# SARS-CoV-2 Vaccine Non-response among Hematopoietic Stem Cell Transplant Patients: A Systematic Review and Meta-analysis

**Afoke Kokogho**
Harvard University
**Trevor A. Crowell**
Henry M. Jackson Foundation
**Paul A. Bain**
Harvard University
**Sudaba Popal**
Lumen Foundation
**Muneerah Aleissa**
Brigham and Women's Hospital
**Jun Bai Park Chang**
Brigham and Women's Hospital
**Deema Aleissa**
Tufts University
**Agho Osamade**
Internal Medicine Solutions
**Lewis A. Novack**
Brigham and Women's Hospital
**August Heithoff**
Brigham and Women's Hospital
**Lindsey R. Baden**
Brigham and Women's Hospital
**Amy C. Sherman**
Brigham and Women's Hospital
**Stephen R. Walsh**
swalsh@bwh.harvard.edu

Brigham and Women's Hospital

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## Abstract

# Background

Hematopoietic stem cell transplant (HSCT) recipients are uniquely vulnerable to adverse outcomes of SARS-CoV-2 infection. Small, mostly observational studies suggest that some HSCT recipients may not generate protective antibody responses following SARS-CoV-2 vaccination. We conducted a meta-analysis to estimate the prevalence and identify predictors of vaccine non-response.

# Methods

A comprehensive search of electronic databases, including MEDLINE (Ovid), Embase (Elsevier), Web of Science Core Collection (Clarivate), the Cochrane Central Register of Controlled Trials (Wiley), and the Cochrane COVID-19 Study Register was conducted on January 20, 2023. We defined a non-response as not achieving a seroconversion (positive anti-S IgG titer) after receiving at least two vaccine doses, indicated by study-specific assay cut-off value. Only studies assessing COVID-19 vaccine induced antibody (anti-S IgG) responses in adult (≥ 18 years) HSCT recipients were included. With 95% confidence intervals (CI) across all studies, a random-effects model was used to combine the pooled effect sizes. Quality and risk of bias assessment were determined using the Newcastle-Ottawa scale and ROBINS-I tool, respectively.

# Results

Out of 903 unique articles identified and 439 screened, 45 were included in this analysis comprising 4568 participants. Pooled absent sero-conversion was 20% (95% CI: 17% − 24%) with significant heterogeneity ($I^2$ = 95.10%) among included studies (1 clinical trial, 1 cross-sectional study, 1 case-control study, and 42 observational cohort studies). Subgroup analyses showed no difference between autologous [0.21 (95%CI 0.12–0.31)] and allogeneic [0.20 (95%CI 0.17–0.24)] transplant recipients. Identified predictors of non-response included time interval between transplantation and vaccination (< 12 months), concurrent anti-CD20 therapy, and specific treatments (high-dose glucocorticosteroid, calcineurin inhibitor, and anti-thymocyte globulin) for graft versus host disease. No publication bias was observed but the Galbraith's plot asymmetry showed evidence of small-study effects.

# Conclusion

Our findings emphasize the significant prevalence of non-responsiveness to SARS-CoV-2 vaccination in HSCT recipients and underscore need for close monitoring and aggressive risk factor management in this immunocompromised population.

## Introduction

Patients with hematological malignancies may undergo hematopoietic stem cell transplantation (HSCT) if they are unable to achieve remission through immunotherapy, chemotherapy, or radiotherapy (1–3). As a result of their disease or treatment, these patients frequently become immunosuppressed, which increases the risk of severe infection with SARS-CoV-2 (4). The availability of coronavirus disease 2019 (COVID-19) vaccines has reduced mortality and disease severity among HSCT recipients (5), however, HSCT recipients have shown variable seroconversion rates and responses following vaccination. Vaccine responsiveness, in terms of neutralizing antibody responses after COVID-19 vaccination, has been shown to correlate with protection in healthy participants (6–11), but immunocompromised individuals were excluded from the large vaccine efficacy studies (12). Existing studies among HSCT recipients have been mostly observational and limited by small sample sizes, but many of these studies have noted that transplant recipients have poor vaccine responses despite multiple doses of the vaccine (13–16). This meta-analysis evaluated the pooled prevalence of this attenuated response to the COVID-19 vaccine among HSCT recipients. We also described the risk factors associated with poor immune response to the COVID-19 vaccines.

## Methods

This report was completed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17).

# Study selection:

To identify studies reporting on COVID-19 vaccine response in HSCT recipients, we searched the electronic databases MEDLINE (Ovid), Embase (Elsevier), Web of Science Core Collection (Clarivate), the Cochrane Central Register of Controlled Trials (Wiley), and the Cochrane COVID-19 Study Register (https://covid-19.cochrane.org). Searches were designed and run by a medical librarian (PAB) and included terms for human stem cell transplants and vaccines against SARS-CoV-2 (**Appendix 1**). Controlled vocabulary terms were included when available. Searches were carried out on January 20, 2023; no date or language limits were applied to the search. In addition, the reference lists of relevant articles and reviews were manually searched to identify additional studies.

# Inclusion and Exclusion Criteria:

Studies were included if they were observational or single-arm vaccination studies and assessed antibody (anti-S IgG) response to COVID-19 vaccines among HSCT recipients aged 18 years or greater. Non-responsiveness or an attenuated response was defined as not achieving the pre-specified assay cut-off for positivity by each included study. Studies that did not enroll HSCT recipients, reported only neutralizing antibody titers, or exclusively reported T-cell responses to the COVID-19 vaccines were excluded.

# Screening and Data Abstraction:

Four reviewers (AK, MA, JP, and LN) independently screened the titles and abstracts of all identified studies for eligibility. Full-text articles were then reviewed for inclusion. Any discrepancies were resolved through discussion (between AK, SRW, and ACS) and consensus. Data were abstracted (by AK, SP, JP, MA, LN, DA, and AH) and organized on a spreadsheet (MS Excel) into five broad categories: study design, participant characteristics, vaccination status, the prevalence of vaccination failure, and predictors of attenuated or blunted vaccine response. Specific data abstracted included: name of the primary author, year of publication, study title, total sample size, duration of the study, type of study, funding source, conflicts of interest, median age of study participants, number of males and females, vaccine type, assay cut-off value of positivity, median anti-S IgG titer, number of autologous transplant and allogeneic transplant recipients, number of HSCT recipients who produced a positive anti-S IgG response, number of allogeneic HSCT responders and non-responders, number of autologous HSCT responders and non-responders, identified risk factors and author contacts (**Supplemental Table 1**).

# Quality Assessment:

The quality of the included studies was assessed using the Newcastle-Ottawa scale for non-randomized studies. Three categories were evaluated: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Each category was rated using specific criteria and a score was given for each study. Studies were considered to be of high quality if they scored 7 or higher on the Newcastle-Ottawa scale (18). A pair of reviewers (AK/SP, MA/DA, LN/AK, JP/AH) independently assessed the quality of each study.

# Risk of bias assessment:

Using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool (19), we assessed this risk of bias in the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each domain was rated as low, moderate, or serious and an overall risk of bias rating was assigned to each study based on the ratings of individual domains. Pairs of reviewers (AK/SP, MA/DA, LN/AK, JP/AH) independently assessed the risk of bias in each included study using the ROBINS-I tool. Disagreements were resolved through discussion and consensus.

# Data Analysis:

A meta-analysis was performed using a random-effects model using Stata (Release 17; College Station, TX: StataCorp LLC.) to estimate the overall prevalence of an attenuated response to SARS-CoV-2 vaccination among HSCT recipients. A funnel plot and regression-based Egger tests were used to investigate publication bias. To quantify the magnitude of small-study effects, regression-based Egger tests were conducted using a random-effects model and residual maximum likelihood (REML) method.

# Results

Electronic data searching identified 903 articles and 439 were screened after duplicates were removed (Fig. 1). Ninety-six reports were selected for full-text examination; 45 reports, representing 45 independent studies, were included in the analysis. The overall prevalence of non-responsiveness to the COVID-19 vaccine among HSCT recipients was 20% (95% CI: 17% − 24%), with significant heterogeneity among included studies (Fig. 2). The random-effects model was used with the REML method, which took into account both within-study and between-study variations in effect size. This heterogeneity was statistically significant, as indicated by a Q-value of 463.51, a p-value of < 0.0001 in the test of homogeneity, and the $\iota^2$ statistic of 95.10%. This strongly suggests that the variation among the study results was not due to chance and there was substantial heterogeneity in the true effects across studies. Finally, the test of ES = 0 indicated that the proportion was significantly different from zero, with a z-value of 10.86 and a p-value of 0.001.

The result of the sub-group analyses showed that the pooled proportion of autologous and allogeneic transplant recipients with a blunted immune response to SARS-CoV-2 vaccination was 0.21 (CI 0.12–0.31) and 0.20 (CI 0.17–0.24), respectively (**Supplementary Figs. 1 and 2**).

# Assessment of Quality and Bias:

The study quality was assessed as mostly either good or fair and studies were mostly prospective or retrospective observational studies. The sample sizes ranged from 22 to 687, with a median of 76 (IQR 56–133). The observation periods ranged from one month to 22 months, with the majority of studies having a duration of two to six months (**Supplemental Table 1**).

Overall, our meta-analysis showed a low to moderate risk of bias of; selection, performance, detection, and attrition using the ROBINS-I tool. Figure 3 shows the funnel plot for the meta-analysis. The plot includes 45 studies and displays the standard error (SE) of the effect size estimate on the horizontal axis and the effect size estimate on the vertical axis. The plot demonstrates a roughly symmetric distribution of studies around the overall effect size estimate, suggesting little evidence of publication bias or other small-study effects. We further explored the presence of publications bias and other small–study effects using the Eggers asymmetry test. The results showed evidence of small-study effects in the meta-analysis. The estimated intercept was 3.94 with a standard error of 0.892. The z-score for the intercept was 4.42 (p = 0.001), indicating that the intercept was significantly different from zero (**Supplementary Fig. 3**).

# Predictors of SARS-CoV-2 Vaccine non-response:

The meta-analysis revealed several risk factors associated with blunted response to COVID-19 vaccination among HSCT recipients (**Supplemental Table 2**). In both allogeneic and autologous HSCT recipients, low anti-S levels were associated with low CD19 + lymphocyte counts and serum IgG levels. Additionally, in the post-transplant period, use of immunosuppressive drugs, presence of graft-versus-host disease (GVHD), and reduced total peripheral, CD4+, CD8+, and CD56 + lymphocyte counts were associated with lack of COVID-19 vaccine response in allogeneic HSCT recipients only.

Univariate analyses showed that HSCT recipients vaccinated within 4.5 years of transplantation, those still receiving immunosuppression, and those with acute or moderate to severe chronic GVHD were more likely to remain seronegative after vaccination. Moreover, the time elapsed since HSCT (transplant within one year), lymphopenia (< 1000 cells/μL), and receipt of immunosuppressive treatment or chemotherapy at the time of vaccination were all associated with poor response.

Anti-CD20 monoclonal antibody administration and prednisone use within one year before vaccination were predictive of poor humoral responses. Inconsistent findings were observed for chronic GVHD and ongoing immunosuppressive therapy, with some studies showing a significant association and others showing no significant difference in serological responses.

Other factors associated with a suboptimal antibody response after the third dose of vaccine included chronic kidney disease, haploidentical donor status, and a lower median lymphocyte count at the third dose. Furthermore, vaccine type, specifically the Pfizer/BioNTech (BNT162b2) mRNA vaccine was associated with a higher response compared to the AstraZeneca (chADOx1-S) recombinant chimpanzee adenovirus vector vaccine, but the sample size was too small to draw definitive conclusions.

# Discussion

Our meta-analysis investigated the prevalence of non-responsiveness to the SARS-CoV-2 vaccine among HSCT recipients. In this study, we found a pooled prevalence of non-responsiveness of 20% (95% CI: 17% – 24%) based on the analysis of 45 studies.

Compared to healthy adults, HSCT recipients and other immunocompromised groups may have a sub-optimal to COVID-19 vaccines (20–24). Studies among solid organ transplant (SOT) recipients and patients with immune-mediated inflammatory diseases were comparable to findings in HSCT recipients (24, 25). However, the extent of this response may differ between the two groups due to differences in the nature and intensity of their immunosuppression. SOT recipients are typically on long-term immunosuppressive therapy to prevent graft rejection, which may lead to a weaker immune response to vaccines (26). A study by Holden et al. reported 65% non-responsiveness in a group of SOT recipients 6 weeks after the second dose vaccination (27), while Kamar et al. reported 32% non-responsiveness after third dose vaccination among SOT recipients (26). Similarly, Boyarsky and Werbel et al. reported in two separate studies, showed 46% and 67% of SOTs failed to respond to the vaccines after second dose vaccinations respectively (28, 29).

A study by Hall et al. reported that only 54% of SOT recipients developed detectable antibodies after two doses of the Moderna mRNA vaccine (30). However, a third dose of the mRNA vaccine was found to significantly increase the proportion of solid organ transplant recipients who developed detectable antibodies (28, 30). In a large meta-analysis comparable to ours, Sakuraba et al. showed 6158 SOT recipients had a poorer response (36% non-responsiveness) compared to HSCT recipients (25). Another meta-analysis by Sakuraba et al. in patients with immune-mediated diseases showed an overall prevalence rate (16.6% non-responsiveness) after two doses comparable to what we observed in HSCT

recipients. Therefore, a significant proportion of transplant patients and immunocompromised groups remain at high risk of severe disease from SARS-CoV-2 infection as well as its complications.

We observed a high (> 75%) heterogeneity among the included studies, as indicated by a Q-value of 463.51 and a p-value of < 0.0001 in the test of homogeneity, and the ι2 statistic (95.10%). This suggests that the variation among the study results is not due to chance, and there is substantial heterogeneity in the true effects across studies. This high heterogeneity in our study may be explained by several factors including the differences in study designs, number of doses of vaccines received, assay type, assay time, use of immunosuppressive agents, and type of transplant. A similarly high (88.9%) overall heterogeneity was observed in a meta-analysis by Sakuraba et al. for similar reasons (25).

Our subgroup analyses revealed that the proportion of autologous and allogeneic transplant recipients with non-response to the COVID-19 vaccination were 0.21 (CI 0.12–0.31) and 0.20 (CI 0.17–0.24), respectively. This strongly suggests that autologous transplant patients may still experience vaccine non-responsiveness, similar to allogeneic bone marrow transplant patients, despite not being on long-term immunosuppressive treatment for graft-versus-host disease (GVHD) (31). The underlying reasons for this non-responsiveness may be multifactorial. Firstly, the autologous transplant procedure itself may temporarily impair the immune system's ability to mount a robust response to vaccines due to the underlying disease, prior treatments such as chemotherapy, or the conditioning regimen used before the transplant (31–33). Additionally, autologous transplant patients may have residual immunodeficiency or immune dysfunction even after recovery, which can affect their ability to generate an adequate antibody response to vaccines, although, this recovery time may be shorter in autologous HSCT recipients compared to those who had allogeneic transplants (34, 35). Furthermore, individual variations among autologous transplant patients, such as pre-existing conditions or overall health status, can also impact their immune function and vaccine responsiveness. It is important for healthcare providers to consider these factors and potentially explore strategies to optimize vaccine responses in autologous transplant patients. This finding emphasizes the need for further research and development of vaccination strategies tailored to HSCT recipients to improve vaccine efficacy.

On visual inspection, our funnel plot analysis demonstrated a roughly symmetric distribution of studies around the overall effect size estimate, indicating little evidence of publication bias or other small-study effects. However, Egger's asymmetry test showed evidence of small-study effects in the meta-analysis, suggesting that caution should be exercised in interpreting the results. To reduce the potential impact of publication bias, future research should include both published and unpublished studies.

Our study adds to the growing body of literature on the prevalence of COVID-19 vaccine failure in immunocompromised individuals and identified several risk factors associated with attenuated or blunted responses to COVID-19 vaccination among HSCT recipients, including low CD19 + lymphocyte counts and serum IgG levels.. The frequent occurrence of non-responsiveness to COVID-19 vaccines in HSCT recipients emphasizes the necessity of further research for effective prophylaxis in this group. Utilizing highly potent neutralizing monoclonal antibodies (mAbs) against SARS-CoV-2 (36) has proven to

be a suitable method for immunocompromised individuals such as HSCT recipients unable to mount a vaccine-induced antibody response (37). Although mAb administration has been effective, the emergence of immune-evasive variants of concern, including the omicron variant (37) has limited their deployment. Further studies are needed to identify potential predictors of blunted or attenuated vaccine response to the COVID vaccines and to develop strategies to improve vaccine efficacy in immunocompromised HSCT recipients who do not respond to COVID-19 vaccines.

# Limitations:

Our meta-analysis has several limitations that may impact the interpretation of the results. A broad range of COVID-19 vaccines have been approved worldwide, however, our analysis included mostly studies involving the use of the Moderna (mRNA-1273) or Pfizer (BNT162b2) vaccine, with very few studies using the Janssen (AD26.COV2.S) or Oxford AZD-1222 / ChAdOx1 nCoV-19 which may have impacted our result. This study may also have been limited by the exclusion of unpublished studies and conference abstracts.

Our primary outcome was focused on the humoral response to the vaccines without assessing T-cell responses. Immune protectiveness to vaccines also depends on the cellular immune responses,although antibody levels are a strong correlate of the risks of SARS-CoV-2 susceptibility (20, 21, 38–40).

Due to limited data on median antibody titer and uniformity in assay type, timing, and threshold for positivity, we could not conduct more subgroup analyses. However, studies showing median titer responses and levels of neutralizing titers of the COVID vaccines should be encouraged despite the challenges with continually evolving strains of SARS-CoV-2.

One important limitation is the high heterogeneity observed between the included studies. As a result, the findings of this meta-analysis should be interpreted with caution. This could have been due to differences in underlying disease, transplant type, transplant conditioning, study size and methods, assay types, and the threshold for positivity. It is worth noting also that the predominant antibody assay for most of the studies used antibody tests marketed by Abbott, Diasorin, and Roche.

Another potential limitation is the reliance on published literature, which may have introduced publication bias into our analysis. In addition, some of the studies included in the meta-analysis were limited by small sample sizes, lack of serological response comparison with healthy individuals, and absence of pre-vaccination status data in some cases.

Lastly, it is important to note that the results of this meta-analysis may be limited to HSCT recipients and may not be generalizable to other populations. Despite these limitations, our meta-analysis provides important insights into the efficacy of COVID-19 vaccines in HSCT recipients.

# Conclusion

Overall, the COVID-19 vaccine did not induce an immune response in about 20% of vaccinated HSCT recipients. This study highlights the most up-to-date estimate of the magnitude of the non-responsiveness to the COVID-19 among HSCT recipients. Most significantly, B-cell ablative therapies, shorter time from transplant to the first vaccination, and specific concurrent immunosuppressive therapies (high-dose glucocorticosteroids, calcineurin inhibitors, and anti-thymocyte globulin) have shown strong associations with non-response to COVID-19 vaccines among HSCT recipients. These findings underscore the importance of monitoring of anti-S IgG titers, and the need to develop alternate protective strategies among unresponsive HSCT recipients.

# Declarations

### Ethics Approval and Consent to Participate:

As this study is a systematic review and meta-analysis of published literature, ethical approval was not required. However, all included studies obtained ethical approval and obtained informed consent from their participants.

### Consent for Publication:

Not applicable.

### Availability of Data and Materials:

All data generated and analysed during this study are included in this published article and its supplementary information files.

### Competing Interests:

SRW has received institutional funding from the National Institute of Allergy and Infectious Diseases/National Institutes of Health; and institutional grants or contracts from Sanofi Pasteur, Janssen Vaccines/Johnson & Johnson, Moderna Tx, Pfizer, Vir Biotechnology, and Worcester HIV Vaccine; has participated on data safety monitoring or advisory boards for Janssen Vaccines/Johnson & Johnson; and his spouse holds stock/stock options in Regeneron Pharmaceuticals. ACS is involved in human immunodeficiency virus (HIV), coronavirus (COVID), and other vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network, COVID Vaccine Prevention Network, International AIDS Vaccine Initiative, Crucell/Janssen, and Moderna.  The other authors have declared no competing interests.

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### Authors' Contributions:

AK, ACS, and SRW wrote the initial draft of the manuscript. All authors reviewed and approved the manuscript. PAB designed and performed the data searches. AK, MA, JP, and LN independently screened the titles and abstracts of all identified studies for eligibility. Data were abstracted by AK, SP, JP, MA, LN, DA, and AH. AK, SP, MA, DA, LN, AK, JP, AH independently assessed the quality and risk of bias of each study.

**Disclaimer:**

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, Henry M. Jackson Foundation for the Advancement of Military Medicine, Brigham and Women's Hospital, Dana-Farber Cancer Institute, or Harvard Medical School.

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# Figures

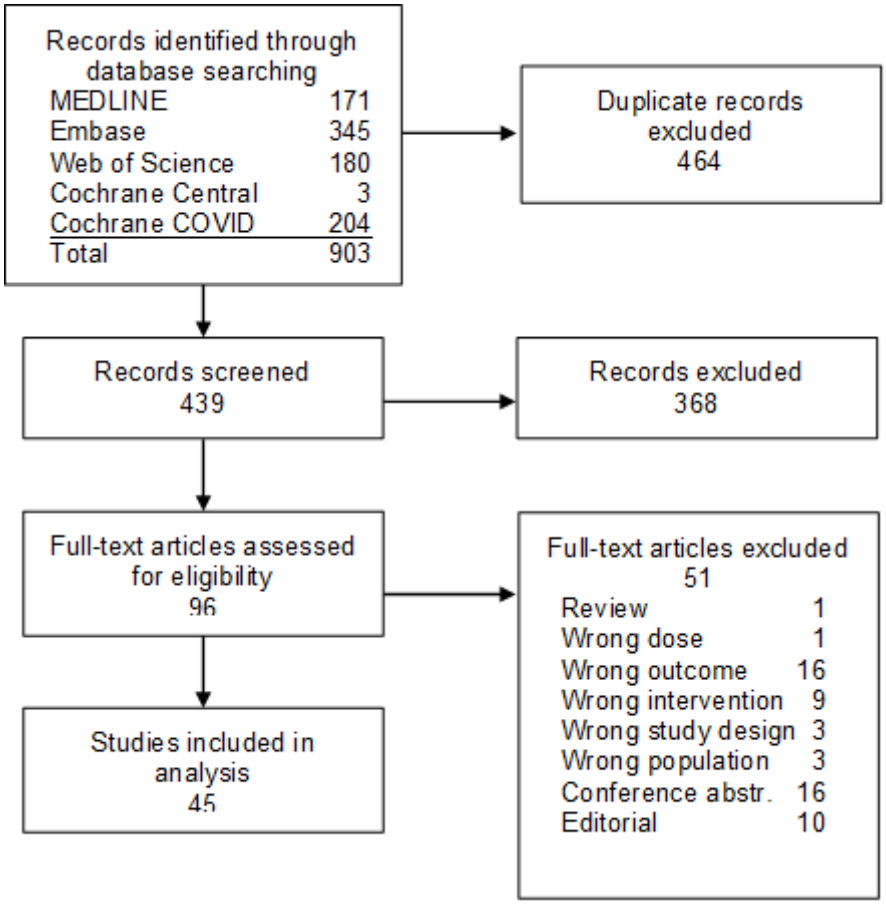


**Figure 1**

Selection of studies

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.pdf
- MetaanalysisSupplementalFigures.pdf
- SupplementalTable1MetaanalysisdataextractionsheetHSCT.xlsx
- SupplementalTable2Predictorsofnonresponse.xlsx