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Review

Influenza Vaccination in Solid Organ Transplant Recipients: Methods to Improve Immunogenicity and Future Directions

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Abstract

Purpose of Review To review the recent literature surrounding immune responses to influenza vaccination in solid organ transplant (SOT) recipients, in addition to reviewing future directions for novel vaccine technologies to help improve immunogenicity in this vulnerable population.

Recent Findings While organ transplantation remains a lifesaving treatment for those with organ failure, infections account for many complications in the post-transplant period. Influenza virus is the most common vaccine-preventable illness, but organ transplant recipients often mount an inferior immune response to vaccination compared to the general population. Due to their impaired immune responses to vaccinations, various studies have examined utilizing different strategies to increase immunogenicity to influenza vaccines in this patient population, including the use of booster doses, high-dose vaccines, and vaccines with adjuvants. Trials with high-dose influenza vaccines and booster doses have shown increased immunogenicity when compared to single standard-dose influenza vaccine. Although these strategies may improve immune responses to influenza vaccines to variable degrees, it is still unknown what the optimal method to provide protection against influenza infection in SOT recipients is. While more studies need to be conducted in the

SOT population, there is promising new influenza vaccine technology development with mRNA vaccines, universal influenza vaccines, and monoclonal antibodies.
Summary As SOT recipients exhibit reduced immunity to vaccines, efforts to increase immunogenicity to influenza vaccine in the transplant population have focused on adjuvanted vaccines, booster doses, and high-dose vaccines. Future directions in this field include mRNA influenza vaccines, universal influenza vaccines, and monoclonal antibodies, but there is no definitive timeline for these products to become available at this time. The authors of this study favor a high-dose influenza vaccination approach for organ transplant recipients, due to ease of administration and demonstrated favorable safety profile.

Introduction

Solid organ transplantation (SOT) offers lifesaving treatment for those with organ failure, with the number of transplantations performed annually in the USA continuing to increase. According to the United Network for Organ Sharing (UNOS), there were 42,880 total solid organ transplants performed in the USA in 2022, with numbers for 2023 on a trajectory to exceed this [1]. Organ transplantation offers improved survival for those with organ failure, particularly for renal and liver recipients who have a mean lifetime survival of over 20 years after transplantation [2]. Even though organ transplantation improves mortality, it carries significant risks associated with both the surgical transplant procedure and the immunosuppression regimens used to prevent rejection.

Infection continues to remain one of the most common complications after transplantation and one of the leading causes of mortality in recipients [3–5]. This phenomenon was particularly highlighted during the COVID-19 pandemic, where excess mortality rates in SOT recipients were up to seven times higher than the general population [6].

One of the most common viral infections that impact organ transplant recipients is influenza virus which remains the most frequent cause of vaccine-preventable illness in SOT recipients [7, 8]. Recipients of SOT are more susceptible to complications related to influenza infection than immunocompetent hosts, including such complications as pneumonia, hospitalization, and mortality [9•]. This has led to an increased effort to optimize vaccine immunogenicity in this population. Current guidelines from the American Society of Transplantation recommend influenza vaccination for all organ transplant recipients over 6 months of age, who are at least 1 month from transplant, with consideration for high-dose vaccine or same-season booster doses in the post-transplant period [10–12].

Immunogenicity of influenza vaccination is characterized by multiple methods. All influenza vaccines currently available in the USA are quadrivalent, containing strains of A/H1N1, A/H3N2, B/Victoria, and B/Yamagata. Hemagglutination inhibition (HI) antibody titers to the specific strains in the vaccine are considered the standard measurement of humoral immunogenicity for influenza vaccines, with seroconversion being defined as a fourfold increase from baseline pre-vaccine HI titers. Seroprotection is defined as an HI titer > 1:40 and correlates with a 50% reduction in contracting the influenza infection in a susceptible population [13–15]. Several studies have demonstrated reduced immunogenicity to influenza vaccination in SOT recipients compared to the general population [16–18]. Multiple factors have been shown to impact immunogenicity including age, timing of vaccination post-transplant, and the use of certain immunosuppression medications, including mycophenolate mofetil [19, 20]. Recent studies investigating SOT recipient antibody responses to various forms of influenza vaccines have been conducted to help determine ways to improve immunogenicity in this population. Most studies evaluating methods to increase immunogenicity of influenza vaccines in SOT recipients have focused on one of the following strategies: (1) same-season booster dose, (2) use of a vaccine with an adjuvant, or (3) vaccines with higher doses of antigen. We aim to review the recent literature

surrounding influenza vaccination in SOT recipients, including possible strategies to increase immunogenicity, as well as provide an overview of future directions for influenza vaccination.

Improving influenza vaccine immunogenicity in SOT recipients

Influenza vaccines with adjuvant

Adjuvants in vaccines serve to augment the immune response to the target antigens. After the 2009 H1N1 influenza virus pandemic, multiple studies involving the H1N1 influenza vaccine using the ASO3 adjuvant described an increase in acute cellular rejection rates and development of human leukocyte antigen (HLA) autoantibodies in solid organ recipients who had been vaccinated [21–23]. These reports highlighted concerns regarding adjuvanted vaccines enhancing the alloimmune response in transplant recipients. An adjuvanted influenza vaccine is currently approved for use in the USA for individuals over 65 years of age. This vaccine contains the oil-in-water emulsion squalene-based adjuvant MF59® (Novartis). A more recent study in kidney transplant recipients who were randomized to receive the 2012–2013 trivalent influenza vaccine, either with or without the MF59 adjuvant, showed seroconversion to at least 1 of 3 influenza antigens in 71% of the recipients who received adjuvanted vaccine, compared to 55.2% of the recipients who received nonadjuvanted vaccine, but this was not statistically significant. Geometric mean titer (GMT) and seroprotection rates were also similar between the two groups; however, a subgroup analysis of younger patients between ages 18 and 64 did note a significant increase in seroconversion rates after receipt of adjuvanted vaccine, which conferred potential benefit in this age group. Furthermore, HLA alloantibodies were not increased in people who received adjuvant vaccinations in this study [24•]. A new study published in 2023 by Mombelli et al. [25••] demonstrated significantly increased seroconversion rates in SOT recipients who received quadrivalent MF59 adjuvant vaccine compared to standard-dose influenza vaccine (60% vs. 42%), while also demonstrating minimal vaccine-associated adverse events.

Booster dosing of influenza vaccines

As stated previously, the American Society of Transplantation vaccination guidelines suggest that booster dose strategies may lead to improved vaccine serologic responses in SOT recipients. A recent study was published by Cordero et al. in 2017 [26••], which randomized SOT recipients to receive standard-dose trivalent influenza vaccine, either a single dose or two doses separated by 5 weeks. The results demonstrated that patients who received two doses had significantly higher rates of seroconversion compared to the single-dose control group for influenza A H1N1, influenza A H3N2, and

influenza B. In addition, there was no increase in adverse effects from the booster dose, which indicates that same-season booster doses are safe and effective.

Given the emergence of the novel SARS-CoV-2 virus and resulting global pandemic in 2019, most of the recent vaccine literature regarding immunogenicity in SOT recipients focuses on COVID-19 vaccinations, including studies on booster doses leading to increased immune response [27–30]. For example, a systematic review with meta-analysis conducted in 2021 including data from 11,713 SOT recipients showed that only 10.4% of recipients had a positive humoral antibody response for anti-spike protein antibodies after a single dose of COVID-19 mRNA vaccine. This value improved to 63.1% of recipients after three doses [29•].

There are several barriers to using the same-season booster dose in clinical practice, namely adherence to vaccination schedule [31–33]. For example, a study by Felzer et al. [31•] investigated influenza vaccination rates among 468 SOT recipients living in four different counties in Minnesota and found that only 57–63% of SOT recipients were adherent to the recommendation for single-dose annual influenza vaccination. Furthermore, they identified that rural location and receipt of lung or liver grafts were associated with reduced rates of influenza vaccination. Another study conducted by Harboe et al. [33] that investigated influenza vaccination rates and hospital admissions for influenza pneumonia among 5745 SOT recipients living in Denmark showed that while influenza vaccination was effective in reducing hospital admissions and complications secondary to influenza virus, only 48% of recipients received annual vaccination. An additional barrier for implementing same-season booster doses is the concern regarding increased risk of antibody-mediated graft rejection (AMR) after vaccination. A multicenter prospective cohort study conducted by Cordero et al. [34•] evaluated AMR in SOT recipients that received influenza vaccination between 2009 and 2013. Results showed that receipt of influenza vaccination was not associated with clinical graft rejection; however, in the 136 participants that received two doses in the same season, the proportion of recipients with detectable HLA class I antibodies increased from 3.8% after one dose to 14.6% after two doses.

High-dose influenza vaccines

The use of high-dose influenza vaccine, which contains four times the amount of influenza antigen as the standard-dose trivalent influenza vaccine, is currently only approved for use in patients 65 years and older. This approval was based on a large efficacy trial conducted by DiazGranados et al. [35••] that compared high-dose vaccination to standard-dose influenza vaccination in elderly patients and successfully demonstrated a 24.2 relative efficacy advantage in preventing laboratory-confirmed influenza infection. High-dose influenza vaccine also produced superior GMT ratio

for influenza A strains and non-inferior GMT ratio for influenza B antigen. A randomized controlled trial comparing high-dose influenza vaccination to standard-dose influenza vaccination in the transplant population was conducted by Natori et al. [36••], which compared immunogenicity and safety outcomes in 161 SOT recipients. Results demonstrated significantly higher seroconversion rates and GMT ratios in those that received high-dose vaccination for all influenza strains tested (A H1N1, A H3N2, and B). In addition, they demonstrated that use of lower doses of mycophenolate (< 2 g daily) was an independent factor associated with seroconversion to at least one vaccine strain. A follow-up study conducted by the same research group [37] collected peripheral blood pre- and post-immunization from 30 high-dose vaccine recipients and 30 standard-dose vaccine recipients from the Natori 2018 study. They reported that the high-dose vaccine elicited significantly increased influenza-specific CD4 + and CD8 + T-cell responses, which provided a novel cellular explanation for the increased immunogenicity reported in their prior study.

A study conducted by Mombelli et al. [38] compared immunogenicity outcomes in kidney and liver transplants randomized to receive either standard-dose influenza vaccine or a double dose of the standard-dose formulation given at the same time. Results of this study were promising and showed a trend toward increased seroconversion rates and GMT with the double-dose vaccine, but these were not statistically significant. However, the incidence of adverse effects was minimal, and there were no cases of vaccine-associated graft rejection, which suggests that while there needs to be further studies investigating this vaccination strategy, it is safe and could be considered when high-dose vaccine formulations are not available. As mentioned during discussion of MF59 adjuvants, the more recent study conducted by the same group [25••] compared seroconversion rates in SOT recipients who received high-dose inactivated influenza quadrivalent vaccine to standard-dose inactivated quadrivalent vaccine and demonstrated that high-dose vaccination led to significantly increased seroconversion rates (66% vs 42%). One potential barrier to this vaccination strategy is that the high-dose influenza vaccination is not commercially approved for use in patients less than 65 years of age, which could lead to a lack of insurance coverage and subsequent cost barriers for off-label use of this product in transplant recipients less than 65 years old.

Future directions

As demonstrated by vaccine development during the COVID-19 global pandemic, the emergence of mRNA vaccine technology has allowed for rapid development of vaccines, and subsequent editing toward varying targets, in addition to favorable safety profile and high efficacy. As previously outlined, there have been several studies showing favorable

immunogenicity responses to COVID-19 mRNA vaccinations in SOT recipients, particularly with use of booster doses. Although not yet studied in immunocompromised populations, there is promising new data from the Moderna-funded phase 1 and 2 trials using mRNA-1010 influenza vaccine in healthy adults. This is a quadrivalent influenza vaccine encoding hemagglutinin surface glycoproteins for A H1N1, A H3N2, B Victoria, and B Yamagata strains. The data published by Lee et al. [39•] demonstrates that a single dose of mRNA vaccination at 25, 50, or 100 mg dose elicits higher hemagglutination inhibition titers than a single standard dose of inactivated seasonal influenza vaccine. While the incidence of solicited adverse effects was higher in the mRNA vaccine cohort in a dose-dependent fashion, there were few safety concerns identified. This product is currently undergoing phase 3 clinical trials. While there will need to be dedicated studies for immunocompromised populations and SOT recipients, this remains a promising technology for increasing vaccine efficacy against seasonal influenza in this population.

Another technology currently in development for preventing influenza infection is use of broadly neutralizing monoclonal antibodies directed at the hemagglutinin stalk, which is shared between the varying influenza strains. This is primarily being developed toward influenza A infections. For example, a monoclonal antibody product by Crucell called CR8020 is currently in phase 2 trials looking at this product both for prevention and treatment of influenza A infections [40, 41]. These products have an unknown timeline to reach approval for clinical use in healthy adults, so therefore remain a distant future possibility for prevention of influenza infection in SOT recipients.

Currently, seasonal vaccines contain three to four strains of influenza which are chosen using variable methods to determine which influenza virus strains are most likely to spread and cause illness during the upcoming influenza season. However, there are also efforts to develop a universal influenza vaccine, which targets the conserved hemagglutinin stem, rather than the hemagglutinin head, which varies with each strain of influenza virus. These vaccines are also in the early stages of development, with results of the phase 1 trial for a H1 hemagglutinin stabilized stem nanoparticle (H1ssF) recently published in April 2023 [42, 43]. The data published by Andrews et al. [42] found that memory B cell responses elicited by H1ssF vaccination were broadly cross-reactive and targeted two conserved epitopes on the H1 stem, while data published by Widge et al. [43] demonstrated that immunization with one or two doses of an H1 hemagglutinin stabilized stem nanoparticle (H1ssF) vaccine was safe in recipients and elicited durable neutralizing antibody responses. The National Institutes of Allergy and Immunology are also currently recruiting participants for a phase 1 clinical trial for an mRNA version of the H1ssF vaccine [44]. This demonstrates that the field of vaccine development remains eager to develop more effective and tolerable vaccinations against influenza virus.

Conclusions

The number of organ transplantations performed is increasing annually, with infections comprising the majority of post-transplant complications. Influenza infection remains the most common vaccine-preventable illness affecting transplant recipients; however, adherence to annual vaccination recommendations and suboptimal immune response compared to the general population serve to reduce vaccines' ability to prevent infection. There are several studied methods to increase immunogenicity in solid-organ transplant recipients, including same-season booster doses, high-dose vaccines, and adjuvanted vaccines. We believe that the most effective strategy currently available to increase vaccine immunogenicity in solid organ transplant recipients includes the high-dose quadrivalent vaccine or the adjuvanted quadrivalent vaccine, which have been shown to have good safety profiles in this population and do not appear to increase the risk of allograft rejection. Same-season influenza vaccine booster dosage also improves immunogenicity, but this strategy may be limited by requiring multiple encounters for vaccination in the same season, when adherence to single annual vaccination is already suboptimal compared to recommendations. While there are many exciting technologies in the pipeline, such as mRNA influenza vaccines, monoclonal antibodies for both prevention and treatment of influenza, as well as universal influenza vaccination targeting the common hemagglutinin stem, these technologies require further clinical trials to demonstrate safety and efficacy, and the timeline for licensure is currently unknown.

Author contributions

EP and LT wrote the main manuscipt text. All authors reviewed the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare no competing interests.

Human and animal rights and informed consent
All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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