of mRNA and conventional vaccines in patients with immune mediated inflammatory disorders. The study by Fan et al, which compared mRNA vaccines with conventional vaccines in non-immunocompromised patients,[142] summarised the safety and efficacy of the three main vaccine platforms (mRNA, non-replicating viral vector, inactivated) reported in phase III trials. When patients with confirmed covid-19 were compared over the total number of participants in each (vaccinated *v* control) group, mRNA vaccines appeared to be the most efficacious after two doses (risk ratio 0.05, 95% confidence interval 0.02 to 0.13) compared with non-replicating viral vector vaccines (0.33, 0.22 to 0.50) and inactivated vaccines (0.32, 0.23 to 0.42). A similar trend could be observed after one dose.

A review suggests that the immune response to the influenza vaccine might not be as strong in immunocompromised patients, yet they appear to derive some benefit from vaccination.[143] These findings reflect what is now being experienced with covid-19 and vaccination.

Limitations of this study

This study has several limitations. Firstly, the included studies are observational. Factors that might influence the immune response to the vaccine, such as comorbidities and age, might not be controlled for between the immunocompromised group and immunocompetent control group. To deal with this limitation, we performed subgroup analyses, which showed no significant effect modification between studies with participants of different median age.

Secondly, the definition of immunocompromised varied between studies. We therefore prespecified the definition of immunocompromised and performed subgroup analyses to assess the difference in seroconversion rates in groups of immunocompromised patients. These analyses showed noticeable differences between organ transplant recipients, people with HIV, and patients with solid cancers, haematological cancers, and immune mediated inflammatory disorders.

Although the seroconversion rate is an indication of an immune response to a vaccine, it is only a proxy for the effects of the vaccine on infection rates and severity of covid-19. Data are still lacking on clinical efficacy endpoints such as covid-19 infection rates in vaccinated immunocompromised populations.

Lastly, the definition of seroconversion and the type of immunoassay used were not standardised across the studies. To deal with this limitation, we performed subgroup analyses to determine the presence of effect modification between studies that used different brands of immunoassays. The findings were inconsistent. Furthermore, vaccine type might influence seroconversion rates after covid-19 vaccination. Given that the studies included in this review predominantly used mRNA vaccines, however, analyses of possible differences were limited.

Conclusion

In this meta-analysis, we have shown that seroconversion rates and antibody titres after covid-19 vaccines are significantly lower in immunocompromised patients than immunocompetent individuals. Among the various groups of immunocompromised patients, organ transplant recipients showed the lowest rates of seroconversion, whereas patients with solid cancers showed the highest. Notably, immunocompromised

patients generally develop lower antibody titres with seroconversion than immunocompetent controls, which raises concern about the adequacy of seroprotection. Additional strategies, such as the administration of a third vaccine dose to the conventional two dose regimen for mRNA covid-19 vaccines would be warranted to confer improved seroprotection for these patients.

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Contributors: ARYBL and SYW contributed equally to this paper and are joint first authors. RS and YYS contributed equally to this paper and are joint last authors. ARYBL, SYW, RS, and YYS conceived and designed the study. ARYBL and SYW selected the articles and extracted data. BKJT, CBT, YHC, ARYBL, and YYS were responsible for statistical analysis. ARYBL and SYW wrote the first draft of the manuscript. RS, YYS, LYAC, SCL, MDM, SHT, and ML provided advice at different stages. All authors approved the final version of the manuscript. RS is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study did not receive specific funding. RS is supported by the National Medical Research Council (NMRC/MOH/000627).

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval. Not required.

Data sharing: No additional data available.

The lead author (RS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: We will disseminate the results to clinicians, patients, and governmental organisations and agencies through social media.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: additional tables 1-20 and additional figures 1-21