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REVIEW

Seasonal influenza vaccine in immunocompromised persons

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ABSTRACT

Immunocompromised persons are at high risk of complications from influenza infection. This population includes those with solid organ transplants, hematopoietic stem cell transplants, solid cancers and hematologic malignancy as well as those with autoimmune conditions receiving biologic therapies. In this review, we discuss the impact of influenza infection and evidence for vaccine effectiveness and immunogenicity. Overall, lower respiratory disease from influenza is common; however, vaccine immunogenicity is low. Despite this, in some populations, influenza vaccine has demonstrated effectiveness in reducing severe disease. Various strategies to improve influenza vaccine immunogenicity have been attempted including two vaccine doses in the same influenza season, intradermal, adjuvanted, and high-dose vaccines. The timing of influenza vaccine is also important to achieve optimal immunogenicity. Given the suboptimal immunogenicity, family members and healthcare professionals involved in the care of these populations should be vaccinated. Health care professional recommendation for vaccination is an important factor in vaccine coverage.

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Introduction

Due to impaired host defenses, immunocompromised persons are at higher risk of morbidity and mortality from vaccine-preventable infections compared to the general population. In addition, frequent contact with the healthcare system also increases the risk of acquisition of certain vaccine-preventable diseases. Influenza is a seasonal RNA virus that causes illness ranging from mild upper respiratory infection to severe lower tract infection and death. Worldwide, influenza epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 250 000 to 500 000 deaths annually.[1] In immunocompetent persons, influenza generally causes upper respiratory tract infection accompanied by fever, myalgias and gastrointestinal symptoms. However, in persons with impaired immunity, influenza can be complicated by progression to lower respiratory infection and can also have unusual manifestations such as rhabdomyolysis and myocarditis.[2,3] In addition, bacterial superinfection can occur in a high percentage of patients with immune compromise (up to one-third in solid organ recipients).[4] Therefore, various expert guidelines recommend annual influenza vaccination for immunocompromised persons. However, expert guidelines are informed primarily by immunogenicity data and extrapolation from the general population; there are limited data for the effectiveness of influenza vaccine in immunocompromised populations. Efficacy studies are generally difficult to perform due to the heterogeneity of the immunocompromised population. There are several types of underlying diseases and a variety of immunosuppressive therapies. Timing of vaccine, optimal schedule and type of influenza vaccine, as well as safety of vaccine are important to consider for immunocompromised persons. A recent systematic review of influenza vaccination in immunocompromised persons showed that vaccine was safe and appeared to lower the odds of influenza-like illness.[5] In this review we will focus on various influenza vaccine strategies in persons with immunocompromise due to organ transplantation, hematopoietic stem cell transplantation, solid tumour and hematologic malignancy, and inflammatory diseases treated with biologic agents (Table 1). A summary of selected studies is presented in Table 2. Influenza in persons infected with human immunodeficiency virus is not discussed in this review and requires separate study.

Influenza vaccines

The annual inactivated influenza vaccine (IIV) has traditionally been a trivalent vaccine containing 15 μg each of two A strains (H1N1 and H3N2) and a B strain. Inactivated influenza vaccine types include either whole inactivated virus, split virus, virosomal or subunit antigen. Since 2012, quadrivalent vaccines containing an additional B strain have been developed to address the issue of annual co-circulation of two B lineages. IIV is recommended for anyone at risk of influenza infection. Some jurisdictions recommend universal vaccination and others suggest vaccination for at-risk groups including children 6 months to 2 years of age, persons $\geq$65 years old, pregnant women, and persons with chronic heart, lung, and neurologic conditions.[6,7] It is also recommended for immunocompromised persons. In a meta-analysis, IIV was shown to have pooled efficacy of 59% in persons aged 18–65 years.[8] However, the efficacy varies by influenza strain and vaccine match in any given year. The

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Table 1. Summary of influenza vaccine studies in various immunocompromised groups.

Seasonal flu vaccine	Solid organ transplant	Hematopoietic stem cell transplant	malignancy	Autoimmune/Inflammatory disease with or without biologic therapy
Standard TIV	•Recommended	•Recommended	•Recommended	•Recommended
Adjuvanted TIV	•Similar immunogenicity as nonadjuvanted[59]	• Similar immunogenicity as standard.[38]	•Not studied	•Not studied
High-dose TIV	• Greater immunogenicity across all vaccine strains (68, 69)	• Greater immunogenicity for H3N2 strain.[37]	• Greater fold increase to: (B antigens in the leukemia group) and (H1 antigens in the solid tumor group).[84]	•Not studied
	• Greater rate of local and systemic reactions	• Greater local reactions		
Live attenuated vaccine	• Contraindicated	• Contraindicated	• Contraindicated during chemotherapy	• Contraindicated on biologic therapy

suboptimal immunogenicity of IIV in the older population has led to the development of newer formulations including adjuvanted vaccines and high-dose vaccines. One available adjuvanted vaccine contains the MF59 compound which is an oil in water emulsion that induces a local inflammatory response when injected together with influenza antigen.[9–11] This allows cytokines and chemokines to attract antigen presenting cells to the site of injection, thereby increasing the potential for an antigen-specific immune response with lower doses of influenza antigen. The adjuvanted vaccine has shown greater immunogenicity than nonadjuvanted vaccine in persons ≥65 years of age and infants/children 6 months-2 years of age.[12–15] Another available formulation of IIV is a high dose influenza vaccine which contains four-times the amount of antigen contained in standard IIV. A large randomized trial of high-dose vaccine vs. standard dose vaccine showed that the high-dose vaccine had 24% greater relative efficacy for influenza prevention in a population of persons ≥65 years. There are no studies directly comparing the high-dose vaccine to the adjuvanted vaccine in the older population. An intradermal influenza vaccine had shown improved immunogenicity in the older population compared to standard intramuscular injection; however, this vaccine is no longer marketed. Finally, the live-attenuated intranasal influenza vaccine is authorized for healthy, non-pregnant people 2 through 49 years of age; however, recent U.S. data show the live vaccine appears to be less effective than IIV.[16] Therefore, pending further evaluation, its use has been suspended in the U.S. in June 2016 although it continues to be available in other countries.

The anticipated antigenic shifts in influenza virus and the 2009 global pandemic of A/H1N1 influenza raised the need for pandemic influenza vaccines. In addition to the use of pandemic H1N1 vaccines during the 2009 pandemic, other H5N1 vaccines have been licensed for similar purposes although not commercially available.[17] Whole inactivated virus (WIV) has been used in pandemic vaccines due to its high intrinsic immunogenicity.[18] Although much literature is available on pandemic vaccines and immunocompromised hosts, this review will primarily focus on seasonal influenza vaccination and discuss pandemic vaccines as they apply to seasonal vaccination. Both pediatric and adult studies are included in this review, although the majority of the clinical data are derived from the adult population.

Several studies have shown that influenza vaccination rates in immunocompromised persons are suboptimal. A large study of patient groups in France showed that influenza vaccination rates in various immunocompromised populations including those with transplant and malignancy ranged 59–72%.[19] Other surveys have reported influenza vaccine uptake rates of 52% in organ transplant patients and 34% in those with inflammatory bowel disease.[20,21] In immunocompromised persons, efficacy data for influenza vaccines are generally lacking. The primary outcomes used by most studies is immunogenicity including seroprotection and seroconversion. A seroprotective titer is generally defined as ≥1:40 (a titer that is associated with a 50% reduction of disease in the population)[22,23] and seroconversion is defined as a 4-fold rise of titer from pre-immunization levels. The definition of seroprotection is generally derived from vaccine immunogenicity in healthy adults; despite its widespread use in trials, it is unknown whether the same cut-off applies to immunocompromised persons. For example, Black et al. showed that children likely require a higher seroprotective level (e.g., ≥1:110).[24] The following sections will highlight studies of influenza vaccination in various immunocompromised hosts. Such studies are intrinsically limited due to relatively small samples sizes and heterogeneity within the study populations; however, general conclusions can be made.

Hematopoietic stem cell transplant

Influenza causes morbidity and mortality in allogeneic and autologous HSCT recipients. Recent studies show lower respiratory infection rates of 7–35% with 5–28% mortality in those that developed lower tract infection.[25,26] Receipt of early antiviral therapy has been important in reducing the rate of lower respiratory tract infection.[26] Prolonged influenza shedding from the respiratory tract is also an issue in this group; studies suggest influenza virus can be detected up to several months following infection especially in patients receiving corticosteroids.[27,28] Guidelines by the Infectious Disease Society of America (IDSA) as well as international guidelines recommend annual influenza vaccine for HSCT recipients.[29] The effectiveness of influenza vaccine in this population was shown by Machado et al. This study retrospectively reviewed 177 HSCT patients in a HSCT program and assessed the risk factors for acquiring influenza and reviewed vaccination records.[30] In multivariate analysis, seasonal exposure and conditioning regimens including total body irradiation (TBI) and melphalan/busulfan were independently associated with an increased risk for influenza, whereas influenza vaccine and steroid therapy

Table 2. Selected studies of influenza vaccine immunogenicity in immunocompromised populations.

Study	Vaccine Formulation	Route of Administration	Study Population	Immunogenicity Outcome	Other outcomes
Hematopoietic Stem Cell Transplant (HSCT)					
Karras et al., 2013[31]	1 dose (n = 33) vs. 2 doses (n = 32) standard TIV 4 weeks apart	Intramuscular	> 60 days post HSCT	No significant differences in seroprotection at 8 weeks for influenza H3N2 (19% vs. 19%), H1N1 (32% vs. 32%) and B (32% vs. 23%).. No differences in seroconversion	
Natori et al., 2017[38]	MF59 adjuvanted (n = 35) vs. nonadjuvanted (n = 32) standard TIV	Intramuscular	> 12 weeks post HSCT	Seroprotection rates after vaccination were similar. Seroconversion to at least one of three influenza vaccine antigens was present in 62.9% vs 53.1% (P = 0.42)	
Halasa et al., 2016[37]	High-dose 60 μg (n = 29) vs. Standard-dose 15 μg (n = 15) TIV	Intramuscular	> 6 months post HSCT	GMTs were higher in the HD group for H1N1 and H3N2. HD group had a higher Seroprotection rate for H3N2; 81% vs. 36% (P = 0.004).	Study not powered for immunogenicity. Greater local reactions in HD vaccine.
Ambati et al., 2015[39]	Virosomal adjuvanted (n = 21) vs. nonadjuvanted standard (n = 30) TIV	Intramuscular	HSCT before and after 6 months post-transplant	Seroprotection rates were poor in both cohorts (23% vs 13.3%).	The delta change of interferon-gamma production in response to influenza A/H1N1and influenza B antigens was significantly greater in individuals who received the virosomal vaccine.
Solid Organ Transplant (SOT)					
Cordero et al., 2017[64]	1 dose (n = 211) vs. 2 doses (n = 213) standard TIV given 5 weeks apart	Intramuscular	> 1 month post SOT	Higher short-term seroconversion rate. Seroprotection at 10 weeks was higher in the booster group: 54% vs 43.2% for A(H1N1) pdm; 56.9% vs 45.5% for A(H3N2); and 83.4% vs 71.8% for influenza B (P < .05).	
Manuel et al., 2007[44]	2 doses (n = 60) TIV given 4 weeks apart	Intramuscular + Intradermal 5 μg	> 3 months post lung transplant	Intradermal booster dose did not significantly improve overall immunogenicity above that achieved with the single intramuscular dose.	
Manuel et al., 2011[70]	TIV Intradermal (n = 41) vs Intramuscular (n = 44)	Intradermal (6 μg) vs. Intramuscular (15 μg)	> 3 months post-lung transplant	Overall seroconversion rate was low, but it was similar between groups. Seroprotection was 39% for H1N1, 83% for H3N2 and 29% for B strain in the intradermal group vs 28% for H1N1, 98% for H3N2 and 58% for B strain in the intramuscular group (p = 0.36 for H1N1, p = 0.02 for H3N2, p < 0.01 for B).	
aluch et al., 2013[46]	TIV ID (n = 107) vs IM (n = 105)	Intradermal (18 μg) vs. Intramuscular (15 μg)	> 3 months post	Similar immunogenicity Certain organ subgroups (liver and kidney patients) had higher response rates for influenza B in the ID vaccine group (p = 0.011).	Response was more likely in those ≥6 months post-transplant (53.2% vs. 19.2%; p = 0.001).
			SOT		
Kumar et al., 2016[59]	MF59 adjuvanted (n = 31) vs. nonadjuvanted (n = 29) standard TIV	Intramuscular	> 3 months post	Geometric mean titers and seroprotection rates were similar between groups.	In a subgroup analysis of the 18–64 year age group, the adjuvanted vaccine showed significantly greater seroconversion rates compared to unadjuvanted vaccines.

(*Continued on next page*)

Table 2. (*Continued*)

Study	Vaccine Formulation	Route of Administration	Study Population	Immunogenicity Outcome	Other outcomes
Natori et al., 2017[69]	High Dose 60μg (n = 84) vs Standard Dose 15μg (n = 77) TIV	Intramuscular	Kidney transplant > 3 months post	Seroconversion to A/ H1N1, A/H3N2 and B strains were higher in HD vs. SD vaccine (p = 0.006, 0.002, 0.028 respectively).	
Magnani et al., 2005[70]	MF59 adjuvanted (n = 21) vs. nonadjuvanted (n = 21) standard TIV	Intramuscular	SOT > 6 months post Heart transplant	No significant difference between groups. Both were associated to a significant increase of antibodies belonging to the IgG and IgM classes to influenza B and of an IgM immune response to influenza A ($p<0.05$).	4 episodes of acute myocardial rejection > 3A were detected during the 6 months of follow-up
GiaQuinta et al., 2015[68]	High Dose 60 μg (n = 23) vs Standard Dose 15 μg (n = 15) TIV	Intramuscular	Pediatric > 6 months post SOT	HD group demonstrated a higher percentage of four-fold titer rise to H3N2 (not powered to compare the immunogenicity).	HD group reported more tenderness and local reactions, fatigue, and body ache
Hojsak et al., 2011[66]	1 dose (n = 18) vs. 2 doses (n = 32) standard TIV given 4–6 weeks apart	Intramuscular	Pediatric > 6 months post Liver Transplant	antibody titers were higher after second vaccination, but not statistically significant (P = 0.198).	
Hematologic Malignancy and Solid Tumour					
Ljungman et al., 2005[80]	1 dose (n = 36) vs. 2 doses (n = 34) standard TIV given 4 weeks apart	Subcutaneous	Haematological malignancies on chemotherapy within 6 months	Seroprotection rates were not improved by two doses compared with one (influenza A virus serotypes H1/N1 18% vs. 22% and H3/N2 26% vs. 14%; influenza B 25% vs. 22%).	
Sanada et al., 2016[81]	2 doses (n = 109) standard TIV given 3–5 weeks apart	Subcutaneous	Solid tumours and haematological malignancy on chemotherapy within 6 months	booster dose did not improve immunogenicity (seroprotction increased by only 10% (H1N1), 8% (H3N2), and 3% (B) after the 2nd vaccine).	
Jamshed et al., 2016[82]	High Dose 60 μg (n = 54) vs Standard Dose 15 μg (n = 51) TIV	Intramuscular	Solid tumours and haematological malignancy on chemotherapy	Significantly improved seroconversion rates with HD for all three strains (26% for H1N1, 22% for H3N2, and 36% for B). Seroprotection rates were equivalent and high in both groups for all three strains	
Hakim et al., 2016[83]	2 doses of HD (60 μg) vs 2 doses SD (15 μg) TIV (1:1) given 21 days apart	Intramuscular	27 with leukemia, 17 with solid tumour, and 41 with HIV	HD TIV was significantly more immunogenic against B antigen in leukemia patients (p = 0.04), and H1 antigen in Solid Tumor patients (p = 0.04).	HD TIV reported more frequent reactogenicity events but not statistically significant
McManus et al., 2014[84]	(HD 60 μg) (n = 34) vs (SD 15 μg) (n = 16) TIV	Intramuscular	Children with acute lymphoblastic leukemia	No significant differences (this study was not powered for immunogenicity)	Nine in the HD group and two in the SD group required two doses of the vaccine.
Inflammatory Disease and Biologic Therapy					
Matsumoto et al., 2015[92]	1 dose (n = 46) vs. 2 doses (n = 43) standard TIV given 3 weeks apart	Subcutaneous	Adult inflammatory bowel disease patients treated with anti-tumor necrosis factor-α agents and/or immunomodulators	No significant difference 3 weeks post-vaccination (geometric mean titers: H1N1, p = 0.09; H3N2: p = 0.99; B: p = 0.94).	

TIV trivalent inactivated vaccine, ID Intradermal, IM Intramuscular, HIV human immunodeficiency virus, HD high-dose, SD standard-dose, HSCT hematopoietic stem cell transplant, SOT solid organ transplant.

showed a protective role. Despite this, the overall immunogenicity of influenza vaccine has been poor in this group and seroprotection / seroconversion rates have ranged from 19–32%.[31] Risk factors for poor response include use of calcineurin inhibitors, chronic GVHD, shorter time post-transplant as well as low IgM levels <0.5 g/L.[32,33]

Timing of vaccination

Timing of vaccination post-transplant has been debated. Earlier studies showed no or poor antibody response when vaccine was given in the first six months of allogeneic transplantation.[34] Guidelines from the IDSA recommend to start influenza vaccination at six months post-transplant and at 4 months if there is a community outbreak of influenza. Guidelines from the European Conference of Infections in Leukemia (ECIL) recommend that influenza vaccination can be given as early as 3-months post-transplant.[35] Pre-transplant vaccination may have some benefit. HSCT recipients who were vaccinated prior to transplant appear to have greater strain-specific antibody responses up to 6 months post-transplant than those who were not vaccinated.[36]

Vaccine dosing

Various dosing strategies have been attempted to improve post-transplant vaccine immunogenicity. Two doses of IIV were given in a randomized controlled trial where patients (>60 days post-transplant) were randomized to receive either one (n = 33) or two (n = 32) influenza vaccine doses, one month apart.[31] However, two doses of influenza vaccine did not improve vaccine-associated T or B cell responses. In this study, the time from transplant to vaccination and absolute CD19+ cell counts, were the strongest predictors of vaccine antibody response. High-dose vaccine was also tested in a randomized trial. In a Phase I safety study,[37] 44 HSCT patients were randomized 2:1, to receive either the high dose (60 μg) or the standard dose (15 μg) trivalent IIV. Both vaccines were found to be safe and well-tolerated in adult HSCT recipients. However, the HD group had a higher frequency of injection-site reactions, with the majority of the reactions being mild. Although the study was not powered to compare immunogenicity, post-vaccination GMTs were higher in the high dose group for H1N1 and H3N2, and the difference reached statistical significance for H3N2 (p = 0.004).

Adjuvants

The MF59 adjuvanted vaccine was studied in a pilot randomized trial with nonadjuvanted vaccine as the comparator. Adjuvanted vaccine demonstrated similar immunogenicity to the non-adjuvanted vaccine and seroconversion rates were 62.9% vs 53.1%.[38] Overall, lower seroconversion rates were associated with the use of calcineurin inhibitors (p < 0.001) and shorter duration from transplantation (p = 0.001). In an attempt to improve immunogenicity, Ambati et al. have attempted to use a virosomal adjuvanted vaccine in a small cohort of HSCT recipients but this did not provide an immunogenicity advantage over subunit vaccine.[39] The virosomal vaccine is no longer available.

In summary, sufficient data exist to show that post-HSCT patients can demonstrate immunogenicity to IIV. Newer vaccine strategies such as high dose vaccines need further study.

Solid organ transplantation

Organ transplant recipients are also at increased risk of morbidity and mortality from influenza[2,4] and influenza vaccine is recommended in guidelines by various national and international bodies including IDSA (Infectious Disease Society of America), AST (American Society of Transplantation), and KDIGO (Kidney Disease Improving Global Outcomes).[29,40,41] In general influenza vaccine may not prevent all cases of influenza but appears to be partly beneficial. In a Spanish cohort of patients with influenza infection,[42] vaccinated patients were less likely to develop pneumonia if they developed influenza infection. A large international study of microbiologically-proven influenza infection in transplant patients showed that the rate of pneumonia in the SOT cohort was 22% and ICU admission occurred in 11% of patients; in the overall cohort (n = 616) that included both SOT and HSCT patients, vaccination in the same season was associated with lower influenza A viral loads and less severe disease including lower rates of pneumonia and ICU admission.[43]

The immunogenicity of influenza vaccine in this group is variable but has been lower than that of the general population and is dependent on various factors including type of transplant and immunosuppression. Lung transplant recipients have traditionally had the lowest levels of seroconversion and range from 7–26%.[44,45] The main barrier to immunogenicity is lifelong immunosuppression given to this population. Mycophenolate mofetil (MMF) has been shown to have a dose-dependent response where higher doses especially those ≥2 grams daily were correlated with lower seroconversion rates.[46–50] A recent meta-analysis confirmed this correlation with MMF and lower rates of seroconversion compared to other immunosuppressants. No significant correlation of low immunogenicity was detected with tacrolimus, sirolimus, cyclosporine, and azathioprine.[51] Induction immunosuppression may not impact vaccine immunogenicity. In a kidney transplant cohort in which thymoglobulin or basiliximab was used as induction therapy, 60 patients were evaluated for the immune response to IIV. There were no significant differences in geometric mean titers for any of the three viral strains between groups.[52] A recent study also showed that immune responses were not significantly different between groups that received basiliximab or ATG in heart and kidney transplant recipients although reported that the median number of influenza-specific memory B-cell (IgG-MBC) did not increase after vaccination.[53]

An anecdotal risk cited for influenza vaccines is the possibility that they may lead to graft rejection. During the H1N1 pandemic of 2009, studies associated the pandemic vaccine with HLA alloupregulation and cellular rejection.[49,54,55] This led to a review of cases by the European Medicines Agency which showed no significant association if controls were used.[56,57] Since the pandemic was widespread, these studies were

confounded by the possibility of influenza infection occurring during the study period. In addition, multiple investigations conducted with seasonal vaccines given to transplant patients have not shown significant associations with HLA antibody production.[46,47,58–60]

Timing of vaccination

Although the above studies show that induction immunosuppression does not appear to have an impact on vaccine responses, guidelines have generally stated to delay the administration of vaccine up to 3 months post-transplant.[40] This is based on previous studies that showed significantly lower antibody titers in transplant recipients vaccinated within six months of transplantation.[61,62] However, a more recent prospective cohort study on 798 SOT recipients who were vaccinated before and after six months (130 vs. 668 respectively) after kidney, heart, and liver transplantation showed similar seroprotective immune response and safety profiles in both groups.[63] Therefore, it may be reasonable to administer influenza vaccine as soon as one month after transplantation.

Vaccine dosing

Various dosing strategies have been attempted to increase influenza vaccine immunogenicity in SOT recipients. A recent RCT was conducted by TRANSGRIPE 1–2 Study Group.[64] In this study, the use of booster dose (5 weeks apart) within the same season of trivalent IIV in SOT patient after one month of transplant was associated with higher short-term seroconversion rates in per-protocol analysis although not in intention to treat group. Seroprotection was greater for two doses in one to two influenza antigens after adjusting for possible confounding factors in the short term, with no difference between the treatment groups 1-year post-vaccination. Based on the low number needed to vaccinate calculated in that study (<10 patients) and the safety of administering two doses of influenza vaccine, the authors suggested that the booster strategy can be considered to increase immunogenicity. In addition, a study of two doses of the influenza A/H1N1 (2009) pandemic vaccine in kidney transplant recipients showed that two doses induced significantly better seroprotection.[65] However, not all studies of booster vaccine have been consistent. A prospective cohort of liver-transplanted children showed that two doses of seasonal influenza vaccine (4-6 weeks apart) yielded no statistically significant benefit of the second dose.[66] In addition an intradermal booster dose of influenza vaccine given to lung transplant recipients 4 weeks after initial vaccination did not show benefit.[44] A meta-analysis was performed on the use of booster vaccinations in the context of a monovalent or trivalent intramuscular influenza vaccine in chronic renal disease patients, including those undergoing hemodialysis, peritoneal dialysis, or kidney transplantation. Nine studies published between 1987 and 2013 were included in the systematic review, and the pooled rate difference (RD) showed that the booster vaccination did not significantly increase the seroprotection rate in patients with hemodialysis, peritoneal dialysis, or a renal transplant.[67] Therefore, the role of booster doses remains controversial. High dose (60 μg) trivalent IIV was studied in a randomized controlled trial of pediatric SOT patients in comparison to standard dose (15 μg). The high-dose influenza vaccine group reported more local reactions, fatigue, and myalgias. However, no severe adverse events or rejection was noted. Seroconversion rates to H3N2 were significantly greater compared to the standard-dose group.[68] Recently, a Canadian randomized trial in 172 adult organ transplant recipients with an age range of 18–86 years showed that high-dose vaccine had greater strain specific geometric mean titers and significantly greater seroconversion rates to all 3 vaccine strains compared to standard dose IIV.[69]

Adjuvants

Another clinical trial in stable outpatient kidney transplanted patients using influenza vaccine containing an oil-in-water emulsion adjuvant (MF-59) versus a nonadjuvanted formulation was done in the 2012–13 season.[59] The adjuvanted vaccine group had comparable immunogenicity compared with the nonadjuvanted vaccine with similar geometric mean titers and seroprotection rates between groups. There were no increases in HLA alloantibodies in patients who received the adjuvanted vaccine. However, in a subgroup analysis of the 18–64 year age group, the adjuvanted vaccine showed greater seroconversion rates compared to unadjuvanted vaccines. A study in heart transplant patients also showed similar immunogenicity of the adjuvanted vs. nonadjuvanted vaccines.[70]

Intradermal vaccines

Intradermal vaccines may improve immunogenicity by increasing exposure of antigen to dermal dendritic cells which act as antigen presenting cells. In a cohort study of 85 lung transplant recipients, patients received the seasonal 2008–9 IIV, containing either 6 μg (intradermal) or 15 μg (intramuscular). Immunogenicity was assessed by using the hemagglutination-inhibition (HI) assay and was overall poor in both groups.[71] Subsequently, a randomized trial was performed comparing a somewhat higher dose (18 μg) of intradermal vaccines compared to standard 15 μg intramuscular vaccine in 212 SOT recipients.[46] The study showed that intradermal vaccine had similar immunogenicity to the standard intramuscular vaccine although non-lung transplants had higher response rates for influenza B in the intradermal vaccine group. Time from transplant (< 6 months), as well as mycophenolate and prednisone doses were significant factors in univariate analysis for poor vaccine responses. This large cohort also showed that IIV did not result in significant HLA alloantibody production.

Taken together, studies indicate that influenza vaccination is safe and effective in SOT recipients. The high-dose vaccine may provide an immunogenicity benefit over standard-dose vaccines and vaccination may protect against severe sequelae of influenza infection.

Solid tumours and hematologic malignancy

Limited recent data are available on the impact of influenza infection in patients with solid tumours or hematologic malignancy. Studies done in the 1990s, primarily in

leukemia patients showed mortality from influenza-related pneumonia to be 11–33%.[72–74] The majority of studies have shown that influenza vaccine is safe in patients with solid and hematological malignancies; studies of effectiveness are limited in this population. A recent prospective, non-interventional cohort study on 806 patients with solid malignancies who were receiving chemotherapy and hematologic patients who had active disease was conducted to examine the effectiveness of the seasonal influenza vaccine. It showed no association between influenza vaccination and the primary outcome (a composite of fever or acute respiratory infections, pneumonia, and/or infection-related chemotherapy interruptions). However, the authors did show that influenza vaccination was associated with significantly lower mortality among cancer patients; the odds ratio for death without vaccination was 2.39 (95% CI, 1.32–4.32).[75] In this cohort, only 48% of patients were vaccinated. Using the same cohort, the authors showed that oncologist and primary care physician recommendation to receive influenza vaccine were the strongest predictors for vaccination.[76] A meta-analysis of the effectiveness of influenza vaccines in adults with cancer was able to find four studies that met the inclusion criteria[77]; the authors concluded that evidence, although weak, does exist to justify vaccination of cancer patients on chemotherapy.

There are more than 50 studies on influenza vaccine immunogenicity in patients with various types of cancers. A meta-analysis was conducted to evaluate both seroconversion ($\geq$ 4 fold rise) and seroprotection ($\geq$ 1:40 hemagglutination inhibition titer) by influenza vaccine[5] in various groups of immunocompromised persons. A review of 12 influenza vaccine immunogenicity studies in cancer patients showed a significantly reduced rate of seroconversion and seroprotection for all three influenza vaccine strains, compared to vaccinated immunocompetent controls (pooled effect size for H1N1 seroconversion, 0.31 95%CI 0.22–0.43).

However, not all cancer chemotherapies are equal in their effect on influenza vaccine response. A recent prospective study to evaluate the immunogenicity of the influenza vaccine in patients with lung cancer undergoing anticancer chemotherapy included 25 patients with lung cancer and 26 patients with chronic obstructive pulmonary disease (COPD) as controls.[78] Lung cancer patients who received trivalent influenza vaccine had post-vaccination seroprotection rates of 84% for both A(H1N1) and A(H3N2), similar to the levels observed in patients with chronic obstructive pulmonary disease, but had significantly lower odds for seroprotection against the B strain. Thus, the response to influenza vaccine may be dependent of the type of influenza strain as well as the type of chemotherapy.

Pediatric data on the subject are limited. A prospective cohort study in children receiving chemotherapy for cancer was conducted during two consecutive influenza seasons.[79] All the patients received trivalent IIV in the 2012–2013 influenza season and quadrivalent IIV in the 2013–2014 influenza season. The seroresponse (defined as a fourfold rise in influenza titer from baseline and/or a titer of $\geq$1:40) rate was 62% (98/157). The seroresponse was not associated with a decreased frequency of influenza infection or influenza-like illness when compared to nonresponders, suggesting that the clinical effectiveness of vaccination may be impacted by multiple factors.

Timing of vaccination

Since immunogenicity of vaccine is variable and generally not measured in clinical practice, the timing of vaccination in relation to chemotherapy is important to achieve optimal vaccine response. Some experts suggest to give annual vaccination at least two weeks prior to chemotherapy; during chemotherapy vaccination could be done at the mid-point of two cycles. Regardless of timing of vaccine, however, there appears to be potential benefit of vaccination.[80]

Vaccine dosing

Studies conducted to determine the immunogenicity of two-dose influenza vaccinations in cancer patients receiving chemotherapy have shown no additional benefit of the second vaccination.[81,82] As with other immunocompromised populations, high-dose vaccine has been studied in a pilot randomized clinical trial including 105 adults younger than 65 years of age receiving cancer chemotherapy.[83] The majority of patients (90%) had solid tumours (mainly breast and gastrointestinal) and more than two-thirds received combination chemotherapy. This study showed that high-dose IIV can be safely administered to patients receiving chemotherapy with greater seroconversion compared to the standard-dose vaccine. The absolute difference (high dose minus standard dose) in the percentage of patients with seroconversion was 26% for H1N1, 22% for H3N2, and 36% for B. This was followed by another randomized, open-label study of high dose IIV compared to the standard-dose vaccine.[84] Eighty-five participants were enrolled in the study: 27 with leukemia, 17 with solid tumor, and 41 with HIV. The high-dose vaccine had significantly greater fold increase in strain-specific antibody titers to B antigens in the leukemia group and to H1 antigens in the solid tumor group. There were no differences in seroconversion or seroprotection between the high-dose and standard dose vaccines in all groups. High-dose vaccine had similar standard dose when in a clinical trial of 50 children with acute lymphoblastic leukemia.[85]

Adjuvants

To our knowledge, there are no studies of MF59 adjuvanted influenza vaccine in patients on chemotherapy.

Taken together, studies suggest that using influenza vaccine is safe for patients with malignancy receiving chemotherapy and high-dose vaccine is a potential strategy to enhance the immune response of patients with malignancy.

Inflammatory disease and biologic therapy

Influenza vaccination is recommended for those with inflammatory diseases including those that are treated with biologic and non-biologic immunosuppressive medications. Inflammatory disease populations include those with rheumatologic

conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). This population also includes those with inflammatory bowel disease (IBD) and dermatologic disease such as psoriasis. In a population at high risk because of exposure to biological therapy for inflammatory arthritides, Brocq et al. showed that information provided by healthcare professionals about inactivated influenza vaccination was an important factor in the decision to be vaccinated.[86] A recent Nationwide Cohort Study conducted in Taiwan compared the incidence of hospitalization, morbidity, and mortality between vaccinated and unvaccinated cohorts of SLE patients.[87] The vaccine cohort had a lower hospitalization rate than the non-vaccine cohort, with an adjusted hazard ratio (aHR) of 0.82 (95% CI 0.73–0.92). The vaccine cohort was also less likely to be admitted to the intensive care unit [aHR 0.55 (95% CI 0.39–0.79)], to be hospitalized for sepsis, bacteremia, or viremia [aHR 0.48 (95% CI 0.32–0.73)], and had a lower risk of death [aHR 0.41 (95% CI 0.27–0.61)]. Immunogenicity studies in the SLE population have shown that as with other populations, antibody responses may depend on the influenza strain. A systematic literature review and meta-analysis of 17 studies in SLE patients showed that there was reduced immunogenicity against influenza A, while the immunogenicity against the B strain was preserved.[88] Another meta-analysis conducted in patients with SLE included 18 studies with 1966 subjects.[89] Compared with the general population, seroprotection rate in SLE patients was significantly decreased in patients for H1N1 [OR 0.36, 95% CI: 0.27–0.50] and H3N2 vaccination (OR 0.48, 95% CI: 0.24–0.93), but not influenza B vaccination (OR 0.55, 95% CI: 0.24–1.25). Subgroup analyses showed that SLE patients using immunosuppressive medications such as corticosteroids, azathioprine and prednisone have significantly lower seroprotection rates, compared with healthy controls. In this study,[89] there was no statistically significant difference in adverse event rates between those with SLE and healthy controls (OR 3.24 (95% CI: 0.62–16.76)).

There are anecdotal concerns that annual influenza vaccine may adversely impact disease activity especially in SLE. However, meta-analysis data have shown that influenza vaccine does not impact the SLE disease activity index.[88]

Persons with inflammatory diseases often receive biologic therapies that include inhibitors of tumour necrosis factor (TNFi) and rituximab. Commonly used TNFi are infliximab, etanercept, certolizumab, and adalimumab. In a meta-analysis of patients with rheumatoid arthritis (RA) receiving biologic therapies, influenza vaccine seroprotection was significantly lower compared to healthy controls for the H1N1 strain, but not for the H3N2 or B strains.[90] Similarly, in a meta-analysis of 9 studies of influenza vaccine in patients with inflammatory bowel disease (IBD), those receiving TNFi therapies (vs. those not on TNFi) had significantly lower seroprotection rates to inactive vaccines including influenza, pneumococcal, and hepatitis B (OR 0.32 (95%CI 0.21–0.49)).

Timing of vaccination

Timing of influenza vaccine was studied in a randomized trial of 137 subjects with inflammatory bowel disease IBD on maintenance infliximab therapy. Subjects were allocated to receive the 2012–13 IIV at the time of infliximab infusion (n = 69) or midway between infusions (n = 68).[91] Serologic protection to influenza vaccine was achieved in 43% to 79% of IBD patients depending on antigen. However, there were no differences in the seroprotection based on vaccine timing relative to infliximab infusion.

Vaccine dosing

Matsumoto et al. performed a study of one vs. two doses of IIV given 3 weeks apart to adult patients with inflammatory bowel disease who were treated with TNFi. No significant differences were noted in immunogenicity between the two groups.[92]

A monoclonal antibody that deserves specific mention is rituximab. This is a chimeric monoclonal antibody directed against the CD20 cell surface molecule located on B cells resulting in B cell depletion and thereby significantly reducing the humoral response to vaccination. To evaluate its effect in a recent study, twenty RA patients on methotrexate (MTX), 23 on Rituximab (RTX) and 28 healthy controls (HC) received trivalent influenza subunit vaccination.[93] All patients had strain-specific increases in antibody titer except for the rituximab group. However, those who had received Rituximab at least 6 months prior to vaccination, had restored IgG responses to vaccine. Although several studies have consistently shown low antibody responses in patients receiving rituximab, one study showed that cell-mediated responses may be preserved.[94–96] Despite the suboptimal vaccine immunogenicity in this group, vaccination should continue to be offered. In these patients, close clinical monitoring and early therapy for influenza infection may be warranted.

Summary

Immunocompromised persons such as those with transplantation, chemotherapy or biologic and nonbiologic therapies are at high risk of the complications of influenza. However, vaccine responses are suboptimal. Timing of vaccination is also important to consider to achieve protective titers. Healthcare workers who regularly work with immunocompromised patients may be a source of influenza transmission and should receive influenza vaccine.[97,98] In addition, close contacts of immunocompromised patients should also be vaccinated. Provider recommendation for vaccination is an important factor that enhances vaccine coverage.

Disclosure of potential conflicts of interest

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