PNEUMOCOCCAL IMMUNIZATION IN ADULT AND PEDIATRIC PATIENTS UNDERGOING CANCER TREATMENT

Effective Date: October, 2017
The recommendations contained in this guideline are a consensus of the Alberta Provincial Tumour Council and members of the Alberta Health Services Province-wide Immunization Program Standards and Quality, and are a synthesis of currently accepted approaches to management, derived from a 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.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

Participation of members of the Alberta Provincial Tumour Council and members of the Alberta Health Services Province-wide Immunization Program Standards and Quality in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Supportive Care Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
BACKGROUND

Streptococcus pneumoniae is a frequent cause of pneumococcal bacteremia, and often attacks individuals with influenza as a secondary infection.¹ There is evidence to suggest that asymptomatic pneumococcal carriage may also affect subsequent influenza virus infections and clinical outcomes.² Individuals over 65 years of age are at greatest risk of fatality from pneumonia combined with influenza, as well as from pneumonia alone; in 2013, the American Lung Association reported that the mortality rate increased from 8.3 deaths per 100,000 people aged 45-64 years to 107.4 deaths per 100,000 people aged 65 years and older.³ Moreover, individuals with underlying medical conditions who are immunosuppressed as a result of their disease or treatments are also at increased risk of complications and death from pneumonia;⁴ in particular, pneumococcal infections are an important cause of morbidity and mortality in adult and pediatric patients with cancer.⁵,⁶ Therefore, immunization of cancer patients with the pneumococcal vaccine may be important in preventing pneumonia. Although the pneumococcal vaccine is provided throughout the year by Public Health and community providers, the influenza season presents an excellent opportunity to assess and immunize eligible persons who have not previously received this immunization or those eligible for a one-time single reinforcing dose. The purpose of this guideline is to describe the use of the pneumococcal vaccine in adult and pediatric patients with solid tumours or hematological cancers such as leukemia, Hodgkin and non-Hodgkin lymphoma, multiple myeloma, and other malignancies.

GUIDELINE QUESTIONS

• What are the recommendations for pneumococcal immunization for adult and pediatric patients with solid tumours or hematologic cancers in Alberta?
• What is the current evidence for response to the pneumococcal vaccine among adult and pediatric patients with cancer receiving chemotherapy or other systemic therapy?
• What is the best timing for administering the pneumococcal vaccine in relation to the therapy cycle?

DEVELOPMENT AND REVISION HISTORY

The 2017 update of this guideline was reviewed and endorsed by members the Alberta Provincial Tumour Team Council, which includes medical and radiation oncologists, surgeons, nurses, hematologists, and allied health care providers, as well as content experts from the Alberta Health Services Province-wide Immunization Program Standards and Quality, Communicable Disease Control. Updated evidence was selected and reviewed by the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed and posted to the website in November 2012. The guideline was revised and reposted in August 2016 and October 2017.

SEARCH STRATEGY

For the original guideline published in 2012, the MEDLINE, PubMed, Cochrane, CINAHL, and EMBASE databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials published between 1965 and October 2012. Websites from health organizations including the World Health Organization, Health Canada, the Public Health Agency of Canada, Alberta Health Services, Alberta Health, the BC Cancer Agency, the National Comprehensive
Cancer Network, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention were also searched for relevant guidance. For the 2017 update, the Medline database was searched according to the following strategy:

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TARGET POPULATION

The recommendations outlined in this guideline apply to children and adults with solid tumours or hematologic malignancies. For current information on immunizations for the general population please refer to the Alberta Health Services Immunization Program Standards Manual at http://www.albertahealthservices.ca/info/Page10802.aspx

RECOMMENDATIONS

The following recommendations have been adapted from existing practice guidelines, policy documents, and consensus statements, including those from the Alberta Health Services Immunization Program Standards Manual, the Alberta Immunization Policy, the Public Health Agency of Canada, and the Centers for Disease Control and Prevention.\(^7\)\(^-\)\(^15\) Evidence from published clinical trials, retrospective reviews, and case study reports was also reviewed and considered.

1. Immunization against *Streptococcus pneumoniae* using pneumococcal vaccine is very important for patients who may be immunosuppressed as a result of their cancer or treatment of their cancer. This includes patients with solid tumours, leukemia, lymphoma, multiple myeloma, and hematopoietic stem cell transplant (HSCT) recipients.

2. Adult and pediatric patients who may be immunosuppressed as a result of their cancer or treatment of their cancer should consult with Public Health Services regarding an immunization schedule for the pneumococcal vaccine.

3. Adult and pediatric patients undergoing HSCT should consult with Public Health Services regarding an immunization schedule for the pneumococcal vaccine starting at 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 immunization.
4. Patients who are treated with rituximab or other B-cell depleting antibodies should have all immunizations postponed until at least six months after the last dose of rituximab.

5. Pneumococcal Conjugate Vaccine (PNEU-C13; Prevnar® 13):
   - PNEU-C13 is provided routinely to all children and adults who are candidates/recipients of solid organ transplants, and HSCT.
   - When both PNEU-C13 and PNEUMO-P vaccines are indicated, it is recommended that the conjugate series/dose be completed prior to administering the PNEUMO-P vaccine:
     - Immunocompromised adults aged 18 years and older who have not previously received PNEU-C13 or PNEUMO-P should receive a dose of PNEU-C13 first, followed by a dose of PNEUMO-P at least eight weeks later.
     - Immunocompromised adults aged 18 years and older who have previously received one or more doses of PNEUMO-P should receive a single dose of PNEU-C13 at least one year or more after the last dose of PNEUMO-P was received.

6. Pneumococcal Polysaccharide Vaccine (PNEUMO-P; Pneumovax® 23):
   - Immunization with PNEUMO-P is recommended for all adult and pediatric patients with solid tumours and hematologic malignancies who have not previously been immunized.
   - A one-time reinforcing dose of PNEUMO-P is recommended only for those individuals at highest risk of invasive pneumococcal disease, including patients who are immunosuppressed as a result of their cancer or treatment of their cancer. This one-time reinforcing dose of PNEUMO-P should be given:
     - Five years after the initial dose (HSCT recipients follow specific spacing recommendations). Refer to the Alberta Health Services Immunization Program Standards Manual, Immunization of Special Populations at the following links:
       - Internal AHS Link: [http://insite.albertahealthservices.ca/11322.asp](http://insite.albertahealthservices.ca/11322.asp)
       - External AHS Link: [http://www.albertahealthservices.ca/info/Page10802.aspx](http://www.albertahealthservices.ca/info/Page10802.aspx)
     - Exception: Individuals will be eligible for a dose of PNEUMO-P vaccine at 65 years of age and older (as long as five years have passed since a previous dose of this vaccine), regardless of the number of doses received prior to 65 years of age.
   - The timing of PNEUMO-P immunization should ideally occur four to six weeks (and at least 14 days) prior to initiation of immunosuppressive therapies such as chemotherapy or radiation. 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 immunization be delayed for three months after completing immunosuppressive chemotherapy (at least one month after stopping high dose steroids).

7. Patients immunized while on immunosuppressive therapy or less than two weeks before starting therapy should be considered un-immunized and should be re-immunized at least three months after discontinuation of therapy. Further discussion with Public Health Services may be appropriate before the patient is re-immunized.

8. Pneumococcal immunizations should not be administered to individuals who:
   - have had an anaphylactic reaction to a previous dose of the vaccine.
   - have a known hypersensitivity to any component of the vaccine.
• are less than two years of age (for PNEUMO-P vaccine) or less than two months of age (for PNEU-C13 vaccine).
• present with a serious acute febrile illness; recommendations should be provided for these individuals to be immunized when their symptoms have resolved. Individuals with non-serious febrile illness may be immunized.

DISCUSSION

Cancer patients are especially susceptible to severe pneumococcal infections, particularly those at risk of poor B-cell function (e.g., chronic lymphocytic leukemia and multiple myeloma) and HSCT recipients, especially those with chronic GVHD.\(^16\) Although evidence from controlled studies addressing pneumococcal immunization in adult and pediatric patients with solid tumours and hematologic malignancies cancer is limited, national and international guidelines and policy statements do support pneumococcal immunization in adult and pediatric immunocompromised populations. The Advisory Committee on Immunization Practices (ACIP) from the Centers for Disease Control and Prevention recommends that children younger than five years old, adults 65 years or older, and people six years or older with immunocompromising conditions should be immunized with the PNEU-C13 vaccine. The committee also recommends immunization with the PNEUMO-P vaccine for adults 65 years or older and for people aged two to 64 years old with immunocompromising conditions.\(^8,9\) Similarly, the Public Health Agency of Canada’s Canadian Immunization Guide 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.\(^7\) However, because of the impact of therapy on immunogenicity, the timing of immunization is an important factor for this population.

The National Comprehensive Cancer Network’s guideline, Prevention and Treatment of Cancer-Related Infections, recommends that patients should ideally be immunized against \textit{S. pneumoniae} at least two weeks before starting chemotherapy or other immunosuppressive therapies. Further, patients should be considered unprotected if they are immunized less than two weeks before starting therapy, and should be re-immunized at least three months after therapy has stopped.\(^17\) The Canadian Immunization Guide is in line with these consensus recommendations, noting that all immunizations should be administered a minimum of two weeks before the initiation of therapy or a minimum of three months after the completion of therapy. This guide also suggests that the immunization schedule may vary with the intensity of the immunosuppressive therapy, underlying disease, and other factors; if treatment is ongoing, immunizations should be administered when the therapy is at the lowest possible level.\(^7\)

In the general pediatric population, there are no efficacy data available for other pneumococcal conjugate vaccines, including PNEU-C13. The efficacy of the PNEUMO-P vaccine is estimated to be between 50 and 80% among the elderly and other high-risk groups, and the efficacy in patients with solid tumours and malignant lymphoma undergoing mild to moderate immunosuppressive chemotherapy has also been reported as good.\(^18,19\) However, the polysaccharide vaccine is less effective than the conjugate vaccine in this group of patients, particularly during treatment.\(^19-24\) Treatment with medications such as methotrexate has also been shown to decrease the immune response to the pneumococcal vaccine.\(^25,26\)

Pediatric and adult cancer patients undergoing hematopoietic stem cell transplantation (HSCT) are immunosuppressed for several months post-transplant, and antibody responses are low post-transplant.\(^16,27-35\) The Alberta Immunization Policy and the Alberta Health Services Immunization Program
Standards Manual both recommend that pediatric and adult HSCT recipients be completely re-immunized post-transplant. The PNEU-C13 vaccine is recommended at six, seven, and eight months post-transplant, while the PNEUMO-P vaccine is recommended at 14 and 24 months post-transplant. Patients with chronic graft-versus-host-disease (GVHD) treated with immunosuppressive drugs should receive PNEU-C13 instead of PNEUMO-P at the 14 and 24 month post-transplant immunizations. In addition, when the recipient is at high risk of GVHD, vaccine response may be improved by donor vaccination. The minimum acceptable interval between PNEU-C13 doses is four weeks and the minimum interval between PNEU-C13 and PNEUMO-P doses is six months.

Patients who are treated with maintenance rituximab or other B-cell depleting antibodies following HSCT should have all immunizations postponed until at least six months after the last dose of rituximab or other B-cell depleting therapies. Berglund and colleagues recently reported the results of a subgroup analysis of rituximab-treated patients among adult outpatients with cancer who were undergoing treatment. Patients treated with rituximab had almost no response to the pneumococcal, influenza A (H1N1), and seasonal influenza vaccines. Specifically, the mean number of serotype-specific protective pneumococcal antibodies (SPP) was not significantly different between the 8 rituximab-treated and 55 non-treated patients before immunization whereas it was significantly increased after immunization for those patients who did not receive rituximab.

GLOSSARY OF ABBREVIATIONS

<table>
<thead>
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<th>Acronym</th>
<th>Description</th>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>GVHD</td>
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<td>Public Health Agency of Canada</td>
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<td>PNEU-C13</td>
<td>13-valent pneumococcal conjugate vaccine</td>
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<tr>
<td>PNEUMO-P</td>
<td>23-valent pneumococcal polysaccharide vaccine</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted in September 2018. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
REFERENCES


APPENDIX A: Additional Resources

Alberta Bone Marrow and Blood Cell Transplant Program. Standard Practice Manual:  

Alberta Health. Manuals and Guidelines for Health Professionals.  
www.health.alberta.ca/professionals/manuals.html

Alberta Health Services. Immunize Alberta:  
www.immunizealberta.ca

Alberta Health Services. Immunization Program Standards Manual:  
external link - www.albertahealthservices.ca/info/Page10802.aspx  
internal link for AHS staff - http://insite.albertahealthservices.ca/11322.asp

Centers for Disease Control and Prevention. Vaccines and Immunizations – Pneumococcal Vaccination:  
www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm

Centers for Disease Control and Prevention. Vaccine Recommendations of the Advisory Committee on  
Immunization Practices (ACIP) – Pneumococcal Disease:  
www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html

Public Health Agency of Canada. Canadian Immunization Guide:  

Public Health Agency of Canada. National Advisory Committee on Immunization (NACI):  