

INFLUENZA AND PNEUMOCOCCAL VACCINATIONS IN PATIENTS UNDERGOING CANCER TREATMENT

Date Developed: November, 2009

The recommendations contained in this guideline are a consensus of members of the Alberta Provincial Tumour Council and represent a synthesis of currently accepted approaches to management, derived from a rapid review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Health Canada estimates that the number of deaths than can be attributed to an epidemic of influenza is between 700 and 2500 annually; these include deaths related to pneumonia due to influenza virus or a secondary pathogen like *Streptococcus pneumoniae*.¹ Individuals over the age of 65 years are greatest risk of fatal complications; however, those with underlying medical conditions, including immunosuppression as a result of disease or treatment, are also at increased risk of complications and death.² Adult and pediatric patients with cancer, either as a result of their underlying disease or secondary to their treatment, are considered immunosuppressed and are therefore included in this high risk group. *Streptococcus pneumoniae* is also a major cause of morbidity and mortality among immunosuppressed individuals.

GUIDELINE GOALS AND OBJECTIVES

To outline the current evidence regarding appropriate vaccination strategies for seasonal influenza and 2009 novel H1N1 influenza for adult and pediatric patients with cancer, and vaccination strategies for *Streptococcus pneumoniae* for adult patients with cancer.

GUIDELINE QUESTIONS

- What is the evidence for response to the influenza and pneumococcal vaccines in adult and pediatric oncology patients receiving chemotherapy or other systemic therapy?
- What is the best timing for administering the vaccines in relation to the therapy cycle?

DEVELOPMENT PANEL

This **guideline** was reviewed and endorsed by a working group comprised of members the Alberta Provincial Tumour Council, which includes medical and radiation oncologists. **Evidence** was selected and reviewed by the working group and the Guideline Utilization Resource Unit.

SEARCH STRATEGY

The MEDLINE (1965 through November 2009), PubMed, Cochrane, CINAHL, and EMBASE databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Websites from health organizations such as the World Health Organization, Health Canada, the Public Health Agency of Canada, Alberta Health Services, the BC Cancer Agency, the National Comprehensive Cancer Network, the American Academy of Pediatrics, the Centers for Disease Control and Prevention, the National Guideline Clearing House, and the Département D'Oncologie Pédiatrique (France) were also searched for relevant guidance.

The search terms for influenza included influenza vaccine AND neoplasms or radiotherapy or therapy or surgery or drug therapy. The search terms for pneumococcal included pneumococcal vaccine AND carcinoma or lymphoma or leukemia or tumour or cancer AND tumour necrosis factor or interleukin or interferon or immunotherapy or systemic therapy OR adjuvant chemotherapy or neoadjuvant chemotherapy or chemotherapy; the search terms for immunocompromised patients included pneumococcal vaccine or influenza vaccine AND cancer or oncology AND immunocompromise*. The search yielded 31 relevant studies on influenza vaccine, 10 relevant studies on pneumococcal vaccine, and 18 relevant studies on immunocompromised patients; 28 of these were included in the evidence tables presented in Appendix B.

RECOMMENDATIONS

The following recommendations have been adapted from existing practice guidelines, including those from Health Canada, the Public Health Agency of Canada, Alberta Health Services, the BC Cancer Agency, the Centers for Disease Control and Prevention, and the American Academy of Pediatrics, as well as from evidence from clinical trials, reviews, and case study reports.

Seasonal and 2009 Novel H1N1 Influenza Vaccination

Adult Patients

1. Annual administration of the **inactivated** seasonal influenza vaccine and the **inactivated** 2009 novel H1N1 monovalent vaccine is indicated for all adult oncology patients. Patients considered to be the highest priority are those on active treatment; the next priority group includes patients who have been treated within the past 1 year. Current recommendations do not support the administration of a second dose of either vaccine in adults during the same influenza season.
2. Age, type and duration of systemic therapy, and curative versus palliative treatment intent do not appear to influence the response of adult patients to the seasonal influenza vaccination. Adult patients with hematologic malignancies may have lower responses to immunization when compared to adult patients with solid tumours. There are no data currently published with regards to response to the novel H1N1 vaccination among oncology patients.
3. Ideally, seasonal and novel H1N1 vaccinations should be given 10-14 days before the start of any immune-suppressing cancer treatment, to allow for sufficient antibody production by the patient. If the patient is actively receiving radiation treatment, vaccines should be ideally administered when blood counts are near the normal range. If this is not possible, the patient can still be vaccinated during a course of chemotherapy or radiotherapy, based on individual clinical judgment incorporating a patient's overall clinical situation
4. For adult patients undergoing blood and marrow transplant (BMT, autologous and allogeneic):
 - a. Administer the inactivated influenza vaccines 10-14 days prior to harvest (allogeneic donor or autologous recipient) or transplant conditioning (allogeneic recipient). **Live vaccines are contraindicated.**
 - b. Immune system recovery post-BMT is variable and requires physician assessment. Only 10 to 30 percent of BMT recipients will have a detectable antibody response to the influenza vaccine at 6 to 24 months post-transplant, while over 60 percent will have a detectable response at 24 months or more post-transplant.
 - c. The influenza vaccinations **should not be administered before 4 months** post-BMT, and should be administered annually to all BMT recipients who are at least 4 months post-BMT. If the vaccine is administered earlier than 6 months post-transplant, regardless of the conditioning intensity, a second dose may be beneficial.
 - d. Close contacts of BMT patients should be strongly encouraged to be vaccinated annually against seasonal influenza, and against novel H1N1 influenza during the 2009/2010 flu season.
5. Immunization of family members and hospital or clinic staff in contact with adult patients is strongly recommended. In many cases, this may be more important than vaccinating the patient themselves, as

some patients may be less likely to respond to the vaccine. Family members and hospital staff should receive both the **inactivated** annual seasonal vaccine, and the novel H1N1 vaccine.

6. Contraindications for seasonal and novel H1N1 influenza vaccinations in adult patients with cancer include:
 - A severe allergy to chicken eggs
 - A previous severe reaction to an influenza vaccination
 - A history of developing Guillain-Barré syndrome (GBS) within 6 weeks of getting an influenza vaccine
 - If there is reason to suspect moderate-to-severe febrile neutropenia, the patient should ideally be immunized after symptoms have diminished

Pediatric Patients

1. Annual administration of the **inactivated** seasonal influenza vaccine is indicated for all pediatric oncology patients over the age of 6 months:
 - Children 9 years or older should receive one dose of the seasonal influenza vaccine
 - Children 6 months through 8 years who have not received seasonal influenza vaccination previously should receive 2 doses of influenza vaccine in the **first year** that they are vaccinated
 - The second dose should be administered 4 or more weeks after the initial dose
 - When only one dose is administered to children aged 6 months to 8 years during their first year of vaccination, 2 doses should be administered only one time in the season that immediately follows
2. Administration of the **inactivated** 2009 novel H1N1 monovalent vaccine is indicated for all pediatric oncology patients over the age of 6 months, as immunosuppression puts this group at a high risk for influenza-related complications. Current recommendations state that *all* children aged 6 months to 3 years should receive two half-doses of the adjuvanted novel H1N1 vaccine, with doses separated by at least 21 days. Children aged 3 to 9 years with *chronic health conditions, including cancer*, should receive two half-doses of the adjuvanted vaccine, with doses separated by at least 21 days. Healthy children aged 3 to 9 years should receive only one half-dose of the adjuvanted vaccine. Children over the age of 10 should receive one full dose of the adjuvanted novel H1N1 vaccine.
3. Although the data is limited, age and type and duration of systemic therapy do not appear to influence the response of pediatric patients to the seasonal influenza vaccination. There are no data currently published with regards to response to the novel H1N1 vaccination among pediatric oncology patients.
4. Current recommendations for pediatric oncology patients suggest that both the seasonal and novel H1N1 vaccinations should ideally be given 10-14 days before the start of the next round of chemotherapy, to allow the patient to develop a sufficient antibody response. If the patient is actively receiving radiation treatment, vaccines should be ideally administered when blood counts are near the normal range. If this is not possible, the patient can still be vaccinated during a course of chemotherapy or radiotherapy, based on individual clinical judgment incorporating a patient's overall clinical situation.
5. For pediatric patients undergoing blood and marrow transplant (BMT, autologous and allogeneic):

- a. Administer the inactivated influenza vaccines 10-14 days prior to harvest (allogeneic donor or autologous recipient) or transplant conditioning (allogeneic recipient). **Live vaccines are contraindicated.**
 - b. Immune system recovery post-BMT is variable and requires physician assessment. Only 10 to 30 percent of BMT recipients will have a detectable antibody response to the influenza vaccine at 6 to 24 months post-transplant, while over 60 percent will have a detectable response at 24 months or more post-transplant.
 - c. The influenza vaccinations **should not be administered before 4 months post-BMT**, and should be administered annually to all BMT recipients who are at least 4 months post-BMT.
 - d. Close contacts of pediatric BMT patients should be strongly encouraged to be vaccinated annually against seasonal influenza, and against novel H1N1 influenza during the 2009/2010 flu season.
6. Annual seasonal influenza (and novel H1N1 influenza during the 2009/2010 flu season) immunization of family members, out-of-home caregivers, and hospital or clinic staff in contact with pediatric oncology patients is strongly recommended. In many cases, this may be more important than vaccinating the patient themselves, as some patients may be less likely to respond to the vaccine. In this situation, only the **inactivated** seasonal influenza and novel H1N1 vaccines should be administered.
7. Contraindications for inactivated seasonal and novel H1N1 immunizations in pediatric patients with cancer include:
- A severe allergy to chicken eggs
 - A previous severe reaction to an influenza vaccination
 - A history of developing Guillain-Barré syndrome (GBS) within 6 weeks of getting an influenza vaccine
 - Age less than 6 months
 - If there is reason to suspect moderate-to-severe febrile illness, children and adolescents should be ideally immunized when symptoms have diminished

Pneumococcal Vaccination

Adult Patients

1. Pneumococcal vaccination should be given to patients who may be immunosuppressed as a result of treatment, including patients actively receiving chemotherapy. This appears to be especially important during the 2009 H1N1 pandemic, as preliminary evidence suggests that pneumococcal pneumonia appears to be over-represented among H1N1 fatalities.
2. Adult patients undergoing BMT (autologous and allogeneic) should receive three to four doses of the pneumococcal conjugate vaccine (PCV) at three to six months post-transplant. When the recipient is at high risk of chronic graft-versus-host disease (GVHD), vaccine response may be improved by donor vaccination.
3. Vaccine Types:
 - a. Pneumococcal polysaccharide vaccine (PPSV): the overall effectiveness at preventing pneumococcal bacteremia is between 50 and 70% in healthy individuals. Of note, it is less effective than the conjugate vaccine in protecting immunosuppressed patients. In particular, it

has been substantially less effective in patients with multiple myeloma, Hodgkin disease, and non-Hodgkin lymphoma, especially during active treatment.

- b. Pneumococcal conjugate vaccine (PCV): evidence from healthy children under two years who have been vaccinated indicates that serotype-specific efficacy is between 94 and 97%.

4. Timing:

- a. Pneumococcal vaccination should be given four to six weeks (and at least 10-14 days) before the start of chemotherapy.
- b. Vaccination during chemotherapy or radiation therapy should be avoided because antibody responses are suboptimal. If this is not possible, and delay of treatment would result in an increased risk of cancer-related complications or death, it is recommended that, for those patients who would likely benefit from the vaccine, vaccination be delayed for three months after completing immunosuppressive chemotherapy.
- c. Patients vaccinated while on immunosuppressive therapy or within the two weeks before starting therapy should be considered unimmunized and should be revaccinated at least three months after discontinuation of therapy.
- d. Pneumococcal vaccination, unlike influenza vaccination, is given as a once-only vaccine; however, re-immunization is recommended in asplenic patients and those with nephrotic syndrome every five to ten years.

5. Contraindications:

- a. Anyone who has had a life-threatening allergic reaction to the vaccine should not get another dose.
- b. Anyone who has a severe allergy to any component of a vaccine should not get that vaccine.
- c. Anyone who is moderately or severely ill when the shot is scheduled may be asked to wait until they recover before getting the vaccine. Someone with a mild illness can usually be vaccinated.
- d. Although there is no evidence that PPSV is harmful to either a pregnant woman or to her fetus, it is not recommended during pregnancy. Pregnant women who have chronic illnesses should consult their provider before being vaccinated. Women who have underlying conditions known to put them at risk of pneumococcal disease should be vaccinated before becoming pregnant, if possible.

6. Factors negatively affecting vaccine efficacy:

- a. Methotrexate use impairs vaccine efficacy most strongly.
- b. Anti-tumour necrosis factor-alpha treatment causes additional immunosuppression.

7. There is no direct evidence regarding the value of pneumococcal vaccination for family members and care givers.

DISCUSSION

In general, there is a paucity of evidence from well-controlled studies on the use of both influenza and pneumococcal vaccinations in adult and pediatric patients with cancer. Articles included in this review repeatedly cite the need for universally accepted guidelines on: the type of vaccine(s) that produces best immunologic response, the number of administrations, the timing of administration in relation to severity of immunosuppression, and the timing of administration in relation to chemotherapy schedules. The recommendations included in the current guidelines are based, in part, on data extrapolated from healthy populations and combined with the best practices and opinions of experts.

Seasonal and 2009 Novel H1N1 Influenza Vaccination

Adult Patients

Annual administration of one dose each of the inactivated seasonal influenza and 2009 novel H1N1 monovalent vaccines is recommended for all adult patients with cancer. Chemotherapy can produce acute and profound immunosuppression in this patient population, although published literature suggests that the degree may differ according to the specific regimen, doses, and duration of treatment. There is currently no strong published evidence to support the administration of a second dose of the seasonal influenza vaccine to adults during the same influenza season, though data specific to adults with cancer is scarce.³ With regards to the novel H1N1 vaccine, the results of a recently completed randomized clinical trial involving 4303 subjects reported that a single dose of the inactive 2009 novel H1N1 vaccine without adjuvant was sufficient to induce a protective immune response in healthy subjects aged 12 to 60 years.⁴ Several recently completed smaller clinical trials have also reported similar findings in healthy populations, and have concluded that only one dose of the novel H1N1 vaccine is needed for adults.^{5,6} Emerging evidence from studies involving healthy populations also supports the importance of receiving **both** the seasonal and novel H1N1 vaccines, as the seasonal influenza vaccine does not appear to induce a cross-reactive antibody response to the 2009 novel H1N1 influenza virus in any age group.⁷

Interpreting the results of influenza vaccine efficacy in adult patients with cancer is difficult, as patient characteristics, cancer types, vaccine strains, and assessment of responses vary between published studies. In a thorough review of the literature, *Arrowood et al.* reported response rates to seasonal influenza vaccination to be between 29 and 88 percent for patients with cancer, and responses were generally higher for patients with solid tumours compared to those with hematologic malignancies.⁸ In a review of 1225 patients from the Surveillance, Epidemiology, and End Results (SEER) and Medicare databases, *Earle et al.* reported that among patients undergoing chemotherapy for stage IV colorectal cancer, those who had been vaccinated had lower rates of influenza and pneumonia than those who were unvaccinated (1.1% versus 3.8%, $p=.004$).⁹ In addition, when compared to their unvaccinated counterparts, the vaccinated patients had significantly fewer interruptions in the chemotherapy cycles, showed a trend towards using fewer health care resources, and were more likely to survive to the next influenza season (HR for death=0.88, 95% CI 0.77 - 0.99). To date, no efficacy studies specific to the 2009 novel H1N1 vaccine in cancer patients have been published.

Although the data regarding influenza frequency in adult patients with cancer is limited, the results of a growing body of literature suggest that patients with cancer who develop influenza are at a high risk for serious complications and death. In a recent review of 11 published studies involving adult patients undergoing chemotherapy treatment or hematopoietic stem cell transplantation (HSCT), *Kunisaki et al.* reported case fatality rates ranging from 11 to 33 percent for the studies involving chemotherapy.¹⁰ With

regards to novel H1N1 influenza, a guidance document released on October 21, 2009 by the Public Health Agency of Canada (PHAC) identifies patients with cancer as being at a higher risk of complications from novel H1N1 influenza, including hospitalization, admission to Intensive Care Units, and death.¹¹ The report cites unpublished surveillance data from the PHAC, and lists persons with chronic health conditions such as cancer as one of the priority groups for the current novel H1N1 vaccination across Canada.

There is some controversy regarding the timing of influenza immunization with respect to chemotherapy administration. The majority of research studies, reviews, and published guidelines included in our review suggest that since immunosuppressive chemotherapy regimens may depress the patients' immune response to vaccines, it is likely most beneficial to immunize patients approximately 10 to 14 days prior to beginning chemotherapy, to allow for sufficient antibody production by the patient;^{2,8,12,13,14,15} If this is not possible, however, administration of the inactivated vaccine *between* chemotherapy cycles has been reported to be safe and is recommended over not receiving vaccination at all,^{2,12,12,16} although the efficacy of the vaccine may be reduced in this situation. In such situations, administration of the vaccine is preferable when therapy is at the lowest level possible.¹² While there is no data currently available specific to the timing of administration of the novel H1N1 vaccine in patients with cancer, recently published clinical trial results addressing the timing of administration of the novel H1N1 vaccine in healthy adults report that the inactivated monovalent vaccine generates antibody responses likely to be associated with protection within 14 days after a single dose is administered;⁶ therefore the recommendations made for seasonal influenza vaccination are likely to apply also to novel H1N1 vaccination in adult patients with cancer.

Adult patients with hematologic malignancies undergoing blood and marrow transplantation (BMT) are at a significant risk for infections prior to immune regeneration. Preparation for both autologous and allogeneic BMT involves intensive high-dose regimens of chemotherapy and/or radiotherapy, which leave the patient acutely and profoundly immunocompromised for several months following transplantation. The impact of seasonal influenza on BMT recipients can be devastating: *Llungman et al.* reported a case fatality rate of 23 percent among over 1900 patients in Europe over 3 flu seasons.¹⁷ It is recommended that both the recipient and donor (for allogeneic transplants) receive seasonal influenza vaccination 10 to 14 days prior to the transplant.^{12,18,19,20} Post-transplant, while only 10 to 30 percent of BMT recipients will have a detectable antibody response to the influenza vaccine at 6 to 24 months, over 60 percent will have a detectable response at 24 months or more post-transplant.²¹ Immune system recovery post-transplant is variable and requires individual assessment by a physician. For example, patients treated with rituximab post-transplant will have a delay in their B-cell recovery by at least 6 months following the final dose.²⁰ In addition, adult transplant patients with chronic graft-versus-host disease (GVHD) may require up to 24 months or more post-transplant to recover CD4+ counts. It is recommended that BMT patients receive annual seasonal influenza vaccinations beginning *at least* 4 months post-transplant.^{12,18,19,20} In this situation, it is especially important that all close contacts of the BMT recipient are also immunized. There are no data currently available addressing the use of the novel H1N1 vaccine in this patient population.

In an effort to reduce the risk of disease transmission, immunization of family members and hospital staff in contact with patients who are high risk for severe or complicated seasonal or novel H1N1 influenza is strongly recommended. The PHAC states that people who are potentially capable of spreading influenza to those who are at high risk should be immunized, regardless of whether the high-risk person has been immunized.¹¹ Furthermore, in their *Guidance Document on the Use of Pandemic Influenza A (H1N1) 2009 Inactivated Monovalent Vaccine*, the PHAC recommends that those who care for patients with chronic health conditions, including cancer, are among the populations of recommended recipients for the H1N1 vaccine in Canada.¹¹ Immunization of family members and hospital staff who are in contact with BMT recipients is also of particular importance, as these patients are severely immunocompromised and cannot

be immunized themselves for at least 4 months post-transplant. In this situation, family members and health care providers should be immunized beginning the season before the transplant and annually for 24 months or more post-transplant.^{18,19,18}

For both the seasonal and novel H1N1 influenza vaccines, adult patients who should not be immunized include those with a severe allergy to chicken eggs, those who have had a previous serious reaction to an influenza vaccine, and those who have previously developed Guillain-Barré syndrome within 6 weeks of getting an influenza vaccination. In addition, for adult oncology patients with moderate-to-severe febrile neutropenia, vaccines should ideally be administered after symptoms have diminished. For the 2009-2010 influenza season, the National Advisory Committee on Immunization states that seasonal and novel H1N1 vaccines may be administered *concurrently* in opposite limbs, and if not administered together, there are no timing restrictions on the administration of the subsequent vaccine.²²

Pediatric Patients

Pediatric oncology patients are highly susceptible to influenza infections and have an increased rate of influenza infection compared to healthy children.²³ In addition, for children under the age of 5 years with chronic health conditions, hospitalization rates have been reported to be significantly higher than for healthy children in the same age group.²⁴ Annual administration of the inactivated seasonal influenza vaccine is indicated for all pediatric oncology patients over the age of 6 months. Current recommendations regarding seasonal influenza vaccine doses in healthy children state that those over the age of 9 years should receive one dose of the inactivated vaccine annually.²⁵ Children aged 6 months through 8 years of age who have not received seasonal influenza vaccination previously should receive 2 doses in the first year that they are vaccinated, with the second dose being administered 4 weeks or more after the first dose. This 2-dose regimen should only be administered one time for the influenza vaccination.

Data regarding the number of doses of the novel H1N1 vaccine that are required for pediatric oncology patients is limited. However, emerging clinical trial results and preliminary recommendations suggest that children aged 6 months to 9 years with *chronic health conditions, including cancer*, should receive 2 half-doses of the inactivated novel H1N1 vaccine separated by at least 21 days, while those aged 10 years or older should receive one full dose of the vaccine.^{4,11,26} The Public Health Agency of Canada (PHAC) also states that the *adjuvanted* version of the novel H1N1 vaccine should be used for children in both age groups because of the potential for enhanced immunogenicity.¹¹

Similar to the literature regarding adult patients with cancer, interpreting the limited published results of influenza vaccine efficacy in pediatric patients with cancer is difficult, as patient characteristics, cancer types, vaccine strains, and assessment of responses vary between published studies. In a recent meta-analysis of 8 controlled clinical trials and 1 randomized controlled trial, *Goossen et al.* reported that immune responses to the seasonal influenza vaccine in children receiving chemotherapy were consistently weaker than in those children who had completed their chemotherapy regimen and in healthy controls.²⁷ Several studies have reported that pediatric oncology patients who have completed their chemotherapy regimens have increased rates of seroconversion, suggesting that the timing of seasonal influenza vaccination with regards to the chemotherapy cycle is an important factor in this population.^{23,28} However, there are currently very limited recommendations regarding the optimal timing of seasonal influenza vaccination for pediatric oncology patients. For the studies included in this review, the ability of children with solid tumours to develop a protective immune response depended on whether the chemotherapy was administered during or within 2 weeks of their immunizations. After cessation of chemotherapy, adequate immune responses were reported within 3 months to 1 year. Similar to the

recommendations made for adults with cancer, it is likely most beneficial to immunize pediatric oncology patients approximately 10 to 14 days prior to beginning chemotherapy, to allow for sufficient antibody production by the patient. There is no data currently available specific to the timing of administration of the novel H1N1 vaccine in pediatric patients with cancer.

The recommendations for pediatric patients undergoing BMT are similar to those made for adult patients, with appropriate adjustments made for vaccine doses.^{18,20} It is recommended that both the recipient and donor (for allogeneic transplants) receive inactivated seasonal influenza vaccination 10 to 14 days prior to the transplant.^{12,18,19} Post-transplant, the majority of recipients will have a detectable antibody response to a vaccine beginning at 4 months, and this response will continue to increase over the next 12 to 24 months. As with adult patients, immune system recovery following transplant is variable, and depends on factors such as the types of therapies administered post-transplant, and the presence of GVHD; therefore individual assessment is required by a physician.²⁰ It is recommended that pediatric BMT patients receive annual seasonal influenza vaccinations beginning no earlier than 4 months post-transplant.^{12,18,19,20,29} There are no data currently available addressing the use of the novel H1N1 vaccine in pediatric patients undergoing BMT.

Similar to the recommendations made for adult patients with cancer, immunization of family members, caregivers, and hospital staff in contact with pediatric patients who are high risk for severe or complicated seasonal or novel H1N1 influenza is strongly recommended. Furthermore, as the novel H1N1 influenza pandemic is proving to be especially severe in healthy pediatric populations under the age of 5 years, reducing the risk of disease transmission to the immunocompromised pediatric patient by ensuring that all of their regular contacts are vaccinated is of heightened importance. To this end, the PHAC recommends that those who care for patients with chronic health conditions, including cancer, are among the populations of recommended recipients for the H1N1 vaccine in Canada.¹¹ Immunization of family members and hospital staff who are in contact with pediatric hematopoietic stem cell transplant recipients is also of particular importance, as these patients are severely immunocompromised and cannot be immunized themselves for at least four months post-transplant. In this situation, family members and health care providers should be immunized beginning the season before the transplant and annually for 24 months or more post-transplant.^{18,19,20}

Neither the seasonal nor the novel H1N1 vaccines are approved for use in Canada by children under the age of 6 months. Other contraindications include: children with moderate-to-severe febrile illness, children with a severe allergy to chicken eggs, children who have previously developed a severe reaction to an influenza vaccination, and children who have previously developed Guillain-Barré syndrome within six weeks of receiving an influenza vaccination. For the 2009-2010 influenza season, the National Advisory Committee on Immunization states that seasonal and novel H1N1 vaccines may be administered *concurrently* in opposite limbs in all populations; if not administered together, there are no timing restrictions on the administration of the subsequent vaccine.²²

Pneumococcal Vaccination

Adult Patients

The Public Health Agency of Canada's *Canadian Immunization Guide* (2006)¹² states that there is no contraindication to the use of any inactivated vaccine in immunosuppressed individuals and that particular attention should be paid to the completion of childhood immunizations, annual influenza immunization, and pneumococcal immunization (with a booster after 3-5 years). However, because of the impact of therapy on immunogenicity, timing of vaccination is an important factor for this population. The *Guide* notes that all vaccinations should be administered a minimum of fourteen days before the initiation of therapy or a minimum of three months after the completion of therapy; however, this may vary with the intensity of the immunosuppressive therapy, underlying disease, and other factors. Further, if treatment is ongoing, vaccines should be given when the therapy is at the lowest possible level.

In the general population, the efficacy of the polysaccharide and conjugate forms of the pneumococcal vaccine have been reported as being 50-70% and 94-97%, respectively.³⁰ Efficacy of the polysaccharide form of the pneumococcal vaccine (PPSV) in patients with solid tumours and malignant lymphoma undergoing mild to moderately immunosuppressive chemotherapy has been reported as being good,³¹ however, it is less effective than the conjugate form of the pneumococcal vaccine (PCV) in individuals with leukemia,^{32,33,34} multiple myeloma,¹⁵ Hodgkin disease, and non-Hodgkin lymphoma, especially during treatment.² Treatment with methotrexate has also been shown to decrease the immune response to the pneumococcal vaccine.^{35,36}

Adult patients with hematologic malignancies undergoing blood and marrow transplantation (BMT) are immunosuppressed for several months following transplantation. As such, it is recommended that autologous and allogeneic BMT recipients receive 3 to 4 doses of the pneumococcal conjugate vaccine (PCV) at 3 to 6 months post-transplant. When the recipient is at high risk of chronic GVHD, vaccine response may be improved by donor vaccination.²⁰ Given the potential benefits of herd immunity, especially for patients undergoing BMT, it is recommended that the family members and care givers of immunosuppressed individuals also receive the pneumococcal vaccine.

The recommendation for immunosuppressed individuals to receive the pneumococcal vaccine may be especially important during the 2009 H1N1 pandemic. Preliminary data from the Centers for Disease Control and Prevention suggests that pneumococcal pneumonia may present as a common co-infection among H1N1 fatalities. Of 77 confirmed cases of 2009 pandemic influenza A (H1N1), 10 had evidence of co-infection with *Streptococcus pneumoniae*.³⁷ However, the cases were not systematically sampled and may not be representative of all pandemic H1N1 deaths or all pandemic H1N1 deaths associated with bacterial pneumonia. Nevertheless, the majority of these patients were candidates for the pneumococcal vaccine because of age (<5 years) or due to underlying medical conditions. Therefore, all people who have existing indications for PPSV should be vaccinated during the 2009 H1N1 influenza pandemic.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
BMT	blood and marrow transplant
CI	confidence interval
GBS	Guillain-Barré syndrome
GVHD	graft-versus-host disease
HR	hazard ratio
HSCT	hematopoietic stem cell transplant
PCV	pneumococcal conjugate vaccine
PHAC	Public Health Agency of Canada
PPSV	pneumococcal polysaccharide vaccine
SEER	Surveillance, Epidemiology, and End Results database

IMPLEMENTATION STRATEGY

- Circulate the guideline internally to Alberta Health Services – Cancer Care staff.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review will be conducted in 2010; however, if new evidence is made available before that time, particularly with regards to the 2009 novel H1N1 influenza vaccine, the guideline will be updated accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

APPENDIX A: ADDITIONAL RESOURCES

Canadian Resources

Alberta Health Services: Physician H1N1 Updates:
<http://www.albertahealthservices.ca/894.asp>

Alberta Health Services – Cancer Care. Lymphoma Guideline:
http://www.cancerboard.ab.ca/Professionals/TreatmentGuidelines/Hematology_Lymphoma/;

Public Health Agency of Canada:
<http://www.phac-aspc.gc.ca/im/index-eng.php>

Public Health Agency of Canada. National Advisory Committee on Immunization (NACI): Statement on Seasonal Trivalent Inactivated Influenza Vaccine (TIV) for 2009-2010:
<http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-dcc-6/index-eng.php>

Public Health Agency of Canada: Canadian Immunization Guide:
<http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php>

Health Canada. It's your Health: Pneumococcal Vaccine (2006):
<http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/med/pneum-eng.php>

BC Cancer Agency: Treatment of Lymphoma, Chronic Lymphocytic Leukemia and Plasma Cell Disorders Including Myeloma:
<http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/default.htm>

International Resources

World Health Organization: Influenza Vaccination:
http://www.wpro.who.int/health_topics/influenza/overview.htm

World Health Organization: Position on Pneumococcal Vaccines (1999):
<http://www.who.int/wer/pdf/1999/wer7423.pdf>

Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP): Use of Influenza A (H1N1) 2009 Monovalent Vaccine:
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5810a1.htm>

Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP): Prevention and Control of Seasonal Influenza with Vaccines (2009):
<http://www.cdc.gov/mmwr/PDF/rr/rr58e0724.pdf>

Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP): Prevention of Pneumococcal Disease (1997):
<http://www.cdc.gov/mmwr/preview/mmwrhtml/00047135.htm>

Centers for Disease Control and Prevention: Pneumococcal Disease Complicating Influenza:
http://www.cdc.gov/h1n1flu/vaccination/provider/provider_pneumococcal.htm

Centers for Disease Control and Prevention: Pneumococcal Disease In-Short (May, 2009):
<http://www.cdc.gov/vaccines/vpd-vac/pneumo/in-short-both.htm#who>

National Comprehensive Cancer Network: Prevention and Treatment of Cancer-Related Infections:
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

American Academy of Pediatrics: Policy Statement: Recommendations for the Prevention and Treatment of Influenza in Children, 2009 –2010:
<http://aappolicy.aappublications.org/cgi/content/abstract/pediatrics;124/4/1216>

Immunization Action Coalition (2009):
<http://www.vaccineinformation.org/pneumchild/recommen.asp>

North of Scotland Cancer Network (2007):
<http://www.noscan-staging.scot.nhs.uk/idoc.ashx?docid=b00551e9-ea50-44b0-a758-b90d7c129be2&version=-1>

Département d'oncologie pédiatrique (France): Immunization for children treated for solid tumors: what are the guidelines?:
<http://www.ncbi.nlm.nih.gov/pubmed/11484458>

APPENDIX B: SELECT EVIDENCE FROM CLINICAL TRIALS AND CASE STUDIES
Table 1. Published Literature on Influenza Vaccination in Adult and Pediatric Patients with Cancer, 2000 to 2009

Author, Year	Study Type	Disease Site	N	Comparisons	Results and Recommendations
<i>Influenza Vaccination in Adult Populations</i>					
<i>Avetisyan et al, 2008</i> ³⁸	comparative study	Hematologic malignancies	18 14	1) Healthy volunteers 2) Allo-SCT patients <ul style="list-style-type: none"> N=5 were < 6 mos post-SCT N=9 were > 6 mos post-SCT N=3 patients on immunosuppression; 2 received tapering doses of cyclosporine, 1 received moderate dose of corticosteroids 	<ul style="list-style-type: none"> 29% of SCT patients demonstrated protective antibody levels to influenza A H1N1 serotype critical period is later than 90 days post-SCT, when patients gradually return to contact with the community and are more exposed to infection by circulating respiratory viruses <i>Authors recommend the influenza vaccination 3 months or longer after allo-SCT, as long as they do not have GVHD or ongoing immuno-suppression</i>
<i>Ljungman et al, 2005</i> ²⁹	open, randomized	Hematologic malignancies	36 34	1) one-dose vaccine 2) two-doses vaccine <ul style="list-style-type: none"> N=59 ongoing chemotherapy against malignancy minimum of 1 week between vaccination and the next scheduled chemotherapy course 	<ul style="list-style-type: none"> Response rates: <ul style="list-style-type: none"> H1N1: 14/70 (20%) H3N2: 14/70 (20%) Influenza B: 16/70 (23%) 4/70 patients responded and became immune to all three influenza subtypes after vaccination Proportion of immune patients after 1-dose vs. 2-doses: <ul style="list-style-type: none"> H1/N: 1 25% vs. 26% (NS) H3/N2: 22% vs. 21% (NS) Influenza B: 14% vs. 18% (NS) Patients with myeloproliferative disorders responded better to H1N1 compared with multiple myeloma patients (p=.002) and patients with lymphoma also responded better than patients with multiple myeloma (p<.001) Trend for better responses in patients with less intensive CT <i>Authors recommend immunization of family members and hospital staff</i>
<i>Machado et al, 2005</i> ³⁹	Prospective cohort study	Hematologic malignancies	134 43	1) < 6 months post-BMT, not eligible for vaccination 2) ≥ 6 months post-BMT, vaccinations recommended by BMT clinic <ul style="list-style-type: none"> Evaluation of the risk factors for influenza infection in a cohort of BMT recipients followed up for 1 year Focus on the <i>clinical benefits</i> of influenza vaccination 	<ul style="list-style-type: none"> 25/134 (18.6%) in group 1 developed influenza 19/43 (compliance rate 44.2%) in group 2 were vaccinated, and vaccine efficacy was 80% 12/24 (50%) unvaccinated in group 2 developed influenza Multivariate analysis: <ul style="list-style-type: none"> Seasonal exposure and conditioning regimens independently associated with increased risk for influenza influenza vaccine and steroid therapy showed a protective role Gender, BMT type, underlying disease and GVHD not associated with risk of influenza infection
<i>Earle et al, 2003</i> ⁹	cohort study	Stage IV colorectal cancer	1225	National Cancer Institute's SEER database and the Center for Medicare and Medicaid Services database were accessed for rates of influenza vaccinations among patients undergoing CT in the months of September – December between 1993 and 1996	<ul style="list-style-type: none"> Patients who developed influenza while undergoing CT: 3.8% unvaccinated vs. 1.1% (vaccinated), p=.004 Influenza vaccination associated with an HR for death of 0.88 (95%CI, 0.77-0.99) <i>68% of patients who were immunized received their vaccination through a primary care physician, yet oncologists are often these patients' most consistent medical contacts. As a result, it is critical that oncologists actively provide routine influenza vaccination to their patients with advanced cancer as part of delivering comprehensive, high-quality cancer care.</i>

Author, Year	Study Type	Disease Site	N	Comparisons	Results and Recommendations
<i>Nordoy et al, 2002</i> ³¹	Controlled clinical trial	Solid tumours or malignant lymphoma	35 38	1) patients on mild or moderate immunosuppressive CT (median age 53 yrs) 2) healthy controls (median age 57 yrs)	<ul style="list-style-type: none"> After 1 vaccination, 25 patients (72%) and 34 controls (87%) were serologically protected against 2 of the 3 flu strains A higher proportion of the patients with solid tumours (81%) than lymphoma (38%) achieved protection Age, duration of CT, and curative vs. palliative treatment did not influence vaccination response
<i>Influenza Vaccination in Pediatric Populations</i>					
<i>Goossen et al, 2007</i> ²⁷	Meta-analysis (Cochrane Review)	Pediatric malignancies	708	<ul style="list-style-type: none"> 8 controlled clinical trials and 1 RCT were included in the review In 5 studies, immune responses to influenza vaccine were compared in 272 children on CT with 166 children not on CT In 3 studies, responses to influenza vaccine were assessed in 204 children on CT compared with responses in 112 healthy children Immune responses in children receiving CT were consistently weaker (four-fold rise of 25% to 52%) than in those children who had completed CT (50% to 86%) and in healthy children (71% to 89%) Concerning adverse effects, 359 pediatric oncology patients received influenza vaccine and the side effects described were mild local reactions and low grade fever Authors concluded that although pediatric oncology patients receiving CT are able to generate an immune response to the influenza vaccine, it is unclear whether this immune response protects them from influenza infection or its complications 	
<i>Bektas et al, 2007</i> ⁴⁰	Case series	Solid tumours	45	Patients aged 1-18 years on CT or within 6 months of completing CT received 2 doses of the trivalent split vaccine 1 month apart	<ul style="list-style-type: none"> Fourfold rise in the percentage of post-vaccination antibody titers was detected for: <ul style="list-style-type: none"> H1N1: 84.4% H3N2: 77.8% Influenza B: 60% Stratification of patients on active CT versus within 6 months of completion of CT in terms of fourfold rise in antibody titers showed a statistically significant difference for only influenza B (p = .34) Post-vaccination protective rates were 86 to 97%
<i>Matsuzaki et al, 2005</i> ²⁸	Controlled clinical trial	Pediatric malignancies	44	Patients with various malignancies received 2 doses of influenza vaccine 2-4 weeks apart	<ul style="list-style-type: none"> Response rates: <ul style="list-style-type: none"> H1N1: 65% H3N2: 40% Influenza B: 46% Patients on CT showed a significantly lower response than those who were immunized after completing CT <ul style="list-style-type: none"> Protection titers: H1N1=42% vs. 90% (p=.006), H3N2=25% vs. 83% (p=.019) For influenza B, patients with low IgG showed a lower response rate than those with higher IgG (29% vs. 61%, p=.040) Multivariate analysis showed that factors associated with lower immune response were: <ul style="list-style-type: none"> H1N1: low IgG (p<.001) and admin. of CT (p=.003) H3N2: admin. Of CT (p=.008) Influenza B: low WBC count (p=.03) and low IgG (p=.030)
<i>Chisholm et al, 2005</i> ²³	Controlled clinical trial	Solid tumours and lymphoma	66	Pediatric patients currently receiving CT or who were within 6 months of completing CT received one or two doses of influenza vaccine, in autumn 2001 and/or 2002	<ul style="list-style-type: none"> Following vaccination: <ul style="list-style-type: none"> 25/64 patients (38%) were protected against all three viruses, representing a full response Protective responses to one or two viral strains were seen in 12/64 (19%) patients

Author, Year	Study Type	Disease Site	N	Comparisons	Results and Recommendations
					<ul style="list-style-type: none"> ○ 27 (41%) patients showed no protective response to vaccination, including 5 patients who remained fully susceptible to all 3 viruses following vaccination • Estimated increases in percentage protected against each viral subtype following vaccination were: <ul style="list-style-type: none"> ○ H1N1: 29% (95% CI 17–42%, p<.0001) ○ H3N2: 22% (95% CI 10–33%, p=.0002) ○ Influenza B: 43% (95% CI 29–57%, p<.0001) • N= 27 patients were transfused with blood and/or platelets during the study: <ul style="list-style-type: none"> ○ N=10 (38%) showed no response to vaccination ○ N=6 (23%) showed a protective response to 1-2 viral subunits ○ N=10 (38%) were protected against all 3 viruses • in multivariate analysis, lymphopenia was associated with improved response for H1N1 (OR=11.4, 95% CI 1.11–117.37; p= .041), though the authors caution that the number of patients with lymphopenia was small • There was no significant difference in response rates among children on treatment and off treatment and by intensity of CT regimen
<i>Porter et al, 2004</i> ⁴¹	Controlled clinical trial	ALL	20 49	1) children with ALL in 1st remission receiving maintenance CT who had completed last delayed intensification at least 4 weeks earlier 2) healthy controls	<ul style="list-style-type: none"> • Although post-immunization geometric mean titres were lower in group 1 versus group 2 children for the H1N1 antigen (p<.001), H3N2 antigen (p=.03), and influenza B antigen (p=.003), at least 60% of children with ALL had at least a 4-fold increase in HAI titres to each of the influenza antigens
<i>Hseih et al, 2002</i> ⁴²	Controlled clinical trial	ALL	25 30 10	1) pediatric patients with ALL in the maintenance stage who received 6-mercaptopurine daily, methotrexate weekly, and reinduction with vincristine and prednisolone 2) pediatric patients with asthma 3) healthy controls previously unvaccinated	<ul style="list-style-type: none"> • group 1 developed significant antibody titers to H3N2 antigen 4 weeks after the 2nd immunization • Seroconversion rates after 2 doses of vaccine were 57.1 to 84.6% and seroresponse rates were between 24 and 60% in group 1 • Compared to group 2, group 1 had less sero-conversion and lower seroresponse rates to H1N1 • Seroconversion and seroresponse rates to Influenza B and H3N2 antigens were comparable in group 1 and group 2 children • Antibody response in group 1 children who received reinduction CT suggests that the therapy did not impair seroresponse rates

Abbreviations: SCT = stem cell transplant, GVHD = graft-versus-host disease, RCT = randomized controlled trial, CT = chemotherapy, NS = not statistically significant, HR = hazard ratio, CI = confidence interval, BMT = blood and marrow transplant, HSCT = hematopoietic stem cell transplant, IgG= immunoglobulin G, WBC = white blood cells, OR = odds ratio, ALL = acute lymphocytic leukemia, HAI = hemagglutination inhibition.

Table 2. Published Literature on Pneumococcal Vaccination in Adult Patients with Cancer

Authors, year	Population	Methods/Treatment	N pts	Outcomes
<i>Vaccination in Patients Receiving Chemotherapy</i>				
Nordøy, et al. 2002 ³¹	Patients with solid tumors and malignant lymphoma undergoing chemotherapy	Patients received vaccination against influenza and pneumococcal disease: 1. Cancer patients (mean age 53 years) 2. Control patients (mean age 57 years) The chemotherapy regimens used were mild or moderately immunosuppressive.	73 total 35 38	Pneumococcal Response: After vaccination with a 23-valent polysaccharide vaccine against pneumococci, most pts and controls achieved protective serum levels of Abs against the different serotypes, with the exception that fewer pts were protected against serotype 4 Affecting Factors: The responses in controls were generally stronger to all serotypes; tumor type did not influence this vaccination response
<i>Vaccination in Patients with Myeloma</i>				
Robertson, et al. 2000 ¹⁵	Patients with multiple myeloma	Clinic attendees offered simultaneous vaccination against influenza, Hib and <i>S. Pneumoniae</i>	52 total - 30 male - 22 female - median age = 55	<i>S. pneumoniae</i>: protective antibody titres at 4-6 weeks in 39%; "good serological response" (i.e., four-fold increase in specific antibodies) in 56% Influenza (H1N1, H3N2, influenza B): 19% fully protected; 59% had poor response to all three; 27% protected against H1N1, 31% protected against H3N2, and 31% protected against influenza B - Receipt of chemotherapy <u>within 7 days prior</u> to vaccination was associated with a poor response to influenza vaccination. - No serious adverse reactions.
<i>Vaccination in Cell Transplantation Patients</i>				
Pao, et al. 2008 ⁴³	Recipients of an allogeneic hemato-poietic cell transplantation (alloHCT)	Patients were vaccinated with pneumococcal vaccine (PNCRM7); median time to vaccination was 1.1 years after HCT.	127 total	Response rate: 62% of pts (45/51 children; 34/76 adults; P < .001) Factors affecting response: Adversely by older age (P < .001) but improved with acquisition of milestones (CD4 > 200/μL, IgG >500 mg/dL, PHA within 60% lower limit of normal (11 of 19 vs. 0 of 8, P < .006). In all patients, higher levels of circulating CD4(+)CD45RA cells correlated with improved PNCRM7 response.
van der Velden, et al. 2007 ⁴⁴	Autologous stem cell transplant recipients	Pneumococcal vaccination consisted of two doses of conjugated vaccine followed by a single dose of polysaccharide vaccine, at 6, 8 and 14 months after transplantation, respectively.	20 total	Response: Mean anti-pneumococcal IgG antibodies sig increased after vaccination; response rate after the full schedule was 78% and 61% for conjugated 7-valent pneumococcal vaccine and non-conjugated 23-valent pneumococcal vaccine, respectively.
Antin, et al. 2005 ⁴⁵	Patients undergoing autologous hematopoietic stem cell transplantation (autoHCT)	Heptavalent pneumococcal conjugate vaccine (PCV7) or no vaccine was given before transplantation; after stem cell reinfusion, all study patients were immunized with PCV7 at 3, 6, and 12 months.	61 total	Response: Serotype-specific pneumococcal antibody concentrations were sig higher in pts immunized with PCV7 before stem cell collection vs. pts not immunized before for 6 of 7 serotypes at 3 & 6 months and 4 of 7 serotypes at 12 months; however, after the 3-dose series of PCV7 after autoHCT, >60% of ALL study patients had protective antibody concentrations to all 7 serotypes
Molrine, et al. 1996 ⁴⁶	Autologous bone marrow transplantation (ABMT) patients	Study patients (n = 12) were immunized before BM harvest with polysaccharide pneumococcal vaccine; comparable ABMT patients not immunized prior to BM harvest (n = 41) also studied; following ABMT, both groups were immunized at 12 and 24 months	53 total	Response: There were no differences in pneumococcal antibody concentrations between the two groups.

Authors, year	Population	Methods/Treatment	N pts	Outcomes
<i>Vaccination in Patients with Leukemia</i>				
<i>Safdar, et al. 2008</i> ³⁴	Patients with chronic lymphocytic leukemia (CLL)	Patients were allocated randomly to receive PPV either alone or with 3 doses of granulocyte-macrophage-colony-stimulating factor (GM-CSF; 250 microg) given before or after vaccination	32 total	<u>Response:</u> A 4-fold rise in IgG to Streptococcus pneumoniae types 4, 6B, 9V, 14, 19F, and 23F occurred in <10% of pts in each group; no diff in mean IgG levels in any of the groups
<i>Sinisalo, et al. 2008</i> ³²	Patients with chronic lymphocytic leukemia (CLL)	Patients (n = 52) were vaccinated with Prevenar 7-valent pneumococcal conjugate vaccine and compared with age- and sex-matched controls (n = 25)	77 total	<u>Response:</u> Antibody response rates to vaccine antigens were lower in pts with CLL vs. controls; however, when vaccine was administered before chemotherapy and development of hypo-gammaglobulinaemia, a sig response to at least six antigens was obtained in almost 40% of the CLL pts
<i>Hartkamp, et al. 2001</i> ³³	Patients with B-cell chronic lymphocytic leukaemia (B-CLL)	Patients were vaccinated with pneumococcal polysaccharide vaccine (Pneumovax-23)	24 total	<u>Response:</u> After vaccination, the number of pts with Ab levels in the protective range against pneumococcal serotypes increased from 9 (38%) to 12 (50%) of 24 patients <u>Affecting factors:</u> Pts w/adequate Ab response had sig less advanced B-CLL, higher gammaglobulin, total IgG-levels and subclasses 2 & 4, lower sol-CD23
<i>Vaccination in Splenectomized Patients and Patients with Lymphoma</i>				
<i>Cherif, et al. 2006</i> ⁴⁷	Pts with hematological diseases undergoing diagnostic or therapeutic splenectomy: Hodgkin lymphoma (n = 26), non-Hodgkin lymphoma (n = 19), immune-mediated cytopenias (n = 28), and others (n = 3)	Patients received 23-valent pneumococcal capsular polysaccharide (Pneumovax N) vaccination Med follow-up: 7.5 years	76 total	<u>Response:</u> Poor response in 21 (28%) pts; good response in 55 pts (72%); Ab levels not improved by revaccination in poor response group <u>Factors:</u> Med age at vaccination sig higher in poor responders (P= 0006); response NOT predicted by gender, disease activity/aggressiveness, previous RT and/or chemo, time b/t splenectomy and vaccination, time b/t chemo/RT and vaccination (1 year)
<i>Kobel, et al. 2000</i> ⁴⁸	Patients with long-term Hodgkin disease (n=3) or allogeneic bone marrow transplant patient (n=1)	Patients received staging splenectomy or total body irradiation and bone marrow transplantation.	4 total	Patients developed severe infections with Streptococcus pneumoniae; current guidelines for preventing infection recommend immunization for patients with Hodgkin disease treated with splenectomy and others with functional hyposplenism; booster vaccine after 5 years is also advised
<i>Petrasch, et al. 1997</i> ⁴⁹	Splenectomized patients with non-Hodgkin's lymphoma (NHL)	Patients had been immunized with a polyvalent pneumococcal vaccine (Pneumovax 23)	11 total	<u>Response:</u> 2+ fold rise in prevaccination titer of Abs against S. pneumoniae elicited in 5/11 pts; no sig diff in level of Abs against S. pneumoniae between lymphoma pts and splenectomy patients due to other reasons was detected
<i>Foss, et al. 1997</i> ⁵⁰	Patients who underwent staging laparotomy with splenectomy for Hodgkin's disease in Norway 1969-80 before pneumococcal vaccine was available	Patients were not immunized preoperatively	325 total	<u>Response:</u> Of 162 pts (49.8%) who died before 1994, 8 (2.4% of total study) died from pneumococcal septicaemia, 16 (6.2%) from infections totally; of 163 patients (50.2%) alive in 1994, 22/158 had been hospitalized for serious infections; 2 with pneumo-coccal septicaemia, 6 with pneumonia
<i>Chan, et al. 1996</i> ⁵¹	Previously treated Hodgkin's disease (HD) patients	Patients were immunized with 7-valent pneumococcal conjugate vaccine (7-OMPC) followed by one dose of 23-valent polysaccharide pneumococcal vaccine (23-PS)	39 total	<u>Response:</u> Mean antibody concentrations after immunization with 23-PS vaccine were sig higher for 5 of 6 serotypes in HD patients primed with 7-OMPC vs. HD pts who received 23-PS only; mean of 6 Ab concentrations was

Authors, year	Population	Methods/Treatment	N pts	Outcomes
		Comparison group: HD patients (n = 57) who received 23-PS vaccine only		sig higher for the primed group at 12.5 µg/mL and 7.76 µg/mL, respectively (P = .015)
<i>Grimfors, et al. 1989</i> ⁵²	Splenectomized patients (11 Hodgkin disease, 13 non-Hodgkin lymphoma, 29 others: hemolytic anemia, thrombocytopenia, post-traumatic pts)	Patients were immunized with a 14-valent vaccine (Pneumovax, MSD); antibodies were mainly restricted to the IgG2 and IgA2 subclasses.	53 total plus 18 controls	<u>Response:</u> Non-Hodgkin lymphoma patients had lower pre-vaccination values to the studied antigens and lower antibody response to vaccination than the other patient groups; 1 vaccinated non-Hodgkin lymphoma patient experienced two episodes of pneumococcal septicaemia, both occurring after chemotherapy which abolished the previously normal IgG2 antibody levels to the pneumococcal antigens
Vaccination in Patients Receiving Methotrexate				
<i>Gelinck, et al. 2008</i> ³⁶	Patients treated with anti-tumor necrosis factor-alpha (anti-TNF) with or without methotrexate	Patients were vaccinated with a 23 valent pneumococcal polysaccharide (PPS) vaccine: 1. Pts treated with immunosuppressives including anti-TNF; 65% pts treated with methotrexate 2. Patients treated with a 41 patients given a similar immunosuppressive regimen without anti-TNF (no anti-TNF group); 76% pts treated with methotrexate 3. Healthy controls	52 41 18	<u>Response (> 2-fold increase in titre):</u> Protection rate defined as post-vaccination titer ≥0.35 µg/ml; Abs against 4 antigens tested: 6B, 9V, 19F, 23F <u>Affecting Factors:</u> Methotrexate impaired vaccine most strongly; anti-TNF caused additional immunosuppression; underlying disease, prednisone, etc. did not cause additional immunosuppression
<i>Visvanathan et al. 2007</i> ⁵³	Patients with rheumatoid arthritis (RA) receiving anti-tumor necrosis factor (TNF) agent to methotrexate (MTX) therapy	Pts received 0.5 ml Pneumovax (pneumococcal vaccine) 34 wks after initiation of study treatment 1. Infliximab 3 mg/kg plus MTX 2. Infliximab 6 mg/kg plus MTX 3. Placebo plus MTX	70 total 20 36 14	<u>Response:</u> No sig diff observed between infliximab + MTX and placebo + MTX groups; 80%-85% pts responded to at least one serotype; however, only 20%-25% pts responded to at least 6 different serotypes; comparable proportions of pts in each group responded to an increasing number (≥1 to ≥6) of different serotypes <u>Affecting Factors:</u> Pts <45 years of age and pts taking oral corticosteroids appeared to respond better than pts 45-65 yrs and pts not taking oral corticosteroids
<i>Kapetanovic et al. 2006</i> ³⁵	Patients with established rheumatoid arthritis (RA) treated with TNF blockers, methotrexate (MTX) or combination of both	Pts received 23-valent vaccine (Pneumovax): 1. Patients with RA 2. Healthy controls Treatment with TNF blockers (etanercept or infliximab) and MTX was given to 50 pts, and 62 pts were treated with TNF blockers alone or with other DMARDs; MTX alone given to 37 pts	149 47	<u>Response (2+ fold rise in Ab titre):</u> Pre-vaccine Ab levels for 23F & 6B were similar in groups; post-vaccine Ab increased sig in all groups <u>Affecting Factors:</u> Pts treated w/TNF blockers without MTX responded better than those treated w/TNF blockers + MTX (P = 0.037 for 23F and P = 0.004 for 6B) or MTX alone (P<0.001 for both 23F & 6B); RA pts given MTX alone had lowest responses; prednisolone did not influence responses

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