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Systematic review

Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review

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ABSTRACT

Background: Available data show that COVID-19 vaccines may be less effective in immunocompromised populations, who are at increased risk of severe COVID-19.

Objectives: We conducted a systematic review of literature to assess immunogenicity, efficacy and effectiveness of COVID-19 vaccines in immunocompromised populations.

Data sources: We searched Medline and Embase databases.

Study eligibility criteria, patients, interventions: We included studies of COVID-19 vaccines after complete vaccination in immunocompromised patients until 31 August 2021. Studies with <10 patients, safety data only and case series of breakthrough infections were excluded.

Methods: Risk of bias was assessed via the tool developed by the National Institutes of Health on interventional and observational studies. Immunogenicity was assessed through non-response rate defined as no anti-SARS-CoV-2 spike protein antibodies, efficacy and effectiveness by the relative reduction in risk of SARS-CoV-2 infection or COVID-19. We collected factors associated with the risk of non-response. We presented collected data by immunosuppression type.

Results: We screened 5917 results, included 162 studies. There were 157 on immunogenicity in 25 209 participants, including 7835 cancer or haematological malignancy patients (31.1%), 6302 patients on dialysis (25.0%), 5974 solid organ transplant recipients (23.7%) and 4680 immune-mediated disease patients (18.6%). Proportion of non-responders seemed higher among solid organ transplant recipients (range 18–100%) and patients with haematological malignancy (range 14–61%), and lower in patients with cancer (range 2–36%) and patients on dialysis (range 2–30%). Risk factors for non-response included older age, use of corticosteroids, immunosuppressive or anti-CD20 agent. Ten studies evaluated immunogenicity of an additional dose. Five studies evaluated vaccine efficacy or effectiveness: three on SARS-CoV-2 infection (range 71–81%), one on COVID-19-related hospitalization (62.9%), one had a too small sample size.

Conclusions: This systematic review highlights the risk of low immunogenicity of COVID-19 vaccines in immunocompromised populations, especially solid organ transplant recipients and patients with haematological malignancy. Despite lack of vaccine effectiveness data, enhanced vaccine regimens may be necessary. **Simon Galmiche, Clin Microbiol Infect 2022;28:163**

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Introduction

A set of COVID-19 vaccines has been rapidly developed with high vaccine efficacy in phase 3 studies. However, these large-scale pre-marketing studies provide little information on vaccine efficacy in immunocompromised populations, while current evidence shows an increased risk of severe COVID-19 in patients with cancer [1], solid organ transplant [2,3], end-stage renal disease [4,5] and rheumatic immune-mediated diseases on immunosuppressive treatment [6].

Available data with other vaccines indicate a lower vaccine immunogenicity and efficacy in immunocompromised patients, such as patients undergoing haemodialysis, solid organ transplant recipients [7,8], patients with cancer or haematological malignancy [9,10] and those with autoimmune inflammatory diseases [11], hence raising the concern of potentially decreased immunogenicity and effectiveness of COVID-19 vaccines.

Several studies have been published in the past few months on the immunogenicity of COVID-19 vaccines in different populations of immunocompromised subjects, leading some countries such as France, and more recently the United States, to recommend an additional dose of vaccine [12,13]. We aimed to summarize available evidence on vaccine immunogenicity and factors associated with non-response to vaccine, efficacy and effectiveness in these populations through a systematic review of literature.

Materials and methods

Objectives and outcomes of interest

We conducted a systematic review of literature until 31 August 2021. The main objective was to assess evidence on COVID-19 vaccine immunogenicity, efficacy and effectiveness in immunocompromised populations. The secondary objectives were to determine factors associated with lack of post-vaccine immunity or low post-vaccine antibody titres, elements of cellular response following vaccination and benefits of additional doses.

Outcomes of interest were vaccine efficacy assessed by the relative reduction in risk of COVID-19 in randomized placebo-controlled trials, vaccine effectiveness, assessed by the relative reduction in risk of SARS-CoV-2 infection in observational studies on RT-PCR-confirmed SARS-CoV-2 infections or in relative reduction in risk of SARS-CoV-2-related hospitalizations or death, and immunogenicity assessed by the rate of non-responders defined as no anti-SARS-CoV-2 spike protein antibodies (IgG, total antibodies if IgG unavailable) as per cut-off defined in each study. If only neutralization assay data were available, we defined non-response as absence of neutralizing antibodies as per cut-off defined in the study. Factors associated with lack of post-vaccine immunity or lower post-vaccine antibody titres, compared with the rest of the population of interest or to a control group (if any), were defined according to associations found in each study.

Inclusion and exclusion criteria

We included reports of COVID-19 vaccine immunogenicity, efficacy and effectiveness in any of the following populations: cancer, haematological malignancy, solid organ transplantation, allogenic stem cell transplantation, autoimmune systemic disease, autoimmune organ specific disease, inflammatory bowel disease, sarcoidosis, autoinflammatory disease, multiple sclerosis, neuromyelitis optica spectrum disease, chronic kidney disease, HIV infection, congenital immunodeficiency, patients undergoing immunosuppressive medications, systemic corticosteroids, monoclonal antibodies. We grouped studies by type of immunosuppressed population.

We included studies of various designs and article types (including preprints, given the rapidly evolving evidence in that field): interventional trials, observational studies and original articles, comments, letters and case series. No language restrictions were imposed.

Exclusion criteria were reports of an incomplete vaccination schedule (i.e. only one dose for all available vaccines except the Ad26.COV2.S Janssen vaccine), review or recommendation articles lacking original data, studies reporting only safety data, case reports, case series reporting fewer than ten patients and case series of breakthrough infections.

Search and data extraction strategies

We searched the databases Medline through PubMed and Embase from inception until 31 August 2021. We used a series of key words and their corresponding Mesh terms for the Pubmed search and the same key words as Emtree terms for the Embase search. Full search strategies are available in supplementary material. One investigator (S.G.) screened titles and abstracts for eligibility. Two investigators (S.G., L.B.L.N.) independently read the selected articles to assess eligibility and met to determine final eligibility. A third investigator (O.L.) split the case in case of persistent discrepancy. We screened grey literature (frequent consultation of core clinical journal websites, abstracts of the congresses of international infectious diseases societies, advisory committee on immunization practice presentations regarding COVID-19 vaccines in immunocompromised populations) and references lists of included reports for further studies. One investigator (S.G.) collected the following data from all selected reports: study type, study population, control group (if any), vaccine used, estimated vaccine efficacy or effectiveness, time from completion of vaccination to measurement of immunogenicity, methods for measurement of immunogenicity, cellular response indicators (if any), neutralization indicators (if any), amount and rate of non-responders (to an additional dose of vaccine if any), factors associated with non-response or lower antibody titres (in multivariable analysis, if any, otherwise in univariable analysis). If studies did not report response status after completion of vaccination schedule for their entire study population, we only considered the subpopulations for whom those data were available.

We collected and synthesized data from studies and created graphs using an Excel spreadsheet. We used STATA/IC 15.1 (College Station, Texas, USA) for further data synthesis.

Risk of bias assessment

We assessed risk of bias through the National Institutes of Health (NIH) quality assessment tools for controlled interventional studies and observational cohorts [14]. Two investigators (S.G., L.B.L.N.) independently assessed risk of bias; discrepancy cases were first discussed between the investigators, then split by a third investigator (P.L.) in case of persistent discordance.

Results

We launched searches on 7 June 2021, again on 21 June 2021, and set up daily e-mail alerts on both databases for subsequent days until 31 August 2021. Searches retrieved 3544 results on Medline and 2373 results on Embase, with 525 duplicates. After title and abstract screening, we retained 271 reports. After full-text reading, grey literature and reference list inspection, 162 studies were included from 170 reports (some reports detailed different timepoints of the same study [15–28] (Fig. 1).

Most studies were prone to some bias; 21 of them were estimated of good quality (Tables S1 and S2). Most frequent sources of bias were lack of definition of population from which participants were included, of sample size calculation and of adjustment on potential confounding factors. The studies on vaccine efficacy or effectiveness were all considered of good or fair quality in the risk of bias assessment.

The vast majority of included studies evaluated vaccines developed by Pfizer (BNT162b2) or Moderna (mRNA-1273). Thirteen studies included patients who received the vaccine developed by Janssen (Ad26.COV2.S) [25–27,29–40], nine included patients vaccinated with the AstraZeneca vaccine (ChAdOx1) [41–49], three included patients receiving the CoronaVac vaccine (Sinovac Biotech) [50–52], and one randomized controlled trial evaluated

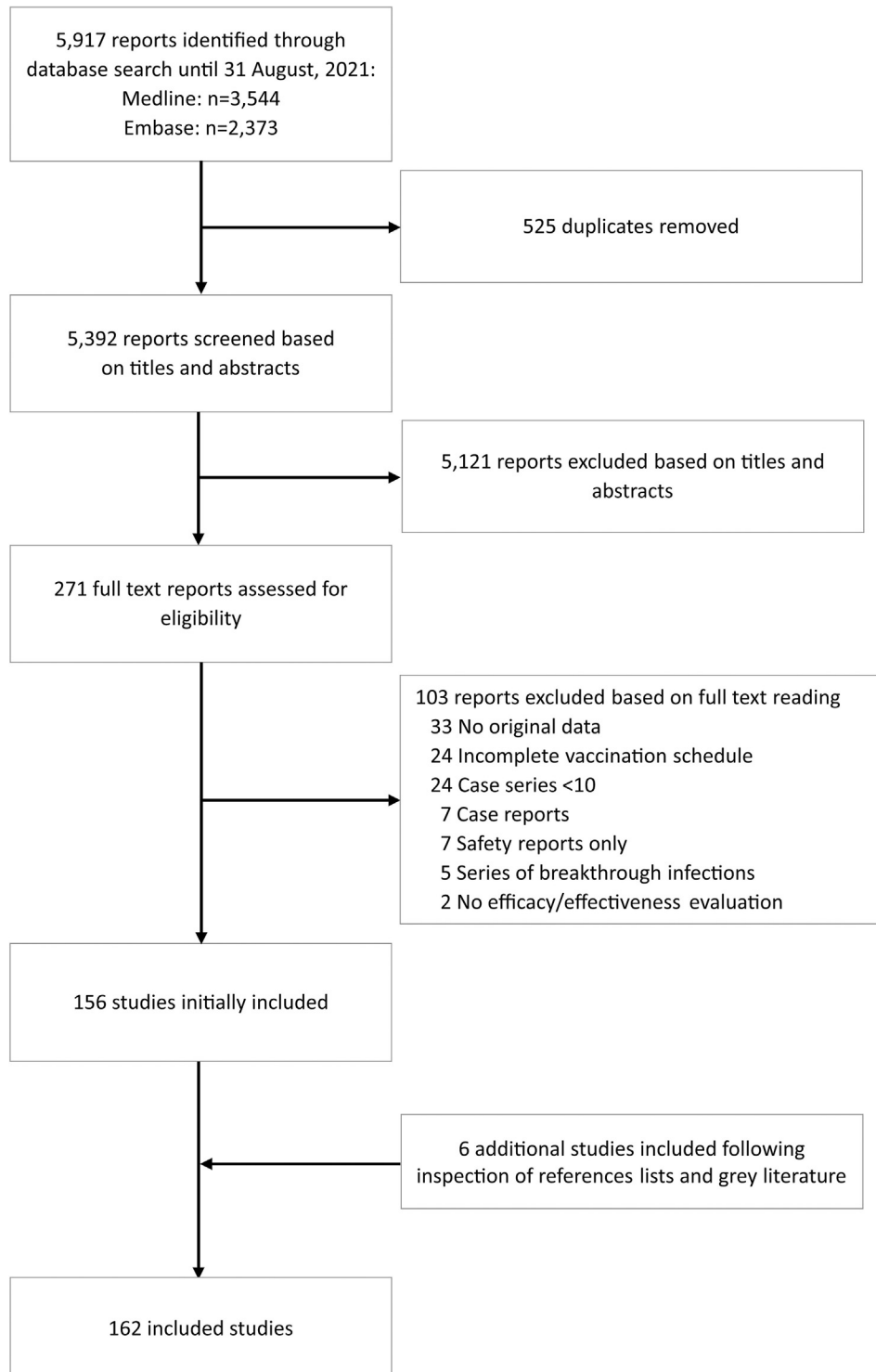


Fig. 1. Flow chart of study selection.

the vaccine developed by Novavax (NVX-CoV2373) vaccine [53]. One study included patients receiving the BBV152-Covaxin (Bharat Biotech) vaccine [44] and one included patients receiving the BBIBP-CorV (Sinopharm) vaccine [54].

Methods of measurement of post-vaccine immunity

Most studies assessed anti-SARS-CoV-2 immunity through an immunoassay to detect antibodies targeted at the spike protein, including some targeting specifically the receptor-binding domain (RBD) of the spike protein. Thirty studies reported neutralization assay results in addition to anti-SARS-CoV-2 antibody assays [34,37,41,48,51,55–79]. Thirty-one studies provided data on cellular immunity [17,21,22,34,37,41,45,46,55–67,72,74–77,79–84].

Immunogenicity data

Most studies ($n = 157$) reported immunogenicity data amounting to 25 209 participants, mainly cancer or haematological malignancy patients (7835, 31.1%), patients on dialysis (6302, 25.0%), solid organ transplant recipients (5974, 23.7%) and immune-mediated disease patients (4680, 18.6%). Eighty-three of those studies included a control population who also received the vaccine or recovering COVID-19 patients.

Cancer and haematological malignancy patients

Forty-three studies reported immunogenicity in patients with haematological malignancy ($n = 6259$, 79.9%) and cancer ($n = 1480$, 18.9%) (Table S3) [30,33,35,42,43,49,52,59,60,70,71,76], [83–113]. Twenty-three of these studies included a control population (overall $n = 1931$) [30,33,42,43,60,71,76,85–89,91,92,96,98,104,106–108,110–112] in which all but 15 participants developed post-vaccine antibodies [43,76,88,106,110,112]. Non-response rates among cancer and haematological malignancy populations ranged from 2% to 61% [30,89,90].

Malignancy-specific treatments were repeatedly associated with non-responder status, whether taken as a whole or specific treatments such as cytotoxic chemotherapy, Bruton tyrosine kinase inhibitors, anti-CD20 treatment or daratumumab-based regimens [30,33,35,42,43,70,71,76,83,85,86,89–92,95,100,102–106,110,112,113] (Table S3).

Patients with haematological malignancy

Non-response rates in patients with haematological malignancy ranged from 14% to 61% [89,101] (Fig. 2A). Patients with chronic lymphocytic leukaemia seemed at high risk of non-response with rates ranging from 28% to 77% [43,70,83,86,89,93,95,103,107,109]. Patients with multiple myeloma were at lower risk of non-response: rates ranged from 5% to 34% [86,88,92–94,103,104,108]. Patients with myeloproliferative neoplasms (chronic myeloid leukaemia and Philadelphia-negative myeloproliferative neoplasms) displayed lower rates of non-response, ranging from 12% to 20% [86,92,101,113]. In patients with lymphoma, non-response rates ranged from 30% to 58%, with the highest rate reported by Ghione et al. [33] in patients largely recently treated (52/86) with B-cell depleting treatment [83,86,93,94,100,107]. Patients with haematopoietic stem cell transplantation (HSCT) displayed non-response rates ranging from 14% to 31% in allogenic HSCT [35,84,102], and showed maintained response rates in Tzarfati et al. [86] (autologous HSCT) and antibody titres in Maneikis et al. [85] (allogenic and autologous HSCT), while they were at increased risk of non-response in Thakkar et al. [30] (mostly autologous HSCT). Only Dhakal et al. provided a non-response rate for patients with autologous HSCT which was estimated at 40% (18/45) [35].

Five studies provided results on cellular immunity, two using an enzyme-linked immunospot (ELISpot) assay [76,84], one with a FluoroSpot assay [60] and one with an interferon-gamma release assay (IGRA) assay [83]. Non-response rates were usually higher in cellular than in antibody response [60,83,84] except in one study [76].

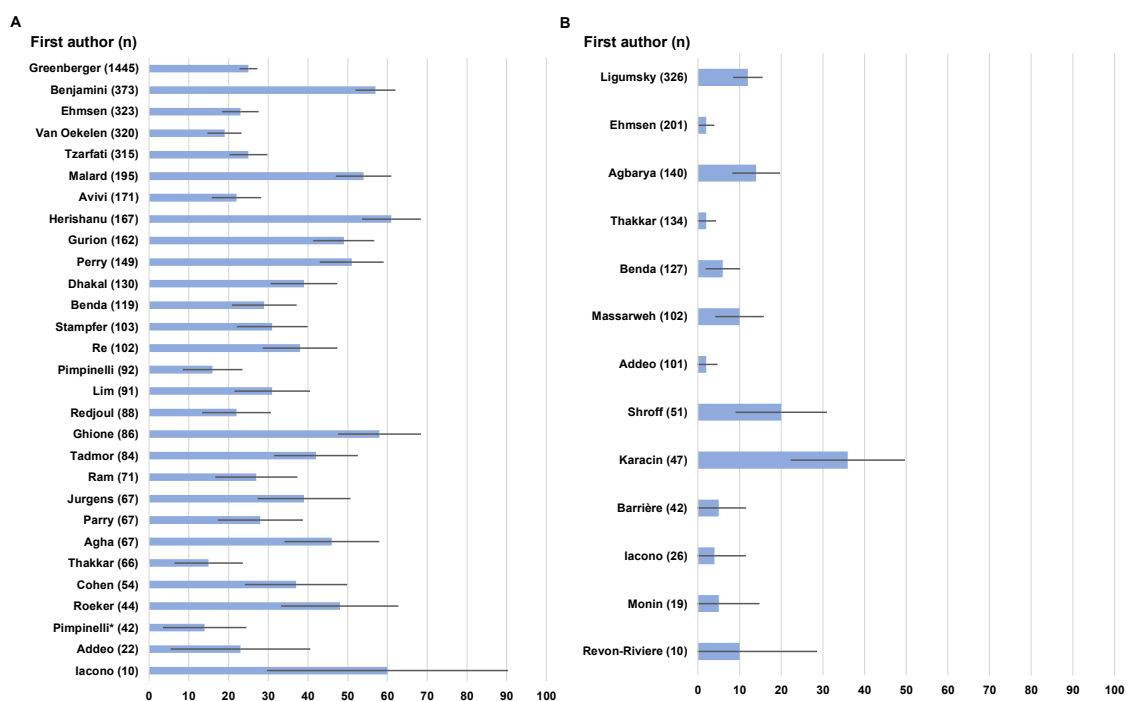


Fig. 2. Rates of non-response in patients with haematological malignancy (A) and cancer (B). Grey dashes represent the 95% CI. The studies are ordered by population size. Only studies with subgroup size $n \geq 10$ are represented.

Patients with cancer

Non-response rates in patients with cancer ranged from 2% to 36% [30,52,83,90] (Fig. 2B). Two large studies found some of the higher rates: Shroff et al. [59] (non-response rate 20%, 10/51) provided binary data on seroconversion only with a neutralization assay, and Karacin et al. [52] (non-response rate 36%, 17/47) included only patients undergoing active specific anti-cancer therapy which possibly contributed to an increased risk of non-response [52,59].

As did Shroff et al., Monin et al. tested for neutralizing antibodies: they found neutralizing antibodies against the wild type and the B.1.1.7 (alpha) variant spike protein in all participants who produced detectable post-vaccine anti-S IgG [59,60].

Both studies, along with Ehmsen et al., reported data on cellular immunity [59,60,83]. In patients without post-vaccine neutralizing antibodies, Shroff et al. found a non-response rate of 60% (6/10) with an ELISpot assay [59]. Non-response rates in Monin et al. were 13% (2/16) in patients with solid cancer and 25% (1/4) of patients with haematological malignancy with a Fluorospot assay [60]. As in patients with haematological malignancy, Ehmsen et al. found a higher non-response rate in cellular (tested via an IGRA assay) than in antibody response: 54% (109/201) vs 2% (4/201) respectively [83].

Patients on dialysis

Thirty-three studies reported immunogenicity in 6302 patients on dialysis (Table S4) [15–17,21,31,38,44,62–64,74,78,80,114–134]. Non-responder rates ranged from 2% to 30% (Fig. 3) [125,126]. Four studies were rated “good” in the risk of bias assessment: they all found low non-response rates ranging from 2% to 5% [21,125,130,133]. Simon et al. found a high non-response rate at 27% (22/80), at least partially explained by the choice of a higher cut-off (29 U/mL) than the one provided by the manufacturer of the serological assay [118,135]. Fifteen studies included a control group ($n = 779$ overall), in which all but nine participants developed post-vaccine antibodies [17,21,63,74,78,80,116,118,120,121,124,126,128,131,134]. Speer et al. performed neutralization assays which showed the same rate of non-response as the anti-S antibody assay: 3/17 (18%) [128]. In a further study, Speer et al. measured neutralizing antibodies in participants with seroconversion: all showed neutralizing antibodies against the B.1.1.7 strain (alpha variant), while only 15/24 had neutralizing antibodies against the B.1.351 strain (beta variant) [78]. Seven studies reported elements of cellular response, using either a flow cytometry technique [21,62,63,80], an ELISpot assay [64] or an IGRA assay [17,21,74]. Non-response rates were lower in T-cell response than antibody response in both Bertrand et al. and Sattler et al. [62,63]. Four studies found opposite results with higher non-response rates in cellular than in antibody response [17,21,64,74].

Treatment with immunosuppressive therapies was associated with non-responder status or lower antibody titres in several studies (Table S4) [62,64,129], as well as older age [17,31,117,118,121,122,124,133] or a lower lymphocyte count [64,124].

Solid organ transplant recipients

Forty-seven studies described immunogenicity across various solid organ transplant populations ($n = 5974$), mostly in kidney transplant recipients ($n = 3534$, 59.2%) (Table S5) [18,20–26,29,34,40,56–58], [62,63,65,66,69,72,73,75,77,79,81,120,126], [136–160]. Twenty-four of those studies included a control group representing overall 1399 participants [21,34,57,63,66,69,72,73,75,79,120,126,142–146,148,149,

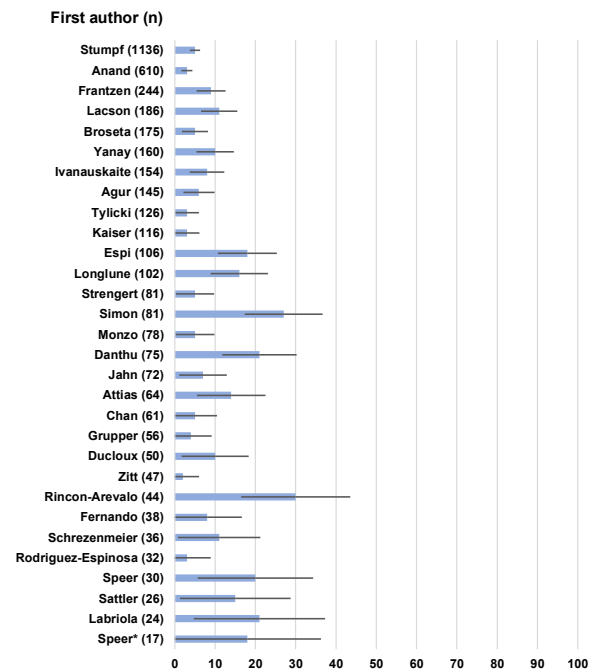


Fig. 3. Rates of non-response in patients on dialysis. We reported the latest endpoint within 30 days following vaccine completion if several endpoints were available. We reported the outcome following second dose in the studies reporting post-vaccine immunity following an additional dose. The studies are ordered by population size. Grey dashes represent the 95% CI. Only studies with subgroup size $n \geq 10$ are represented. *Speer et al. [128].

151,152,154–156], among whom only 12 did not mount a post-vaccine antibody immunity [21,69,145,155]. Non-responder rates ranged from 18% to 100% [40,149,152] (Fig. 4): 35–98% in kidney transplant recipients, 19–63% in liver transplant recipients, 25–88% in heart transplant recipients and 59–100% in lung transplant recipients (for studies with subgroup size $n \geq 10$) (Fig. 5).

Eleven studies reported results of neutralization assays [34,63,66,69,72,77,79,126,145]. Non-response rates were close to those in anti-S assays in most studies [63,72,77,126], while several studies performed the assay only in anti-spike antibody positive participants who mostly tested positive in neutralization assays [69,79,145].

Fourteen studies included data on T-cell immunity, assessed through an ELISpot assay [56–58,62,65,75,81], flow cytometry [21,34,63,72,79] or an IGRA assay [21,66]. Most studies found lower non-response rates in cellular than in antibody response [56–58,62,63,72,79,81], while two studies found higher non-response rates in cellular than in antibody response [21,65].

Solid organ transplant-specific treatments (calcineurin inhibitors, antimetabolites, corticosteroids) were often associated with a higher non-response rate or lower antibody titres [20,21,24,40,56,62,65,69,72,75,81,136,138–142,144,145,148,154–157,159,160] (Table S5). Older age and lower estimated glomerular filtration rate were repeatedly associated with a non-responder status [21,24,79,120,138,142,144,155]. We found conflicting results regarding the impact of time since transplantation on vaccine response: seven studies found higher non-response rates or lower antibody titres in patients with recent transplantation, Rozen-Zvi et al. [138] found a longer time from transplantation was associated with lower antibody titres [21,62,79,139,141,143,155,160].

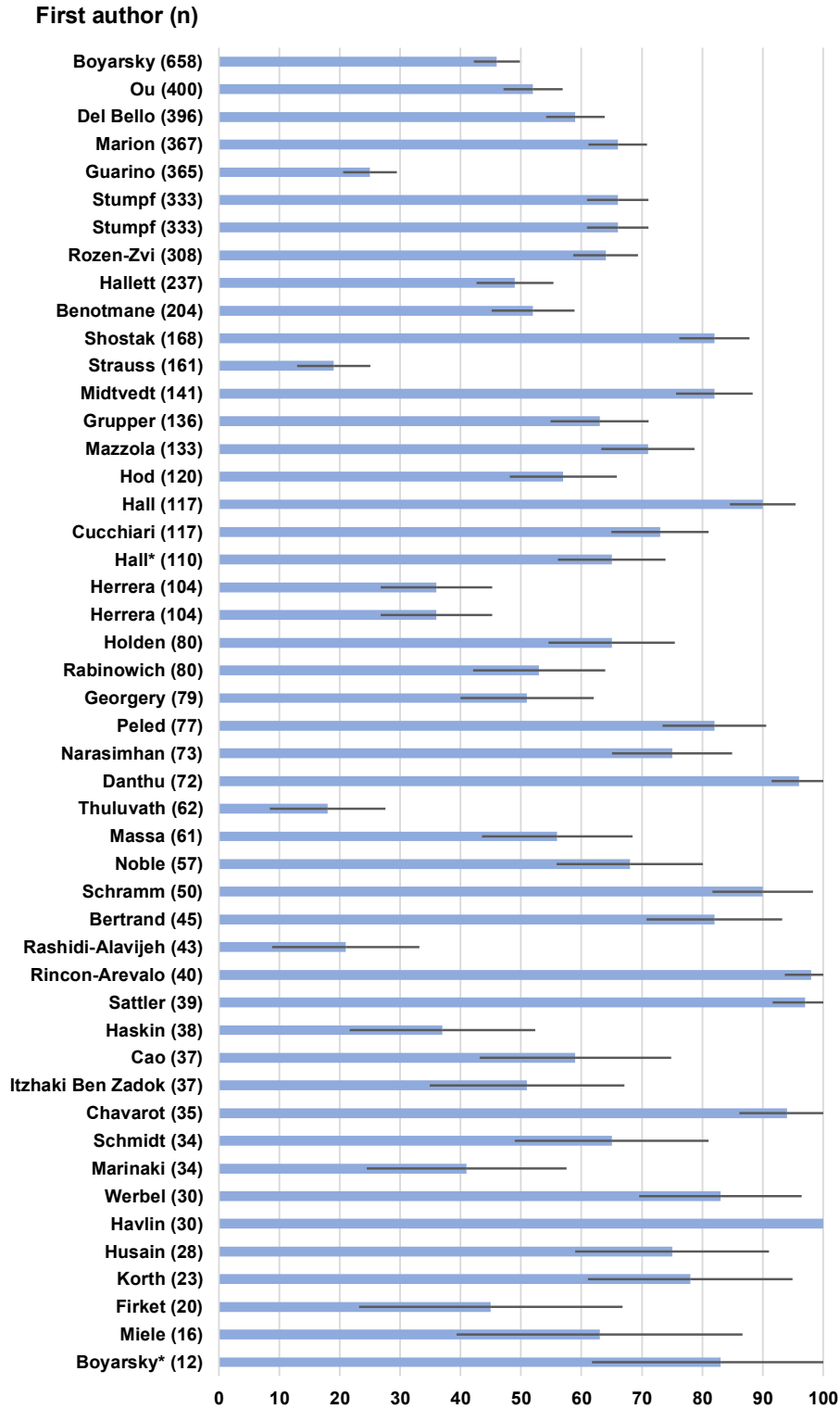


Fig. 4. Rates of non-response in solid organ transplant recipients. We reported the latest endpoint within 30 days following vaccine completion if several endpoints were available. We reported the outcome following second dose in the studies reporting post-vaccine immunity following an additional dose. Grey dashes represent the 95% CI. The studies are ordered by population size. *Hall et al. [72]. *Boyarsky et al. [29].

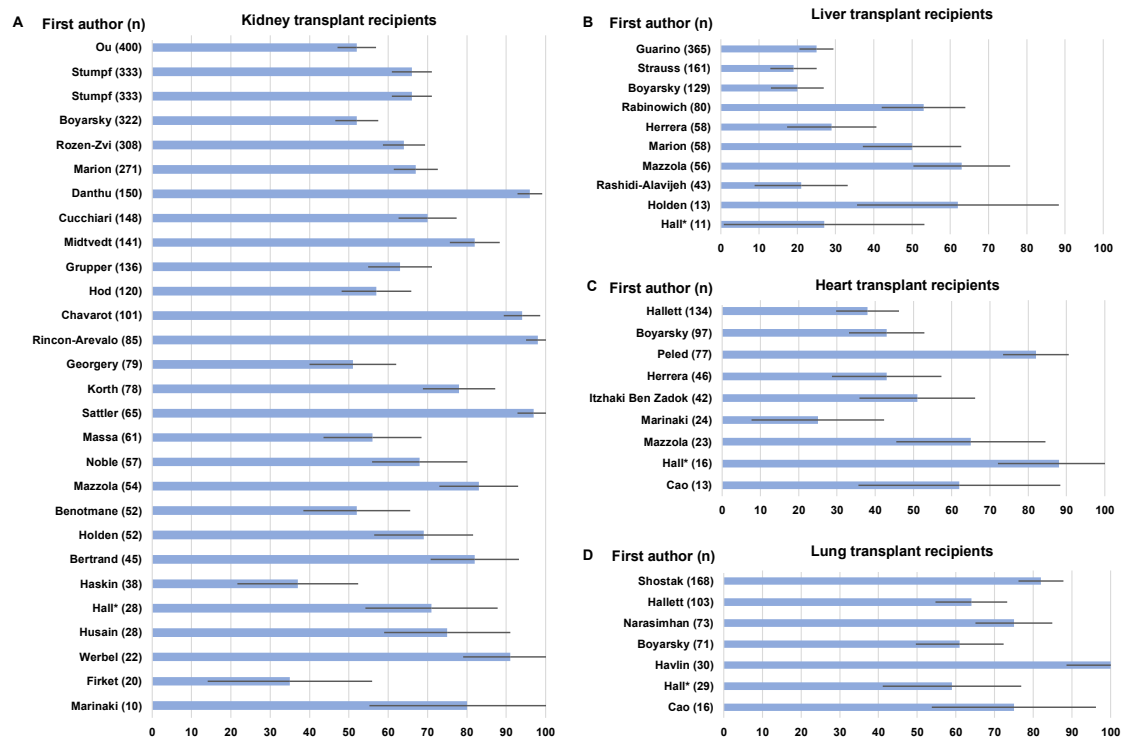


Fig. 5. Rates of non-response in solid organ transplant recipients: kidney (A), liver (B), heart (C) and lung (D). We reported the latest endpoint within 30 days following vaccine completion if several endpoints were available. We reported the outcome following second dose in the studies reporting post-vaccine immunity following an additional dose. Grey dashes represent the 95% CI. The studies are ordered by population size. Only studies with subgroup size $n \geq 10$ are represented. *Hall et al. [72].

Inflammatory immune-mediated diseases

Thirty-one studies reported immunogenicity in 4680 patients with inflammatory immune-mediated diseases (Table S6) [27,28,32,36,37,39,45–47,50,51,54,55,82,161–178]. Main represented groups included rheumatoid arthritis ($n = 665$), inflammatory bowel diseases ($n = 476$) and multiple sclerosis ($n = 231$). Twenty of those studies had a control group [32,37,45–47,50,51,55,161–164,166,167,169,171,172,174,177,178] ($n = 1609$), among which 16 participants failed to mount a post-vaccine antibody response [47,50,51,55,163,164].

Non-response rates ranged from 0% to 63% (Fig. 6) [36,39,55,168,171,172,177]. Among the studies with the highest non-response rates, Mrak et al. included only patients on rituximab, Connolly et al. [36] included 48 participants with ANCA-associated vasculitis, of whom 44 received rituximab, and Achiron et al. and Guerrieri et al. found high rates (respectively 47% and 50%) in patients with multiple sclerosis (MS) [164,168]. Six studies tested participants' sera with neutralization assays [32,37,51,163,172,174], one tested neutralization on a SARS-CoV-2 spike protein bearing the N501Y mutation (present in the alpha variant) [32]. Two studies provided non-response rates which were either the same as with anti-S IgG assay (0%, 0/26 [172]) or higher (44%, 375/859 vs. 29%, 245/859 with the anti-S assay [51]).

Six studies included elements of cellular response, using a flow cytometry technique [46,55], an ELISpot assay [37,45,178] or an IGRA assay [82]. Haberman et al. found activated CD8+ T-cells in all 24 participants who were not receiving methotrexate but in none of the 18 patients who were receiving methotrexate [55]. Predecki et al. and Mrak et al. found lower non-response rates in cellular than in antibody response, while Benucci et al. found detectable

T-cell response in four patients with no antibodies or low titres [45,82,178].

Specific treatments of the inflammatory disease negatively impacted post-vaccine response: B-cell depleting agents [28,50,161–165,169,175], methotrexate and other disease-modifying antirheumatic drugs (DMARDs) or corticosteroids [28,50,51,55,161–163,176]. When analysed, impact of TNF inhibitors varied across studies: while some found an association with a lower risk of non-response or no impact on response or antibody titres [28,46,161,163], two studies found they were associated with absence of seroconversion or low antibody titres [51,171].

Other immunosuppressed populations

Five studies conducted in people living with HIV found low non-response rates ranging from 0 to 4% [48,68,179] (among those, two studies were estimated of good quality in the risk of bias assessment [48,68]) or comparable antibody titres compared to an HIV-negative population [41,67].

Two studies by Hagin et al. and Abo-Helo et al. reported results of immunogenicity of the BNT162b2 vaccine in patients inborn errors of immunity (mostly common variable immunodeficiency): non-response rates were respectively 23% (6/26) and 27% (4/15) [61,180].

Lustig et al. reported immunogenicity data in 2607 healthcare workers who received BNT162b2, among whom 74 with an autoimmune disease and 12 with another immunosuppression were evaluated following the second dose [181]. Immunosuppression, but not autoimmune diseases, was associated with lower antibody titres. Kageyama et al. found a non-response rate of 4% (1/23) in healthcare workers who received corticosteroids [182].

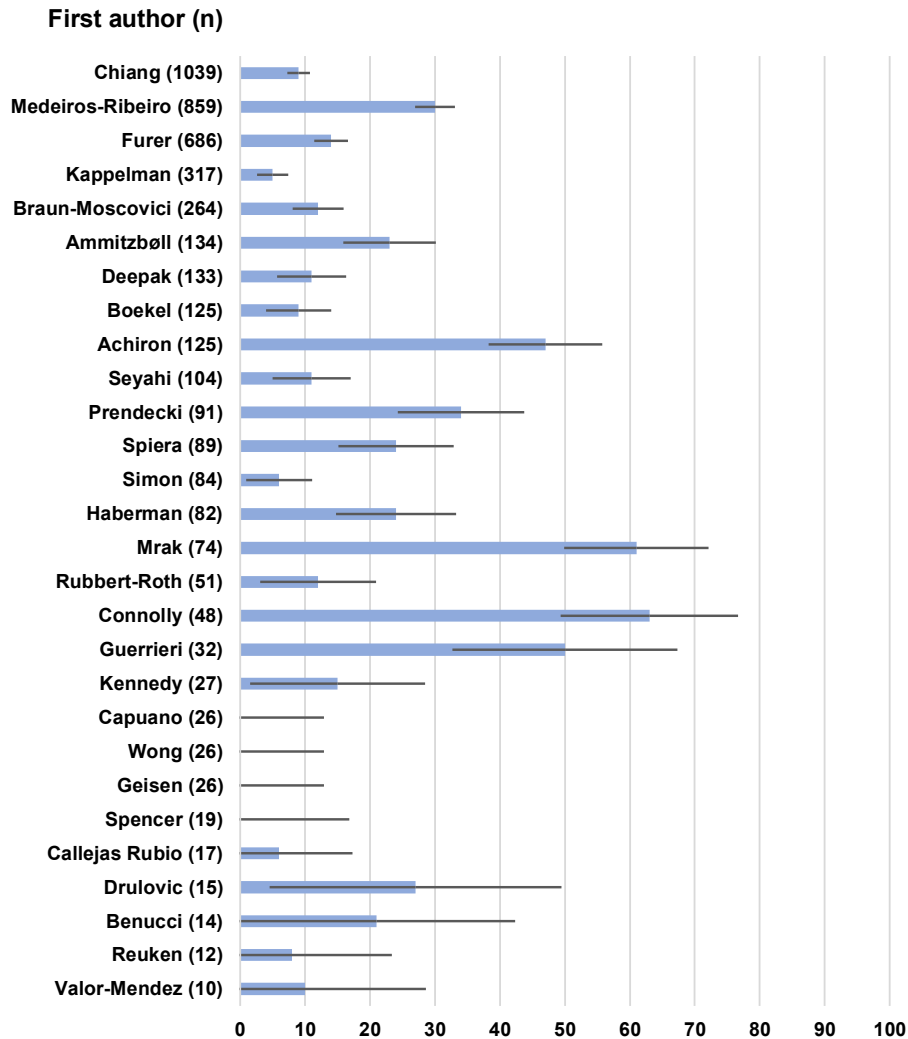


Fig. 6. Rates of non-response in patients with autoimmune inflammatory diseases. Grey dashes represent the 95% CI. The studies are ordered by population size.

Effect of an additional dose of vaccine

Ten studies reported the effect of an additional dose following a complete vaccination [16,19,22,23,25,26,75,77,129,153,157]. Seven were conducted in solid organ transplant recipients [22,23,25,26,75,77,153,157] (Table S5): non-response rates following the additional dose in the initially non-responders ranged from 51% to 68% [75,153]. Hall et al. conducted a randomized placebo-controlled trial (the only study rated “good” in the risk of bias assessment among those studying an additional dose), testing a third dose of the Moderna vaccine in 117 solid organ transplant recipients, and showed a lower non-response rate in the vaccine arm (45%, 27/60) than in the placebo arm (82%, 47/57) [77]. Alejo et al. continued the study by Werbel et al. and offered a fourth dose of vaccine to 18 patients of whom 50% (3/6) of the non-responders after the third dose showed positive antibody testing after the fourth dose [25,26]. Three studies were conducted in patients with end-stage renal disease [16,19,129]: non-response rates following the additional dose among the initially non-responders ranged from 50% to 60% (Table S4).

Effect of vaccine type

Immunogenicity varied across vaccine type: the Pfizer [21,38,39,103,130,159] and Janssen vaccines [38,39] were repeatedly associated with non-response status or lower antibody titres compared than the Moderna vaccine. Two studies found higher odds of non-response when vaccinated with the Janssen vaccine compared with the two mRNA vaccines [27,40].

Vaccine efficacy and effectiveness data

Five studies reported data in immunosuppressed populations [53,183–186]. A randomized controlled trial of the Novavax vaccine against the B.1.351 (beta) variant reported outcomes in a subgroup of 148 HIV-positive participants who were seronegative for SARS-CoV-2 at baseline. Efficacy could not be estimated in the group of people living with HIV: only six events occurred in this subgroup (four in the 76 participants in the vaccine group and two in the 72 participants in the placebo group) [53]. Nonetheless, vaccine efficacy estimates were lower when including participants living with

HIV (efficacy: 49.4%, 95% CI 6.1–72.8) than when analysis was restricted to HIV-negative participants (efficacy: 60.1%, 95% CI 19.9–80.1). Other phase 3 randomized controlled trials did not include immunosuppressed patients or did not provide subgroup analysis results [187–190]. Three observational retrospective studies estimated effectiveness on RT-PCR-proven SARS-CoV-2 infection in immunocompromised patients: a study in patients with inflammatory bowel diseases reported an 80.4% vaccine effectiveness of mRNA vaccines [184], an Israeli cohort included patients with immunosuppression (no further details) with a reported effectiveness of 71% (95% CI 37–87%), notably lower than across the entire study population (90%, 95% CI 79–95%) [183], and a study in solid organ transplant recipients found an incidence rate ratio of 0.19 (95% CI 0.049–0.503) [186]. One study evaluated effectiveness on COVID-19-related hospitalizations in a test-negative design and found an effectiveness of 62.9% (95% CI 20.8–82.6%) in an immunocompromised population (no further details), lower than across the non-immunocompromised population (91.3%, 95% CI 85.6–94.8%) [185].

Discussion

This review is the first to report available data on COVID 19 vaccination in different populations of immunocompromised patients. It highlights lower immunogenicity of COVID-19 vaccines in these patients than estimated in most previous clinical studies conducted in healthy volunteers [191–193]. Non-response rate varies widely and is higher in solid organ transplant recipients (especially lung and renal transplant recipients), patients with haematological malignancy (most of all patients with chronic lymphocytic leukaemia), and lower in patients with cancer, patients on dialysis and with varying levels across different immune-mediated diseases (seemingly higher in patients with MS), possibly due to differences in therapeutics. These variations are consistent with findings in other vaccines (influenza, pneumococcal and hepatitis B vaccines) among solid organ transplant recipients [194,195] and patients with haematological malignancies [196,197], while patients on dialysis often display satisfying immunogenicity [198] or higher than solid organ transplant recipients [199]. Only a few studies provided information on cellular immunity and neutralization assays. While some seemed to indicate a better cellular response than humoral antibody response [45,56–58, 62,63,72,76,79,81], others found opposite results [17,21,60,64, 65,74,76,83,84]. Lack of standardization of assays to detect T-cell immunity and various performances across different techniques (flow cytometry or ELISpot/fluorospot) may partly explain these discrepancies [200]. Further data on T-cell-mediated immunity are needed to determine to which extent post-vaccine immunity is compromised.

The majority of included studies involved mRNA-based vaccines. This is the consequence of the early availability of those vaccines, with data suggesting high immunogenicity in healthy volunteers and elderly, of particular interest in immunocompromised patients who are at high risk of severe COVID-19 [191]. As mRNA vaccines are being used for the first time, those are the first data we have on mRNA vaccines in immunocompromised populations. We only included studies on full vaccination schedules, thus data on ChAdOx1 nCoV-19 are still scarce, given the extended interval between the two doses implemented in some national vaccination campaigns [201]. Immunogenicity data suggesting higher immunogenicity of mRNA-based vaccines (especially the Moderna vaccine) than adenovirus-based vaccines warrant further investigation [27,30,38–40,170].

Risk factors for non-response status often included older age, which is consistent with data provided by phase 1 and 2 studies of

COVID-19 vaccines [191,192], as well as in other vaccines such as influenza, pneumococcal and hepatitis B vaccines [202–205]. Immunosuppressive therapy and biological agents, especially B-cell depleting agents, often negatively impact immune responses to COVID-19 vaccines. These reports are consistent with immune response to other vaccines in populations receiving such treatments, mycophenolate [194] and anti-CD20 agents (in a rheumatological indication [206,207], haematological malignancy [208,209] or multiple sclerosis [210]), methotrexate [211], while TNF inhibitors variously affect immunogenicity [211,212].

This systematic review of literature highlights currently missing data. We identified only five articles on vaccine efficacy or effectiveness in immunosuppressed populations. Estimates of effectiveness appear lower than in the general population [183,213,214], which is consistent with the findings of this review regarding a diminished immunogenicity and reports of more breakthrough infections observed in these populations [215–217]. Data on variants of concern include the dedicated randomized controlled trial [53] and the study by Chodick et al. which took place during periods of high local prevalence of the alpha variant [183]. However, data on the delta variant are still missing, and studies in the general population suggest a reduced effectiveness against SARS-CoV-2 infection (but not against severe forms) with this variant [218,219]. No study has yet reported effectiveness nor efficacy of an additional dose of vaccine in immunocompromised populations. Further studies with longer follow-up will help determine long-term immunogenicity. Literature data are still scarce if existent in many immunocompromised populations, including patients with inborn errors of immunity, allogenic stem cell transplantation and people living with HIV. A search of the [ClinicalTrials.gov](https://www.clinicaltrials.gov) database on 31 August 2021 revealed two ongoing randomized controlled trials in immunocompromised populations: one comparing the Moderna and Pfizer vaccines in solid organ transplant recipients and people living with HIV, and one in patients with chronic kidney disease and dialysis comparing the Moderna and Pfizer vaccines as third dose after two doses of mRNA vaccines. Other phase 2 or phase 3 studies evaluating currently not approved COVID-19 vaccines include people living with HIV.

This review has certain limitations. The included studies assessed post-vaccine antibody response through various anti-Spike protein assays, performed at different timepoints. Heterogeneity in populations and methods used to assess immunogenicity and frequent lack of details on included populations make it difficult to perform meta-analysis with currently available data, which is why we chose not to do so. Most included studies were observational with a small sample size, thus permitting little adjustment on confounding. We could not perform additional analyses of factors associated with non-response as individual data were mostly unavailable, thus we reported those as mentioned by the authors. Large studies with standardized assays allowing comparisons are needed [220]. Nonetheless, this review provides a comprehensive understanding of the current evidence to help decision-making regarding vaccination strategies in immunocompromised patients.

Targeted strategies might prove interesting in those populations, such as additional doses (currently recommended in France [12]), as suggested by some data presented in this review [16,24,26,129]. Other approaches such as heterologous vaccination [221,222], increased doses (as in hepatitis B vaccine [223,224]) might enhance immunogenicity, while prophylactic administration of monoclonal antibodies [225] or 'cocooning' vaccination of relatives and healthcare workers offer potential alternatives [226].

Overall, this systematic review highlights a diminished immunogenicity of COVID-19 vaccines, including mRNA-based vaccines, in immunocompromised populations, with varying levels across

different types of immunodepression. Alternative strategies are necessary to provide sufficient protection to these patients.

Transparency declaration

Dr Loubet reports personal fees from Pfizer, non-financial support from Sanofi Pasteur, non-financial support from Pfizer, personal fees from AstraZeneca, outside the submitted work. Dr Luong Nguyen reports personal fees from Pfizer, outside the submitted work. Other authors do not report any competing interests. Dr Wittkop reports grants and contracts from ANRS-MIE and Sidaction to the institution. Pr Launay reports grants and contracts from Pfizer, GSK, Janssen, Sanofi Pasteur, GSK, consulting fees from Pfizer, Janssen, Sanofi Pasteur, support for attending meetings and/or travel from Pfizer, Janssen, Sanofi Pasteur and participation on a data safety monitoring board or advisory board for Sanofi Pasteur and MSD, all unrelated to the submitted work.

Data availability

Extracted data are available almost entirely in the review (including supplementary information). Remaining data regarding the serological assays are available on request.

Author contributions

S.G., L.B.L.N., P.L. and O.L. designed the review. S.G. screened titles and abstract for eligibility. S.G. and L.B.L.N. independently assessed articles for inclusion. O.L. split the case in case of discrepancy. S.G. and L.B.L.N. independently assessed risk of bias of included studies. P.L. split the case in case of discrepancy. S.G. extracted data from the included studies. S.G. and L.B.L.N. jointly verified figures extracted from the studies. S.G., L.B.L.N., P.L. and O.L. drafted the first versions of the manuscript. E.T., X.d.L. and L.W. critically reviewed the manuscript. All authors received and approved the current version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.09.036>.

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