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Influenza in Immunosuppressed Populations:

A Review of Infection Frequency, Morbidity, Mortality, and Vaccine Responses

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Abstract

Patients that are immunosuppressed might be at risk of serious influenza-associated complications. As a result, multiple guidelines recommend influenza vaccination for patients infected with HIV, who have received solid-organ transplants, who have received haemopoietic stem-cell transplants, and patients on haemodialysis. However, immunosuppression might also limit vaccine responses. To better inform policy, we reviewed the published work relevant to incidence, outcomes, and prevention of influenza infection in these patients, and in patients being treated chemotherapy and with systemic corticosteroids. Available data suggest that most immunosuppressed populations are indeed at higher risk of influenza-associated complications, have a general trend toward impaired humoral vaccine responses (although these data are mixed), and can be safely vaccinated—although longitudinal data are largely lacking. Randomised clinical trial data were limited to one study of HIV-infected patients with high vaccine efficacy. Better trial data would inform vaccination recommendations on the basis of efficacy and cost in these at-risk populations.

Introduction

The influenza virus is among the most common human respiratory viruses. In the USA, for example, influenza can result in the admission of over 225 000 patients to hospital[1] and 36 000 deaths every year.[2] High rates of influenza infection and complication rates are suggested to occur among people with impaired immune defences. Immunosuppression can result from many different biological mechanisms, ranging from rare congenital immunodeficiencies to more common causes such as immunosuppressive drugs or HIV infection.

Despite prevailing concerns about the risk of influenza infection in patients with immunosuppression, the actual rate and effect of infection in this population are not well characterised. Whether people that are immunocompromised would be even more susceptible

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Contributors

KMK was the primary author of the paper and extracted the data from the search of published work. KMK and ENJ both contributed to the search of published work. ENJ contributed primary writing and critical revisions to the manuscript.

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to new viruses, such as the recent swine-origin influenza A H1N1 strain,[3] without the benefit of previous exposure, is an area for investigation. Moreover, although influenza vaccination is widely recommended for people that are immunosuppressed, the same immune dysfunction that can increase the risk and consequences of influenza infection might also compromise vaccine responses and effectiveness. These distinctions are particularly important in settings of vaccine shortages or in response to a new pandemic, where selective and prioritised allocation of vaccine is necessary. To better inform influenza vaccination policies for immunocompromised populations, we reviewed the published work relevant to influenza infection and vaccination in patients with HIV infection, recipients of solid-organ transplants (SOTs), recipients of haemopoietic stem-cell transplants (HSCTs), patients receiving chemotherapy, patients on chronic haemodialysis, and patients receiving corticosteroids. These conditions affect about 3 million people in the USA (about 1% of the total US population), and the worldwide HIV epidemic affects about 33 million people (table 1).

The primary purpose of this Review is to identify and summarise the incidence and mortality rates of influenza infection among adults who are immunocompromised, as well as the risks of vaccination, the ability of vaccine to elicit appropriate immune responses, and the clinical effectiveness of vaccination in these populations. We also summarise guidelines on influenza vaccination of these populations, limitations of the available data, and alternative approaches to influenza control.

HIV/AIDS

An estimated 1·3 million (480 000 to 1·9 million) people are living with HIV/AIDS in North America. Worldwide, the epidemic affects an estimated 33·2 million (30·6 million to 36·1 million) people.[4] Influenza is a common cause of respiratory illness in adults with HIV.[10] Because both antibodies and T cells play a crucial part in viral immune responses, patients infected with HIV might be expected have severe and prolonged influenza infections, as reported in several early case series and anecdotal reports.[11-14]

Two large studies done before the widespread use of highly active antiretroviral therapy (HAART) confirmed high numbers of hospital admissions and mortality from influenza in patients with HIV/AIDS (table 2).[15,16] A study analysing data from an administrative database[17] showed that cardiopulmonary hospitalisation rates of patients with HIV/AIDS decreased by 53% during the HAART era. However, the reported hospitalisation rate still exceeded that of the general US population, and was similar to that of other high-risk populations for whom the US Centers for Disease Control (CDC) recommends influenza vaccination.[18] Although HAART seems to reduce the number of patients with HIV/AIDS treated for influenza in hospital, much of the world's population living with HIV/AIDS are in resource-limited areas such as sub-Saharan Africa, where antiretroviral drugs are available to less than 10% of those in need of treatment.[19]

Yearly influenza vaccination for adults infected with HIV is recommended by the CDC and the Infectious Disease Society of America,[18,20,21] although this recommendation has not received universal support. Initial concerns that immunisation enhances HIV replication by vaccine-induced CD4+ T cell activation[22] have been supported by some,[23-30] but not all,[31-38] studies. Moreover, rises in plasma HIV RNA that occur do so only transiently and then return to baseline over several weeks, typically without associated changes in CD4+ T cell counts, time to AIDS, or death over 8 years of follow-up in one retrospective analysis.[39] No prospective studies have looked at the long-term effect of influenza vaccination on disease progression or the effect of annual vaccination over multiple years.

Although influenza vaccination of patients with HIV/AIDS seems to be safe, the T-cell dysfunction caused by HIV might be expected to diminish the immune response to influenza

vaccination. Indeed, multiple studies have shown lower antibody responses in patients infected with HIV compared with the uninfected people in the control group,[23,35,36,40-44] although responses in one study were similar.[33] The prediction that patients with low CD4+ counts or with a diagnosis of AIDS would have the most limited antibody responses to immunisation is supported by several studies,[32,41,43,45] but not all reports (figure).[35,36,44] Most of these studies are limited by small sample sizes, particularly for patients with very low CD4+ counts; the five studies reporting responses in patients with CD4+ counts of less than 200 CD4+ T cells per μL included only 55 patients. Two recent HAART-era studies showed vaccine response to be related to HIV RNA levels rather than CD4+ counts.[55,56]

Clinical protection from disease (immunity), rather than antibody response, is the ideal outcome for vaccine studies. An outbreak investigation at a residential facility for people with AIDS, found fewer and less severe influenza cases in people previously vaccinated than in those not vaccinated.[57] Two prospective, but nonrandomised, studies identified substantially fewer episodes of laboratory-confirmed influenza in vaccinated patients with HIV (6·1%) than in unvaccinated patients (21·2%),[56] and a lower frequency of influenza in patients who were simultaneously vaccinated for influenza and pneumococcus than in those who declined vaccination.[58] The only randomised, double-blind, placebo-controlled study showed a 20% absolute reduction in risk of respiratory symptoms (from 49% to 29%, p=0·04) and 100% protection (95% CI 73-100%) against laboratory-confirmed symptomatic influenza (p<0·001) among patients infected with HIV receiving influenza vaccine compared with those receiving placebo.[33] Two systematic reviews identifying the same four clinical outcome studies cited above, conclude that influenza vaccination of adults infected with HIV might be effective despite variable antibody responses.[59,60] Both reviews highlight the limited data available and the need for more and larger randomised trials (only one has been done to date) to confirm how effective and safe vaccination is in this large population of patients, particularly among those with very low CD4+ counts.

Solid-organ transplantation

Patients receiving SOTs are treated with immunosuppressive drugs that alter multiple immune mechanisms.[61] Therefore, those patients might have more severe influenza infections and compromised responses to vaccination. As of the end of 2004, 153 245 people in the USA were living with a functioning transplanted solid organ.[5] Over 27 000 transplantations are done every year in the USA, nearly 90% of which are kidney, liver, and heart procedures.[5]

A retrospective review of patients that received organ transplants admitted to hospital with influenza between 1990 and 2000 reported high numbers of patients who received lung transplants compared with patients that received liver and renal transplants (table 2).[62] These increased rates might be because of either increased surveillance of recipients of lung transplants, decreased secretory antibodies in the allograft lung, epithelial injury, or impaired lymphatic drainage of the allograft lung—the primary site of influenza infections. Other studies in recipients of lung transplants with acute viral respiratory symptoms have identified influenza in 3%,[63] 16%,[64] and 48%[65] of viral illnesses during times when influenza is circulating in the community.

Prevention of influenza infection in recipients of SOTs is a crucial issue. Influenza infection has been reported to cause acute kidney allograft rejection,[66-68] and both acute[62,69] and chronic lung allograft rejection.[69-71] Despite these potentially devastating consequences of infection in recipients of SOTs, influenza vaccination in this population could stimulate a T-cell response, thus leading to organ rejection. Multiple studies of kidney[72-80] and heart[47,81-85] transplantation have not linked allograft rejection to influenza vaccination. However, all studies were underpowered to derive firm conclusions on safety.

The effectiveness of influenza vaccination of recipients SOTs is also widely debated. Despite some evidence for comparable influenza vaccine responses in recipients of kidney[72,80,86,87] and liver[88] transplants and control individuals, most published data suggest that antibody responses are diminished in recipients of SOTs, whether the transplanted organ is a kidney,[48,73,75,76,78,79,89,90] liver,[91-93] heart,[47,83,92,94] or lung[46,95] (figure). The particular immunosuppressive regimen might contribute to the size of any impairment. Azathioprine, for example, might have less effect on serological responses than mycophenolate mofetil[46,76,86] or ciclosporin.[77,90] Indeed, mycophenolate mofetil use has been associated with lower serological response rates compared with other immunosuppressive drugs.[55,72] Data that recipients of SOTs treated with sirolimus and those treated with a calcineurin inhibitor (tacrolimus or ciclosporin) had similar serological responses to each other[96] might have been underpowered (n=32 patients) to detect substantial differences. Despite their lower overall response rates to influenza vaccination, many recipients of SOTs do mount an appropriate immune response. Evidence of the clinical effectiveness of immunisation is lacking for recipients of SOTs.

The American Society of Transplantation recommends influenza vaccination every year for all recipients of SOTs, beginning about 6 months after transplantation.[97] 6 months was chosen because immunosuppressive protocols generally have been tapered substantially by that time and a recent study showed lower antibody titres in recipients of kidney transplants vaccinated within 6 months of transplantation.[48] Despite these recommendations, among 1800 recipients of SOTs transplanted between 1995-2005, nearly half were unvaccinated.[98]

Bone-marrow transplantation

An estimated 35 000 people receive autologous (reimplanted from the same person) and 20 000 allogeneic (from a genetically similar donor) HSCTs every year worldwide.[7] Preparation for stem-cell infusion generally requires high doses of chemotherapy, radiation, or both to prevent allograft rejection from residual host immune cells, destroy any residual malignant cells in patients receiving HSCTs for malignancies, and provide marrow space for donor stem-cell engraftment. These intensive pretransplantation regimens leave patients acutely and profoundly immunocompromised for up to several months after transplantation. Additional complications, such as delayed engraftment and graft-versus-host disease (GVHD), can predispose these patients to more prolonged immune dysfunction.

The frequency of influenza among recipients of HSCTs is quite low (range of 0·2-2·8%; table 3).[100-105] However, among patients with respiratory symptoms during a local epidemic, influenza frequency is as high as 23-29%.[104,105] Individual reports have suggested an increased frequency of influenza illness among recipients of allogeneic HSCTs compared with recipients of autologous HSCTs.[101,102] However, the largest analysis so far—a 12-year, single-centre, retrospective analysis of 4797 patients—found no association between donor type and risk of influenza within the first 120 days after transplantation.[103] In this same analysis, the presence of GVHD was not associated with increased risk of influenza infection. Additionally, influenza might have devastating consequences in recipients of HSCTs. The largest report (37 European centres, three influenza seasons, over 1900 patients) cited a case fatality rate of 23% (table 3).[101]

Very few controlled studies of influenza vaccination in recipients of HSCTs have been done, making vaccine responses and efficacy difficult to establish. One study found overall poor serological responses to influenza vaccine: from 0% in nine recipients of allogeneic transplants to 32% in 41 recipients of autologous transplants.[109] The difference in serological response rates by donor type was not statistically significant in this small study. Another study similarly showed blunted responses to influenza vaccine for recipients of HSCTs compared with healthy

controls (29-34% vs. 46-62%, respectively),[110] but again, small sample sizes limited statistical power. Addition of granulocyte-macrophage colony-stimulating factor to the vaccination regimen did not improve serological responses.

In addition to regimen, appropriate timing might be important for the immunogenicity of influenza vaccination after giving HSCTs. One series showed that vaccination within the first 6 months resulted in a complete lack of serological response in all ten patients.[111] For vaccination within 7-24 months after receipt of HSCT, the response rate was 13% and reached 64-71% for vaccination 2 years after the procedure.

We found only one retrospective report of the clinical effectiveness of influenza vaccination in recipients of HSCTs.[112] Among patients with respiratory symptoms who received a nasal wash or aspirate, 134 people were unvaccinated (because of being less than 6 months from transplantation), and 25 of them (19%) developed influenza. Among the 43 patients who were beyond 6 months from transplantation, influenza was diagnosed in 50% of the 24 unvaccinated patients (because of non-compliance with the programme), but only 11% of the 19 vaccinated patients. No prospective or randomised studies have been done to confirm or quantify vaccine efficacy in this population at high risk for adverse outcomes with influenza.

The CDC, Infectious Disease Society of America, and American Society of Blood and Marrow Transplantation have jointly published guidelines for influenza vaccination of recipients of HSCTs,[113] as has the European Group for Blood and Marrow Transplantation.[114] Both sets of guidelines support influenza vaccination beginning around 6 months after transplantation, but they differ in the recommended periodicity of immunisation (lifelong in the US guidelines vs. individually assessed duration in the European guidelines). Unfortunately, no data exist to help resolve this difference, since most studies have only investigated the effect of a single dose given in one influenza season. No study has looked at the long-term risks or benefits of annual influenza vaccination in this immunosuppressed population.

Malignancies and chemotherapy

Some 1·4 million patients will be diagnosed with new haematological and invasive solid-organ cancers in the USA in 2009,[8] many of whom will require treatment with chemotherapy. Similar to preparation for HSCT, chemotherapy can produce acute and profound immunosuppression, although the degree differs depending on the chemotherapy drugs, doses, and total duration of therapy. An estimated number of patients receiving chemotherapy every year is not available.

Information about influenza frequency among adults receiving chemotherapy is quite limited. Among patients with cancer admitted to hospital with respiratory symptoms during times of a circulating influenza epidemic, 21-33% might test positive for influenza.[108,106] Similar to results in recipients of HSCTs, influenza mortality is very high among patients with cancer. Four different studies reported case fatalities of 11%, 25%, 27%, and 33% (table 3).[99,107,108] The available data are too limited to distinguish frequency and mortality differences among patients with different malignancies and different chemotherapeutic regimens.

As in the HSCT population, humoral responses to influenza vaccination seem rarer among adults undergoing chemotherapy for cancer compared with the general population (figure).[49,50,115-117] Vaccine responses were similar between nine patients with breast cancer and 19 healthy women, although the small size of this study means the results cannot be generalised.[118] Serological responses among patients with solid tumours can exceed those among patients with haematological malignancies,[51,115] but not in all studies.[119] Each of these studies had small sample sizes. Patients with lymphoma, in particular, seem to have some of the poorest humoral responses.[115,120-122] Vaccine efficacy trials with clinical infections as an outcome are lacking.

Timing of vaccination in relation to chemotherapy might be an important determinant of response. Humoral responses might be enhanced when influenza vaccination is given between chemotherapy cycles (where the blood count is lowest) rather than concurrent with chemotherapy dosing (93% vs. 50% with four-fold rise in titre to H1N1, respectively).[119] Similarly, poor vaccine response might be related to receiving chemotherapy within 7 days before to vaccination.[123] No unique adverse events have been identified for influenza vaccination among patients with malignancies.

No consensus guidelines on influenza immunisation for patients with malignancies exist. Two review articles[124,125] recommended vaccination every year timed to occur either more than 2 weeks before receiving chemotherapy or between chemotherapy cycles.

Haemodialysis

By the end of 2006, 327 754 people were on chronic haemodialysis in the USA, with projected increases in prevalence.[6] The complex and multifactorial causes of immune dysfunction in patients on haemodialysis include defects in complement activation, neutrophil function, and B-cell and T-cell function.[126-128] Infections are the second leading cause of death in patients receiving dialysis.[6] Compared with the general population, pulmonary infection kills more patients on dialysis[129] and mortality rates from sepsis are higher.[130] However, we were unable to find any data on the specific frequencies of influenza infections and influenza-specific mortality rates in this population.

The frequency and magnitude of humoral responses to influenza vaccine among patients on dialysis can be similar to[131-136] or lower than those among people in control groups (figure).[52-54,73,137-139] Despite potentially impaired antibody responses, a 2-year analysis of US Medicare claims data found that vaccinated patients on dialysis had a substantially lower chance of any-cause hospital admission and any-cause death than unvaccinated patients on dialysis.[140] This finding might indicate clinical effectiveness of vaccinating this population, but its observational design might also reflect differences in the underlying clinical status among patients vaccinated and unvaccinated. No unique adverse events related to influenza vaccine have been identified in patients on dialysis.

The CDC and authors of other reviews all recommend influenza vaccination every year for patients on haemodialysis.[18,141,142] However, only about 60% of US patients on haemodialysis were vaccinated in 2006.[6] Many patients with end-stage renal disease also eventually undergo renal transplantation. As previously discussed, acute kidney allograft rejection can result from influenza infection.[66-68] Thus, patients on dialysis awaiting transplantation should be vaccinated to limit the risk of an influenza episode after transplantation.

Systemic corticosteroids

Many patients use systemic corticosteroids to treat a wide variety of disorders, particularly inflammatory and autoimmune disorders such as asthma, rheumatoid arthritis, and inflammatory bowel disease. Some patients receive corticosteroids for short periods, whereas others remain on chronic therapy. The prevalence of corticosteroid use is not well known. Of the total British adult population, an estimated 0·9% (or about 409 000 adult Britons) are using oral corticosteroids at any given time, with an estimated 93 000 adults using more than 7·5 mg of prednisone daily for more than 6 months.[9] Corticosteroid use at any time was described in 2·2-9·2% of 42 500 participants in seven large cohort studies (age 55-80 years), with current use in 2-3% of participants in three of those cohorts.[143]

Corticosteroids alter immune function through direct effects on gene transcription and have broad effects on non-lymphoid and lymphoid cells.[144] Corticosteroid use predisposes patients

to infections, particularly with doses higher than 10 mg/day and cumulative doses higher than 700 mg,[145] but the additional risk specific for influenza posed by either chronic or short-term corticosteroid use has not been established.

Few influenza vaccination studies have been done on patients treated with corticosteroids. Four of nine studies of influenza vaccination in adult patients with rheumatoid arthritis and systemic lupus erythematosus, diseases frequently treated with systemic corticosteroids, showed impaired immune responses in patients with these rheumatological diseases compared with healthy controls,[146-149] whereas five studies found no such differences.[150-154] The power to detect small differences was limited by small sample sizes. Corticosteroids were often given in combination with other immune-modulating drugs, so the interpretation of isolated corticosteroid effects on immune response is limited. These studies also suggested that influenza vaccination does not induce a flare of the underlying rheumatological condition, though small sample sizes and limited follow-up restrict the ability to make firm conclusions on long-term safety.

Among patients with chronic lung disease, antibody responses to influenza vaccine were equivalent among 25 patients treated with corticosteroids and 14 who were not.[155] Similarly, humoral responses were independent of inhaled corticosteroid use (even high-dose inhaled corticosteroid use) in one study of 294 patients with asthma receiving influenza vaccine[156] and another of 162 patients with chronic obstructive pulmonary disease taking inhaled steroids (87 patients), oral steroids (33), and no steroids (42).[157]

Evidence suggests that for patients taking corticosteroids—either oral or inhaled, and either chronically or for a transient period—influenza vaccination is both safe and often serologically immunogenic, but the vaccine's clinical effectiveness in this population has not been well tested.

Limitations and challenges

Among all immunosuppressive conditions discussed, very few data exist on the prevention of clinical influenza infection by vaccination. Most studies have focused on the surrogate outcome of humoral antibody responses. However, a positive humoral response can be defined in multiple ways, most commonly a haemagglutination inhibition titre of 1:40 or greater, or a four-fold or greater rise in titres after vaccination. The limitations of these definitions become apparent, for example, in a patient who has a prevaccination titre of 1:20 that rises to 1:40. This hypothetical patient would be counted as a positive response by use of the 1:40 titre or greater criterion, but as a negative response with the four-fold rise criterion. Additionally, standard influenza vaccination includes antigens for three strains of influenza virus (H1N1, H3N2, and B). Thus, one must not only select a titre criterion, but also decide if a positive vaccine response should require titre response to one, two, or all three strains. Annual reformulation of vaccine also results in differing antigenicity of each year's vaccine, making comparisons across studies difficult. Additionally, in some years, strains can remain unchanged from previous years. Thus, a study participant who had been vaccinated against the same strain the previous year might have a different response than a participant naive to that strain. For all these reasons, interpretation of influenza vaccine studies using humoral outcomes is challenging.

Cell-mediated immunity might also play an important part in the heightened risk of infection in the immunosuppressed populations we have reviewed. The small number of studies of cellular responses to influenza vaccination, in relatively small numbers of immunosuppressed individuals, showed impaired cellular responses among six patients[158] and 14 patients[159] after receipt of HSCTs, intact cellular responses in 65 kidney transplant recipients,[160] and impaired[161] and intact[162] cellular responses among lung transplant recipients. The latter study cited yearly variation in vaccine strain as one possible contributor to the discrepancy between

study results in similar populations.[162] Cellular immunity remains an important area for investigation, but the responses remain a surrogate outcome without clear correlations with clinical outcomes.

The best possible studies are those based on clinical outcome, but such studies with influenza vaccination in immunosuppressed individuals face substantial challenges. Unlike research on other common vaccinations (such as hepatitis B or *Streptococcus pneumoniae)*, influenza vaccination research is faced with unpredictable yearly variation in circulating strains of virus. For example, if a study was done in a year when the circulating strain was not in that year's vaccine, one would expect little protective effect from the vaccine, and one would likely discount any such study as flawed by factors outside of investigators' control. Achieving adequate statistical power might also be difficult when studying the clinical effects of influenza vaccination in immunosuppressed individuals. Because most single centres lack large numbers of these patients, multicentre studies might be needed. Nevertheless, the one randomised, double-blind, controlled trial in patients with HIV showed a reduction in clinical respiratory illness, such that the result was significant with only 102 patients in the study.[33] Allocation concealment (ie, adequacy of blinding) might also be difficult when comparing placebo vaccination with influenza vaccination, which might be associated with local reactions.[18] Placebo-controlled studies might also raise ethical concerns, given the large number of professional societies recommending influenza vaccination for these patients. An alternative approach would be to compare standard vaccines with newer vaccines or antiviral drugs.

We found little evidence of harm from influenza vaccination, but most studies were small and with limited follow-up. These studies had limited power to detect rare (but potentially serious) adverse events. In addition, we found almost no data on the effects of ongoing annual vaccination that most professional societies recommend (table 4).

Other options to control influenza infection

The priority for control of influenza is focused on generating effective antibody responses with vaccines.[13] Progress is being made to increase the scale, duration, and breadth of vaccine responses to haemagglutinin and neuraminidase in healthy and immunocompromised populations.[163,164] Concerns that the cold-adapted live, attenuated vaccine would pose a risk to people that are immunocompromised have proven unfounded so far, but efficacy studies in adults that are immunocompromised have not been done. Driven in large part by concern about an impending influenza pandemic, areas of vaccine development include the use of standard and new adjuvants ranging from alum to toll-like receptor agonists, use of viral-like particles, other viral vectors, and DNA vaccines. Moreover, the role of more conserved antigens shared by many influenza strains, such as matrix proteins, nucleoproteins, and polymerases, might serve as targets for CD4+ and CD8+ cytototoxic T-cell responses to attenuate, if not prevent, infection and serious disease from diverse strains over time.

Chemoprophylaxis with antiviral drugs provides an immediate and immune-independent intervention to prevent seasonal influenza-related illness, as well as during family and institutional outbreaks, in both healthy and immunocompromised hosts. Indeed, chemoprophylaxis can be effective in controlling outbreaks among recipients of HSCTs.[165] Of equal or greater importance in this setting, are proactive and consistent infection control precautions in facilities and by employees, as proposed in ongoing plans for pandemic influenza.[166,167] Use of antiviral drugs might also help reduce mortality in patients that are immunocompromised, as suggested by an observational study of 19 recipients of HSCTs with influenza, of whom 87% received oseltamivir and none died.[168]

Conclusions

We encourage further clinical trials with relevant clinical outcome measures, as opposed to surrogate outcomes like vaccine-induced antibody titres. We would particularly welcome randomised trials comparing standard influenza vaccine with active comparators such as modified vaccines[55] or antiviral prophylaxis with or without vaccination. Such data would greatly enhance our ability to make more informed vaccination recommendations for this population, particularly in situations of vaccine shortage or pandemic influenza.

Search strategy and selection criteria

Relevant articles were identified by searches of Medline (1966-2009) with the medical subject heading terms “influenza, human”, “influenza A virus”, “influenza B virus”, or “influenza vaccines”, combined with the following associated disease terms: “HIV”, “HIV-1”, “dialysis”, “renal dialysis”, “organ transplantation”, “transplantation”, “bone marrow transplantation”, “neoplasms”, “glucocorticoids”, “adrenal cortex hormones”, “prednisone”, and “prednisolone”. Additional relevant articles were identified by cross-referencing citations from articles identified by the Medline searches. Articles selected for inclusion reported adult influenza frequency, complications, serological or clinical responses to vaccination, or recommendations and guidelines. Because live vaccines are not recommended for immunocompromised patients, we included only articles reporting outcomes related to inactivated vaccine. Only English-language reports were included.

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References

1. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the united states. JAMA 2004;292:1333–40. [PubMed: 15367555]
2. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179–86. [PubMed: 12517228]
3. Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Science 2009;324:1557–61. [PubMed: 19433588]
4. UNAIDS. AIDS epidemic update. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO); Geneva: [accessed July 1, 2009]. 2007 2007http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007/default.asp
5. Port FK, Merion RM, Finley MP, Goodrich NP, Wolfe RA. Trends in organ donation and transplantation in the United States, 1996-2005. Am J Transplant 2007;7:1319–26. [PubMed: 17428282]
6. US Renal Data System. USRDS 2008 Annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: [accessed July 1, 2008]. 2008 http://www.usrds.org/2008/view/default.asp
7. Center for International Blood and Marrow Transplant Research. Report on state of the art in blood and marrow transplantation. [accessed July 1, 2009]. http://www.cibmtr.org/SERVICES/Observational_Research/Summary_Slides/index.html

8. Horner, MJ.; Ries, LAG.; Krapcho, M. SEER cancer statistics review, 1975-2006. National Cancer Institute; Bethesda, MD: [accessed July 1, 2009]. 2009 at alhttp://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data
9. van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM 2000;93:105–11. [PubMed: 10700481]
10. Klein MB, Lu Y, DelBalso L, Cote S, Boivin G. Influenza virus infection is a primary cause of febrile respiratory illness in HIV infected adults, despite vaccination. Clin Infect Dis 2007;45:234–40. [PubMed: 17578785]
11. Cohen JP, Macauley C. Susceptibility to influenza A in HIV-positive patients. JAMA 1989;261:245. [PubMed: 2909018]
12. Thurn JR, Henry K. Influenza A pneumonitis in a patient infected with the human immunodeficiency virus (HIV). Chest 1989;95:807–10. [PubMed: 2647422]
13. Safrin S, Rush JD, Mills J. Influenza in patients with human immunodeficiency virus infection. Chest 1990;98:33–37. [PubMed: 2361409]
14. Radwan HM, Cheeseman SH, Lai KK, Ellison IR. Influenza in human immunodeficiency virus-infected patients during the 1997-1998 influenza season. Clin Infect Dis 2000;31:604–06. [PubMed: 10987729]
15. Neuzil KM, Reed GW, Mitchel EF Jr, Griffin MR. Influenza-associated morbidity and mortality in young and middle-aged women. JAMA 1999;281:901–07. [PubMed: 10078486]
16. Lin JC, Nichol KL. Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome. Arch Intern Med 2001;161:441–46. [PubMed: 11176770]
17. Neuzil KM, Coff ey CS, Mitchel EF Jr, Griffi n MR. Cardiopulmonary hospitalizations during influenza season in adults and adolescents with advanced HIV infection. J Acquir Immune Defic Syndr 2003;34:304–07. [PubMed: 14600576]
18. Fiore AE, Shay DK, Haber P, et al. Prevention and control of influenza: recommendations of the advisory committee on immunization practices (ACIP), 2007. MMWR Recomm Rep 2007;56:1–54. [PubMed: 17625497]
19. UNAIDS. Report on the global AIDS epidemic 2006: A UNAIDS 10th anniversary special edition. Joint United Nations Programme on HIV/AIDS (UNAIDS); Geneva: [accessed July 1, 2009]. 2006 http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2006/
20. Aberg JA, Gallant JE, Anderson J, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2004;39:609–29. [PubMed: 15356773]
21. Kaplan JE, Masur H, Holmes KK, et al. An overview of the 1999 US public health service/infectious diseases society of America guidelines for preventing opportunistic infections in human immunodeficiency virus-infected persons. Clin Infect Dis 2000;30(suppl 1):S15–28. [PubMed: 10770912]
22. Ho DD. HIV-1 viraemia and influenza. Lancet 1992;339:1549. [PubMed: 1351231]
23. Staprans SI, Hamilton BL, Follansbee SE, et al. Activation of virus replication after vaccination of HIV-1-infected individuals. J Exp Med 1995;182:1727–37. [PubMed: 7500017]
24. O'Brien WA, Grovit-Ferbas K, Namazi A, et al. Human immunodeficiency virus-type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. Blood 1995;86:1082–89. [PubMed: 7620162]
25. Rosok B, Voltersvik P, Bjerknes R, Axelsson M, Haaheim LR, Asjo B. Dynamics of HIV-1 replication following influenza vaccination of HIV+ individuals. Clin Exp Immunol 1996;104:203–07. [PubMed: 8625509]
26. Tasker SA, O'Brien WA, Treanor JJ, et al. Effects of influenza vaccination in HIV-infected adults: a double-blind, placebo-controlled trial. Vaccine 1998;16:1039–42. [PubMed: 9682356]
27. Gunthard HF, Wong JK, Spina CA, et al. Effect of influenza vaccination on viral replication and immune response in persons infected with human immunodeficiency virus receiving potent antiretroviral therapy. J Infect Dis 2000;181:522–31. [PubMed: 10669335]

28. Kolber MA, Gabr AH, De La Rosa A, et al. Genotypic analysis of plasma HIV-1 RNA after influenza vaccination of patients with previously undetectable viral loads. AIDS 2002;16:537–42. [PubMed: 11872996]
29. Fuller JD, Craven DE, Steger KA, Cox N, Heeren TC, Chernoff D. Influenza vaccination of human immunodeficiency virus (HIV)-infected adults: Impact on plasma levels of HIV type 1 RNA and determinants of antibody response. Clin Infect Dis 1999;28:541–47. [PubMed: 10194075]
30. Banic S, Koren S, Tomazic J, et al. Influenza vaccination of human immunodeficiency virus 1-infected patients receiving antiretroviral therapy. Acta Virol 2001;45:39–44. [PubMed: 11394576]
31. Glesby MJ, Hoover DR, Farzadegan H, Margolick JB, Saah AJ. The effect of influenza vaccination on human immunodeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. J Infect Dis 1996;174:1332–36. [PubMed: 8940228]
32. Fowke KR, D'Amico R, Chernoff DN, et al. Immunologic and virologic evaluation after influenza vaccination of HIV-1-infected patients. AIDS 1997;11:1013–21. [PubMed: 9223736]
33. Tasker SA, Treanor JJ, Paxton WB, Wallace MR. Efficacy of influenza vaccination in HIV-infected persons: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;131:430–33. [PubMed: 10498559]
34. Sullivan KM, Dykewicz CA, Longworth DL, et al. Preventing opportunistic infections after hematopoietic stem cell transplantation: The Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation practice guidelines and beyond. Hematology Am Soc Hematol Educ Program 2001:392–421. [PubMed: 11722995]
35. Amendola A, Boschini A, Colzani D, et al. Influenza vaccination of HIV-1-positive and HIV-1-negative former intravenous drug users. J Med Virol 2001;65:644–48. [PubMed: 11745926]
36. Zanetti AR, Amendola A, Besana S, Boschini A, Tanzi E. Safety and immunogenicity of influenza vaccination in individuals infected with HIV. Vaccine 2002;20(suppl 5):B29–32. [PubMed: 12477415]
37. Iorio AM, Francisci D, Camilloni B, et al. Antibody responses and HIV-1 viral load in HIV-1-seropositive subjects immunised with either the MF59-adjuvanted influenza vaccine or a conventional non-adjuvanted subunit vaccine during highly active antiretroviral therapy. Vaccine 2003;21:3629–37. [PubMed: 12922092]
38. Durando P, Fenoglio D, Boschini A, et al. Safety and immunogenicity of two influenza virus subunit vaccines, with or without MF59 adjuvant, administered to human immunodeficiency virus type 1-seropositive and seronegative adults. Clin Vaccine Immunol 2008;15:253–59. [PubMed: 18003811]
39. Sullivan PS, Hanson DL, Dworkin MS, Jones JL, Ward JW. Effect of influenza vaccination on disease progression among HIV-infected persons. AIDS 2000;14:2781–85. [PubMed: 11125897]
40. Ragni MV, Ruben FL, Winkelstein A, Spero JA, Bontempo FA, Lewis JH. Antibody responses to immunization of patients with hemophilia with and without evidence of human immunodeficiency virus (human T-lymphotropic virus type III) infection. J Lab Clin Med 1987;109:545–49. [PubMed: 3572201]
41. Nelson KE, Clements ML, Miotti P, Cohn S, Polk BF. The influence of human immunodeficiency virus (HIV) infection on antibody responses to influenza vaccines. Ann Intern Med 1988;109:383–88. [PubMed: 2970238]
42. Miotti PG, Nelson KE, Dallabetta GA, Farzadegan H, Margolick J, Clements ML. The infl uence of HIV infection on antibody responses to a two-dose regimen of influenza vaccine. JAMA 1989;262:779–83. [PubMed: 2787416]
43. Kroon FP, Rimmelzwaan GF, Roos MT, et al. Restored humoral immune response to influenza vaccination in HIV-infected adults treated with highly active antiretroviral therapy. AIDS 1998;12:F217–23. [PubMed: 9863863]
44. Brydak LB, Hryniewicz HJ, Machala M, Horban A. Humoral response to influenza vaccination in HIV-infected patients. Clin Drug Invest 1999;17:441–49.
45. Iorio AM, Alatri A, Francisci D, et al. Immunogenicity of influenza vaccine (1993-94 winter season) in HIV-seropositive and -seronegative ex-intravenous drug users. Vaccine 1997;15:97–102. [PubMed: 9041673]

46. Hayney MS, Welter DL, Francois M, Reynolds AM, Love RB. Influenza vaccine antibody responses in lung transplant recipients. Prog Transplant 2004;14:346–51. [PubMed: 15663020]
47. Dengler TJ, Strnad N, Buhring I, et al. Differential immune response to influenza and pneumococcal vaccination in immunosuppressed patients after heart transplantation. Transplantation 1998;66:1340–47. [PubMed: 9846520]
48. Birdwell KA, Ikizler MR, Sannella EC, et al. Decreased antibody response to influenza vaccination in kidney transplant recipients: a prospective cohort study. Am J Kidney Dis 2009;54:112–21. [PubMed: 19185404]
49. Feery BJ, Sullivan JR, Hurley TH, Evered MG. Immunization with influenza vaccine in patients with haematological malignant disease. Med J Aust 1977;1:292–94. [PubMed: 859489]
50. Gribabis DA, Panayiotidis P, V B, Hannoun C, Pangalis GA. Influenza virus vaccine in B-cell chronic lymphocytic leukaemia patients. Acta Haematol 1994;91:115–18. [PubMed: 8091931]
51. Stiver HG, Weinerman BH. Impaired serum antibody response to inactivated influenza A and B vaccine in cancer patients. Can Med Assoc J 1978;119:733–35. [PubMed: 709474]
52. Beyer WE, Versluis DJ, Kramer P, Diderich PP, Weimar W, Masurel N. Trivalent influenza vaccine in patients on haemodialysis: impaired seroresponse with differences for A-H3N2 and A-H1N1 vaccine components. Vaccine 1987;5:43–48. [PubMed: 3577356]
53. Rautenberg P, Teifke I, Schlegelberger T, Ullmann U. Influenza subtype-specific IgA, IgM and IgG responses in patients on hemodialysis after influenza vaccination. Infection 1988;16:323–28. [PubMed: 3065242]
54. Antonen JA, Hannula PM, Pyhala R, Saha HH, Ala-Houhala IO. Pasternack AI. Adequate seroresponse to influenza vaccination in dialysis patients. Nephron 2000;86:56–61. [PubMed: 10971154]
55. Evison J, Farese S, Seitz M, Uehlinger D, Furrer H, Mühlemann K. Randomized, double-blind comparative trial of subunit and virosomal influenza vaccines for immunocompromised patients. Clin Infect Dis 2009;48:1402–12. [PubMed: 19361304]
56. Yamanaka H, Teruya K, Tanaka M, et al. Efficacy and immunologic responses to influenza vaccine in HIV-1-infected patients. J Acquir Immune Defi c Syndr 2005;39:167–73.
57. Fine AD, Bridges CB, De Guzman AM, et al. Influenza A among patients with human immunodeficiency virus: an outbreak of infection at a residential facility in New York City. *Clin Infect Di*s 2001;32:1784–91. [PubMed: 11360221]
58. Ranieri R, Veronelli A, Santambrogio C, Pontiroli AE. Impact of influenza vaccine on response to vaccination with pneumococcal vaccine in HIV patients. *AIDS Res Hum Retroviruse*s 2005;21:407–09. [PubMed: 15929703]
59. Atashili J, Kalilani L, Adimora AA. Efficacy and clinical effectiveness of influenza vaccines in HIV-infected individuals: a meta-analysis. *BMC Infect Di*s 2006;6:138. [PubMed: 16965629]
60. Anema A, Mills E, Montaner J, Brownstein JS, Cooper C. Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis. HIV Med 2008;9:57–61. [PubMed: 18199173]
61. Gangappa S, Kokko KE, Carlson LM, et al. Immune responsiveness and protective immunity after transplantation. Transpl Int 2008;21:293–303. [PubMed: 18225995]
62. Vilchez RA, McCurry K, Dauber J, et al. Influenza virus infection in adult solid organ transplant recipients. Am J Transplant 2002;2:287–91. [PubMed: 12096793]
63. Gottlieb J, Schulz TF, Welte T, et al. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. Transplantation 2009;87:1530–37. [PubMed: 19461490]
64. Hopkins P, McNeil K, Kermeen F, et al. Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. Am J Respir Crit Care Med 2008;178:876–81. [PubMed: 18658110]
65. Weinberg A, Zamora MR, Li S, Torres F, Hodges TN. The value of polymerase chain reaction for the diagnosis of viral respiratory tract infections in lung transplant recipients. J Clin Virol 2002;25:171–75. [PubMed: 12367651]

66. Keane WR, Helderman JH, Luby J, Gailiunas P, Hull AR, Kokko JP. Epidemic renal transplant rejection associated with influenza A victoria. Proc Clin Dial Transplant Forum 1978;8:232–36. [PubMed: 386316]

67. Gabriel R, Selwyn S, Brown D, et al. Virus infections and acute renal transplant rejection. Nephron 1976;16:282–86. [PubMed: 175308]

68. Briggs JD, Timbury MC, Paton AM, Bell PR. Viral infection and renal transplant rejection. BMJ 1972;4:520–22. [PubMed: 4566016]

69. Khalifah AP, Hachem RR, Chakinala MM, et al. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med 2004;170:181–87. [PubMed: 15130908]

70. Billings JL, Hertz MI, Savik K, Wendt CH. Respiratory viruses and chronic rejection in lung transplant recipients. J Heart Lung Transplant 2002;21:559–66. [PubMed: 11983546]

71. Garantziotis S, Howell DN, McAdams HP, Davis RD, Henshaw NG, Palmer SM. Influenza pneumonia in lung transplant recipients: clinical features and association with bronchiolitis obliterans syndrome. Chest 2001;119:1277–80. [PubMed: 11296201]

72. Scharpe J, Evenepoel P, Maes B, et al. Influenza vaccination is efficacious and safe in renal transplant recipients. Am J Transplant 2008;8:332–37. [PubMed: 18162092]

73. Cavdar C, Sayan M, Sifi l A, et al. The comparison of antibody response to influenza vaccination in continuous ambulatory peritoneal dialysis, hemodialysis and renal transplantation patients. Scand J Urol Nephrol 2003;37:71–76. [PubMed: 12745749]

74. Wyzgal J, Brydak LB, Zygier D, Paczek L, Rowinski W, Grochowiecki T. Study on efficacy of influenza vaccination in renal allograft recipients. Transplant Proc 2002;34:572–75. [PubMed: 12009628]

75. Sanchez-Fructuoso AI, Prats D, Naranjo P, et al. Influenza virus immunization effectivity in kidney transplant patients subjected to two different triple-drug therapy immunosuppression protocols: mycophenolate versus azathioprine. Transplantation 2000;69:436–39. [PubMed: 10706057]

76. Smith KG, Isbel NM, Catton MG, Leydon JA, Becker GJ, Walker RG. Suppression of the humoral immune response by mycophenolate mofetil. Nephrol Dial Transplant 1998;13:160–64. [PubMed: 9481733]

77. Versluis DJ, Beyer WE, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. Transplantation 1986;42:376–79. [PubMed: 3532450]

78. Kumar SS, Ventura AK, VanderWerf B. Influenza vaccination in renal transplant recipients. JAMA 1978;239:840–42. [PubMed: 342736]

79. Stiver HG, Graves P, Meiklejohn G, Schroter G, Eickhoff TC. Impaired serum antibody response to inactivated influenza A and B vaccine in renal transplant recipients. Infect Immun 1977;16:738–41. [PubMed: 330394]

80. Carroll RN, Marsh SD, O'Donoghue EP, Breeze DC, Shackman R. Response to influenza vaccine by renal transplant patients. BMJ 1974;2:701–03. [PubMed: 4605057]

81. Fraund S, Wagner D, Pethig K, Drescher J, Girgsdies OE, Haverich A. Influenza vaccination in heart transplant recipients. J Heart Lung Transplant 1999;18:220–25. [PubMed: 10328147]

82. Kimball P, Verbeke S, Flattery M, Rhodes C, Tolman D. Influenza vaccination does not promote cellular or humoral activation among heart transplant recipients. Transplantation 2000;69:2449–51. [PubMed: 10868658]

83. Kimball P, Verbeke S, Tolman D. Influenza vaccination among heart transplant recipients. Transplant Proc 2001;33:1785–86. [PubMed: 11267511]

84. Kobashigawa JA, Warner-Stevenson L, Johnson BL, et al. Influenza vaccine does not cause rejection after cardiac transplantation. Transplant Proc 1993;25:2738–39. [PubMed: 8356730]

85. Magnani G, Falchetti E, Pollini G, et al. Safety and efficacy of two types of influenza vaccination in heart transplant recipients: A prospective randomised controlled study. J Heart Lung Transplant 2005;24:588–92. [PubMed: 15896757]

86. Keshtkar-Jahromi M, Argani H, Rahnavardi M, et al. Antibody response to influenza immunization in kidney transplant recipients receiving either azathioprine or mycophenolate: a controlled trial. Am J Nephrol 2008;28:654–60. [PubMed: 18322360]

87. Briggs WA, Rozek RJ, Migdal SD, et al. Influenza vaccination in kidney transplant recipients: cellular and humoral immune responses. Ann Intern Med 1980;92:471–77. [PubMed: 6987929]

88. Burbach G, Bienzle U, Stark K, et al. Influenza vaccination in liver transplant recipients. Transplantation 1999;67:753–55. [PubMed: 10096534]

89. Versluis DJ, Beyer WE, Masurel N, Weimar W. Influenza vaccination in dialysis and transplant patients. Antiviral Res 1985;(suppl 1):289–92. [PubMed: 3909959]

90. Huang KL, Armstrong JA, Ho M. Antibody response after influenza immunization in renal transplant patients receiving cyclosporin A or azathioprine. Infect Immun 1983;40:421–24. [PubMed: 6339408]

91. Soesman NM, Rimmelzwaan GF, Nieuwkoop NJ, et al. Efficacy of influenza vaccination in adult liver transplant recipients. J Med Virol 2000;61:85–93. [PubMed: 10745238]

92. Blumberg EA, Albano C, Pruett T, et al. The immunogenicity of influenza virus vaccine in solid organ transplant recipients. Clin Infect Dis 1996;22:295–302. [PubMed: 8838186]

93. Duchini A, Hendry RM, Nyberg LM, Viernes ME, Pockros PJ. Immune response to influenza vaccine in adult liver transplant recipients. Liver Transpl 2001;7:311–13. [PubMed: 11303290]

94. Admon D, Engelhard D, Strauss N, Goldman N, Zakay-Rones Z. Antibody response to influenza immunization in patients after heart transplantation. Vaccine 1997;15:1518–22. [PubMed: 9330462]

95. Mazzone PJ, Mossad SB, Mawhorter SD, Mehta AC, Schilz RJ, Maurer JR. The humoral immune response to influenza vaccination in lung transplant patients. Eur Respir J 2001;18:971–76. [PubMed: 11829104]

96. Willcocks LC, Chaudhry AN, Smith JC, et al. The effect of sirolimus therapy on vaccine responses in transplant recipients. Am J Transplantation 2007;7:2006–11.

97. American Society of Transplantation. Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant 2004;4(suppl 10):160–63.

98. Harris K, Baggs J, Davis RL, et al. Influenza vaccination coverage among adult solid organ transplant recipients at three health maintenance organizations, 1995-2005. *Vaccin*e 2009;27:2335–41. [PubMed: 19428848]

99. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. Am J Med 1997;102:2–9. [PubMed: 10868136]

100. Ljungman P. Respiratory virus infections in bone marrow transplant recipients: The European perspective. Am J Med 1997;102:44–47. [PubMed: 10868142]

101. Ljungman P. Respiratory virus infections in stem cell transplant patients: the European experience. Biol Blood Marrow Transplant 2001;7(suppl):5S–7S. [PubMed: 11777102]

102. Hassan IA, Chopra R, Swindell R, Mutton KJ. Respiratory viral infections after bone marrow/peripheral stem-cell transplantation: The Christie Hospital experience. Bone Marrow Transplant 2003;32:73–77. [PubMed: 12815481]

103. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 2004;39:1300–06. [PubMed: 15494906]

104. Machado CM, Boas LS, Mendes AV, et al. Low mortality rates related to respiratory virus infections after bone marrow transplantation. Bone Marrow Transplant 2003;31:695–700. [PubMed: 12692610]

105. Whimbey E, Elting LS, Couch RB, et al. Influenza A virus infections among hospitalized adult bone marrow transplant recipients. Bone Marrow Transplant 1994;13:437–40. [PubMed: 8019468]

106. Yousuf HM, Englund J, Couch R, et al. Influenza among hospitalized adults with leukemia. *Clin Infect Di*s 1997;24:1095–99. [PubMed: 9195063]

107. Schepetiuk S, Papanaoum K, Qiao M. Spread of influenza A virus infection in hospitalised patients with cancer. Aust N Z J Med 1998;28:475–76. [PubMed: 9777122]

108. Elting LS, Whimbey E, Lo W, Couch R, Andreeff M, Bodey GP. Epidemiology of influenza A virus infection in patients with acute or chronic leukemia. Support Care Cancer 1995;3:198–202. [PubMed: 7655781]

109. Gandhi MK, Egner W, Sizer L, et al. Antibody responses to vaccinations given within the fi rst two years after transplant are similar between autologous peripheral blood stem cell and bone marrow transplant recipients. Bone Marrow Transplant 2001;28:775–81. [PubMed: 11781630]

110. Pauksen K, Linde A, V H, et al. Granulocyte-macrophage colony stimulating factor as immunomodulating factor together with influenza vaccination in stem cell transplant patients. Clin Infect Dis 2000;30:342–48. [PubMed: 10671339]
111. Engelhard D, Nagler A, Hardan I, et al. Antibody response to a two-dose regimen of influenza vaccine in allogeneic T cell depleted and autologous BMT recipients. Bone Marrow Transplant 1993;11:1–5. [PubMed: 8431706]
112. Machado CM, Cardoso MR, da Rocha IF, Boas LS, Dulley FL, Pannuti CS. The benefi t of influenza vaccination after bone marrow transplantation. Bone Marrow Transplant 2005;36:897–900. [PubMed: 16170332]
113. Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 2000;49:1–125.
114. Ljungman P, Engelhard D, de la Camara R, et al. Vaccination of stem cell transplant recipients: Recommendations of the infectious diseases working party of the EBMT. Bone Marrow Transplant 2005;35:737–46. [PubMed: 15750612]
115. Shildt RA, Luedke DW, Kasai G, El-Beheri S, Laham MN. Antibody response to influenza immunization in adult patients with malignant disease. Cancer 1979;44:1629–35. [PubMed: 498034]
116. Nordoy T, Aaberge IS, Husebekk A, et al. Cancer patients undergoing chemotherapy show adequate serological response to vaccinations against influenza virus and *Streptococcus pneumoniae*. Med Oncol 2002;19:71–78. [PubMed: 12180483]
117. Rapezzi D, Sticchi L, Racchi O, Mangerini R, Ferraris AM, Gaetani GF. Influenza vaccine in chronic lymphoproliferative disorders and multiple myeloma. Eur J Haematol 2003;70:225–30. [PubMed: 12656745]
118. Brydak LB, Guzy J, Starzyk J, Machala M, Gozdz SS. Humoral immune response after vaccination against influenza in patients with breast cancer. Support Care Cancer 2001;9:65–68. [PubMed: 11147146]
119. Ortbals DW, Liebhaber H, Presant CA, Van Amburg AL 3rd, Lee JY. Influenza immunization of adult patients with malignant diseases. Ann Intern Med 1977;87:552–57. [PubMed: 921082]
120. Lo W, Whimbey E, Elting L, Couch R, Cabanillas F, Bodey G. Antibody response to a two-dose influenza vaccine regimen in adult lymphoma patients on chemotherapy. Eur J Clin Microbiol Infect Dis 1993;12:778–82. [PubMed: 8307050]
121. Mazza JJ, Yale SH, Arrowood JR, et al. Efficacy of the influenza vaccine in patients with malignant lymphoma. Clin Med Res 2005;3:214–20. [PubMed: 16303886]
122. Brydak LB, Machala M, Centkowski P, Warzocha K, Bilinski P. Humoral response to hemagglutinin components of influenza vaccine in patients with non-Hodgkin malignant lymphoma. Vaccine 2006;24:6620–23. [PubMed: 16870313]
123. Robertson JD, Nagesh K, Jowitt SN, et al. Immunogenicity of vaccination against influenza, streptococcus pneumoniae and haemophilus influenzae type B in patients with multiple myeloma. Br J Cancer 2000;82:1261–65. [PubMed: 10755398]
124. Arrowood JR, Hayney MS. Immunization recommendations for adults with cancer. Ann Pharmacother 2002;36:1219–29. [PubMed: 12086557]
125. Melcher L. Recommendations for influenza and pneumococcal vaccinations in people receiving chemotherapy. Clin Oncol (R Coll Radiol) 2005;17:12–15. [PubMed: 15714923]
126. Descamps-Latscha B. The immune system in end-stage renal disease. Curr Opin Nephrol Hypertens 1993;2:883–91. [PubMed: 7922228]
127. Descamps-Latscha B, Herbelin A. Long-term dialysis and cellular immunity: a critical survey. Kidney Int Suppl 1993;41:S135–42. [PubMed: 8320907]
128. Haag-Weber M, Horl WH. Uremia and infection: Mechanisms of impaired cellular host defense. Nephron 1993;63:125–31. [PubMed: 8450902]
129. Sarnak MJ, Jaber BL. Pulmonary infectious mortality among patients with end-stage renal disease. Chest 2001;120:1883–87. [PubMed: 11742917]
130. Naqvi SB, Collins AJ. Infectious complications in chronic kidney disease. Adv Chronic Kidney Dis 2006;13:199–204. [PubMed: 16815225]

131. Jordan MC, Rousseau WE, Tegtmeier GE, Noble GR, Muth RG, Chin TD. Immunogenicity of inactivated influenza virus vaccine in chronic renal failure. Ann Intern Med 1973;79:790–94. [PubMed: 4761907]

132. Hodges GR, Davis JW, Lewis HD Jr, et al. Response to influenza A vaccine among high-risk patients. South Med J 1979;72:29–32. [PubMed: 366766]

133. Osanloo EO, Berlin BS, Popli S, et al. Antibody responses to influenza vaccination in patients with chronic renal failure. Kidney Int 1978;14:614–18. [PubMed: 748672]

134. Ortbals DW, Marks ES, Liebhaber H. Influenza immunization in patients with chronic renal disease. JAMA 1978;239:2562–65. [PubMed: 660788]

135. Song JY, Cheong HJ, Ha SH, Kee SY, Jeong HW, Kim WJ. Active influenza immunization in hemodialysis patients: comparison between single-dose and booster vaccination. Am J Nephrol 2006;26:206–11. [PubMed: 16699258]

136. Scharpe J, Peetermans WE, Vanwalleghem J, et al. Immunogenicity of a standard trivalent influenza vaccine in patients on long-term hemodialysis: an open-label trial. Am J Kidney Dis 2009;54:77–85. [PubMed: 19339089]

137. Versluis DJ, Beyer WE, Masurel N, Diderich PP, Kramer P, Weimar W. Intact humoral immune response in patients on continuous ambulatory peritoneal dialysis. Nephron 1988;49:16–19. [PubMed: 3380215]

138. Versluis DJ, Beyer WE, Masurel N, Weimar W, Kramer P, Diderich PP. Value of booster immunisation with influenza vaccine in patients undergoing haemodialysis. BMJ 1987;294:348. [PubMed: 3101868]

139. Vogtlander NP, Brown A, Valentijn RM, Rimmelzwaan GF, Osterhaus AD. Impaired response rates, but satisfying protection rates to influenza vaccination in dialysis patients. Vaccine 2004;22:2199–201. [PubMed: 15149777]

140. Gilbertson DT, Unruh M, McBean AM, Kausz AT, Snyder JJ, Collins AJ. Influenza vaccine delivery and effectiveness in end stage renal disease. Kidney Int 2003;63:738–43. [PubMed: 12631142]

141. Johnson DW, Fleming SJ. The use of vaccines in renal failure. Clin Pharmacokinet 1992;22:434–46. [PubMed: 1587056]

142. Rangel MC, V C, Euler GL, Strikas RA. Vaccine recommendations for patients on chronic dialysis. the Advisory Committee on Immunization Practices and the American Academy of Pediatrics. Semin Dial 2000;13:101–07. [PubMed: 10795113]

143. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004;19:893–99. [PubMed: 15125788]

144. Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. Ann Intern Med 1993;119:1198–208. [PubMed: 8239251]

145. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989;11:954–63. [PubMed: 2690289]

146. Ristow SC, G DR Jr, Condemi JJ. Influenza vaccination of patients with systemic lupus erythematosus. Ann Intern Med 1978;88:786–89. [PubMed: 666135]

147. Williams GW, Steinberg AD, Reinertsen JL, Klassen LW, Decker JL, Dolin R. Influenza immunization in systemic lupus eruthematosus: a double-blind trial. Ann Intern Med 1978;88:729–34. [PubMed: 352210]

148. Abu-Shakra M, Press J, Varsano N, et al. Specific antibody response after influenza immunization in systemic lupus erythematosus. J Rheumatol 2002;29:2555–57. [PubMed: 12465151]

149. Holvast A, Huckriede A, Wilschut J, et al. Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease. Ann Rheum Dis 2006;65:913–18. [PubMed: 16322083]

150. Brodman R, Gilfi llan R, Glass D, Schur PH. Influenza vaccine response in systemic lupus erythematosus. Ann Intern Med 1978;88:735–40. [PubMed: 307353]

151. Louie JS, Nies KM, Shoji KT, et al. Clinical and antibody responses after influenza immunization in systemic lupus erythematosus. Ann Intern Med 1978;88:790–92. [PubMed: 307356]

152. Herron A, Dettleff G, Hixon B, et al. Influenza vaccination in patients with rheumatic diseases: safety and efficacy. JAMA 1979;242:53–56. [PubMed: 312949]

153. Chalmers A, Scheifele D, Patterson C, et al. Immunization of patients with rheumatoid arthritis against influenza: a study of vaccine safety and immunogenicity. J Rheumatol 1994;21:1203–06. [PubMed: 7966058]

154. Del Porto F, Lagana B, Biselli R, et al. Influenza vaccine administration in patients with systemic lupus erythematosus and rheumatoid arthritis safety and immunogenicity. Vaccine 2006;24:3217–23. [PubMed: 16466833]

155. Kubiet MA, Gonzalez-Rothi RJ, Cottey R, Bender BS. Serum antibody response to influenza vaccine in pulmonary patients receiving corticosteroids. Chest 1996;110:367–70. [PubMed: 8697835]

156. Hanania NA, Sockrider M, Castro M, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. J Allergy Clin Immunol 2004;113:717–24. [PubMed: 15100679]

157. de Roux A, Marx A, Burkhardt O, et al. Impact of corticosteroids on the immune response to a MF59-adjuvanted influenza vaccine in elderly COPD-patients. Vaccine 2006;24:1537–42. [PubMed: 16288937]

158. Avetisyan G, Ragnavolgyi E, Toth GT, Hassan M, Ljungman P. Cell-mediated immune responses to influenza vaccination in healthy volunteers and allogeneic stem cell transplant recipients. Bone Marrow Transplant 2005;36:411–15. [PubMed: 15980884]

159. Avetisyan G, Aschan J, Hassan M, Ljungman P. Evaluation of immune responses to seasonal influenza vaccination in healthy volunteers and in patients after stem cell transplantation. Transplantation 2008;86:257–63. [PubMed: 18645488]

160. Lindemann M, Witzke O, Lutkes P, et al. ELISpot assay as a sensitive tool to detect cellular immunity following influenza vaccination in kidney transplant recipients. Clin Immunol 2006;120:342–48. [PubMed: 16631409]

161. Mazzone PJ, Mossad SB, Mawhorter SD, Mehta AC, Mauer JR. Cell-mediated immune response to influenza vaccination in lung transplant recipients. J Heart Lung Transplant 2004;23:1175–81. [PubMed: 15477112]

162. Hayney MS, Moran J, Wiegert NA, Burlingham WJ. Lung transplant patients' T cell responses to influenza vaccine viruses between seasons. Vaccine 2008;26:2596–600. [PubMed: 18420314]

163. Tosh PK, Poland GA. Emerging vaccines for influenza. Expert Opin Emerg Drugs 2008;13:21–40. [PubMed: 18321146]

164. Nichol KL, Treanor JJ. Vaccines for seasonal and pandemic influenza. J Infect Dis 2006;194(suppl 2):S111–18. [PubMed: 17163383]

165. Vu D, Peck AJ, Nichols WG, et al. Safety and tolerability of oseltamivir prophylaxis in hematopoietic stem cell transplant recipients: a retrospective case-control study. Clin Infect Dis 2007;45:187–93. [PubMed: 17578777]

166. US Department of Health and Human Services. HHS pandemic influenza plan. [accessed July 1, 2009]. http://www.hhs.gov/pandemicfl u/plan/

167. WHO. WHO global influenza preparedness plan: the role of WHO and recommendations for national measures before and during pandemics. World Health Organization; Geneva: 2005.

168. Khanna N, Steff en I, Studt JD, et al. Outcome of influenza infections in outpatients after allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis 2009;11:100–05. [PubMed: 19175540]

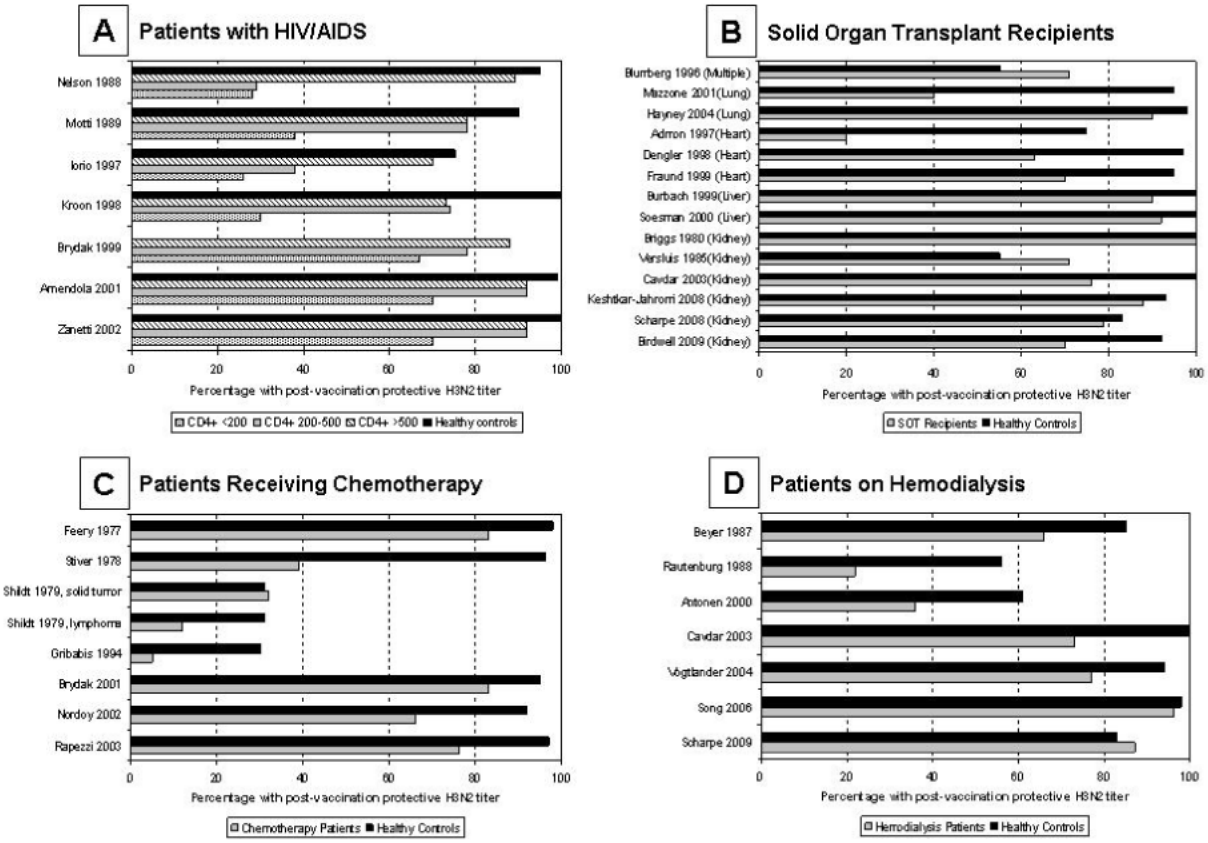

Figure. Percentage of immunosuppressed patients and healthy controls with protective postvaccination influenza titres

Data are only presented for proportions of patients with H3N2 serotype of influenza A, which is typically associated with higher risk of admission to hospital and death than the H1N1 serotype or influenza B.[1,2] Protective haemagglutination inhibition (HI) titre for studies was 1:40 or greater unless otherwise noted. Studies without healthy control groups are not presented. No studies provided data on haemopoietic stem-cell transplant recipients relevant to these figures. Also excluded are data for corticosteroid users, because of inability to extract relevant data for figures. Results in patients with HIV infection (A), stratified by CD4+ T cell counts, and healthy controls. Fowke and colleagues[32] not shown, because CD4 strata were not readily integrated with more conventional CD4 strata above. Brydak and colleagues[44] did not include healthy control group, but data were provided for CD4 strata, and therefore included. Results in solid-organ transplant recipients and healthy controls (B): Hayney and colleagues[46] data extracted from published figures. Dengler and colleagues[47] reported percentage with either HI titer 1:40 or greater or with four-fold or greater rise in HI titre postvaccination. Birdwell and colleagues[48] reported HI titer of 1:32 or greater. Results in patients treated with chemotherapy for malignancies and healthy controls (C): Feery and colleagues[49] and Gribabis and colleagues[50] data extracted from published figures. Stiver and colleagues[51] reported HI titre of 1:32 or greater. Results in patients on hemodialysis and healthy controls (D): Beyer and colleagues[52] reported HI titre of 1:100 or greater. Rautenburg and colleagues[53] data extracted from published figures and reported IgG titre of 1:2 or greater. Antonen and colleagues[54] data extracted from published figures.

Table 1
Estimated prevalence of selected immunosuppressive conditions

	Condition	USA	Worldwide/Other
Chronic immunosuppressive conditions	HIV/AIDS[4]	1,300,000[a, *]	33,200,000[a]
	Solid Organ Transplant[5]	153,245[c]	Data not found
	Hemodialysis[6]	314,162[b]	Data not found
Transient immunosuppressive conditions	Hematopoetic Stem Cell Transplant (annual procedures)[7]	18,720[b, *]	45,000[b]
	Cancer (new cases)[**8]	1,479,350[e]	Data not found
Either chronic or transient	Corticosteroid use[9]	Data not found	409,000 in U.K.[d]

Superscript letters indicate data for years as follows

[a] 2007

[b] 2005

[c] 2004

[d] 1996

[e] estimate for 2009

[*] Data for all of North America

[**] Data for hematologic and invasive solid organ cancers only; excludes in-situ malignancie

Table 2

Incidence of influenza in general and immunosuppressed populations

Author	Data source	Population	n	Outcome	# Outcomes/1000 person-years in disease (+) population (95% CI)	# Outcomes /1000 person-years in control (95% CI)
Thomp son2	National Center for Health Statistics Database	General population	nr	Influenza-associated deaths[b]	n/a	All ages: 0.03 (nr) ≥65 y/o: 0.22 (nr)
Thomp son1	National Hospital Discharge Survey	General population	nr	Influenza-associated hospital admissions[c]	n/a	All ages: 0.52 (nr) >65 y/o: 2.81 (nr)
Neuzil15	Tennessee Medicaid Database, women 15-64 y/o for HIV and for controls.	HIV, Pre-HAART	1,725,712 person-years of data	Combined, excess hospital admissions and deaths	1973-1993: 33.4 (nr)	0.4 (nr)
Lin16	National Center for Health Statistics Database, ≥13 y/o. for AIDS, 25-54 y/o for controls	AIDS, Pre-HAART	149,256 person-years of data	Excess deaths from pneumonia or influenza during influenza seasons[a]	1991-1992: 1.26 (1.07-1.45) 1992-1993: 1.47 (1.28-1.65) 1993-1994: 0.94 (0.80-1.08)	0.01 (0.009-0.01) 0.009 (0.009-0.01) 0.009 (0.008-0.009)
Neuzil17	Tennessee Medicaid Database. HIV+, 15-50 y/o.	HIV, Post-HAART	7,368 person-years of data	Excess hospital admissions Excess deaths	1995-1996, pre-HAART: 48 (16-81) 1996-1999, post-HAART: 5 (-0.5-11) 0.5 (-4.8-5.7)	n/a
Vilchez62	University of Pittsburgh Transplant Program Database.	Organ Transplant	3,569 organ transplants over 10 years	Hospital admissions	Lung Tx: 4.18 - 41.8 (nr)[d] Liver Tx: 0.28 - 2.8 (nr)[d] Kidney Tx: 0.43 - 4.3 (nr)[d]	n/a

n/a : not applicable

nr: not reported or data not collected

[a] Excess deaths calculated as difference between deaths during influenza season and prior to influenza season

[b] Data reported are for underlying pneumonia and influenza deaths. Data for all-cause deaths showed rates of 0.20 for all ages, and 1.32 for ≥65 y/o.

[c] Data reported are for influenza or pneumonia listed under any diagnosis. Data for influenza as primary diagnosis showed 0.37 endpoints/1000 person-years for all ages.

[d] Ranges provided because complete person-years data not reported.

Table 3

Influenza frequency and case fatality in HSCT and cancer patients

Author	Population and Setting	Influenza Years	# of patients under observation	Frequency of influenza[†]	Case fatality
Couch99	HSCT, hospitalized, single center	1992-1995	nr	nr	5/20 (25%)
Couch99	Leukemia, hospitalized, single center	1992-1995	nr	nr	9/27 (33%)
Ljungman100	HSCT, single center.[*]	1989-1996	545	15 (2.8%)	2/15 (13%)
Ljungman101	Allogeneic HSCT , 37 European Centers[*] Autologous HSCT, 37 European Centers[*] Allogeneic HSCT, 37 European Centers[*] Autologous HSCT, 37 European Centers[*]	1997-1998 1997-2000	819 1154 >819 >1154	14 (1.7%) 2 (0.2%) nr nr	4/14 (29%) 0/2 (0%) 7/30 (23%) 2/9 (22%)
Hassan102	Allogeneic HSCT, single center[*] Autologous HSCT, single center[*]	1996-2001	230 396	5 (2.2%) 0 (0%)	1/5 (20%)
Nichols103	HSCT, 120 days within transplantation date only, single center[*]	1989-2002	4797	62 (1.3%)	6/62 (10%)
Machado104	HSCT, respiratory symptoms present, single center[*]	2001-2002	179	41/179 (23%)	0/41 (0%)[a]
Whimbey105	HSCT, hospitalized, local influenza epidemic present, respiratory symptoms present, single center	1991-1992	28	8/28 (29%)	1/8 (13%)
Yousuf106	Leukemia, hospitalized, local influenza epidemic present, respiratory symptoms present, single center	1993-1994	45	15/45 (33%)	4/15 (27%)
Schepetiuk107	Nosocomial outbreak in oncology ward, single center	1997	19	nr	2/19 (11%)
Elting108	Leukemia, local influenza epidemic present, respiratory symptoms present, single center.	1991-1992	37	4/37 (11%)	1/4 (25%)

nr = not reported

[†] Frequencies are those reported during the total observation period (column 3—influenza years)

[*] outpatient/inpatient status not specified.

[a] only reported mortality from pneumonia, not all-cause mortality

Table 4

Recommendations for influenza vaccination of selected immunocompromised populations

Population	Inactivated influenza vaccine recommended?	Timing of initial vaccination	Recommendations for subsequent vaccination	Sources of recommendations
HIV infection	Yes	Not specified	Annual	CDC, IDSA
Solid organ transplantation	Yes	6 months following transplantation	Annual	American Society of Transplantation
Bone marrow transplantation	Yes	Approximately 6 months following transplantation	Annual or individually assessed	CDC, IDSA, American Society of Blood and Marrow Transplantation, European Group for Blood and Marrow Transplantation
Malignancy or chemotherapy	No guidelines available	n/a	n/a	n/a
Hemodialysis	Yes	Not specified	Annual	CDC
Systemic corticosteroids	No guidelines available	n/a	n/a	n/a

CDC = US Centers for Disease Control and Prevention. IDSA = Infectious Diseases Society of America. n/a = not applicable.