Infect Dis Ther
https://doi.org/10.1007/s40121-024-01052-8

ORIGINAL RESEARCH

COVID-19 Vaccination Recommendations for Immunocompromised Patient Populations: Delphi Panel and Consensus Statement Generation in the United States

Kira Zhi Hua Lai · Stuart Greenstein · Rajesh Govindasamy · Jaya Paranilam · Joseph Brown · Samantha Kimball-Carroll

Received: June 17, 2024 / Accepted: September 9, 2024

ABSTRACT

Introduction: The United States Advisory Committee on Immunization Practices (ACIP) and the Centers for Disease Control (CDC) recommend COVID-19 vaccines for all immunocompromised individuals. Certain disease groups are at increased risk of comorbidity and death for which disease-specific recommendations should be considered. The objective of the Delphi panel of experts was to summarize expert consensus on COVID-19 vaccinations for patients with rheumatologic disease, renal disease, hematologic malignancy and solid organ transplant (SOT) in the US.

Methods: A two-stage Delphi panel method was employed, starting with qualitative interviews with key opinion leaders (KOLs) in the four disease areas ($n=4$ KOLs, $n=16$ total) followed by three rounds of iterative revision of disease-specific COVID-19 vaccine recommendations. Final consensus was rated after the third round. Statements addressed primary and booster dosing (e.g., number and frequency) and other considerations such as vaccine type or heterologous messenger ribonucleic acid (mRNA) vaccination. Following the Delphi Panel, an online survey was conducted to assess physician agreement within the disease areas ($n=50$ each, $n=200$ total) with the consensus statements.

Results: Moderate to strong consensus was achieved for all primary series vaccination statements across disease groups, except one in hematology. Similarly, moderate to strong consensus was achieved for all booster series statements in all disease areas. However, statements on antibody titer measurements for re-vaccination considerations and higher dosages for immunocompromised patients did not reach agreement. Overall, approximately 62%–96% of physicians strongly agreed with the primary and booster vaccine recommendations. However, low agreement (29%–69%) was found among physicians for time interval between disease-specific treatment and vaccination, recommendations for mRNA vaccines, heterologous mRNA vaccination, antibody titer measurement and higher vaccine dosage for immunocompromised groups.

Conclusion: Consensus was achieved for disease-specific COVID-19 vaccine recommendations concerning primary and booster series vaccines and was generally well accepted by practicing physicians.

K. Z. H. Lai · J. Paranilam · J. Brown · S. Kimball-Carroll (✉)
ICON Clinical Research, Dublin 18, Ireland
e-mail: Samantha.kimball@iconplc.com

S. Greenstein
Westchester Medical Center, Transplant Surgery, 100 Woods Road, Valhalla, NY 10595, USA

R. Govindasamy
UPMC Hamot Medical Center, Erie, PA 16550, USA

Published online: 10 October 2024

Keywords: Vaccines; Severe acute respiratory syndrome coronavirus 2; SARS-CoV-2; Coronavirus disease 2019; COVID-19; Rheumatologic disease; Renal disease; Hematologic malignancy; Solid organ transplant; Immunocompromised

Key Summary Points

Why carry out this study?

Vaccination against severe acute respiratory acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the most effective way to prevent COVID-19 and related severe outcomes.

Guidelines for vaccination in the US are for all groups of immunocompromised individuals when the management of COVID-19 in patients with disease-specific requirements may be required.

What was learned from the study?

Delphi panel methodology was utilized to gain insights into the disease-specific recommendations for vaccination against COVID-19 in patients with rheumatologic disease, renal disease, hematologic malignancy and solid organ transplant recipients.

Five statements addressing primary series recommendations and four booster series statements achieved moderate to strong consensus among panelists of all four disease areas except one primary series statement in hematology.

A survey of practicing physicians within each disease found that physicians agreed with the consensus statements for primary (62%–96%) and booster series (64%–92%) vaccine recommendations.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), was classified as a global pandemic in 2020. The most effective way to prevent COVID-19 and related severe outcomes is vaccination. In the USA, two types of COVID-19 vaccines were approved, which includes mRNA-1273 (Spikevax®, Moderna, Inc., Cambridge, MA, USA) [1] and BNT162b2 (Comirnaty®, Pfizer/BioNTech, New York, NY, USA/Mainz, Germany) [2], both utilizing the novel messenger ribonucleic acid (mRNA) technology, as well as Nuvaxovid (Novavax), which employs a tradition protein subunits [3].

Although vaccination was shown to lower the risk of infection and severe COVID-19 outcomes [4], the COVID-19 pandemic has still disproportionally impacted immunocompromised individuals [5]. Adults who are immunocompromised are at 2.68 greater adjusted odds of being hospitalized with COVID-19 compared with immunocompetent individuals [6]. Numerous systematic reviews and meta-analyses consistently demonstrated that conditions such as rheumatic disease, hematologic malignancies, renal disease and solid organ transplant (SOT) increase patients' risk of hospitalization, intensive care unit (ICU) admission or death from COVID-19 [7–10]. The increased risks of disease severity and complications are mainly caused by underlying immunocompromised state and therapies used for specified diseases, such as immunomodulating medications like T-cell suppressors and B-cell depleting agents; both of these factors are associated with increased severity of infection and mortality [11, 12] and blunt immune response to COVID-19 vaccines [11, 13–15].

As of Spring 2024, the Center for Disease Control and Prevention (CDC) recommends a two-dose primary series vaccination for all people who are 6 months and older for the prevention of COVID-19 and provides specific guidance on vaccine administration for those who are in these specific populations [16]. Nevertheless, current COVID-19 vaccine guidelines are general and not specific to distinct immunocompromised states, despite their higher risk of morbidity and mortality, and there remains a lack of definitive understanding and guidelines of the appropriate type of vaccines, dosing schedules and frequency of booster doses for specific groups of immunocompromised groups.

As COVID-19 is becoming endemic, national healthcare systems are now tasked with recommending the best use of available vaccines for distinct populations specific to their own geographic regions. Therefore, this study aims to understand the consensus recommendations for COVID vaccination for immunocompromised populations within four immunocompromised states: rheumatic disease, hematologic malignancies, renal disease and SOTs, to inform guidelines for immunocompromised populations.

A Delphi Panel methodology was utilized to gauge the Key Opinion Leaders (KOLs) agreement, incorporate insights and revise accordingly to achieve consensus recommendations for patients in the four disease states. The development process followed a rigorous and formal methodology, was based on disease and US-specific literature reviews, incorporated panelist expertise from specialists in the four disease states, integrated input from related medical experts in other disciplines (e.g., infectious disease, epidemiology) and included direct participation by healthcare professionals in the US to elucidate their insights and preferences regarding the consensus statements.

METHODS

A similar methodology is presented elsewhere for the European Union panel (https://doi.org/10.1007/s40121-024-01051-9).

Modified Delphi Panel: Overview and Approach

To understand the consensus recommendations from experts providing vaccination recommendations, a non-random sampling process consistent with standard Delphi Panel approaches was utilized to select experts for this panel. The Delphi technique is a scientific method to organize and manage a structured group communication process to derive consensus. A modified two-phase, online consensus process was undertaken to establish consensus on a set of disease-specific recommendations for COVID-19 vaccination in immunocompromised populations similar to that used by the American College of Rheumatology [17] (Fig. 1). The expert panel was selected through a targeted list of relevant KOLs through a local third-party representative, whose panel members were not related to the study sponsor or funder. The participants were blinded to the sponsor of the study, and the sponsor has no access to personal information of the participants at the time of data collection. An expert panel consisting of four key opinion leaders (KOLs) in the area of infectious disease, rheumatology, organ transplant, hematology/oncology or nephrology from the US were selected in the Delphi panel. In each specified disease area, three treatment area specialists in the disease area and one infectious disease specialist were included. The selection of KOLs was primarily based on clinical expertise and research engagement on the specified disease population. The group was selected based on six criteria: (1) the KOL must have at least 100 patients, (2) at least 50 immunocompromised patients, (3) scored at least 5 points on a 7-point COVID knowledge questionnaire, (4) spends at least 25% of his/her working hours performing clinical management, (5) had at least one published article and (6) had at least five scientific engagements on the specified disease area (defined as published articles, conference presentations, contributions to policies created or updated, treatment guidelines written or updated, lectures or panels led, principal investigator of clinical trials and participation in advisory boards). Panel members were remunerated for their participation.

Ethical Approval

This study was designed in compliance with the standards of the professional associations code of ethical conduct (GDPR, Insights Association, ESOMAR, GRBN, Intellus Worldwide and country-specific privacy and data protection laws). This study did not involve patients or collect any patient information. This study was specifically designed to capture professional opinion.

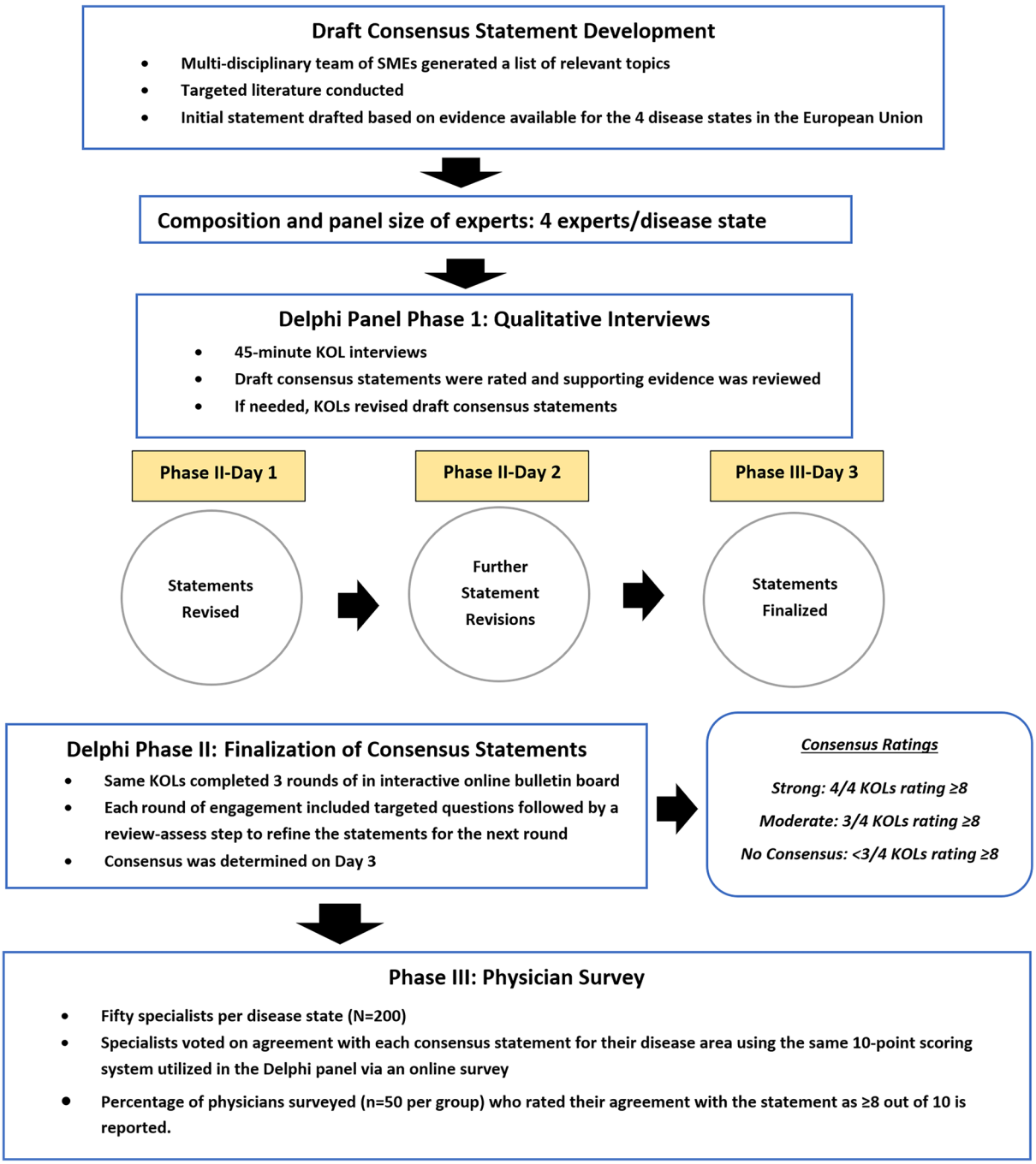

Fig. 1 Delphi panel: Overview and approach [also presented here: https://doi.org/10.1007/s40121-024-01051-9]. *SME* subject matter expert, *KOL* key opinion leader

Delphi Panel Preparation: Development of Draft Consensus Statements

A multidisciplinary team of subject matter experts (SMEs) of individuals from epidemiology, immunology, evidence synthesis and a medical director with specific expertise in infectious disease, vaccinology and immune deficiencies identified key topics to serve as themes for the consensus statement. Topics identified consisted of three domains of interest: first, primary/initial vaccination series (e.g., need for vaccination, number of vaccines); second, booster/updated vaccinations (e.g., frequency); third, additional vaccination considerations (e.g., value of antibody titer, vaccine type). The Health Economics Outcomes Research (HEOR) team summarizes the discussion from the SMEs to refine their search criteria and tactics.

A systematic review and meta-analysis previously conducted by the authors evaluated the comparative clinical effectiveness of COVID-19 vaccination in immunocompromised individuals [4]. The search outcomes from the systematic review were used as a point of reference for the generation of the initial statements. To supplement these references, a targeted literature review was conducted to include US-specific evidence, and all relevant papers addressing COVID-19 vaccinations in the immunocompromised population were included. Up to five supporting articles for each statement topic were collated in an Excel database with summary of data for each reference. We used the following hierarchy for evidence gathering listed from strongest to weakest. Systematic literature review or meta-analysis: real-world evidence that met the following criteria: population included the immunocompromised disease in scope, large sample size, equal distribution of different vaccines covered; clinical trials in priority order: randomized double blind, single blind, open-label; cohort studies; recommendations/reviews published by disease-specific groups (e.g., European Hematology Associations) and government bodies (e.g., Centers for Disease Control).

With the results from the targeted literature review, a draft consensus statement for each of the four disease-specific groups was revised based on the supporting evidence [4, 9, 13, 17–75]. Subsequently, a draft consensus statement was created for each disease group to present to KOLs.

Delphi Panel Phase 1: Qualitative Interviews

Forty-five-minute interviews were conducted with four KOLs per disease group in the US. KOLs first rated their agreement with a statement on a scale of 1–10, where 1 = do not agree at all and 10 = significantly agree. Trained moderators reviewed each draft statement (~ 15 statements) with KOLs (~ 3–4 min per statement) to obtain feedback on supporting resources/information and ways to improve accuracy of statements and further define and refine wording. In some cases, additional literature search and review were performed when respondents requested more supporting evidence. Respondents were asked to rework statements to provide a higher level of agreement. Once reworded, the statements were reassessed by KOLs using the same rating scale.

Delphi Panel Phase 2: Consensus Statement Rating

The same KOLs completed three rounds of interactive online bulletin boards, each lasting 30 min, over 3 separate days. Each round included targeted questions followed by a review to refine the statement for the next round if consensus was not achieved. Final consensus was determined by the results of day 3. The strength of the consensus was determined by the following rating: strong rating was defined as all four KOLs have a rating ≥ 8, moderate rating was defined as three out of four KOLs have a rating ≥ 8, and no consensus was defined as fewer than three out of four KOLs providing a rating of ≥ 8.

Delphi Panel Phase 3: Physician Survey

An online survey was conducted to assess physician agreement with the final consensus statements developed by KOLs prior to publication. Fifty specialists per disease area were

recruited to take part in the survey from the US ($N = 200$). Specialists voted on agreement with each consensus statement for their disease area using the same 10-point scoring system utilized in the Delphi panel via an online survey and were asked for explanations for their rating as optional. Percentage of physicians surveyed ($n = 50$ per group) who rated their agreement with the statement as ≥ 8 out of 10 is reported.

Characteristics of Delphi Expert Panel Member

Three KOLs in the US with experience in each disease-specific area (e.g., autoimmune rheumatic disease, renal disease, SOT or hematology/oncology) were recruited for the Delphi Panel and were supported by an infectious disease specialist. Table 1 describes the clinical and research experiences of the selected KOLs.

Table 1 KOL experience and engagement in research/ clinical activity

KOL experience	Rheumatology KOLs ($n = 4$) mean	Hematology KOLs ($n = 4$) mean	Renal disease KOLs ($n = 4$) mean	Solid organ transplant KOLs ($n = 4$) mean
Patients treated over the past 12 months	*1125*	*950*	*725*	*319*
Immunocompromised patients treated over the past 12 months	*333*	*278*	*344*	*213*
Patients on dialysis over the past 12 months	*N/A*	*N/A*	*93*	*N/A*
SOT performed over the past 12 months ($n = 3$)	*N/A*	*N/A*	*N/A*	*75*
Patients who have undergone SOT in the past 12 months	*N/A*	*N/A*	*N/A*	*N/A*
Published articles in the past 5 years*	*5*	*9*	*11*	*7*
Policies and treatment guidelines created or updated in the past 5 years	*5*	*13*	*14*	*5*
Published articles in the disease area in the past 5 years	*2*	*13*	*5*	*7*
Speaking engagements (conferences, lectures, or panel discussions)	*5*	*8*	*5*	*2*
Policies and treatment guidelines created or updated	*2*	*2*	*4*	*4*

KOL key opinion leader, *SOT* solid organ transplant, *IC* immunocompromised, *N/A* not applicable

*Total number for each group

Published articles, policies created or updated, treatment guidelines written or updated, led lectures or panels, clinical trial involvement, clinical trial advisory board participation

RESULTS

Primary/Initial Series COVID-19 Vaccinations

KOLs in each disease state panel across the US were presented a total of five statements focused on primary/initial series COVID-19 vaccinations. Statements were modified to be specific for each disease state and further revised among KOLs during the Delphi panel to address disease-specific considerations. Consensus statements for immunocompromised patient groups are presented in Table 2.

Disease Burden

All four KOLs in each of the disease areas indicated moderate to strong consensus.

KOLs in the area of renal and SOT achieved strong consensus that patients in the respective disease area are at an increased risk of hospitalization and death due to COVID-19. However, KOLs in rheumatic conditions and hematologic malignancies only achieved moderate consensus. Physicians from all disease areas strongly agreed with the consensus statement (84%–96%), indicating that patients in these disease areas have a low immune response and are at high risk of severe disease complications.

Primary/Initial Series Safety

All four KOLs in each respective disease state indicated moderate to strong consensus.

Most of the KOLs agreed that COVID-19 vaccines are safe and well tolerated among the disease-specific populations, with strong consensus achieved in rheumatology, nephrology and SOT and moderate consensus in hematologic malignancies. All physicians surveyed strongly agree with the KOL consensus (88%–92%), stating that the vaccines are well tolerated among patients and align with clinical evidence and experience.

Need for Vaccination

All KOLs from four disease states indicated moderate to strong consensus statements in their respective disease areas.

KOLs in nephrology and SOT achieved strong consensus on the recommendations for COVID-19 vaccination, while KOLs in rheumatology and hematologic malignancies indicated moderate consensus. Physicians surveyed across the four disease states strongly agreed with the KOLs' consensus statements (80%–96%), indicating that the vaccine could prevent severe disease complications from COVID-19, especially in those who are immunocompromised, and that this recommendation aligns with evidence and guidelines.

Number of Doses

All four of the respective disease state KOLs indicated moderate to strong consensus, with KOLs from rheumatology, renal and SOT achieving a strong consensus and KOLs from hematologic malignancies reaching moderate consensus about the number of doses recommended for primary series COVID-19 vaccinations. Physicians surveyed in renal disease strongly agreed with the statement (80%), while physicians in rheumatology (78%) and SOT (72%) moderately agreed. Physicians in the area of hematologic malignancies were not in a high level of agreement with the consensus statement (62%), stating that the recommendation depends on the patient's level of immunosuppression.

Frequency of Initial Vaccine

Three of the four disease-state KOLs indicated moderate to strong consensus, with KOLs from the area of hematologic malignancies failing to reach consensus on the statement for a three-dose primary series with at least 28 days between doses and completed within a 6-month period. Surveyed physicians in nephrology (70%) and rheumatology (72%) moderately agreed with the statement, while physicians in the areas of hematologic malignancies (69%) and SOT (62%) were not in a high level of agreement, stating that the recommendation depends on

Table 2 Consensus statement for primary COVID-19 vaccine series for immunocompromised patients

Topic: primary series	Statement by disease group	Expert consensus[1]	Physician agreement[2]
Disease-specific COVID-19 risk: increased risk of COVID-19 complications in immunocompromised population	Rheum: immunocompromised patients with autoimmune inflammatory rheumatic diseases are at a higher risk of hospitalization and death due to COVID-19 infection compared to patients with no rheumatic conditions	Moderate	90%
	Hem: immunocompromised patients with hematologic malignancies are at a higher risk of hospitalization and mortality compared to immunocompetent adults with the disease	Moderate	96%
	Renal: patients with renal immunodeficiencies, including chronic kidney disease, who have contracted COVID-19, are at a higher risk of mortality than immunocompetent individuals	Strong	96%
	SOT: SOTR currently taking immunosuppressive medication who have contracted COVID-19 have a higher risk of hospitalization, mechanical ventilation, and mortality against non-immunocompromised individuals	Strong	84%

Table 2 continued

Topic: primary series	Statement by disease group	Expert consensus[1]	Physician agreement[2]
Primary series safety: COVID-19 vaccines are considered safe and well tolerated in immunocompromised patients	Rheum: COVID-19 vaccines are considered safe and well tolerated only producing mild to moderate adverse events in immunocompromised patients with autoimmune inflammatory rheumatic diseases	Strong	92%
	Hem: although COVID mRNA vaccines may cause mild to moderate side effects, they are generally safe and well tolerated by immunocompromised patients with hematologic malignancies	Moderate	92%
	Renal: COVID-19 vaccines are well tolerated by patients receiving dialysis, only producing mild to moderate side effects	Strong	90%
	SOT: SOTR currently taking immunosuppressive medication are able to tolerate COVID-19 vaccines safely only producing mild to moderate adverse events	Strong	88%

Table 2 continued

Topic: primary series	Statement by disease group	Expert consensus[1]	Physician agreement[2]
Need for vaccination: recommendations to receive the COVID-19 vaccines in immunocompromised patients	Rheum: immunocompromised patients with autoimmune inflammatory rheumatic diseases are recommended to receive the COVID-19 vaccine to reduce the risk of infection and severe outcomes	Moderate	96%
	Hem: it is recommended to vaccinate immunocompromised patients with hematologic malignancies to reduce the risk of infection and severe outcomes. This group includes higher risk subpopulations that mount a lower immune response and are more prone to severe and critical COVID-19	Moderate	94%
	Renal: patients receiving dialysis, or who have chronic kidney disease, are recommended to be vaccinated against COVID-19 to reduce potential severe disease complications	Strong	96%
	SOT: SOTR currently taking immunosuppressive medication are recommended to receive the COVID-19 vaccine to reduce risk of infection and severe outcomes	Strong	80%

Table 2 continued

Topic: primary series	Statement by disease group	Expert consensus[1]	Physician agreement[2]
Number of doses in primary series: three-dose primary series of COVID-19 vaccines to reduce potential serious disease complications	Rheum: patients with autoimmune inflammatory rheumatic disease on immunomodulatory therapy are advised to take at least 3 primary/initial doses of the COVID-19 vaccine to confer the best protection to reduce potential serious disease complications	Strong	78%
	Hem: immunocompromised patients with hematologic malignancies are recommended to receive a three-dose primary series of COVID-19 vaccines to reduce the risk of infection and severe outcomes	Moderate	69%
	Renal: patients receiving dialysis are recommended to receive an extended primary series of 3 vaccinations to reduce potential severe disease complications	Strong	80%
	SOT: SOTR currently taking immunosuppressive medication are recommended to receive an initial (primary) series of three doses to reduce potential serious disease complications	Strong	72%

Table 2 continued

Topic: primary series	Statement by disease group	Expert consensus[1]	Physician agreement[2]
Frequency of doses in primary series: time interval between three doses of COVID-19 vaccine	Rheum: it is recommended three doses (primary series) for immunocompromised patients that should be completed within 4 months with each dose at least 28 days apart Primary series should be administered as 2 doses, 28 days apart and a third dose 3–6 months after the 2nd dose	Moderate	72%
	Hem: immunocompromised patients with hematologic malignancies would benefit from a three-dose series completed over the course of 6 months and at least 28 days between each dose	None	69%
	Renal: immunocompromised patients are recommended to complete a 3 dose primary vaccine series within 4 months, with at least 28 days between each dose	Strong	70%
	SOT: COVID-19 vaccine primary series should be administered as 2 doses 28 days apart and a third dose 3–6 months after the 2nd dose. However, this regimen ideally NOT be administered the first 2 to 4 weeks of initiating immunomodulatory/immunosuppressive medications	Moderate	62%

Rheum rheumatologic conditions, *Hem* hematologic malignancies, *Renal* renal disease, *SOT* solid organ transplant, *SOTR* solid organ transplant recipients, *mRNA* messenger ribonucleic acid

[1]Strong: 4 of 4 rated the statement ≥ 8 out of 10; moderate: 4 of 4 rated the statement ≥ 8 out of 10; none: < 3 rated the statement ≥ 8 out of 10

[2]Percentage of physicians surveyed ($n = 50$ per group) who rated their agreement with the statement as ≥ 8 out of 10

the patient's level of immunosuppression and expressing uncertainty about the guidelines surrounding the timing between vaccinations.

COVID-19 Booster Vaccinations

KOLs from each disease state panel across the US were presented with four statements focused on COVID-19 booster vaccine considerations. Final consensus statements reached for respective immunocompromised patient groups are presented in Table 3.

Booster Vaccine Safety

All four disease state KOLs indicated moderate to strong consensus, with KOLs from renal and SOT achieving strong consensus and KOLs from rheumatology and hematologic malignancies indicating moderate consensus on the safety and tolerability of mRNA booster vaccines. Surveyed physicians in the area of rheumatic conditions, hematologic malignancies and renal disease strongly agreed with the consensus (range: 82%–88%), while physicians in SOT indicated moderate validation (74%). Most physicians agreed that the statement aligns with evidence and their clinical experience.

Need for Booster Vaccination

All four disease state KOLs indicated moderate to strong consensus, with KOLs from rheumatic conditions, renal disease and SOT achieving strong consensus and KOLs from hematologic malignancies in achieving moderate consensus on the recommendation of a COVID-19 booster to reduce disease severity. Physicians across all disease areas agreed with the recommendation (range: 80%–92%), stating that booster recommendation aligns with clinical guidelines.

Frequency of Booster Doses

All four disease state KOLs indicated moderate to strong consensus that immunocompromised patients should receive a booster COVID-19 vaccine within a range of a 3–12 months. KOLs from nephology and SOT achieved strong consensus and KOLs from rheumatic conditions and hematologic malignancies indicated moderate consensus. The timing for booster vaccines differed among the four disease states: 6–12 months for rheumatic conditions and SOT, 12 months for renal disease and 3 to 6 months after the initial three-dose primary series for hematologic malignancies. HCPs from renal disease strongly agreed (82%) with the statement and physicians from rheumatic conditions moderately agreed (78%). However, physicians in hematologic malignancies (65%) and SOT (64%) only achieved moderate agreement with the recommendations, expressing uncertainty about the specified booster timing for SOT (6–12 months) and hematologic malignancies (3–6 months). Additionally, some physicians in hematologic malignancies noted that the timing of booster dose might depend on the phase of the treatment.

Booster Recommendation

All four disease state KOLs indicated moderate to strong consensus that immunocompromised patients with previous exposure to COVID-19 should receive a booster COVID-19 to reduce disease complications. KOLs from nephrology and SOT achieved strong consensus and KOLs from rheumatic conditions and hematologic malignancies achieved moderate consensus. Physicians in each disease state strongly agreed with the statement (range: 84%–90%), except for SOT physicians, who moderately agreed (74%) noting that there is a lack of long-term evidence supporting the duration of natural immunity and that the timing of booster administration post-infection should be considered.

Additional Vaccine Considerations

Four KOLs in each disease state panel across the US were presented up to six statements that addressed additional considerations for COVID-19 vaccine recommendations. Revised statements and consensus for the four immunocompromised patient groups are presented in Table 4.

Table 3 Consensus statements for booster COVID-19 vaccine for immunocompromised patients

Topic: booster series	Statement by disease group	KOL consensus	Physician agreement
Booster vaccine safety: mRNA booster vaccines are safe and well tolerated in immunocompromised patients	Rheum: mRNA booster vaccines are safe and well tolerated, only producing mild to moderate adverse events in patients with autoimmune inflammatory rheumatic diseases currently taking immunosuppressive treatment	Moderate	82%
	Hem: Although COVID mRNA boosters may cause mild to moderate side effects, they are generally safe and well tolerated by immunocompromised patients with hematologic malignancies	Moderate	88%
	Renal: mRNA booster vaccines are safe and well tolerated by patients who are receiving dialysis, only producing mild to moderate side effects	Strong	88%
	SOT: COVID-19 mRNA booster vaccines are safely tolerated by SOTR currently taking immunosuppressive medication only producing mild to moderate adverse events	Strong	74%
Need for booster vaccination: A COVID-19 booster vaccine is recommended to reduce disease complications in immunocompromised patients	Rheum: Immunocompromised patients with autoimmune inflammatory rheumatic diseases are recommended to receive booster doses to reduce potential severe disease complications from COVID-19 infection	Strong	86%
	Hem: Immunocompromised patients with hematologic malignancies are recommended to receive COVID-19 boosters to reduce the risk of infection and severe outcomes	Moderate	92%
	Renal: Dialysis patients are recommended to receive a booster vaccine following their primary series to provide continued reduction of potential severe disease complications	Strong	88%
	SOT: SOTR currently taking immunosuppressive medication are recommended to receive COVID-19 booster doses after the initial series to reduce risk of infection and severe outcomes	Strong	80%

Table 3 continued

Topic: booster series	Statement by disease group	KOL consensus	Physician agreement
Frequency of booster doses: Time interval of at least 6 to 12 months between doses of COVID-19 vaccine boosters	Rheum: COVID-19 updated vaccines (booster) is recommended in patients with autoimmune inflammatory rheumatic diseases every 6–12 months after completing the regular vaccination. Timing should consider the patients' disease, treatment, risk and comorbidities	Moderate	78%
	Hem: Immunocompromised patients with hematologic malignancies are recommended to receive a booster dose every three to six months after the primary series	Moderate	65%
	Renal: Patients receiving dialysis are recommended to receive an annual dose of the most updated COVID-19 vaccine to reduce the risk of severe infection and severe disease outcomes	Strong	82%
	SOT: SOTR currently taking immunosuppressive medication are recommended to receive a COVID-19 booster dose every 12 months to reduce risk of infection and severe outcomes	Strong	64%

Table 3 continued

Topic: booster series	Statement by disease group	KOL consensus	Physician agreement
Boosters and COVID-19 infection: Patients with previous exposure to COVID-19 infection are recommended to take booster doses to reduce disease complications	Rheum: Patients with autoimmune inflammatory rheumatic disease currently on immunomodulatory therapy with previous exposure to COVID-19 infection are recommended to take booster dose to reduce infection severity and outcomes	Strong	84%
	Hem: It is recommended for immunocompromised patients with hematologic malignancies with prior COVID-19 exposure to be vaccinated against the disease, despite some level of immunity being provided by the previous infection	Moderate	86%
	Renal: Patients receiving dialysis who have previously experienced COVID-19 may develop some level of immunity against the disease; however, it is still recommended for such patients to be vaccinated against the disease	Strong	90%
	SOT: SOTR with previous exposure to COVID-19 infection are recommended to take booster dose to reduce risk of infection and severe outcomes	Strong	74%

KOL key opinion leader, *mRNA* messenger ribonucleic acid, *Rheum* rheumatologic conditions, *Hem* hematologic malignancies, *Renal* renal disease, *SOT* solid organ transplant, *SOTR* solid organ transplant recipients

[1]Strong: 4 of 4 rated the statement ≥ 8 out of 10; moderate: 4 of 4 rated the statement ≥ 8 out of 10; none: < 3 rated the statement ≥ 8 out of 10

[2]Percentage of physicians surveyed ($n = 50$ per group) who rated their agreement with the statement as ≥ 8 out of 10

Table 4 Additional vaccine considerations

Topic: additional considerations	Statement by disease group	KOL consensus	Physician agreement
Disease-specific criteria	Rheum: A gap of 28 days in immunomodulatory treatment is recommended after COVID-19 vaccines to enhance their efficacy in patients with autoimmune inflammatory rheumatic disease	Moderate	56%
	Hem: Immunocompromised patients with hematologic malignancies undergoing anti-CD20 antibody therapy can achieve higher seropositivity rates when the interval between therapy and vaccination exceeds 6 months	Moderate	69%
	Renal: Not tested	Not tested	Not tested
	SOT: SOTR are recommended to receive any COVID-19 vaccination at least 2 weeks before initiation of immunosuppressive therapy	Strong	62%
Recommendation for mRNA vaccines: mRNA vaccines are recommended over other current COVID-19 vaccine types for immunocompromised patients	Rheum: mRNA vaccines are recommended over other current COVID-19 vaccine types for patients with autoimmune inflammatory rheumatic diseases currently taking immunosuppressive treatment. If a patient is unable to take an mRNA Covid-19 vaccine, another option is available	Moderate	50%
	Hem: mRNA vaccines are preferred over other vaccine platforms for immunocompromised patients with hematologic malignancies	Moderate	57%
	Renal: mRNA vaccines are recommended over other vaccine types for patients with renal immunodeficiencies	Moderate	64%
	SOT: COVID-19 mRNA vaccines are preferred over other vaccine platforms (e.g., vector, IAV) for SOTR currently taking immunosuppressive medication	Moderate	50%

Table 4 continued

Topic: additional considerations	Statement by disease group	KOL consensus	Physician agreement
Heterologous mRNA recommendation: mRNA vaccine regime is recommended in those who were initiated with a non-mRNA vaccine	Rheum: Among immunocompromised patients with autoimmune inflammatory rheumatic diseases, if a vaccine regimen is initiated with a non-mRNA vaccine, continuation with heterologous mRNA regimen is recommended to confer protection against the risk of severe outcomes from COVID-19 infection	None	52%
	Hem: Among immunocompromised patients, if a vaccine regimen is initiated with a non-mRNA vaccine, continuation with a heterologous mRNA regimen is recommended to confer protection against COVID-19 infection	None	53%
	Renal: Among immunocompromised patients, if a vaccine regimen is initiated with a non-mRNA vaccine, continuation with heterologous mRNA regimen is recommended to reduce potential severe disease complications	Strong	56%
	SOT: Among immunocompromised patients, if a COVID-19 vaccine regimen is initiated with a non-mRNA vaccine, continuation with heterologous mRNA regimen is recommended to reduce risk of infection and severe outcomes	Moderate	44%

Table 4 continued

Topic: additional considerations	Statement by disease group	KOL consensus	Physician agreement
Role of measuring antibody titers: Measurement of antibody titters to assess immunity and the need for re-vaccination	Rheum: Antibody titers can be optionally measured in immunocompromised and high-risk patients with autoimmune inflammatory rheumatic diseases such as those with comorbidities to help assess the risk/benefit ratio and the need for re-vaccination in patients	None	52%
	Hem: Regular antibody measurements for neutralizing antibodies can be considered for immunocompromised patients with hematologic malignancies, as their vaccine response is variable and influenced by emerging strains, and higher antibody titers are correlated with reduced risk of subsequent infections	None	55%
	Renal: order to understand the durability of vaccine protection, severely high-risk kidney transplant patients currently taking immunosuppressive medications should be evaluated for antibody response at baseline, as well as after each vaccination, to evaluate whether there has been an appropriate increase in antibody levels	None	42%
	SOT: SOTR currently taking immunosuppressive medication can optionally be evaluated for COVID-19 seroconversion at baseline and 4–6 weeks after each vaccination to inform physician decision making	None	46%

Table 4 continued

Topic: additional considerations	Statement by disease group	KOL consensus	Physician agreement
Higher dose for immunocompromised: Higher dosage of COVID-19 vaccines in immunocompromised patients	Rheum: Immunocompromised patients with autoimmune inflammatory rheumatic disease are suggested to be administered a higher dose of vaccines to confer protection against the risk of severe outcomes from COVID-19 infection	None	32%
	Hem: Immunocompromised patients with hematologic malignancies are recommended to be administered a higher dosage of vaccines to confer protection against COVID-19	None	29%
	Renal: Patients with renal immunodeficiencies are recommended to be administered a higher dosage of vaccines to reduce risk of infection and potential severe disease outcomes	None	48%
	SOT: Higher doses of COVID-19 vaccination provides greater protection in SOTR taking immunosuppressive medication	None	32%

Table 4 continued

Topic: additional considerations	Statement by disease group	KOL consensus	Physician agreement
Specific guidelines for disease area: The disease area should have specific recommendations for COVID-19 vaccinations	Rheum: Immunocompromised patients with autoimmune inflammatory rheumatic diseases (under active follow-up by a rheumatologist) should have specific recommendations for COVID-19 vaccinations rather than recommendations focused on the broader immunocompromised population	Moderate	58%
	Hem: Immunocompromised patients with hematologic malignancies should have specific recommendations for COVID-19 vaccinations rather than recommendations focused on the broader immunocompromised population	None	49%
	Renal: Immunocompromised patients with renal immunodeficiencies should have specific recommendations for COVID-19 vaccinations rather than recommendations focused on the broader immunocompromised population	Moderate	58%
	SOT: Not tested	Not tested	Not tested

KOL key opinion leader, *Rheum* rheumatologic conditions, *Hem* hematologic malignancies, *Renal* renal disease, *SOT* solid organ transplant, *SOTR* solid organ transplant recipients, *mRNA* messenger ribonucleic acid

[1]Strong: 4 of 4 rated the statement ≥ 8 out of 10; moderate: 4 of 4 rated the statement ≥ 8 out of 10; none: < 3 rated the statement ≥ 8 out of 10

[2]Percentage of physicians surveyed ($n = 50$ per group) who rated their agreement with the statement as ≥ 8 out of 10

Disease State-Specific Criteria

All of the KOLs in the assessed disease area achieved moderate to strong consensus.

KOLs in SOT achieved strong consensus on the recommendation to receive any COVID-19 vaccination at least 2–4 weeks before the starting immunosuppressive therapy. However, HCPs in the area of SOT had low level of agreement (62%) with the recommendations, noting that there is lack of evidence to support this practice and that the recommendation is not applicable to all patients. KOLs in rheumatology were in moderate agreement for the recommendation to have a 28-day gap in immunomodulatory treatment after COVID-19 vaccines; similarly, physicians in rheumatology (56%) also achieved a moderate level of agreement with the recommendation, with physicians stating that the recommendation depends on the medication in use. Lastly, for hematologic malignancies, KOLs achieved moderate agreement on the statement that patients can achieve higher seropositivity rates when there is a 6-month gap between CD20 antibody therapy and vaccination, and a similar level of agreement was found among physicians (69%), with most physicians expressing there is lack of evidence to support this claim.

Recommendation for mRNA Vaccines

All four KOLs across all disease states achieved moderate consensus on the recommendations of mRNA over other vaccine types. However, physicians across all disease areas had a low level of agreement with the statement (range: 50–57%), noting that there is lack of evidence supporting using mRNA vaccines over other available vaccines, and they were not sure about the recommendation. In addition, this recommendation is not present in current clinical guidelines.

mRNA Booster Vaccine Recommendation (Heterologous/ Homologous)

KOLs from two disease areas achieved moderate to strong consensus, but KOLs in rheumatology and hematologic malignancies failed to achieve consensus on the recommendation of administrating mRNA vaccine in patients who initiated with a non-mRNA vaccine. Physicians across all diseases expressed a low level of agreement with this approach (range 44%–56%), with most respondents stating that there is a lack of evidence to support this claim.

Role of Measuring Antibody Titers

KOLs across all disease areas did not reach a consensus on the recommendation of measuring antibody titers to assess immunity and the need for re-vaccination. Similarly, only 42%–55% of physicians agreed with the consensus statement, noting the impracticality of performing antibody titers in patients as well as the lack of evidence to support the causal relation between seroconversion and level of disease severity protection. One physician in hematology stated that antibody testing would not impact their decision-making, as they would recommend vaccination for patients in all high-risk populations.

Higher COVID-19 Vaccine Dosing

KOLs across all disease areas did not reach a consensus on the recommendation of providing a higher dosage of COVID-19 vaccines in immunocompromised patients. Similarly, only 29%–48% of physicians surveyed agreed to the consensus statement, with most physicians stating that there is a lack of evidence to support increasing dosing for immunocompromised patients and that it is not currently included in clinical guidelines. Some physicians also noted that the decision might vary depending on the patient's disease and treatment, while others mentioned that increasing the dose is recommended for flu vaccines but were unsure about the recommendations and evidence for COVID-19 vaccines.

Specific Guidelines for Disease Area

Two of the three disease state KOLs indicated moderate consensus, with KOLs in rheumatology and nephrology indicating moderate agreement and KOLs in hematologic malignancies failing to reach consensus on providing specific guidelines for the respective

immunocompromised populations. HCPs from all disease areas did not think disease-specific COVID-19 guidelines were necessary, noting that a standard recommendation for immunocompromised patients would be sufficient across all immunocompromised groups.

DISCUSSION

In a Delphi process involving two phases, we established a disease-specific consensus statement on COVID-19 vaccinations for immunocompromised patients with rheumatologic conditions, hematologic malignancies, renal disease and SOT in the US. Additionally, this study summarizes expert perspectives on COVID-19 vaccination guidelines related to the primary vaccine series, booster vaccine, and vaccine considerations concerning dosing, heterogeneous vaccination, vaccine schedules and clinical considerations with specific therapies used in rheumatology, renal disease, SOT, and hematologic malignancies. KOLs in rheumatology, nephrology and SOT achieved consensus on all nine statements regarding the primary and booster series, while KOLs in hematology reached consensus on eight of nine statements.

Overall, KOLs from all disease areas agreed that immunocompromised patients have a higher disease burden of COVID-19. KOLs agreed that primary COVID-19 vaccines are safe and well tolerated in specific disease populations, with strong support for vaccination to prevent severe disease complications. While there is consensus on a three-doses primary vaccine series, opinions vary slightly regarding the timing and frequency of initial vaccine administration, particularly in hematologic malignancies, because of differing levels of immunosuppression among patients. Overall, there is clear consensus among physicians and KOLs on the importance and effectiveness of COVID-19 vaccination in these vulnerable patient populations. Similarly, strong consensus was achieved for booster vaccine safety and the need for booster vaccination, which aligns with the March 2024 recommendations from the CDC recommending that people who were previously vaccinated and are immunocompromised should receive an updated dose of COVID-19 vaccine [76]. Our study also showed moderate consensus on the frequency of booster doses and timing of vaccination post-infection; however, uncertainty exists among physicians in hematologic malignancies and SOT relating to the specified timing between booster vaccines. Additionally, physicians in hematology noted that the timing of booster dose might depend on the phase of the treatment. Although the CDC does not have disease-specific recommendations for the timing of vaccination, it is acknowledged that immunosuppressive regimens may vary, allowing HCPs to use clinical judgment to determine vaccination timing outside the recommended intervals [76].

Considerations for vaccination beyond primary and booster series did not achieve the same level of consensus or agreement among physicians. mRNA vaccines were a novel approach for prevention of COVID-19 at the onset of the pandemic, and evidence has provided support for their use in immunocompromised populations. There was moderate consensus among all four disease groups that mRNA vaccines are recommended over other current COVID-19 vaccine types for these immunocompromised patients. Despite evidence from a recent systematic literature review and meta-analysis of 80 global studies that reported immunocompromised individuals who were administered mRNA vaccines induced higher immunity after the second dose compared to vector vaccines [77], physicians surveyed had low levels of agreement with this statement (50–67%). Experts' perspectives on other vaccine considerations were examined through statements pertaining to regular measurement of antibody titers, higher dosing and the need for disease-specific guidelines that were not recommended by the expert panels. Both KOLs and physicians disagreed on regular measurements of antibody titers and providing higher vaccine dosages for immunocompromised patients. The main reason for disagreement on antibody titer measurements was the impracticality in a clinical setting; in addition, some physicians expressed the lack of direct relationship between immunogenicity measures with infection and infection severity. The

CDC also does not recommend antibody testing for the assessment of vaccine-mediated immune response and stated that it should not be used for vaccine decision-making [76].

Regarding the introduction of specific vaccination guidelines for each of the disease areas, consensus was lacking among KOLs and were deemed unnecessary by HCPs, who favored a standardized recommendation for all immunocompromised populations.

Lastly, KOLs in SOT, rheumatology and hematologic malignancies showed moderate to strong consensus on the timing of COVID-19 vaccines regarding disease-specific treatments and therapeutics, with approximately 56–69% of physicians agreeing with the statement. The consensus statement recommends a timing of 28 days between vaccination and immunomodulatory treatments for rheumatologic conditions and 6 months for CD-20 therapy, which is longer than the CDC guidelines. The CDC recommends administering vaccines at least 2 weeks before starting or resuming immunosuppressive therapies and 4 weeks for those receiving B-cell therapies [76]. Nonetheless, the CDC acknowledges that immunosuppressive regimens may vary and states that clinical judgments regarding the timing of vaccination can be made outside the recommended dosing intervals. This aligns with physicians' feedback that recommendation of spacing out treatments with vaccines largely depends on individual patients' clinical situation and the treatment statuses. Additionally, some physicians expressed that there are insufficient evidence and guidelines to support the specific recommendations. Considering the differing opinions and insufficient guidance on the timing of COVID-19 vaccination regarding immunosuppressive therapies, specific guidelines for commonly used immunosuppressive therapies, such as B- and T-cell therapies, chemotherapy, high-dose corticosteroids, hematopoietic cell transplantation (HCT) and anti-CD20 drugs, may help healthcare providers make more informed clinical decisions.

The Delphi methodology offers the strength of the reiterative process, with each round of KOL review revising and refining statements, increasing the degree of consensus and, in some cases, reaching unanimity. The Delphi panel participants were able to offer anonymous responses during the group process while being able to view other participant responses. This study was conducted among a group of experts within each disease area across the US.

There are several limitations despite the robust nature of the Delphi method. We recruited KOLs that met specific criteria primarily based on strong clinical expertise and extensive research engagement to build a representative expert panel, but the number of KOLs ($n=4$ for each group) may limit the true representation. Furthermore, the wealth and rapid evolution of literature in this area limited our ability to perform a formal systematic review with stringent criteria for levels of evidence owing to the sheer volume of COVID-19-related publications. However, we have utilized the references from a recently published systematic review and meta-analysis conducted by our authors [4] and further supplemented the search outcomes with a targeted literature review in each disease area. This approach ensures up-to-date evidence (published after January 1, 2022) was provided for the specific immunocompromised populations relevant to the initial statement items. We sought region-specific evidence for the US populations, but this was not always available and was substituted with the highest level of evidence possible. Additionally, we recognize that not all forms of COVID-19 preventative interventions, such as monoclonal antibodies, were examined in this study. However, this is outside the scope of our research and may warrant future studies summarizing their clinical use in immunocompromised populations.

CONCLUSIONS

Disease-specific COVID-19 vaccination statement consensus driven by Delphi methodology in the four disease areas in this study were supported by a broad group of stakeholders. Our goal was to provide guidance to healthcare providers treating patients with rheumatologic conditions, renal disease, hematologic malignancy and SOTR on the use of COVID-19 vaccines and boosters considering disease-specific issues such

as immunosuppressive therapies. Moderate to high levels of agreement among surveyed physicians were found for primary and booster series recommendations. Furthermore, our findings suggest that KOLs felt the mRNA vaccines may be superior to other types of vaccines when used in specific immunocompromised populations. This study emphasizes the need for COVID-19 vaccines, including supplemental/booster dosing for patients across all four immunocompromised disease areas (i.e., rheumatologic disease, renal disease, hematologic malignancy and SOTR), within the framework of personalized medicine and shared decision-making with patients.

ACKNOWLEDGEMENTS

We thank all of the disease experts and physicians that participated in the Delphi panel and the online survey.

Author Contributions. Samantha Kimball-Carroll and Joseph Brown were involved in study conception and design. Material preparation and interpretation of results was performed by Kira Zhi Hua Lai, Jaya Paranilam, Joseph Brown and Samantha Kimball-Carroll. Stuart Greenstein and Rajesh Govindasamy participated in the Delphi panel. The manuscript was drafted by Kira Zhi Hua Lai and Samantha Kimball-Carroll. All authors commented on drafts of the manuscript and read and approved the final manuscript.

Funding. A grant (grant number: 7700053394) was obtained by ICON for this study from Moderna Inc. To avoid any conflict of interest, per terms of grants agreement, Moderna only provided high-level input on the populations of interest and the general need for guidelines. Moderna was not involved in the design, conduct of the study, interpretation of results or writing of this manuscript. ICON team independently from Moderna determined the focus of the surveys and interviews and generated the summary statements; was responsible for selecting the KOLs; was responsible for creating inclusion/exclusion of final panel members; conducted data collection and interviews; facilitated the process of the Delphi panel and developed the manuscripts. The journal's Rapid Service Fee was paid for with the study grant.

Data Availability. All data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. Kira Zhi Hua Lai, Jaya Paranilam, Joseph Brown, Samantha Kimball-Carroll are employed by ICON Plc and have previously worked with Moderna Inc. Stuart Greenstein and Rajesh Govindasamy have nothing to declare.

Ethical Approval. This study was designed in compliance with the standards of the professional associations code of ethical conduct (GDPR, Insights Association, ESOMAR, GRBN, Intellus Worldwide, and country specific privacy and data protection laws). This study did not involve patients or collect any patient information. This study was specifically designed to capture professional opinion.

REFERENCES

1. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–16.

2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15.

3. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med. 2021;385(13):1172–83.

4. Wang X, Haeussler K, Spellman A, Phillips LE, Ramiller A, Bausch-Jurken MT, et al. Comparative effectiveness of mRNA-1273 and BNT162b2 COVID-19 vaccines in immunocompromised individuals: a systematic review and meta-analysis using the GRADE framework. Front Immunol. 2023;14:1204831.

5. Panel C-TG. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health; 2024.

6. Ridgway JP, Tideman S, French T, Wright B, Parsons G, Diaz G, et al. Odds of hospitalization for COVID-19 after 3 vs 2 doses of mRNA COVID-19 vaccine by time since booster dose. JAMA. 2022;328(15):1559–61.

7. Ao G, Wang Y, Qi X, Nasr B, Bao M, Gao M, et al. The association between severe or death COVID-19 and solid organ transplantation: a systematic review and meta-analysis. Transplant Rev (Orlando). 2021;35(3): 100628.

8. Chen CY, Shao SC, Chen YT, Hsu CK, Hsu HJ, Lee CC, et al. Incidence and clinical impacts of COVID-19 infection in patients with hemodialysis: systematic review and meta-analysis of 396,062 hemodialysis patients. Healthcare (Basel). 2021;9(1):47.

9. Conway R, Grimshaw AA, Konig MF, Putman M, Duarte-García A, Tseng LY, et al. SARS-CoV-2 infection and COVID-19 outcomes in rheumatic diseases: a systematic literature review and meta-analysis. Arthritis Rheumatol. 2022;74(5):766–75.

10. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136(25):2881–92.

11. Moor MB, Suter-Riniker F, Horn MP, Aeberli D, Amsler J, Möller B, et al. Humoral and cellular responses to mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell-depleting therapy (RituxiVac): an investigator-initiated, single-centre, open-label study. Lancet Rheumatol. 2021;3(11):e789–97.

12. MacKenna B, Kennedy NA, Mehrkar A, Rowan A, Galloway J, Matthewman J, et al. Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies: a nationwide cohort study in the OpenSAFELY platform. Lancet Rheumatol. 2022;4(7):e490–506.

13. Lee A, Wong SY, Chai LYA, Lee SC, Lee MX, Muthiah MD, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. BMJ. 2022;376: e068632.

14. Shen C, Risk M, Schiopu E, Hayek SS, Xie T, Holevinski L, et al. Efficacy of COVID-19 vaccines in patients taking immunosuppressants. Ann Rheum Dis. 2022;81(6):875–80.

15. Stumpf J, Siepmann T, Lindner T, Karger C, Schwöbel J, Anders L, et al. Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: A prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. Lancet Reg Health Eur. 2021;9: 100178.

16. (ACIP) ACoIP. ACIP evidence to recommendations for use of an additional COVID-19 vaccine dose in immunocompromised people. In: Control USCfD, editor. 2024.

17. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American college of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: Version 4. Arthritis Rheumatol. 2022;74(5):e21–36.

18. Au WY, Cheung PPH. Effectiveness of heterologous and homologous Covid-19 vaccine regimens: living systematic review with network meta-analysis. BMJ. 2022;377: e069989.

19. Espi M, Charmetant X, Barba T, Mathieu C, Pelletier C, Koppe L, et al. A prospective observational study for justification, safety, and efficacy of a third dose of mRNA vaccine in patients receiving maintenance hemodialysis. Kidney Int. 2022;101(2):390–402.

20. Ferreira VH, Ierullo M, Mavandadnejad F, Kurtesi A, Hu Q, Hardy WR, et al. Omicron BA.4/5 Neutralization and T-cell responses in organ transplant recipients after booster messenger RNA

vaccine: a multicenter cohort study. Clin Infect Dis. 2023;77(2):229–36.

21. Gagelmann N, Passamonti F, Wolschke C, Massoud R, Niederwieser C, Adjallé R, et al. Antibody response after vaccination against SARS-CoV-2 in adults with hematological malignancies: a systematic review and meta-analysis. Haematologica. 2022;107(8):1840–9.

22. Gatti M, Rinaldi M, Bussini L, Bonazzetti C, Pascale R, Pasquini Z, et al. Clinical outcome in solid organ transplant recipients affected by COVID-19 compared to general population: a systematic review and meta-analysis. Clin Microbiol Infect. 2022;28(8):1057–65.

23. Ge C, Du K, Luo M, Shen K, Zhou Y, Guo K, et al. Serologic response and safety of COVID-19 vaccination in HSCT or CAR T-cell recipients: a systematic review and meta-analysis. Exp Hematol Oncol. 2022;11(1):46.

24. Grainger R, Kim AHJ, Conway R, Yazdany J, Robinson PC. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. Nat Rev Rheumatol. 2022;18(4):191–204.

25. Haarhaus M, Duhanes M, Leševic N, Matei B, Ramsauer B, Da Silva RR, et al. Improved immunologic response to COVID-19 vaccine with prolonged dosing interval in haemodialysis patients. Scand J Immunol. 2022;95(5): e13152.

26. Hovd M, Åsberg A, Munthe LA, Heldal K, Reisæter AV, Vaage JT, et al. Humoral vaccine response and breakthrough infections in kidney transplant recipients during the COVID-19 pandemic: a nationwide cohort study. EClinicalMedicine. 2023;60: 102035.

27. Ito Y, Honda A, Kurokawa M. COVID-19 mRNA vaccine in patients with lymphoid malignancy or anti-CD20 antibody therapy: a systematic review and meta-analysis. Clin Lymphoma Myeloma Leuk. 2022;22(8):e691–707.

28. Joudeh AI, Lutf AQ, Mahdi S, Tran G. Efficacy and safety of mRNA and AstraZeneca COVID-19 vaccines in patients with autoimmune rheumatic diseases: a systematic review. Vaccine. 2023;41(26):3801–12.

29. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med. 2021;385(7):661–2.

30. Kelly JD, Leonard S, Hoggatt KJ, Boscardin WJ, Lum EN, Moss-Vazquez TA, et al. Incidence of severe COVID-19 illness following vaccination and booster with BNT162b2, mRNA-1273, and Ad26. COV2.S vaccines. JAMA. 2022;328(14):1427–37.

31. Lane S, Yeomans A, Shakir S. Systematic review of spontaneous reports of myocarditis and pericarditis in transplant recipients and immunocompromised patients following COVID-19 mRNA vaccination. BMJ Open. 2022;12(7): e060425.

32. Ma BM, Tam AR, Chan KW, Ma MKM, Hung IFN, Yap DYH, et al. Immunogenicity and safety of COVID-19 vaccines in patients receiving renal replacement therapy: a systematic review and meta-analysis. Front Med (Lausanne). 2022;9: 827859.

33. Manley HJ, Li NC, Aweh GN, Hsu CM, Weiner DE, Miskulin D, et al. SARS-CoV-2 vaccine effectiveness and breakthrough infections among patients receiving maintenance dialysis. Am J Kidney Dis. 2023;81(4):406–15.

34. Mehrabi Nejad M-M, Moosaie F, Dehghanbanadaki H, Haji Ghadery A, Shabani M, Tabary M, et al. Immunogenicity of COVID-19 mRNA vaccines in immunocompromised patients: a systematic review and meta-analysis. Eur J Med Res. 2022;27(1):23.

35. Mehrabi Nejad M-M, Shobeiri P, Dehghanbanadaki H, Tabary M, Aryannejad A, Haji Ghadery A, et al. Seroconversion following the first, second, and third dose of SARS-CoV-2 vaccines in immunocompromised population: a systematic review and meta-analysis. Virol J. 2022;19(1):132.

36. Noori M, Azizi S, Abbasi Varaki F, Nejadghaderi SA, Bashash D. A systematic review and meta-analysis of immune response against first and second doses of SARS-CoV-2 vaccines in adult patients with hematological malignancies. Int Immunopharmacol. 2022;110: 109046.

37. Piechotta V, Mellinghoff SC, Hirsch C, Brinkmann A, Iannizzi C, Kreuzberger N, et al. Effectiveness, immunogenicity, and safety of COVID-19 vaccines for individuals with hematological malignancies: a systematic review. Blood Cancer J. 2022;12(5):86.

38. Raja MA, Mendoza MA, Villavicencio A, Anjan S, Reynolds JM, Kittipibul V, et al. COVID-19 in solid organ transplant recipients: a systematic review and meta-analysis of current literature. Transplant Rev (Orlando). 2021;35(1): 100588.

39. Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. Clin Microbiol Infect. 2021;27(8):1173.e1.

40. Schietzel S, Anderegg M, Limacher A, Born A, Horn MP, Maurer B, et al. Humoral and cellular immune responses on SARS-CoV-2 vaccines in patients with anti-CD20 therapies: a systematic review and meta-analysis of 1342 patients. RMD Open. 2022;8(1): e002036.

41. Tenforde MW, Patel MM, Ginde AA, Douin DJ, Talbot HK, Casey JD, et al. Effectiveness of severe acute respiratory syndrome coronavirus 2 messenger RNA vaccines for preventing coronavirus disease 2019 hospitalizations in the United States. Clin Infect Dis. 2022;74(9):1515–24.

42. Thakkar A, Pradhan K, Duva B, Carreno JM, Sahu S, Thiruthuvanathan V, et al. Study of efficacy and longevity of immune response to third and fourth doses of COVID-19 vaccines in patients with cancer: a single arm clinical trial. Elife. 2023. https://doi.org/10.7554/eLife.83694.

43. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430–6.

44. Kabbani D, Yotis DM, Ferreira VH, Shalhoub S, Belga S, Tyagi V, et al. Immunogenicity, safety, and breakthrough severe acute respiratory syndrome coronavirus 2 infections after coronavirus disease 2019 vaccination in organ transplant recipients: a prospective multicenter Canadian Study. Open Forum Infect Dis. 2023. https://doi.org/10.1093/ofid/ofad200.

45. Cdc. COVID-19 Vaccination. Centers for Disease Control and Prevention. 2020.

46. Hause AM. Safety monitoring of COVID-19 mRNA vaccine first booster doses among persons aged ≥12 years with presumed immunocompromise status — United States, January 12, 2022–March 28, 2022. MMWR Morb Mortal Wkly Rep. 2022; https://doi.org/10.15585/mmwr.mm7128a3

47. Chuleerarux N, Manothummetha K, Moonla C, Sanguankeo A, Kates OS, Hirankarn N, et al. Immunogenicity of SARS-CoV-2 vaccines in patients with multiple myeloma: a systematic review and meta-analysis. Blood Adv. 2022;6(24):6198–207.

48. Ku JH, Sy LS, Qian L, Ackerson BK, Luo Y, Tubert JE, et al. Vaccine effectiveness of the mRNA-1273 3-dose primary series against COVID-19 in an immunocompromised population: a prospective observational cohort study. Vaccine. 2023;41(24):3636–46.

49. Cheng H, Peng Z, Si S, Alifu X, Zhou H, Chi P, et al. Immunogenicity and safety of homologous and heterologous prime-boost immunization with COVID-19 vaccine: systematic review and meta-analysis. Vaccines. 2022;10(5):798.

50. Angkasekwinai N, Juthamas P, Leelahavarong P, Sarayuth K, Chatkamol P, Natthakan C, et al. Binding and neutralizing antibody levels and vaccine efficacy/effectiveness compared between heterologous and homologous primary series COVID-19 vaccination: A systematic review and meta-analysis. 2022;40(4):321–36.

51. CDC. Data & Surveillance | CDC. 2024.

52. Azeem MI NA, Shanmugasundaram U, Cheedarla N, Potdar S, Manalo RJ, Moreno A, Switchenko JM, Cheedarla S, Doxie DB, Radzievski R, Ellis ML, Manning KE, Wali B, Valanparambil RM, Maples KT, Baymon E, Kaufman JL, Hofmeister CC, Joseph NS, Lonial S, Roback JD, Sette A, Ahmed R, Suthar MS, Neish AS, Dhodapkar MV, Dhodapkar KM. Impaired SARS-CoV-2 Variant Neutralization and CD8+ T-cell Responses Following 3 Doses of mRNA Vaccines in Myeloma: Correlation with Breakthrough Infections | Blood Cancer Discovery | American Association for Cancer Research. Blood Cancer Discov. 2023;4(2):106–117).

53. (OIAC) OIAC. Ontario Immunization Advisory Committee (OIAC). Public Health Ontario.

54. COVID-19 vaccine effectiveness against omicron (B.1.1.529) variant infection and hospitalisation in patients taking immunosuppressive medications: a retrospective cohort study - PMC.

55. Lin Y-C, Lai T-S, Lin S-L, Chen Y-M, Chu T-S, Tu Y-K. Outcomes of coronavirus 2019 infection in patients with chronic kidney disease: a systematic review and meta-analysis. Ther Adv Chronic Dis. 2021;12:2040622321998860.

56. Singh J, Malik P, Patel N, Pothuru S, Israni A, Chakinala RC, et al. Kidney disease and COVID-19 disease severity—systematic review and meta-analysis. Clin Exp Med. 2022;22(1):125–35.

57. Mehta N, Shah S, Paudel K, Chamlagain R, Chhetri S. Safety and efficacy of coronavirus disease-19 vaccines in chronic kidney disease patients under maintenance hemodialysis: a systematic review. Health Sci Rep. 2022;5(4): e700.

58. Peiyao R, Mengjie Y, Xiaogang S, Wenfang H, Danna Z, Yuqun Z, et al. Immunogenicity and safety of SARS-CoV-2 vaccine in hemodialysis patients: a systematic review and meta-analysis. Front Public Health. 2022;10: 951096.

59. CDC. COVID-19 Vaccine: For Public Health Jurisdictions and Dialysis Partners | CDC. 2023.

60. Affeldt P, Koehler FC, Brensing KA, Gies M, Platen E, Adam V, et al. Immune response to third and fourth COVID-19 vaccination in hemodialysis patients and kidney transplant recipients. Viruses. 2022;14(12):2646.

61. Ontario Immunization Advisory Committee (OIAC) | Public Health Ontario.

62. Notarte KI, Catahay JA, Peligro PJ, Velasco JV, Ver AT, Guerrero JJ, et al. Humoral response in hemodialysis patients post-SARS-CoV-2 mRNA vaccination: a systematic review of literature. Vaccines. 2023;11(4):724.

63. S O, K T, M A, Ar O, Mr A, Z A, et al. Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey. Nephrol Dialysis Transplant Eur Renal Assoc 2020;35(12).

64. Beilhack G, Monteforte R, Frommlet F, Reindl-Schwaighofer R, Strassl R, Vychytil A. Durable anti-SARS-CoV-2 antibody response after mRNA-1273 booster in peritoneal dialysis patients during the omicron wave. Vaccines. 2023;11(6):1121.

65. Berar-Yanay N, Freiman S, Shapira MA, Saffoury A, Elemy A, Hamze M, et al. Waning humoral response 3 to 6 months after vaccination with the SARS-COV-2 BNT162b2 mRNA vaccine in dialysis patients. J Clin Med. 2022;11(1):64.

66. Tenforde MW. Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19–associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults — VISION Network, Nine States, September–November 2022. MMWR Morb Mortal Wkly Rep. 2022;71.

67. Taheri S. Efficacy and safety of booster vaccination against SARS-CoV-2 in dialysis and renal transplant patients: systematic review and meta-analysis. Int Urol Nephrol. 2023;55(4):791–802.

68. Chen J-J, Lee TH, Tian Y-C, Lee C-C, Fan P-C, Chang C-H. Immunogenicity rates after SARS-CoV-2 vaccination in people with end-stage kidney disease: a systematic review and meta-analysis. JAMA Netw Open. 2021;4(10): e2131749.

69. Montez-Rath ME, Garcia P, Han J, Cadden L, Hunsader P, Morgan C, et al. SARS-CoV-2 Infection during the omicron surge among patients receiving dialysis: the role of circulating receptor-binding domain antibodies and vaccine doses. J Am Soc Nephrol. 2022;33(10):1832.

70. Parker EPK, Horne EMF, Hulme WJ, Tazare J, Zheng B, Carr EJ, et al. Comparative effectiveness of two- and three-dose COVID-19 vaccination schedules involving AZD1222 and BNT162b2 in people with kidney disease: a linked OpenSAFELY and UK Renal Registry cohort study. The Lancet Regional Health – Europe. 2023;30.

71. Risk M, Hayek SS, Schiopu E, Yuan L, Shen C, Shi X, et al. COVID-19 vaccine effectiveness against omicron (B.1.1.529) variant infection and hospitalisation in patients taking immunosuppressive medications: a retrospective cohort study. Lancet Rheumatol. 2022;4(11):e775–84.

72. Sood A, Tran M, Murthy V, Gonzalez E. Immunogenicity and safety of SARS-CoV-2 vaccination in patients with rheumatic diseases: a systematic review and meta-analysis. JCR J Clin Rheumatol. 2022;28(8):381.

73. Bjørlykke KH, Ørbo HS, Tveter AT, Jyssum I, Sexton J, Tran TT, et al. Four SARS-CoV-2 vaccine doses or hybrid immunity in patients on immunosuppressive therapies: a Norwegian cohort study. Lancet Rheumatol. 2023;5(1):e36–46.

74. CDC. Recommended update (2023–2024 Formula) COVID19-vaccination-recommendations.

75. Mojadadi M-S, Javadinia SA, Attarian F, Samami E, Sobhani M. Anti-SARS-CoV-2 spike IgG following injection of the third dose vaccine: a systematic review with meta-analysis of heterologous versus homologous vaccination. Front Public Health. 2023;10: 960598.

76. Control. CoD. COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised | CDC. 2024.

77. Mehrabi Nejad MM, Shobeiri P, Dehghanbanadaki H, Tabary M, Aryannejad A, Haji Ghadery A, et al. Seroconversion following the first, second, and third dose of SARS-CoV-2 vaccines in immunocompromised population: a systematic review and meta-analysis. Virol J. 2022;19(1):132.