<table>
<thead>
<tr>
<th>Program Name:</th>
<th>Vaccines: Beyond the Basics</th>
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Introduction

Vaccines are one of the most important advances in public health and are estimated to have saved more lives in Canada over the past 50 years than any other health intervention.¹ Immunization programs are responsible for the elimination, containment or control of infectious diseases that were once common in Canada.¹

Immunization is important at every stage of life in Canada and globally. As more Canadians travel to international destinations, primary care healthcare professionals are increasingly going to be asked to provide advice to reduce their overall risk of acquiring travel-related illnesses.

This vignette program explores four common situations where vaccines are recommended. The last vignette reviews the importance of immunization prior to commencement of immunosuppressive therapy (including biologic modifiers) and screening for latent tuberculosis.

Pre-Post Course Survey

1. Please rate your current comfort level discussing vaccines not covered by your provincial immunization program. (1 not at all comfortable, 5 very comfortable)
2. How often do you recommend vaccines that are not paid for by your provincial immunization program? (1- never, 5 to every eligible patient)
3. Please provide your current comfort level discussing basic travel health immunizations. (1 not at all comfortable, 5 very comfortable)
4. Do you currently offer travel services in your practice? (1 never, 5 all of my patients that are travelling)
5. How often do you refer patients that are travelling to a travel health clinic? (1 never, 5 all of my patients that are travelling)
6. How time consuming do you find immunization discussions with your patients? (1 not more than a standard consult, 5 – very time consuming)
7. How would you rate your ability to comfortably discuss the benefits and risks of the quadrivalent influenza vaccine with your patients? (1=poor, 5=excellent)
8. How comfortable are you assessing a patient for latent tuberculosis infection? (1 not at all comfortable, 5 very comfortable)
Vignette #1 – Beyond C, Protecting Your Patients Against Meningococcal Disease

Meet Jason
Rebecca W. is in to see you with her son Jason (17 yo). He is heading to the University of British Columbia in the fall. He is going to be living in residence. Due to his performances in high school sports, he is being encouraged to try out for a variety of university sports team.

Jason received a letter from the university recommending that his immunization records are reviewed to ensure everything is up-to-date. Upon reviewing Jason’s immunization schedule, you ask him if he would like to receive a vaccine to protect him against a leading cause of bacterial meningitis. His mother is surprised to hear that he is not already protected as she clearly remembered him getting a meningitis vaccine in grade 6.

You explain that Jason was protected against a type of this disease, but not other types and the protection can decrease over time. You explain that there are vaccines that will protect against other types or strains of meningococcus. Both Jason and Rebecca would like to hear more about the vaccine. Rebecca has been worried about meningitis since there were a few recent outbreaks in the news in some of the universities in the United States.

Learning Objectives
Upon successful completion of this continuing education program, you will be better able to:

1. Discuss the epidemiology of invasive meningococcal disease (IMD) in Canada
2. Review the clinical presentation of IMD
3. Assess patients for potential risk factors for IMD
4. Review the different available meningococcal vaccines
5. Discuss the role of the healthcare professional in recommending vaccines that are not covered by the provincial/territorial immunization program
Post Test

Based on your current knowledge, please indicate if the following statements are true or false

1. The most common meningococcal serogroups responsible for IMD are A, B, C, W, Y
   
a. True
   b. False

2. The incubation period of meningococcal disease is 3 to 4 days, with a range of 2 to 10 days
   
a. True
   b. False

3. Invasive meningococcal disease is easy to diagnose at early presentation as the clinical presentation is so unique
   
a. True
   b. False

4. Conjugated meningococcal vaccines produce a more robust immune response compared to polysaccharide vaccines
   
a. True
   b. False

5. The estimated lifetime risk of a patient developing invasive meningococcal disease (IMD) is:
   
a. 1 in 120
   b. 1 in 540
   c. 1 in 1900
   d. 1 in 5400

6. The quadrivalent meningococcal vaccine currently protects against which types of meningococcal disease?
   
a. A,B,C,Y
   b. A,B,W,Y
   c. A,C,W,Y
   d. A,C,W,Z

**Neisseria meningitidis**

*N. meningitidis* is an aerobic, gram-negative diplococcus bacteria.\(^2\) The outer membrane contains several protein structures that enable the bacteria to interact with the host cells.\(^2\) The bacteria is surrounded by a polysaccharide capsule that is necessary for pathogenicity because it helps the bacteria resist phagocytosis and complement-mediated lysis. The outer membrane proteins and the capsular polysaccharide make up the main surface antigens of the organism.\(^2\)

Meningococci are classified by using serologic methods based on the structure of the polysaccharide capsule.\(^2\) In Canada, almost all invasive disease is caused by one of five serogroups: A, B, C, W, and Y. The relative importance of each serogroup depends on geographic location, as well as other factors, such as age.\(^2\)
Since the introduction of universal childhood immunization with serogroup C meningococcal conjugate vaccine, the incidence of serogroup C has declined (0.41 per 100,000 in 2002 to 0.07 per 100,000 in 2006). \(^3\) Serogroup B now accounts for the majority of infections in Canada. \(^3\) From 2007 to 2011, serogroup B incidence has fluctuated between 0.27 and 0.40 cases per 100,000 per year. \(^4\) The incidence of serogroup Y disease has remained stable over time, with an annual average incidence of approximately 0.09 per 100,000. \(^3\) The annual incidence of W-135 disease remains steady at 0.01–0.05 per 100,000, and one or two cases of serogroup A disease occur each year and are usually travel-related. \(^3\)

The age groups with the highest risk for IMD in order of frequency are: \(^5\)

- Children under 1 year of age
- Adolescents and young adults (12 to 24 years of age) \(^6\)
- Children 1-4 years of age

**Clinical Practice Tip:**
The serogroups responsible for IMD can vary from country-to-country. Travellers previously immunized with meningococcal serogroup C immunization will many times not have adequate protection when travelling to other parts of the world. \(^7\) It is also important to remember that the vaccine antibody titres can decrease with time and may not provide adequate protection several years after immunization. NACI recommends that travellers going to destinations where risk of meningococcal transmission is high should be vaccinated with the quadrivalent meningococcal vaccine. \(^6\)

### Pathogenesis and Transmission

The most common form of meningococcal infection is the carrier state, where colonization occurs in up to 10% of healthy individuals. The bacteria resides and multiplies in the nasopharynx. A person may remain a carrier for up to six months and remain asymptomatic. In a small proportion (less than 1%) of colonized persons, the organism penetrates the mucosal cells and enters the bloodstream. \(^2\) The bacteria spread by way of the blood to many organs. In about 50% of bacteremic persons, the organism crosses the blood–brain barrier into the cerebrospinal fluid and causes purulent meningitis. An antecedent upper respiratory infection may be a contributing factor. \(^2\)

*N. meningitidis* is transmitted by droplet aerosol or secretions from the nasopharynx of colonized persons. The bacteria are extremely fragile outside the body and are transmitted from an infected person (including carriers) to another person through close, direct contact such as kissing, coughing and sneezing. Transmission can also occur through saliva when sharing items such as cigarettes, lipstick, food and drinks, etc. \(^8\) Outbreaks of meningococcal infection have occurred in dormitories at universities due to so many individuals living in such close quarters.
Clinical Presentation

The incubation period of meningococcal disease is 3 to 4 days, with a range of 2 to 10 days.\textsuperscript{2}

IMD is very difficult to diagnose at clinical presentation and is challenging to distinguish from more common but less serious illnesses.\textsuperscript{9} A trial assessing 448 pediatric IMD cases found that many children have only non-specific symptoms in the first 4-6 hours of infection, but are close to death by 24 hours.\textsuperscript{10} They found that only 51\% of children were sent to hospital after the first consultation.\textsuperscript{10}

Approximately 40\% of patients with clinical manifestations of meningococcal disease have meningitis alone, 40\% have both meningitis and septicemia, 10-15\% have septicemia alone and 5\% have other infections (pneumonia, arthritis or otitis media).\textsuperscript{11} The most common symptoms of IMD are reviewed in table 1.

### Table 1 – Clinical Presentation of patients with IMD\textsuperscript{9}

- Symptoms include:
  - the sudden development of fever
  - drowsiness
  - irritability or agitation
  - intense headache
  - nausea
  - vomiting
  - stiff neck and
  - photophobia
- Most commonly, invasive disease results in meningitis and/or septicemia, in addition to a characteristic non-blanching petechial or purpuric rash.

Morbidity and Mortality of IMD

Meningitis is the most common presentation of IMD and results from the spread of the organism through the blood.\textsuperscript{2} Meningococci can be isolated from the blood in up to 75\% of persons with meningitis. The case-fatality rate of invasive meningococcal disease is 9\% to 12\%, even with appropriate antibiotic therapy.\textsuperscript{2}

Meningococcal sepsis occurs in 5 to 20\% of IMD patients.\textsuperscript{9} It presents with an abrupt onset of fever and a petechial or purpuric rash, which may progress to purpura fulminans, and is often associated with the rapid onset of hypotension, acute adrenal hemorrhage and multiorgan failure.\textsuperscript{9}

Despite treatment with appropriate antibiotics and optimal care, the overall case fatality rates have remained stable over the past 20 years, at 9 to 12\%, with a rate of up to 40\% among patients with meningococcal sepsis.\textsuperscript{9}

Approximately 17 individuals (five children and 12 adults) die from meningococcal disease every year in Canada with an additional 35 (19 children and 16 adults) experiencing significant sequelae.\textsuperscript{5} Long-term sequelae occur in 21-33\% of pediatric survivors.\textsuperscript{12,13} Table 2 lists some of the sequelae in pediatric survivors of IMD. Unfortunately, these impairments are likely to not improve over time and pose a burden for survivors long-term.
Table 2 – Sequelae seen in Pediatric Survivors of IMD\textsuperscript{12,13}

- Deafness
- Amputations
- Scarring
- Neurological dysfunction
- Renal dysfunction
- Reduced IQ and memory
- Impaired executive function

Patient Counselling Tip:
- Each week in Canada, on average, one individual dies or develops a new significant disability as a result of IMD.\textsuperscript{5} Clinicians can explain to patients and parents that the estimated lifetime risk of a patient developing IMD from any meningococcal serogroup is 1 in 1900.\textsuperscript{5}

Risk Factors of IMD

The interaction between the host and the meningococcus determines if the infection will be contained (asymptomatic carrier) or lead to rapidly progressive and sometimes fatal IMD.\textsuperscript{14} In a few patients, upper respiratory acquisition of the bacteria is rapidly followed by IMD.\textsuperscript{14} Many of the patients at highest risk of IMD have underlying immune dysfunction or are exposed to patients with IMD.\textsuperscript{15} Risk factors for IMD are highlighted in table 3.

Clinical Practice Tip:
Although there are risk factors for meningococcal infection, many of the cases of IMD occurred in otherwise healthy children, adolescents and adults.

Table 3 – Risk Factors for IMD\textsuperscript{15,16}

<table>
<thead>
<tr>
<th>Host Factors:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons with asplenia or functional hyposplenism (including sickle cell disease)</td>
<td></td>
</tr>
<tr>
<td>Persons who have complement, properdin, factor D or primary antibody deficiencies (genetic factors)</td>
<td></td>
</tr>
<tr>
<td>Persons with acquired complement deficiency (eg. Patients receiving eculizumab, HIV)</td>
<td></td>
</tr>
<tr>
<td>Active and passive smoking</td>
<td></td>
</tr>
<tr>
<td>Concurrent respiratory infection</td>
<td></td>
</tr>
<tr>
<td>Recent influenza infection</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure Factors:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Close contacts of an infected person are at increased risk</td>
<td></td>
</tr>
<tr>
<td>Concurrent upper respiratory tract infection</td>
<td></td>
</tr>
<tr>
<td>Household crowding (e.g. dormitory)</td>
<td></td>
</tr>
<tr>
<td>Lower socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>During outbreaks, bar or nightclub patronage and alcohol use have also been associated with higher risk for disease</td>
<td></td>
</tr>
<tr>
<td>Travellers to areas with significant crowding (e.g. Hajj pilgrimage)</td>
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</table>
Meningococcal Vaccines

There are three meningococcal vaccine types in Canada. These include:

- Meningococcal polysaccharide vaccine (ACWY)
- Meningococcal conjugated vaccine (ACWY), (C)
- Meningococcal Multicomponent Serogroup B Vaccine

The vaccines currently available in Canada are listed in Table 4.

Meningococcal Polysaccharide Vaccine

The serogroups of meningococcal disease are classified according to the polysaccharide capsule surrounding the bacterium.\(^\text{17}\) The first vaccines developed in the 1960’s against serogroups A and C were based on the capsular polysaccharide.\(^\text{17}\) Subsequently, polysaccharide vaccines were introduced against W and Y.\(^\text{17}\) Currently a quadrivalent polysaccharide vaccine covering serogroups A, C, Y and W is available in Canada.

Polysaccharide vaccines are poorly immunogenic in children younger than 2 years of age (with the exception of the serogroup A component).\(^\text{17}\) Polysaccharide vaccines lead to short-lived immunity with no memory response.\(^\text{17}\) There may be a reduced antibody response with subsequent booster doses (a phenomenon known as “hyporesponsiveness”).\(^\text{17}\) The Canadian Pediatric Society discourages the use of meningococcal polysaccharide vaccine because of its lower immunogenicity.

Meningococcal Conjugated Vaccines

With the shortfalls of polysaccharide vaccines, researchers developed conjugate meningococcal vaccines.\(^\text{17}\) With a conjugated vaccine, the polysaccharide is bound to a protein carrier (usually diphtheria or tetanus toxoid carrier) to enhance the immune response.\(^\text{17}\) This conjugation leads to a memory response and gives more long-term immunity.\(^\text{17}\) The first conjugated meningococcal vaccines developed were conjugated serogroup C polysaccharide vaccines.\(^\text{17}\) In 2001, the meningococcal serogroup C conjugated vaccine was authorized for use in Canada.\(^\text{16}\) This vaccine has decreased the prevalence of serogroup C in Canada and throughout the world.

With the success of the conjugated serogroup C vaccine, a conjugated serogroup A, C, Y and W was introduced.\(^\text{18}\) These vaccines provide significant antibody response for each of the serogroups in the vaccine.\(^\text{16}\) However, studies have shown that effectiveness of the conjugated quadrivalent vaccines also wanes over time. The American Academy of Pediatrics recommends that adolescents who receive their first dose of quadrivalent meningococcal vaccine at age 13 through 15 years should be considered for a 1-time booster, preferably at age 16 through 18 years, to provide additional protection during the period of increased risk.

Meningococcal Multicomponent Serogroup B Vaccine

The latest meningococcal vaccine approved for use in Canada is the meningococcal serogroup B vaccine. This vaccine is different than other vaccines in that it is not based on the polysaccharide capsule of the
bacteria. The vaccine is a novel multicomponent meningococcal serogroup B (4CMenB) vaccine created through a process of reverse vaccinology. Through this process, potential vaccine targets (i.e., antigens) are identified and developed by sequencing the meningococcal serogroup B genome. It contains antigens against some of the other outer surface targets of the bacteria.19

Unlike the conjugated vaccines that target all of the strains of a serogroup (ACWY), the meningococcal serogroup B vaccine protects against certain B strains of the bacteria. Based on serological testing, it was predicted that antibodies produced by the vaccine would cover two-thirds of the types of meningococcal serogroup B in Canada.20

The Pan-Canadian Public Health Network recommendations for use of the multicomponent meningococcal B vaccine in Canada are limited by the lack of evidence and the range of uncertainty of the underlying assumptions, particularly those concerning the vaccine’s coverage of circulating strains, herd immunity, effectiveness and potential adverse effects of vaccination at the population level. Currently, it is not recommended to include the multicomponent meningococcal serogroup B (4CMenB) vaccine in routine immunization programs for Canadian infants, children, adolescents and adults. Immunization of individuals 2 months of age and older should be considered if they are at high risk of meningococcal B disease, if they have been in close contact with a case of invasive meningococcal disease caused by serogroup B, or if they are at risk during invasive meningococcal disease outbreaks caused by serogroup B \textit{N. meningitidis}.4

<p>| Table 4 – Current Meningococcal Vaccines in Canada |</p>
<table>
<thead>
<tr>
<th>Description</th>
<th>Vaccine</th>
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</thead>
<tbody>
<tr>
<td>Quadrivalent (A, C, Y, W) meningococcal polysaccharide vaccine</td>
<td>Menomune®</td>
</tr>
<tr>
<td>Meningococcal C conjugate vaccines</td>
<td>Menjugate®</td>
</tr>
<tr>
<td></td>
<td>NeisVac-C®</td>
</tr>
<tr>
<td></td>
<td>Meningitec®</td>
</tr>
<tr>
<td>Quadrivalent (A, C, Y, W) meningococcal conjugate vaccines</td>
<td>Menactra®</td>
</tr>
<tr>
<td></td>
<td>Menveo™</td>
</tr>
<tr>
<td></td>
<td>Nimenrix™</td>
</tr>
<tr>
<td>Meningococcal serogroup B vaccine</td>
<td>Bexsero™</td>
</tr>
</tbody>
</table>

Efficacy, Effectiveness and Immunogenicity

The Canadian Immunization Guide provides clinicians with some data on efficacy and immunogenicity to provide patients regarding the different vaccines available in Canada.

Clinical Practice Tip:
When discussing vaccines with patients, some may ask about vaccine efficacy. Many of the new vaccines are approved in Canada based on \textbf{immunogenicity data}. This data shows that sufficient antibodies are generated and thus is likely to lead to protection. Some other vaccines have \textbf{efficacy data}, due to higher use in the population. This data shows the effectiveness of a vaccine to reduce the illness in the target recipients. Although immunogenicity is likely a marker for efficacy, these two terms cannot be used interchangeably.
Efficacy and Effectiveness

A study of meningococcal conjugate C vaccine demonstrated effectiveness in infants of 97% within one year of vaccination, decreasing to 68% after 1 year. Longer term vaccine effectiveness requires administration of a booster dose in the second year of life for those immunized in infancy.\(^6\)

The Canadian Immunization guide states that there is data demonstrating that the vaccine effectiveness of Menactra\(^\circledR\) within 3 to 4 years of vaccination in adolescents is 80% to 85%; however, effectiveness wanes over time. There is no efficacy or effectiveness data available for Menveo\(^\text{TM}\) or Nimenrix\(^\text{TM}\).\(^6\)

Vaccine effectiveness measured at an individual level may underestimate the impact of the program on meningococcal disease burden in the community due to the additional benefit conferred by herd immunity through the decrease of nasopharyngeal carriage.

Immunogenicity

Meningococcal conjugated vaccines (C, ACWY) are immunogenic in infants and toddlers but those vaccinated in infancy show a waning immune response. Vaccination with conjugate meningococcal vaccine primes the immune system for memory and induces good antigenic responses; however, antigenic response may not be sufficient to prevent disease after exposure and circulating antibodies are thought to be essential.\(^6\)

Conjugate meningococcal vaccines do not result in hyporesponsiveness and have been shown to overcome the hyporesponsiveness evident with polysaccharide meningococcal vaccine usage.\(^6\)

For the meningococcal serogroup B vaccine, it was predicted that 66% of B strains in Canada would be covered by the vaccine.\(^20\) It was estimated that 26%, 29% and 11% of strains would be covered by one, two, and three of the vaccine antigens, respectively.\(^20\)

Vaccines that are Recommended but Not Funded by the Provincial Immunization Program

Some clinicians are unsure of their obligation to discuss new vaccines not funded by provincial immunization programs.

The Canadian Medical Protective Association (CMPA) has provided some guidance on whether a physician is obliged to recommend a vaccine. An important factor to consider is if the vaccine in the patient’s circumstances is considered the standard of care by other healthcare professionals in the community.\(^21\) If a case were to come before a court regarding vaccine administration, the court might look to standards expressed in:\(^21\)

- Medical publications
- The common practice of other physicians
- Recommendations made by professional bodies or health organizations (e.g. National Advisory Committee on Immunization or the Canadian Paediatric Society)

Specific circumstances such as outbreaks of a particular infection may also influence the standard of care.\(^21\)
With the delay in vaccine coverage under provincial/territorial immunization programs (average-6.5 years) there can be a significant delay from when a vaccine is recommended by the National Advisory Committee on Immunization (NACI) and when it is included in the province’s publically funded schedule.  

By not discussing and offering the patient a unfunded vaccine, the clinician can be placing this individual at risk of a vaccine-preventable disease. Clinicians are encouraged to discuss the risk of the disease, the pros/cons of the vaccine and allow the patient/parent to determine if it is the most appropriate option. Once offered, clinicians should document the patient’s decision and address any questions they have regarding the vaccine.

Clinical Practice Tip:
NACI currently recommends protection against IMD in adolescents and young adults (age 12-24 years). Give adolescents (routinely at 12 years of age) and young adults one dose of either Men-C conjugated vaccine or Men-ACYW conjugated vaccine, even if previously vaccinated as an infant or toddler.

Revisit our Patient

Based on your discussion with Jason and Rebecca, she is going to check with her insurance company to see if the meningococcal B vaccine is covered. Even if it is not covered, she wants Jason to get it. She says that she wants to do everything she can to make sure he is as safe as possible when he is away at university.

Key Learning Points
1. There are serogroups other than C that cause invasive meningococcal disease (IMD)
2. The age groups with the highest risk of IMD are children < 1 year of age, children 1-4 years of age and adolescents
3. IMD can be challenging to diagnose early in the course of the disease
4. Approximately one Canadian every week either dies or suffers a new disability from IMD
5. The lifetime risk of a person in Canada developing IMD is 1 in 1900
6. Although there are risk factors for IMD, many cases occur in healthy patients
7. Meningococci are transmitted person-to-person by mucosal contact with respiratory droplets from the nose and throat of infected persons. Close contact with a patient (e.g. household contacts or living in close quarters) or sharing personal items (e.g. utensils, personal items) can increase the risk of transmission
8. The quadrivalent conjugated vaccines provide significantly higher immune and memory response compared to the polysaccharide vaccine
9. There is a difference between immunogenicity data and efficacy data
10. Clinicians should consider recommending vaccines not funded by provincial/territorial programs to ensure their patients are protected against serious diseases
Discussion Forum:

1. The effectiveness of meningococcal vaccines wanes over time, even the conjugated vaccines. The Advisory Committee on Immunization Practices in the United States (ACIP) and the Joint Committee on Vaccination and Immunisation (JCVI) in the United Kingdom, now recommend a booster for adolescents. Would you recommend the booster dose to your young adult patients given this information?

2. With invasive meningococcal disease (IMD) having such significant negative outcomes, what strategy do you use to start the discussion of IMD protection with your patients?

3. Current Infant public immunization programs only offer coverage against strain C. However, strain predominance causing meningococcal disease changes from year to year and strain C is not the only threat. What do you feel is the most effective way for clinicians to start the discussion with patients on recommended but unfunded vaccines?
Vignette #2 – Protecting Travellers from Common Water/Food Borne Illnesses

Meet your Patient – Paul

Paul (28 yo) is in to see you for a refill of his asthma medications. He has a few questions on how he should transport his inhalers on an airplane and how to adjust his medications while away.

When you ask him about the details of his trip, he says he is travelling to Costa Rica at the end of the month (2.5 weeks from now). He plans to fully immerse himself in the culture and is really looking forward to zip-lining in the rain forest.

You ask him if he went to a travel clinic. He says that this is a last minute trip and he only thought you would need a travel consult if you were taking a trip to the Far-East or to Africa. In addition, there are no travel clinics in your area. He thought you would be able to provide advice – and potentially also link him to other resources so he could learn how to remain healthy in order to enjoy each day of his vacation.

He has brought his travel itinerary to show you. His recommended Canadian immunizations are up-to-date, including the seasonal influenza vaccine. He had not previously travelled outside of Canada. In your province, Paul received his hepatitis B vaccine through the school immunization program. He also has been offered pneumococcal polysaccharide and conjugated vaccine for pneumococcal coverage.

You feel that he is at an elevated risk of food/water borne illness in Costa Rica. You decide to review the lifestyle recommendations (e.g. food/water precautions) and additional vaccines to reduce his risk of food and water-borne infections.

Learning Objectives

Upon successful completion of this continuing education lesson, you will be better able to:

1. Review the most common food/water borne travel related illnesses
2. Discuss the role of dietary modifications to reduce the risk of food/water borne diseases
3. Explore the role of hepatitis A, typhoid, and travellers’ diarrhea immunization to reduce the risk of these infections
4. Customize your prevention strategies for a particular patient
Post Test

1. Using bottled water only while travelling will adequately protect all patients from food/water-borne illness
   a. True
   b. False

2. Case fatality of hepatitis A in adults > 50 years is approximately 2%
   a. True
   b. False

3. Typhoid fever can occur in travellers to South Asia, the Caribbean, South/Central America and Africa
   a. True
   b. False

4. With increasing frequency of antibiotic resistance, typhoid fever can be significantly difficult to treat
   a. True
   b. False

5. Which of the following travel vaccines can be administered the day of travel and still protect the patient from the infectious disease?
   a. Hepatitis A vaccine
   b. Hepatitis B vaccine
   c. Yellow fever
   d. Traveller’s diarrhea/cholera vaccine

6. Which of the following statements regarding gastrointestinal travel related illness is TRUE?
   a. The case fatality of hepatitis A infection is > 20% for all adults
   b. Mexico is a low-risk region of travel for traveller’s diarrhea
   c. All water is best to be avoided during travel
   d. Patients with achlorhydria (e.g. proton pump inhibitors) are at greater risk of acquiring S. typhi infections

Water/Food-Borne Illness

The most common illnesses among travellers are generally caused by eating food or drinking beverages contaminated by bacteria, parasites, or viruses. This is due to poor hygiene, inadequate sanitation and lack of or inadequate water treatment infrastructure in many parts of the world. Bottled water has become the convenient solution for most travellers, but in some places it may not be superior to tap water. Where untreated surface or well water is used and there is no sanitation infrastructure, the risk of waterborne infection is high. Poor hygiene practice in local restaurants is likely a very large contributor to the risk for travellers’ diarrhea. The pathogens in the contaminated water and food are the major causes of travellers’ diarrhea, hepatitis A and typhoid fever.
Clinical Practice Tip:
Even travellers who completely avoid contaminated water may still be exposed to these pathogens through the food they consume or inhaling or swallowing contaminated water while bathing, showering, or participating in recreational activities such as swimming or snorkeling. In some areas it is very difficult to reduce exposure to the microorganisms in water and food.

Common Food/Water Travel Related Illnesses

Travellers’ Diarrhea
Diarrhea is the most common medical problem affecting travellers to developing countries. Attack rates range from 30% to 70% of travellers, depending on the destination and season of travel. Bacterial pathogens are the predominant risk, thought to account for 80%–90% of travellers’ diarrhea (TD). Enterotoxigenic *Escherichia coli* is the most common bacteria associated with travellers’ diarrhea. Viral infections account for 5-8% of infections. Protozoal infections account for approximately 10% of illnesses.

The incubation period for bacterial and viral pathogens is 6–48 hours whereas protozoal pathogens have an incubation period of 1–2 weeks or longer. Bacterial travellers’ diarrhea presents with the sudden onset of bothersome symptoms that can range from mild cramps and urgent loose stools to severe abdominal pain, fever, vomiting, and bloody diarrhea. Viral infections present very similarly to bacterial causes. Protozoal diarrhea generally has a more gradual onset of low-grade symptoms, with 2–5 loose stools per day.

Untreated uncomplicated bacterial diarrhea lasts 3–5 days. Viral gastroenteritis lasts 2–3 days. Protozoal diarrhea can persist for weeks to months without treatment.

Clinical Practice Tip:
For further information on the management of Travellers’ diarrhea, clinicians are encouraged to review the treatment recommendations in the *2016 CDC Yellow Book Chapter on Travellers’ Diarrhea*

Hepatitis A
Hepatitis A is another infectious agent that is commonly transmitted through contaminated water, ice, or shellfish harvested from sewage contaminated water, or from contaminated raw fruits, vegetables or other food. Hepatitis A is shed in the feces of infected people, and can also be acquired through direct person-to-person contact.

The average incubation period is 28 days (range 15–50 days). Infection may be asymptomatic or may range in severity from a mild illness lasting 1–2 weeks to a severely disabling disease lasting several months. In children < 6 years, the infection is mostly (70%) asymptomatic. In adults and older children, signs and symptoms include:

- Anorexia
- Nausea
- Fever
- Fatigue
- Abdominal discomfort, followed within several days by jaundice

The virus is present in bile, blood, stools and liver during the late incubation period and the early acute phase of the illness.

Approximately 25% of adult cases are hospitalized. Treatment is supportive. The average duration of illness is 1 month, but lethargy and weakness can last up to 12 months. The overall case fatality rate is 0.1% to 0.3%, but can reach 1.8% in adults over 50 years of age. Individuals with chronic liver disease have an increased risk of progressing to fulminant hepatic failure resulting in death.\textsuperscript{29}

The period of infectiousness is highly variable but is typically from 2 weeks before onset of symptoms until a week or so after the onset of jaundice. The virus may remain infectious in the environment for several weeks. Viral shedding can be greatly prolonged in immunocompromised persons.\textsuperscript{27} Infants and children (who are often asymptomatic) may shed the virus for up to 6 months after infection.\textsuperscript{25}

**Clinical Practice Tip:**
Most patients infected with hepatitis A will not present with symptoms until after they have returned from their holiday. It is important to assess previous travel and immunization status of all patients presenting with jaundice and other hepatic symptoms. Post-exposure prophylaxis of exposed contacts of the person with hepatitis A can prevent further cases of Hepatitis A.

**Typhoid Fever**
Typhoid fever is a potentially severe and life-threatening febrile illness that is caused by the bacterium *Salmonella enterica* serotype Typhi.\textsuperscript{30} It is usually acquired during travel to a typhoid endemic country.\textsuperscript{31}

Exposure to the causative pathogen is normally through ingestion of water or food that has been contaminated by feces from an ill individual or a chronic carrier.\textsuperscript{31}

The incubation period of typhoid infection is generally 6–30 days, but incubation can vary from 3 days to 3 months.\textsuperscript{30} The clinical course of typhoid ranges from mild illness with low-grade fever to severe systemic disease with abdominal perforation, abdominal hemorrhage and extraintestinal manifestations such as meningitis and endocarditis that, if untreated, can be fatal.\textsuperscript{31}

The onset of illness is insidious, with gradually increasing fatigue and a fever that increases daily from low-grade to as high as 38°C–40°C by the third to fourth day of illness. Headache, malaise, and anorexia are nearly universal.\textsuperscript{30} Abdominal pain, constipation or diarrhea, hepatosplenomegaly, evanescent rose spots (blanching erythematous, slightly raised lesions, especially on the trunk) are not uncommon.\textsuperscript{30}

Hospitalization in North America and Europe is common (75%-90%) with a mean length of stay ranging from 6–10 days. Antibiotic therapy can be life-saving, however typhoid fever can be significantly difficult to treat due to the increasing frequency of antibiotic resistance. The case fatality rate is approximately 10% for untreated cases in low income settings and <1% for patients receiving care in high income countries.\textsuperscript{31}

An estimated 22 million cases of typhoid fever and 200,000 related deaths occur worldwide each year.\textsuperscript{30}
Clinical Practice Tip:
Typhoid fever, travellers’ diarrhea and hepatitis A are transmitted by the fecal-oral route. If a patient is at risk of one of these infections, depending on the epidemiology of infectious diseases in the travel destination(s), protection against one or more of these infectious may be warranted.

Epidemiology of Water/Food Borne Illnesses

Travellers’ Diarrhea
The destination is the most significant factor in determining the overall risk of travellers’ diarrhea. The travellers’ diarrhea risk categories are reviewed in table 1.

<table>
<thead>
<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>Eastern Europe</td>
<td>Asia</td>
</tr>
<tr>
<td>Canada</td>
<td>South Africa</td>
<td>The Middle East</td>
</tr>
<tr>
<td>Australia</td>
<td>Some of the Caribbean islands</td>
<td>Africa</td>
</tr>
<tr>
<td>New Zealand</td>
<td></td>
<td>Mexico</td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td>Central and South America</td>
</tr>
<tr>
<td>Countries in Northern and Western Europe.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Travellers’ diarrhea occurs equally in male and female travellers. Factors that may be associated with a higher probability of acquiring travellers’ diarrhea include adventurous eating habits, gastric hypochlorhydria, immunodeficiency diseases, and the relative lack of gut immunity seen in younger individuals.

Hepatitis A
Hepatitis A is common throughout the developing world. Although the incidence of Hepatitis A has decreased over the past two decades, it remains one of the most common vaccine-preventable diseases in travellers to developing countries.

It is estimated that 44% to 55% of reported cases are linked to travel. Low-budget travellers, volunteer and humanitarian workers, and Canadian-born children of new Canadians returning to their country of origin to visit friends and relatives, may be at increased risk. Many reported cases of hepatitis A have no identifiable risk factors.

Typhoid Fever
The risk of typhoid fever is highest for travellers to southern Asia (6–30 times higher than for all other destinations). Other areas of risk include:

- East and Southeast Asia
- Africa
- The Caribbean
- Central and South America
Clinical Practice Tip:
Travellers visiting friends and relatives (VFRs) in areas with increased prevalence of food and water borne infections are a high risk group. Many of these travellers developed immunity during childhood to ‘travel-related illnesses’. However, with time away from their birth country, immunity decreases and they and their Canadian-born children may be at increased risk of many travel related illnesses. When presented with an immigrant who is returning to their country of birth, provide them with up-to-date Canadian recommended immunizations and consider referring them to a travel clinic.

Non-Pharmacological Recommendations to Prevent Water/Food Borne Illness

The most common illnesses among travellers are generally caused by eating food or drinking beverages contaminated by bacteria, parasites, or viruses. To reduce the risk of these illnesses all international travellers should be encouraged to be selective about the food and beverages they consume.

Food
All raw food is subject to contamination. Raw or undercooked meat, fish, and shellfish can carry various gastrointestinal pathogens. This is particularly the case in areas where hygiene and sanitation are inadequate. Travellers should be advised to avoid:

- Salads
- Uncooked vegetables
- Unpasteurized fruit juices
- Unpasteurized milk and milk products (cheese and yogurt)

Foodborne illness is more prevalent than waterborne disease. Particular attention should be given to the choice of foods. Travellers should wash their hands with soap and water before eating, after using the bathroom or changing diapers, after caring for someone who is ill, and after direct contact with preschool-age children, animals, or feces. If soap and water are not available, they should use a hand sanitizer containing at least 60% alcohol.

The most common recommendation provided to travellers is to:

- “Boil it, Cook it, Peel it or Forget it”

Unfortunately, studies show that travellers who practice these rules may still become ill. This is likely due to poor hygiene practices in local restaurants.

Beverage
In many parts of the world, tap water may contain disease-causing contaminants, including viruses, bacteria, and parasites. Tap water in some places may be unsafe for drinking, preparing food and beverages, making ice, cooking, and brushing teeth. In areas where tap water may be contaminated, commercially bottled water from an unopened, factory-sealed container or water that has been adequately disinfected should be used for brushing teeth and other oral hygiene.
Beverages made with boiled water and served steaming hot (such as tea and coffee) are generally safe to drink.\(^3^2\) When served in unopened, factory-sealed cans or bottles, carbonated beverages, commercially prepared fruit drinks, water, alcoholic beverages, and pasteurized drinks generally can be considered safe.\(^3^2\) Because water on the outside of cans and bottles may be contaminated, they should be wiped clean and dried before opening or drinking directly from the container.\(^3^2\) Because ice may be made from contaminated water, travellers in areas with unsafe tap water should request that beverages be served without ice.\(^3^2\)

Longer-term travellers or those who prefer not to use bottled water due to environmental concerns can use water purification methods for ensuring safe water. Water bottles with filters and various easy to use disinfectant drops or tablets can be found in travel clinics. For more in depth and up-to-date discussion of water purification clinicians can see [Chapter 2 in the 2016 CDC Yellow Book](http://www.cdc.gov/yellowbook/).  

**Clinical Practice Tip:**

When asked questions about safe beverages to consume while travelling, clinicians can suggest that commercially prepared sealed carbonate beverages due to their bactericidal acid environment are generally safe.\(^2^6\)

Table 2 contains a list of recommendations to reduce the risk of food borne illnesses.

### Table 2 – Government of Canada Food and Beverage Recommendations for Travellers\(^3^3\)

- Boil it, cook it, peel it or forget it!
- Always wash your hands before eating or preparing food. It is also important to remember to wash your hands after using the bathroom, changing diapers, or having contact with animals or sick people.
- Use alcohol-based hand sanitizer if soap and water are not available. It’s a good idea to always keep some sanitizer with you when you travel.
- Only eat foods that are well cooked and served hot. Avoid food served at room temperature.
- Avoid raw or undercooked (rare) meats and fish, including shellfish.
- Only eat fruits and vegetables if you have washed them in safe water or peeled them yourself.
- Avoid salads, or other items that are made with fresh produce.
- Avoid food from street vendors.
- Drink water only if it has been boiled or disinfected or if it is in a commercially sealed bottle.
- Use ice made only from purified or disinfected water.
- Commercially sealed beverages in cans or bottles and served unopened, such as carbonated drinks, and drinks made with boiled water and served steaming hot, such as coffee and tea, are generally safe.
- Brush your teeth with purified or bottled water.
- Avoid unpasteurized dairy products and fruit juices.
Vaccines to Prevent Travel Related Common Food/Water Borne Illnesses

Travellers’ Diarrhea

The pathogen that most commonly causes travellers’ diarrhea is enterotoxigenic *E. coli* (ETEC).\textsuperscript{34} Many strains of ETEC produce a heat-labile enterotoxin that is similar to the cholera toxin.\textsuperscript{34} This is the reason that the oral inactivated cholera vaccine (Dukoral\textsuperscript{®}) that contains killed whole cell *Vibrio cholera* and the non-toxic cholera toxin B-subunit has been shown to provide moderate protection against diarrhea caused by ETEC.\textsuperscript{34}

The vaccine has approximately 50% efficacy against diarrhea caused by ETEC and overall protection against travellers’ diarrhea of 23%.\textsuperscript{34} The vaccine can be considered for some travellers who:

- Are at an increased risk of acquiring travellers’ diarrhea (e.g. those with gastric hypochlorhydria, children 2 years of age and older),
- Have chronic illnesses for whom there is an increased risk of serious consequences from travellers’ diarrhea (e.g. chronic renal failure, congestive heart failure, diabetes mellitus, inflammatory bowel disease)
- Are immune suppressed due to HIV infection or other immunodeficiency states or those that cannot tolerate a brief illness (e.g. business travellers, adventure travellers going to remote areas).\textsuperscript{34}

The primary and booster immunization schedule for the oral vaccine is provided in table 3. The vaccine is well tolerated. In clinical trials the rates of adverse effects did not differ significantly between the vaccine and placebo group.\textsuperscript{34} The most common reported adverse events were abdominal pain (16%), diarrhea (12%), nausea (4%), and vomiting (3%).\textsuperscript{34}

<table>
<thead>
<tr>
<th>Table 3 – Dosage of the Oral Vaccine for Travellers’ Diarrhea\textsuperscript{34}</th>
<th>Adults and children aged ≥ 2 years</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary immunization</td>
<td>2 doses at least 1 week but &lt; 6 weeks apart</td>
<td>If &gt; 6 weeks elapse between doses, restart the primary immunization. Children aged 2 to 6 years: one-half the amount of buffer solution is discarded, and the remaining part is mixed with the entire contents of the vaccine vial.</td>
</tr>
<tr>
<td>Booster*</td>
<td>1 dose every 3 months if ongoing risk</td>
<td>If &gt; 5 years have passed since primary immunization or the last booster dose, restart primary series.</td>
</tr>
</tbody>
</table>

*Note: Booster schedule for cholera protection differs from traveller diarrhea protection*
Clinical Practice Tip:
It takes approximately 1 week after the second dose of the oral vaccine for travellers’ diarrhea to provide protection against travellers’ diarrhea. The vaccine can be considered if the person takes it orally 2 weeks prior to travel.\(^\text{34}\)

The oral vaccine for travellers’ diarrhea does not require a medical prescription except in the province of Quebec. Travellers should either purchase this oral vaccine at a travel clinic, or speak to their local pharmacist so that the pharmacist will have time to obtain the oral vaccine for travellers’ diarrhea when needed.

Hepatitis A
Hepatitis A is one of the most common vaccine preventable diseases in travellers. Protection against hepatitis A is recommended for all travellers to developing countries, especially to rural areas or places with inadequate sanitary facilities.\(^\text{29}\) CATMAT recommends that all non-immune travellers to developing countries should receive an inactivated hepatitis A vaccine.\(^\text{28}\)

There are a number of vaccines for hepatitis A. Some of these vaccines are combined with other antigens to protect against other disease states.\(^\text{29}\) The currently available vaccines are listed in table 4.

<table>
<thead>
<tr>
<th>Vaccine Targeting</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Avaxim®, Avaxim® Pediatric, Havrix® 1440, Havrix® 720, Vaqta®, Vaqta® Pediatric/Adolescent</td>
</tr>
<tr>
<td>Hepatitis A and Typhoid</td>
<td>Vivaxim®</td>
</tr>
<tr>
<td>Hepatitis A and B</td>
<td>Twinrix®, Twinrix® Junior</td>
</tr>
</tbody>
</table>

Currently available hepatitis A vaccines given prior to travel are at least 85-90% effective in preventing clinical illness.\(^\text{29}\) Due to the long incubation period for the hepatitis A virus, most of the vaccines listed in table 4 (the only exception is the combination hepatitis A and B vaccine, which contains a lower dose of hepatitis A antigen) can be administered up to the day of departure and still provide protection for travellers.\(^\text{29}\)

The combination vaccines can be excellent choices for patients who are likely to be exposed to multiple travel related illnesses. There is currently a vaccine that protects against both hepatitis A and B and a vaccine that protects against typhoid and hepatitis A. In patients that require protection for two conditions, these combinations vaccines can be both cost effective and improve adherence to the regimen.
Clinical Practice Tip:
It is important for clinicians to know the immunization schedule of their province/territory of practice or of the patients’ province/territory when they were receiving childhood immunizations. Many youth and young adults will have been immunized against hepatitis B through the province’s/territory’s public immunization program and will not need to be reimmunized again to travel.

Table 5 reviews the administration schedules of each of the vaccines that offer protection against hepatitis A.

<table>
<thead>
<tr>
<th>Name of Vaccine</th>
<th>Dosing Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avaxim™</td>
<td>0.5 mL IM 0, 6-36 months</td>
<td>≥ 12 years old</td>
</tr>
<tr>
<td>Avaxim™ Pediatric</td>
<td>0.5 mL IM 0, 6-36 months</td>
<td>1-15 years old</td>
</tr>
<tr>
<td>Havrix™ 1440</td>
<td>1.0 mL IM 0, 6-12 months</td>
<td>≥ 19 years old</td>
</tr>
<tr>
<td>Havrix™ Jr. 720</td>
<td>0.5 mL IM 0, 6-12 months</td>
<td>1-18 years old</td>
</tr>
<tr>
<td>Vaqta®</td>
<td>1.0 mL IM 0, 6-18 months</td>
<td>≥18 years old</td>
</tr>
<tr>
<td>Vaqta® Pediatric/Adolescent</td>
<td>0.5 mL IM 0, 6-18 months</td>
<td>1-17 years old</td>
</tr>
</tbody>
</table>

**Combination Vaccines**

<table>
<thead>
<tr>
<th>Name of Vaccine</th>
<th>Dosing Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twinrix® Adult</td>
<td>1.0 mL IM 0, 1, 6 months</td>
<td>≥ 19 years old</td>
</tr>
<tr>
<td>Twinrix® Junior</td>
<td>0.5 mL IM 0, 1, 6 months</td>
<td>1-18 years old</td>
</tr>
<tr>
<td>Vivaxim™</td>
<td>1.0 mL IM 0, 6-36 months*</td>
<td>≥ 16 years old</td>
</tr>
</tbody>
</table>

* - booster doses can be either a hepatitis A (6-36 months) or the combination vaccine (month 36)

The combination hepatitis A/B vaccine has a rapid schedule for adults where the vaccine is given at days 0, 7, 21 and 360. This alternative schedule can be used in patients presenting between 21 and less than 28 days prior to travel. If the patient presents < 21 days prior to travel they should receive a monovalent hepatitis A or the hepatitis A/typhoid vaccine and the hepatitis B vaccine separately. The combination hepatitis A/B vaccine has a lower dose of hepatitis A antigen than the other vaccines and thus will not offer full protection against hepatitis A if started this late before a trip, but also has an accelerated regimen to offer more rapid protection.

The adverse effects of hepatitis A vaccines are mild and transient. Local reactions such as soreness and redness at the injection site happen in approximately 50% of recipients. Headache and malaise have also been infrequently reported.

Clinical Practice Tip:
Consider developing a recall method for travel vaccines requiring booster doses. Many patients will forget these doses and this will reduce the long-term protection of these vaccines. If you are not a physician working in a travel clinic, it would be important to know that the local pharmacist does have the travel vaccines noted above available, so that the traveller can purchase the vaccines just prior to coming to your office to have the vaccine(s) administered.
Typhoid Vaccine

Generally, Canadians who acquire typhoid fever do so when travelling in a typhoid endemic country.\textsuperscript{31} Globally, it is estimated that more than 90\% of typhoid cases and deaths occur in Asian countries, predominantly in South Asia.\textsuperscript{35} CATMAT suggests that typhoid vaccine be used for Canadian travellers visiting South Asia.\textsuperscript{31} The estimated risk of developing travel associated typhoid is about 1/3000 travellers for travel to South Asia (high risk), 1/50,000-1/100,000 for travel to Sub-Saharan Africa, North Africa and the Middle East, or South America (intermediate risk) and <1/300,000 for travel to the Caribbean and Central America (low risk).\textsuperscript{35}

CATMAT recommended that the decision of whether or not to use typhoid vaccination for destinations other than South Asia might be influenced by other factors of travel associated typhoid infection such as:\textsuperscript{31}

- Pediatric travel
- Visiting friends and relatives
- Longer duration of travel
- The presence of achlorhydria or use of acid suppression therapy
- Patient preference and risk tolerance

All vaccine efficacy studies were performed in populations living in endemic areas; this data has been extrapolated to travellers. Efficacy of typhoid vaccine (oral and intramuscular formulations) in preventing typhoid is approximately 50\%.\textsuperscript{35} Typhoid vaccines protect against \textit{Salmonella typhi}, but not \textit{Salmonella paratyphi}.

The current Canadian typhoid vaccines are reviewed in table 6.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Brand name} & \textbf{Parenteral inactivated vaccines (capsular polysaccharide vaccines)} & \textbf{Oral, live attenuated vaccine} & \textbf{Combined hepatitis A and inactivated typhoid vaccine} \\
\hline
\textbf{Indicated ages} & \begin{tabular}[c]{@{}l@{}}Typhim Vi\textsuperscript{®} \& \\Typherix\textsuperscript{®}\end{tabular} & \begin{tabular}[c]{@{}l@{}}Vivotif\textsuperscript{®}\end{tabular} & \begin{tabular}[c]{@{}l@{}}Vivaxim\textsuperscript{®}\end{tabular} \\
\hline
\textbf{Protection begins} & \begin{tabular}[c]{@{}l@{}}≥ 2 years of age\end{tabular} & \begin{tabular}[c]{@{}l@{}}≥ 5 years of age\end{tabular} & \begin{tabular}[c]{@{}l@{}}≥ 16 years of age\end{tabular} \\
\hline
\textbf{Dose and schedule} & 14 days following vaccination & 7 days following last dose & 14 days following vaccination \\
\hline
\textbf{Route of administration} & Intramuscular injection once & Orally in a series of doses & Intramuscular injection once \\
\hline
\textbf{Contraindications} & Individuals with hypersensitivity or anaphylaxis to any component of the vaccine or its container. & Pregnancy & Individuals with hypersensitivity or anaphylaxis to any component of the vaccine or its container. \\
\hline
\end{tabular}
\caption{Typhoid Vaccines Authorized for Use in Canada\textsuperscript{35}}
\end{table}
coated capsule.

Individuals with an acute gastrointestinal condition or inflammatory bowel disease and in immunocompromised persons.

Ty21a vaccination should be completed before commencing treatment with antibiotics.

Chloroquine, mefloquine and malarone do not influence the immune response of Ty21A and can be administered at any interval. When using any other antimalarial, immunization should precede antimalarial prophylaxis using the 3 day interval.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Re-immunization</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid</td>
<td>Every 3 years</td>
<td>The adverse effects of typhoid vaccines are generally mild. The most common adverse effects of the injectable formats are injection site tenderness, induration, redness or pain, fever, headache, general malaise or myalgia. The oral typhoid vaccine’s most common adverse effects include abdominal pain, nausea, diarrhea, vomiting, fever, headache and rash.</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Every 7 years</td>
<td>Hepatitis A - boost with a single dose of hepatitis A vaccine 6 months to 36 months later for long term protection. Typhoid - re-immunize with a single dose of typhoid vaccine injection every 3 years if at risk. The combination vaccine can be used after 3 years if boosters are needed for both hepatitis A and typhoid.</td>
</tr>
</tbody>
</table>

35
Clinical Practice Tip:

In immunocompromised individuals, primary immunization and/or reimmunization may be contraindicated, depending on the underlying cause of the immunocompromise or the type of vaccine.

In immunocompetent individuals, it is generally safe to revaccinate (unless they have developed allergies related to vaccine[s]). This reduces the risk of the traveller not being adequately protected due to waning immunity. If the person reported receiving previous doses, confirmation through written or electronic records is recommended. Patients often verbally report incorrectly having received previous doses of vaccines.

Travel Health Recommendations in Primary Care

It is quite common for travellers to developing countries to not go to a travel clinic prior to a trip. This can place them at increased risk of travel-related illnesses. Also many patients will present in primary care wanting to receive immunizations and protection only days prior to travel. With water/food-borne illnesses being some of the most common travel-related illnesses and the vaccines being generally well-tolerated, primary care clinicians should consider discussing them with travellers. Food/beverage recommendations should be provided to all patients. Primary care clinicians should consider providing information regarding each of the vaccines and allowing the patient to determine if they feel they can benefit from the different vaccines.

Combination vaccines are encouraged if the patient requires protection against multiple vaccine-preventable diseases as it is convenient and may be less expensive.

Revisit our Patient

You discuss with Paul the importance of asthma control while away on holidays. You recommend that he bring his inhalers in their original containers in his carry-on luggage so that they are available to him, in case his luggage is delayed or lost. Fortunately, he is travelling to a country in the same time zone. Therefore, there would not need to be special adjustments to the timing of his asthma medications. You also recommend that he purchase health insurance for Canadians travelling outside of Canada in case he does require emergency care in Costa Rica.

You review the food/beverage recommendations for his trip. He did not even realize that there were serious diseases where he was travelling. He was glad to hear about the different available vaccines. He would like to do everything he can to minimize his risk of getting sick. You discuss the protection of each condition and mention that he has sufficient time prior to his trip. You feel that with the right diet strategy and appropriate immunizations, he will be doing everything he can to protect himself from these travel-related diseases.

You remind Paul that prior to any future trips it is a good idea to see a travel clinic at least 4 weeks prior to departure so they can assess his vaccination status and discuss non-vaccine preventable illness.
Key Learning Points

1. The major travel related illnesses associated with inadequate water and sanitation are travellers’ diarrhea, hepatitis A and typhoid fever
2. Travellers’ diarrhea occurs in approximately 30-70% of travellers
3. Dietary changes are many times not effective at protecting against water/food borne illnesses. Poor hygiene practice in local restaurants is likely a large contributor to the risk for travellers’ diarrhea
4. Hepatitis A is commonly transmitted through contaminated food and water
5. An estimated 22 million cases and 200,000 related deaths worldwide are associated with typhoid fever
6. The case fatality rate with Hepatitis A in patients > 50 years is 1.8%
7. When presented with a patient who is travelling to an area where food-borne illnesses are common, consider protection against several vaccine-preventable diseases including hepatitis A, typhoid and Enterotoxigenic E. coli/cholera
8. Before recommending hepatitis A vaccine for travellers, it is important to ask about their hepatitis B immunization status. Many young travellers are already protected against hepatitis B. If not, the combination vaccine with both hepatitis A and B is recommended if there is enough time prior to departure.

Discussion Forum:

1. How do you discuss the risk of travel-related illnesses with your patients? Do you refer your patients to travel clinics in your community or do you usually manage travel health related questions?
2. What type of education do you require to improve the travel health education you provide your patients?
Vignette #3 – Yellow Fever Risk in The Americas – It Is Not Just in Africa

Meet our Patient – David

David (41 yo) and his wife Laura are planning a vacation to the Amazon rain forest in Brazil. They are looking forward to the incredible trip. They have planned to stay at a floating lodge down the river from Manaus in the heart of the Amazon. Their trip is booked in 4 months.

David was seen at a travel clinic earlier this week regarding the upcoming trip. They suggested a variety of vaccines to prevent infectious diseases. Due to his travel itinerary, he would be a candidate for the yellow fever vaccine. There were quite a few recommendations.

He wants to know what you think. He would love to hear your thoughts if he should receive this vaccine or should he just skip it.

Learning Objectives

Upon successful completion of this continuing education module, you will be better able to:

1. Discuss the transmission and epidemiology of yellow fever
2. Be familiar with the clinical presentation and disease course of yellow fever infection
3. Review the non-pharmacological recommendations to reduce the risk of yellow fever
4. Counsel a patient on the requirement or recommendation for the yellow fever vaccine prior to entering certain countries, as well as precautions and contraindications associated with yellow fever vaccine administration.

Post Test

1. Yellow fever vaccine should only be administered to patients travelling to countries where proof of immunization is required for entry
2. The risk of yellow fever is increased when travelling to countries during the dry season
   a. True
   b. False

3. The yellow fever vaccine has a seroconversion rate of 95% to 99%
   a. True
   b. False

4. The yellow fever vaccine is currently indicated for healthy persons over 9 months of age
   a. True
   b. False

5. You have a patient who is travelling to an area where yellow fever is endemic. Which of the following is/are a Committee to Advise on Tropical Medicine and Travel (CATMAT) recommendation to prevent being bitten by infected mosquitoes?
   a. Choosing an insect repellent containing 20-30% DEET for adults
   b. Using air-conditioning when possible
   c. Wear loose fitting, full length and light-coloured garments
   d. All of the above

6. Your patient requires the yellow fever vaccine. Which of the following is TRUE?
   a. It is an inactivated travel vaccine
   b. It is required at least 14 days prior to entry to all countries with endemic yellow fever
   c. It cannot be administered at the same time as any other vaccines
   d. The vaccine can only be administered in approved yellow fever vaccination centres

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**The Yellow Fever Virus**

The yellow fever virus is a single-stranded RNA virus. Yellow fever is a vector-borne illness transmitted by the bite of an infected mosquito. The World Health Organization (WHO) estimates that approximately 200,000 yellow fever cases occur each year, resulting in up to 30,000 deaths.

There are three transmission cycles which describe the occurrence of yellow fever. These cycles are reviewed in table 1.

<table>
<thead>
<tr>
<th>Table 1 – Transmission Cycles of Yellow Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jungle transmission</td>
</tr>
<tr>
<td>- Occurs in the jungle environments</td>
</tr>
<tr>
<td>- Multiple mosquito species (including <em>Aedes</em> and <em>Haemagogus</em> species) transmit the virus between non-human primate hosts</td>
</tr>
<tr>
<td>- Humans are infected sporadically</td>
</tr>
<tr>
<td>- Humans living and working within or near the jungle are at risk of acquiring the disease</td>
</tr>
</tbody>
</table>

| Urban transmission                          |
| - Occurs in more metropolitan areas where *Aedes aegypti* mosquito acts as the main vector |
| - Urban yellow fever cycles usually result in an epidemic after the virus has been introduced either by an infected mosquito or a human carrying the yellow fever virus. |
| - Due to the greater population density, can result in explosive epidemics |

| Intermediate                                 |
| - Occurs in smaller rural villages, where humans and monkeys live in |
Humans infected with the yellow fever virus experience the highest levels of viremia and can transmit the virus to mosquitoes shortly before onset of fever and for the first 3–5 days of illness.\(^\text{36}\) Given the high level of viremia, blood borne transmission theoretically can occur via transfusion or needlesticks.\(^\text{36}\)

### The Traveller’s Yellow Fever Risk

Yellow fever is endemic and intermittently epidemic in parts of Africa and South America.\(^\text{37}\) While the mosquito vectors are present in Asia, there have been no documented cases of transmission on this continent.\(^\text{37}\) Most yellow fever disease in humans is due to jungle or intermediate transmission cycles. Urban yellow fever occurs periodically in Africa and sporadically in the Americas.\(^\text{36}\) Table 2 reviews the countries with risk of yellow fever transmission.

<table>
<thead>
<tr>
<th>Africa</th>
<th>Central and South America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>Argentina†</td>
</tr>
<tr>
<td>Benin</td>
<td>Bolivia†</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Brazil†</td>
</tr>
<tr>
<td>Burundi</td>
<td>Colombia†</td>
</tr>
<tr>
<td>Cameroon</td>
<td>Ecuador†</td>
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<tr>
<td>Central African Republic</td>
<td>French Guiana</td>
</tr>
<tr>
<td>Chad†</td>
<td>Guyana</td>
</tr>
<tr>
<td>Congo, Republic of the Côte d’Ivoire</td>
<td>Panama†</td>
</tr>
<tr>
<td>Democratic Republic of the Congo†</td>
<td>Paraguay</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>Peru†</td>
</tr>
<tr>
<td>Ethiopia†</td>
<td>Suriname</td>
</tr>
<tr>
<td>Gabon</td>
<td>Trinidad and Tobago†</td>
</tr>
<tr>
<td>Gambia, The</td>
<td>Venezuela†</td>
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<tr>
<td>Ghana</td>
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<tr>
<td>Guinea</td>
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<td>Guinea-Bissau</td>
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<td>Kenya†</td>
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<td>Liberia</td>
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<td>Mali†</td>
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<td>Mauritania†</td>
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<td>Niger†</td>
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<td>Nigeria</td>
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<td>Rwanda</td>
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<td>Senegal</td>
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<td>Sierra Leone</td>
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<tr>
<td>Sudan†</td>
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</tr>
<tr>
<td>South Sudan</td>
<td></td>
</tr>
<tr>
<td>Togo</td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td></td>
</tr>
</tbody>
</table>

\(^\dagger\) - In these countries only a portion of the country has a risk of yellow fever transmission

Note: Eritrea, Rwanda, São Tomé and Príncipe, Somalia, Tanzania, Zambia are countries with low potential exposure to yellow fever, but may be considered in patients if extended rural exposure.

It is very difficult to estimate the patient’s risk of acquiring yellow fever.\(^\text{37}\) Along with the travel destination, the season of travel, occupational/recreational activities and local yellow fever virus activity all determine a traveller’s risk. These factors are reviewed in table 3.

**Table 3 – Factors Influencing a Traveller’s Risk of Yellow Fever**\(^\text{37,38}\)

<table>
<thead>
<tr>
<th>Destination</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A traveller’s destination influences yellow fever risk in many ways</td>
</tr>
<tr>
<td></td>
<td>Yellow fever is one of the few communicable diseases that has international regulations that govern its control</td>
</tr>
<tr>
<td></td>
<td>Some countries require proof of immunization against yellow fever for travellers arriving from or transiting through a yellow fever endemic</td>
</tr>
</tbody>
</table>
Some countries where yellow fever circulates do not require vaccination for entrance (e.g. Brazil) and therefore unvaccinated travellers may be at greater risk, especially if visiting a yellow fever risk area.

**Season**
- Vertical transmission occurs with the yellow fever virus from female mosquito to her larvae. The number of mosquitoes generally increases during and following the ‘wet season’.
- Transmission in rural West Africa is seasonal:
  - An elevated risk during the end of the rainy season and the beginning of the dry season (usually July–October).
  - It may be episodically transmitted even during the dry season in both rural and densely settled urban areas.
- The risk for infection in South America is highest during the rainy season (January–May, with a peak incidence in February and March).

**Occupational & Recreational activities**
- Outdoor activities which expose travellers to mosquitoes during prime biting hours (daytime) can increase risk of yellow fever transmission.

**Local yellow fever virus activity**
- Yellow fever virus activity fluctuates.
- There have been sporadic outbreaks in the last few years in Africa and South America.
- These risks should all be taken into consideration by travellers and travel health practitioners during pre-travel consultation to determine the need for yellow fever vaccination.

---

### Clinical Practice Tip:
A traveller's yellow fever risk is based on their travel itinerary, time of travel and the activities within the area of risk. Up-to-date epidemiology data is important to make informed choices. Making a recommendation not to immunize the traveller, solely based on the countries to be visited, and not areas of yellow fever risk within the country could place a traveller at elevated risk of yellow-fever or of unnecessary vaccination.

---

### Clinical Presentation, Morbidity and Mortality
The clinical presentation of yellow fever varies in severity from asymptomatic to fatal.\(^{37}\) For patients who develop symptoms, the incubation period is usually 3-6 days.\(^{37}\) The initial illness presents as a nonspecific influenza-like syndrome with a sudden onset of:

- Fever
- Chills
- Headache
- Back pain
- Muscle and joint pain
- Prostration
- Photophobia
- Nausea and vomiting.
- Mild jaundice that worsens as disease progresses
- Epigastric pain
- Faget’s sign may be present (slow weak pulse, contrasting with high fever)

In an estimated 85% of yellow fever cases, the disease resolves without intervention. In the remaining 15% of patients, these symptoms are followed by a brief remission between hours to a day. Then, the condition worsens and the disease advances in the liver eventually leading to multi-organ failure – including renal failure, hemorrhagic symptoms, and thrombocytopenia.

The case-fatality ratio for severe cases with hepatic and renal dysfunction is 20%–50%.  

Clinical Practice Tip:
There are no specific treatments for patients with yellow fever viral infection. Any options are designed to reduce the symptoms or supportive to provide life saving interventions.  

For this reason, patients should be aware of the risk of the infection and the role of immunization to prevent the morbidity and mortality from yellow fever.

Non-Pharmacological Prevention Strategies
The Committee to Advise on Tropical Medicine and Travel (CATMAT) stresses the importance of strategies to reduce the risk of vector transmission.  

A summary of the CATMAT recommendations for arthropod protection is provided in table 4.

| Address to Arthropods | Avoid travelling during the season when infection transmission is most likely to occur
<table>
<thead>
<tr>
<th></th>
<th>Reduce being outside during peak biting hours (Note: The mosquitoes that transmit yellow fever are active throughout the day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Barriers</td>
<td>Use screening on doors and windows, close eaves, eliminate holes in roofs and walls and close other gaps around a building</td>
</tr>
<tr>
<td></td>
<td>Wear appropriate clothing (e.g., full length, loose fitting and light-coloured garments)</td>
</tr>
<tr>
<td>Chemical Barriers</td>
<td>Repellents that contain DEET (20-30%) or icaridin/picaridin (20%) should be the first choice for adults</td>
</tr>
<tr>
<td></td>
<td>Repellents that contain icaridin/picaridin (20%) should be the first choice for children aged six months to twelve years. Lower DEET concentrations can be used second-line in children</td>
</tr>
<tr>
<td></td>
<td>For travel outside of Canada to endemic/epidemic areas, the risk for arthropod-associated diseases (AAD) likely outweighs the risk of an adverse reaction to DEET or icaridin/picaridin. In such situations and if vectors cannot be otherwise excluded (e.g., through use of insecticide-treated netting), use of up to 10% DEET or 10% icaridin/picaridin should be considered for infants under six months of age.</td>
</tr>
<tr>
<td></td>
<td>Do not use repellent and sunscreen combination products.</td>
</tr>
<tr>
<td></td>
<td>It is preferable to apply sunscreen first and allow it to penetrate the skin</td>
</tr>
</tbody>
</table>
before applying repellent.

<table>
<thead>
<tr>
<th>Bed Nets</th>
<th>Use insecticide-treated nets for protection against arthropod bites and related diseases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clothing Treatment</td>
<td>Use insecticide-treated clothing to protect against the bites of vectors and nuisance arthropods.</td>
</tr>
</tbody>
</table>
| Do NOT use any of these unproven methods | Electronic (ultrasonic) devices  
Wristbands, neckbands, and ankle bands impregnated with repellents  
Electrocuting devices ("bug zappers")  
Odour-baited mosquito traps  
Citrosa plant (geranium houseplant)  
Orally administered vitamin B1  
Skin moisturizers that do not contain an approved repellent active ingredient. |

Yellow Fever Vaccine

Yellow fever is preventable by a relatively safe, effective vaccine. The vaccine used in Canada, is a live attenuated preparation grown in chick embryos inoculated with the 17D yellow fever virus strain in Canada. The vaccine has a seroconversion rate of 95% to 99%; immunity persists for more than 10 years following vaccination.

The vaccine is recommended for healthy persons 9 months of age to less than 60 years of age. It may be considered in infants 6 to 8 months of age and in people aged 60 years and over travelling to areas where risk of yellow fever is highest.

In Canada, the yellow fever vaccine can only be administered at designated Yellow Fever Vaccination Centres. A list of these centres can be found on the Public Health Agency of Canada’s website. For some countries (table 5) an International Certificate of Vaccination or Prophylaxis is required prior to entry. The certificate of vaccination is valid for a period of 10 years, commencing 10 days after the initial vaccination or immediately upon re-immunization. Re-immunization should be considered at 10 year intervals; however there is evidence that seroconversion bestows longer protection and may be lifelong.

The vaccine can be co-administered with other vaccines. Since it is a live-attenuated vaccine, it can be given on the same day with another live attenuated vaccine, but if the patient has received a live attenuated parenteral vaccine in the previous 28 days, the yellow fever vaccine should be delayed until 28 days have elapsed.

**Clinical Practice Tip:**

In 2013, the World Health Organization published a document that one dose of the yellow fever vaccine was sufficient for life-long protection and a booster dose was not required. This recommendation has not yet been approved by all countries requiring yellow fever documentation prior to entry. Travellers to countries where yellow fever is endemic should check with their country of travel and the travel clinic to determine the yellow fever vaccine requirements for entry.
Table 5 – Countries that require proof of yellow fever vaccination from all arriving travellers†

- Angola
- Benin
- Burkina Faso
- Burundi
- Cameroon
- Central African Republic
- Congo
- Côte d’Ivoire
- Democratic Republic of the Congo
- French Guiana
- Gabon
- Guinea-Bissau
- Liberia
- Mali
- Niger
- Rwanda
- Sierra Leone
- Togo

† - Country requirements for yellow fever vaccination are subject to change at any time; therefore, travellers should check with the destination country’s embassy or consulate before departure.

A number of rare, but serious reactions to yellow fever vaccination have been documented. As with any therapy, there are major and minor adverse events associated with a certain percentage of the population receiving the intervention. The goal of any therapy is to employ it only when the benefits of the intervention outweigh potential harms.

Yellow fever vaccine is generally well tolerated. Reactions to the vaccine are usually mild and transient in nature and include headaches, myalgias and low-grade fevers. Reactions usually begin a few days after vaccination and last five to ten days post dose. There is a wide variability (2-30%) in the frequency of report of mild adverse events. Less than one percent of recipients had to curtail daily activities due to an adverse event following vaccination.

Although rare, there have been a range of serious adverse events which have been recorded following yellow fever vaccination, occurring up to one month after vaccination. These are reviewed in Table 6.

Table 6 – Serious Adverse Events with the Yellow Fever Vaccine

<table>
<thead>
<tr>
<th>Hypersensitivity Reaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- These are rare events</td>
</tr>
<tr>
<td></td>
<td>- Immediate type hypersensitivity reactions (rash, urticaria, asthma, anaphylaxis) can occur.</td>
</tr>
<tr>
<td></td>
<td>- Anaphylaxis after yellow fever vaccine is reported to occur at a rate of 1.8 cases per 100,000 doses administered</td>
</tr>
<tr>
<td></td>
<td>- Hypersensitivity reactions occur primarily in people with sensitivity to egg proteins and/or chicken. The gelatin stabilizer used in the vaccine has also been implicated</td>
</tr>
<tr>
<td></td>
<td>- People with allergies to eggs, chicken, or gelatin should not receive the vaccine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yellow fever associated neurotropic disease (YEL-AND)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- YEL-AND was once a syndrome characterized by fever and encephalitis in young children</td>
<td></td>
</tr>
<tr>
<td>- YEL-AND now describes a grouping of clinical syndromes: meningoencephalitis, auto-immune involvement of the central nervous system and/or auto-immune involvement of the peripheral nervous system (Guillain Barré syndrome) and rarely bulbar and Bell palsy, which can present in any age group, between four and 23 days post vaccination</td>
<td></td>
</tr>
<tr>
<td>- Studies suggest that older age is a risk factor</td>
<td></td>
</tr>
<tr>
<td>- Reported rate of 0.8 cases per 100,000 doses of yellow fever vaccine administered</td>
<td></td>
</tr>
</tbody>
</table>
WHO reports that there have been 26 proven or probable cases of YEL- AND since 1945, with two fatalities.

Rate is double for those over age 60 and quadruples for those over age 70. When infants and elderly are not given the vaccine, recent surveillance data suggest population-based incidence rates drop close to zero.\(^\text{42}\)

### Yellow Fever Vaccine Associated Viscerotropic Disease (YEL-AVD)

- Characterized by severe illness and multi-organ failure, similar to that seen in yellow fever disease.
- YEL-AND tends to develop 2 to 5 days post-vaccination.
- Seen almost exclusively with primary vaccination.
- Recent analysis estimates risk of developing YEL-AVD to be 0.5-6 per 1 million doses, risk of death being 0.5 per 1 million doses.\(^\text{42}\)
- These reactions have been linked to host characteristics including older age (≥60 years) and thymus disease associated with abnormal immune function (e.g. thymoma and myasthenia gravis).
- Since the initial cases of YEL-AVD were published in 2001, >60 confirmed and suspected cases have been reported through the world.

Despite the emerging information on YEL-AND and YEL-AVD, the yellow fever vaccine is highly effective and generally safe. The important message here is to ensure that the exact reason for vaccination is understood (risk of exposure versus international regulations). It is also crucial to avoid exposing travellers to the very small, but non-negligible, risk of yellow fever vaccination if there is no actual risk or requirement for vaccination.

There are several precautions and contraindications to yellow fever vaccine use. These are reviewed in Table 7.

### Table 7 – Contraindications and Precautions to the Yellow Fever Vaccine\(^\text{41}\)

**Contraindications**

- Infants younger than 6 months of age
- Hypersensitivity to any of the vaccine components, including eggs, egg products, chicken proteins, or gelatin.
- Altered immune status:
  - Thymus disorder associated with abnormal immune cell function, such as thymoma or myasthenia gravis
  - HIV infection including individuals with the CD4 T-lymphocyte values <200 mm\(^3\) or <15% of total lymphocytes for children aged <6 years
  - Other immunodeficiencies including primary immunodeficiencies, malignant neoplasms and transplantation
  - Immunosuppressive and immunomodulatory therapies – as current or recent radiation therapies or drugs may suppress or modulate the immune response

**Precautions**

- Infants aged 6-8 months of age
- Adults 60 years of age and older, particularly if this is the first dose of yellow fever vaccine given
- HIV infection – asymptomatic individuals with CD4 T-lymphocyte values 200-499/mm\(^3\) or 15-24% of total lymphocytes for children aged <6 years
- Pregnancy
- Breastfeeding. Three YEL-AND cases have been reported in exclusively breastfed infants whose mothers were vaccinated with yellow fever vaccine.
All 3 infants were aged <1 month at the time of exposure. Until more information is available, yellow fever vaccine should be avoided in breastfeeding women.

Exemption certificates may be provided to patients for whom the vaccine is contraindicated and must travel; however, risks need to be reviewed with patients and avoidance of travel to these destinations need to be considered. Clinicians interested in reading more on the use of the yellow fever vaccine in these populations are referred to the CATMAT Statement for Travellers and Yellow Fever where each of these high-risk conditions are discussed in detail.

Revisit our Patient – David

You provide David with information regarding yellow fever and the vaccine. You explain that although Brazil does not require proof of the vaccine for entry, it does not mean the country is free of yellow fever. Due to the World Cup of Soccer in Brazil in 2014 – and the Summer Olympic and Paralympic Games in Brazil in 2016, the Ministry of Health Secretariat of Health Surveillance of the Government of Brazil has listed the yellow fever vaccine recommendations by state and municipalities. Yellow fever vaccine is recommended for Amazonas.

You explain that based on his activities in the Amazon region of Brazil, and from your knowledge of his medical history in which he has no contraindications or precautions for yellow fever vaccine, you would recommend that he receive the yellow fever vaccine to prevent a potentially severe and fatal disease.
Key Learning Points

1. Yellow fever is endemic in parts of Africa, Central and South America
2. The destination of travel is one factor that determines the patient’s yellow fever risk. Other factors to consider include the season of travel, activities planned in the country and local yellow fever activity.
3. Some countries require proof of yellow fever vaccination to enter their country. This does not always correlate with the traveller’s actual risk of acquiring the disease.
4. There are no specific treatments for yellow fever infections. The case fatality can be 20-50%
5. The yellow fever vaccine has a seroconversion rate of between 95-99%
6. Although yellow fever vaccine is generally well tolerated, a number of rare, but serious reactions to yellow fever vaccine have been documented
7. Yellow fever vaccine is recommended for healthy travellers (9 months to less than 60 years of age) passing through, visiting or living in areas where yellow fever is considered endemic, or if yellow fever immunization is required to enter the country.
8. The yellow fever vaccine is only administered at designated yellow fever vaccination centres. These centres also provide an International Certificate of Vaccination or Prophylaxis that will accompany the traveller. The certificate of vaccination is valid for a period of 10 years, commencing 10 days after the initial vaccination or immediately upon re-immunization.
9. For those people who cannot be vaccinated, the traveller may be provided with a waiver outlining the medical reason for not receiving the vaccination at the Yellow Fever Vaccination Centre. This is a Certificate of Medical Contraindication to Vaccination issued by the Public Health Agency of Canada.

Discussion Forum

1. Some patients underestimate their risk of travel-related illnesses. How do you encourage your patients to ensure they are properly immunized against these diseases?
2. Do you currently recommend the yellow fever vaccine for your patients who are travelling to endemic areas? What tools would you require to make travel-related immunization recommendations in your practice?
Vignette #4 – Influenza Vaccine - Quadrivalent or Trivalent: What’s the Difference?

Meet our Patient – Ashley
Ashley (34 yo) is in to see you for a refill for her son Adam’s (5 yo) fluticasone inhaler. You ask her if she has received her flu shot for this season.

She says that she never gets the flu shot. She feels that she is in good health and has heard the vaccine is associated with serious adverse effects and is not very effective. She is worried that the flu shot may make her sick as she is currently looking after her own kids as well as her elderly parents.

You feel there is a great educational gap and decide to discuss the role of influenza prevention for Ashley and her family.

Learning Objectives
Upon successful completion of this continuing education lesson, you will be better able to:

1. Discuss the clinical presentation, complications and at risk populations for influenza
2. Review some of the most common myths associated with influenza and vaccination
3. Discuss the different influenza vaccine options
4. Explore the differences between trivalent and quadrivalent influenza vaccines
Post Test

1. It is estimated that between 10-20% of the population will become infected with influenza each year  
   a. True  
   b. False  

2. Approximately 50% of eligible Canadians receive the influenza vaccine each year  
   a. True  
   b. False  

3. Influenza B is unpredictable and can account for up to 67% of all reported influenza cases in some seasons  
   a. True  
   b. False  

4. The influenza vaccine should be delayed in a patient with a cough or cold  
   a. True  
   b. False  

5. Which of the following groups does NACI consider a high priority for influenza immunization?  
   a. Obese patients with BMI ≥ 40  
   b. Patients aged 5-64 years  
   c. Patients aged 6-59 months  
   d. Answers A and C are correct  

6. You discuss the role of quadrivalent inactivated influenza vaccine with a patient. Which of the following statements is TRUE?  
   a. It has a similar safety profile as the trivalent inactivated influenza vaccine  
   b. It has coverage for 3 strains of influenza type A  
   c. The vaccine is only indicated for use in children  
   d. All of the above  

Influenza

Influenza infections are caused by influenza A and B viruses.

Influenza A viruses are classified into subtypes based on two surface proteins: haemagglutinin (H) and neuraminidase (N). Three subtypes of haemagglutinin (H1, H2, and H3) and two subtypes of neuraminidase (N1 and N2) are recognized among influenza A viruses that have caused widespread human disease. Having immunity to haemagglutinin and neuraminidase proteins reduces the likelihood of infection and lessens the severity of disease if infection does occur.

Influenza B has evolved into two antigenically distinct lineages (B/Yamagata and B/Victoria) that contribute variably to influenza outbreaks each year. The behavior of influenza B is less predictable as there have been seasons with minimal circulation (0.8%) and seasons with high circulation (up to 67%). There is little or no cross-reactive protection between the influenza B lineages. Good protection against the circulating influenza B virus relies on correctly predicting the prevalent influenza B lineage in any season. In recent years, the ability to predict the predominating lineage of influenza B has only been correct 50% of the seasons from 2001 to 2011. This is the primary rationale behind the introduction of the new quadrivalent influenza vaccine.
Influenza viruses are continuously evolving. Over time, antigenic variation of strains occurs with influenza A subtype or B lineage. These changes are known as antigenic drift and antigenic shift (Table 1). Antigenic drift and shift and changes in circulating strains are the primary reasons for requiring annual influenza immunization.

<table>
<thead>
<tr>
<th>Table 1 – Differences between Antigenic Drift and Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antigenic Drift</strong></td>
</tr>
<tr>
<td>• Minor antigen changes that occur constantly as a result of mutations involving the genes encoding the H and N antigens</td>
</tr>
<tr>
<td>• Common in the influenza virus as its genes are RNA-based and are more prone to mutations than viral genes made of DNA</td>
</tr>
<tr>
<td>• Good resource to explain this concept to patient is – Antigenic Drift</td>
</tr>
<tr>
<td><strong>Antigenic Shift</strong></td>
</tr>
<tr>
<td>• Occurs only occasionally, and refers to an abrupt, major change that produces a novel human influenza A virus</td>
</tr>
<tr>
<td>• Can occur through bird or swine to human transmission or through mixing of human and animal influenza virus genes to create a new human influenza A virus</td>
</tr>
<tr>
<td>• New viruses are unlike any human influenza viruses that have been circulating in the past. Antigenic shift is the most common reason for influenza pandemics and epidemics</td>
</tr>
<tr>
<td>• Good resource to explain this concept to patient is – Antigenic Shift</td>
</tr>
</tbody>
</table>

Clinical Presentation and Complications

Most healthy adults may be able to infect others beginning 1 day before symptoms develop and up to 5 to 7 days after becoming sick. Some people, especially young children and people with weakened immune systems, might be able to infect others for an even longer period of time.

The clinical presentation will depend on the patient’s previous exposure to antigenically related influenza viruses.

Most experts believe that influenza viruses spread mainly by droplets made when people with influenza cough, sneeze or talk. These droplets can land in the mouths or noses of people who are nearby. Less often, a person might also get influenza by touching a surface or object that has influenza virus on it and then touching their own mouth, eyes or possibly their nose. The influenza virus then starts to replicate at the cellular lining of the nose and pharynx. The infection leads to varying degrees of destruction of cells within the nasopharynx, trachea, bronchi and bronchioles. The incubation period for influenza is usually 2 days, but can vary from 1 to 4 days.

The most common clinical presentation is outlined in table 2.

It is estimated that between 10-20% of the population will become infected with influenza each year. Many patients view influenza as a minor illness, but in reality influenza is a serious infection leading to up to 20,000 hospitalizations and approximately 4,000 deaths in Canada annually.
Clinical Practice Tip:
The majority of influenza complications occur in elderly patients, those with underlying medical conditions and children under 2 years of age. Although a healthy individual may not feel they require the influenza vaccine for themselves, it is important to remind them that if they become infected with the flu, they can transmit it to a family member, co-worker or friend who may be at a high risk of influenza complications.

Table 2 – Common symptom presentation and potential complications of influenza

<table>
<thead>
<tr>
<th>Symptom Presentation</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sudden onset of:</strong></td>
<td>• Secondary bacterial pneumonia (most common cause of death due to influenza)</td>
</tr>
<tr>
<td>o Fever (although not always present)</td>
<td>• Worsening of pre-existing medical conditions</td>
</tr>
<tr>
<td>o Headache</td>
<td>• Otitis media</td>
</tr>
<tr>
<td>o Myalgia</td>
<td>• Sinus infections</td>
</tr>
<tr>
<td>o Fatigue</td>
<td>• Myositis in children with influenza B infection, primarily in the calf muscles</td>
</tr>
<tr>
<td>o Anorexia</td>
<td>• Myocarditis</td>
</tr>
<tr>
<td>o Cold symptoms</td>
<td>• Encephalitis</td>
</tr>
<tr>
<td>o Pharyngitis</td>
<td>• Severe cough</td>
</tr>
<tr>
<td>o Severe cough</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms common in infants and children</strong></td>
<td></td>
</tr>
<tr>
<td>o High fever (&gt;40°C/104°F) without other symptoms</td>
<td></td>
</tr>
<tr>
<td>o Croup</td>
<td></td>
</tr>
<tr>
<td>o Febrile seizures</td>
<td></td>
</tr>
<tr>
<td>o Fever, vomiting, abdominal pain and diarrhea with or without respiratory symptoms</td>
<td></td>
</tr>
</tbody>
</table>

Patients at Risk

Current immunization programs should be primarily focused on those at high risk of influenza-related complications, those capable of transmitting influenza to individuals at high risk of complications and those who provide essential community services (Table 3).

NACI also recommends influenza immunization for ALL Canadians 6 months of age and older due to the significant illness and societal costs that occur in people who may not be considered at high risk of complications (i.e. healthy people aged 5 to 64 years).

Table 3 – NACI Recommended Influenza Vaccine Recipients

<table>
<thead>
<tr>
<th>People at high risk of influenza-related complications or hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adults (including pregnant women) and children with the following chronic health conditions:</td>
</tr>
<tr>
<td>o Cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma);</td>
</tr>
<tr>
<td>o Diabetes mellitus and other metabolic diseases;</td>
</tr>
<tr>
<td>o Cancer, HIV or AIDS, immune compromising conditions (due to underlying disease and/or therapy including chronic corticosteroids);</td>
</tr>
</tbody>
</table>
- Renal disease;
- Anemia or hemoglobinopathy;
- Conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration;
- Neurological and neurodevelopmental conditions including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy or spinal cord injury
- Morbid obesity (BMI≥40); and
- Children and adolescents with conditions treated for long periods with acetylsalicylic acid.

- People of any age who are residents of nursing homes and other chronic care facilities.
- People ≥65 years of age.
- All children 6 to 59 months of age.
- Healthy pregnant women (the risk of influenza-related hospitalization increases with length of gestation, i.e. it is higher in the third than in the second trimester)
  - This will not only protect the pregnant woman, but also the infant during the first 6 months of life
- Aboriginal Peoples.

### People capable of transmitting influenza to those at high risk

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - Household contacts of individuals at high risk, as listed in the section above;
  - Household contacts of infants <6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine; and
  - Members of a household expecting a newborn during the influenza season.
- Those providing regular child care to children ≤ 59 months of age, whether in or out of the home.
- Those who provide services within closed or relatively closed settings to persons at high risk (e.g. crew on a ship).

### Others

- People who provide essential community services.
- People in direct contact during culling operations with poultry infected with avian influenza.

---

### The Influenza Vaccine

**Far from Optimal Uptake**

It is estimated that 29.3% of Canadians were immunized against influenza in 2013.\(^{49}\) This is an increase from the immunization rate in 2012 (28.9%) but lower than the level in 2011 (30.2%).\(^{49}\) In provinces such as Ontario and Alberta with universal immunization programs, less than 1 in 3 Canadians aged 12 and older are immunized against influenza.\(^{49}\)
All influenza vaccines authorized for use in Canada are immunogenic, safe and associated with minimal adverse effects.

Vaccine Effectiveness

Multiple studies have shown that the influenza vaccine is efficacious. The efficacy is higher against laboratory-confirmed influenza than that defined by clinical outcomes. In healthy adults, inactivated vaccine:

- Efficacy against laboratory-confirmed influenza was 80%
- Effectiveness against influenza-like illness was 30% when the vaccine strain matched the circulating strains and circulation was high

Overall the vaccine efficacy in healthy adults is estimated to be 50% during select seasons of vaccine mismatch.

The vaccine effectiveness in elderly people is about half that of healthy younger adults. Even with the reduced effectiveness, systematic reviews have demonstrated that the influenza vaccine decreases the incidence of pneumonia, hospital admissions, and deaths in elderly individuals. It has also been shown to reduce exacerbations in persons with chronic obstructive pulmonary disease (COPD).

There is less data on the effectiveness of influenza vaccine in children. In one study in Canada, vaccinating children 3-15 years of age resulted in a community level vaccine efficacy of 59% against polymerase chain reaction (PCR)-confirmed influenza, compared with communities where children received hepatitis A vaccine as a control. In a US study, provision of live-attenuated influenza vaccine to all eligible children, resulting in a school-wide vaccine coverage of 48% was associated with significant decreases in medically attended acute respiratory illness rates among adults in the community, despite a mismatch between vaccine and circulating strains. These findings have been replicated over several years, and they are consistent with early studies suggestive of the role of children in transmitting influenza in the community.

Contraindications and Precautions

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Inactivated intramuscular vaccines</th>
<th>Live attenuated nasal influenza vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>People who have had an anaphylactic reaction to a previous dose</td>
<td></td>
<td>Children &lt;24 months of age due to increased risk of wheezing</td>
</tr>
<tr>
<td>People who have had an anaphylactic reaction to any of the vaccine components†</td>
<td></td>
<td>Individuals with severe asthma (as defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing) or those with medically attended wheezing in the 7 days prior to vaccination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children and adolescents (2-17 years of age) currently receiving aspirin or aspirin-containing therapy. It is recommended that aspirin-containing products in children &lt;18</td>
</tr>
</tbody>
</table>
An accredited version is available online at www.rxBriefCase.com until July 27, 2016

43 years of age be delayed for four weeks after receipt of LAIV.
- Pregnant women, because it is a live attenuated vaccine and there is a lack of safety data at this time; however, it is not contraindicated in nursing mothers.
- Persons with immune compromising conditions, due to underlying disease and/or therapy

Precautions

- Severe lower respiratory symptoms within 24 hours of a previously administered influenza vaccine dose
- Guillain-Barré Syndrome (GBS) - the risk of GBS is about one excess case per million doses of vaccine. GBS can be triggered by influenza infection itself. Risk from the vaccine has to be balanced against the risk of influenza

- If significant nasal congestion is present that might impede delivery to the nasopharyngeal mucosa, the nasal vaccine should be deferred until nasal symptoms have improved
- Recipients should avoid close association with persons with severe immune compromising conditions for at least two weeks following immunization, because of the theoretical risk of shedding and transmitting the live influenza virus
- Should not be administered until 48 hours after antiviral agents active against influenza (oseltamivir and zanamivir) are stopped

† - Possible exception is egg-allergy where the influenza vaccine has been given in some patients safely. The protocol for administering the vaccine to a patient with an egg allergy is reviewed annually in the NACI statement on influenza immunization

Adverse Effects

Inactivated influenza vaccine cannot cause influenza, as the vaccine does not contain a live virus. With the intramuscular injection, increased soreness at the injection site lasting up to two days is very common, but rarely interferes with normal activity. Healthy adults receiving inactivated influenza intramuscular vaccine show no increase in the frequency of fever or other systemic symptoms compared with those receiving placebo.

The inactivated intramuscular vaccine is safe and well tolerated in healthy children. Mild local reactions, primarily soreness at the vaccination site, occur in ≤7% of healthy children who are <3 years of age. Fever may be observed in ≤12% of immunized children 1 to 5 years of age.

Live attenuated intranasal influenza vaccine is different from other products in that it contains live-attenuated (weakened) virus. The most common adverse effects are nasal congestion and runny nose. Wheezing was reported more frequently in children < 24 months, and for this reason it is not indicated in children < 2 years of age. Shedding of the virus can occur post-vaccination. The frequency of shedding decreases with increasing age and time since vaccination. Shedding is generally below the levels needed to transmit infection, although in rare instances, the shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons.
Differences between Influenza Vaccines

There are three main forms of influenza vaccine.

1. Trivalent inactivated intramuscular influenza vaccine (has antigens for 2 strains of influenza A and 1 strain of influenza B)
2. Trivalent live attenuated intranasal influenza vaccine (has antigens for 2 strains of influenza A and 1 strain of influenza B)
3. Quadrivalent inactivated intramuscular influenza vaccine (has antigens for 2 strains of influenza A and 2 strains of influenza B)

Currently NACI recommends influenza vaccine as first-line for Canadians 6 months and over. The intranasal influenza vaccine is currently recommended first-line for patients 2-17 years with the inactivated intramuscular vaccine as an acceptable alternative. The quadrivalent inactivated influenza vaccine was just launched in Canada in 2014. The current NACI 2014/2015 influenza recommendation is that if there is a limited supply of the quadrivalent products that they should be prioritized to children and adolescents as they have a higher infection rate with influenza B.

Myths of Influenza and the Influenza Vaccine

There are many patient myths regarding influenza and the vaccines. These myths are commonly believed by many members of the general public and some healthcare providers. They are thought to have a significant impact on annual influenza immunization rates.

Clinicians must be aware of these myths and be able to address them effectively with evidence-based answers. Table 5 reviews many of the common myths regarding the vaccines and information that can be provided to patients and parents.

<table>
<thead>
<tr>
<th>Myth</th>
<th>Key Points</th>
</tr>
</thead>
</table>
| I am young and healthy, I don’t need the flu shot | • Influenza is a highly contagious infection that can readily infect patients through airborne transmission, or indirectly through touching surfaces contaminated with the virus, and then touching their eyes, nose or mouth.  
• For the 2013 influenza season, patients aged 20-44 and 44-64 made up the largest categories of positive influenza specimens (26.4% and 25.9%, respectively)  
• Although this group is not as likely to develop complications from influenza, they can transmit the virus to higher risk groups such as children, pregnant women and the elderly  
• Many young patients with an influenza infection will not be able to work or go to school due to symptoms. This could impact them financially or academically |
| Vaccine causes influenza      | • Trivalent and quadrivalent inactivated vaccines contain destroyed influenza virus  
• There is NO risk of influenza infection from these vaccines as it CANNOT replicate upon injection |
The only exception is the live attenuated influenza intranasal vaccine. The influenza strains in this product are cold-adapted and temperature sensitive, so they replicate in the nasal mucosa rather than in the lower respiratory tract. In healthy children and adults they do not produce classic influenza-like illness.

**Vaccine is associated with many adverse effects**

- For the inactivated influenza vaccine, the most common adverse event is soreness at the injection site lasting up to two days. It rarely interferes with normal activity. Healthy adults receiving this vaccine show no increase in the frequency of fever or other systemic symptoms compared with those receiving placebo.
- The inactivated influenza vaccine is safe and well tolerated in healthy children. Mild local reactions, primarily soreness at the vaccination site, occur in ≤7% of healthy children who are <3 years of age. Fever may be observed in ≤12% of immunized children 1 to 5 years of age.
- The live attenuated influenza nasal vaccine has a different adverse effect profile. The most common adverse effects are nasal congestion and runny nose. Wheezing was reported more frequently in children < 24 months and for this reason it is not indicated in children < 2 years of age.

**Vaccine is not effective**

- The influenza vaccine has demonstrated efficacy in studies in both laboratory confirmed influenza and when used in clinical settings. The efficacy in laboratory confirmed influenza is estimated to be 80% in healthy adults and 30% against influenza-like illness. There are several reasons a patient immunized with the vaccine may still develop a flu-like condition:
  - Some people can become ill from other respiratory viruses besides influenza (such as rhinoviruses), which are associated with the common cold, cause symptoms similar to flu, and also spread and cause illness during the flu season.
  - It is possible to be exposed to influenza viruses shortly before or after being vaccinated. The patient may be exposed prior to the body mounting a significant antibody response.
  - The circulating strains of influenza virus do not match the viral strains in the vaccine.
  - The vaccine is not 100% effective in preventing influenza. This is especially the case in the elderly and immunocompromised patients.
- The vaccine efficacy in elderly patients is half that of healthy adults. Even with a reduced efficacy in elderly patients, the vaccine has been shown to reduce hospital admissions, complications such as pneumonia, and death in that age group. Consideration to induce an enhanced immune response in the elderly may be use of the adjuvant influenza vaccine.
- The new quadrivalent vaccine is designed to address the two distinct lineages of influenza B. This induces antibodies against both types and thus could potentially increase protection from influenza B. This vaccine also protects against two strains of influenza A.
- It is important to remind patients that the most effective way to prevent influenza is the vaccine.
### Quadrivalent Influenza Vaccine

Quadrivalent influenza vaccine has antigens for four strains of influenza versus the traditional three. This broader coverage contains antigens for two strains of influenza A and 2 strains of influenza B. It is available in both the parenteral and intranasal formats.

This vaccine is being increasingly used in different parts of the world as it is difficult to predict which of the two antigenically different strains of influenza B will predominate during the influenza season. Quadrivalent influenza vaccines will be offered in several Canadian provincial public programs starting in fall 2015.

Laboratory confirmed influenza has shown that the percentage of B strains out of the total cases is quite variable from one season to the next (average 17% range 0.1% to 53%).\(^4^4\) Between 2001 and 2011 the choice of influenza B strain included in the trivalent vaccine was accurately predicted in only 5 of the 10 seasons.\(^4^6\) This lack of coverage is placing patients at risk of influenza type B and potentially decreasing the effectiveness of the influenza vaccine. Using data from the previous ten influenza seasons, researchers feel the additional protection with the quadrivalent vaccine is expected to result in: \(^5^4\)

- Fewer cases of influenza (range: 1-321 per 100,000)
- Fewer hospitalizations due to influenza (range: 0.06-2.7 per 100,000)
- Fewer deaths (range: 0.001-0.16 per 100,000)

The safety and immunogenicity of the quadrivalent vaccine was evaluated in an open-label trial.\(^5^5\) It was found that the vaccine was as safe and immunogenic as the licensed trivalent inactivated vaccine.

NACI reviewed the use of quadrivalent vaccine in their 2014-15 Statement on Seasonal Influenza Vaccine. They recommend that if the quadrivalent vaccine is in limited supply, that healthcare professionals consider offering it to children and adolescents as influenza B occurs more frequently in this group. There is also a higher number of hospitalizations and deaths in children due to influenza B compared to adults.\(^4^4\)

NACI has indicated the quadrivalent vaccine could be utilized in any patient where trivalent was an option (≥6 months of age), where the patient wanted broader coverage or where the clinician felt it was a better option for a patient.

### Influenza Vaccine Selection

Clinicians should consider offering each of the different influenza options to their patients to allow them to select their best option. Table 6 provides some factors to consider when selecting a specific influenza vaccine.
Table 6 – Factors that can be Considered when Selecting an Influenza Vaccine

<table>
<thead>
<tr>
<th>Factor</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age</td>
<td>Some vaccines are indicated in infants as young as 6 months and others are indicated in older children and adults</td>
</tr>
<tr>
<td>Patient’s immune status</td>
<td>The live attenuated intranasal influenza vaccine is NOT recommended in patients with compromised immune status, including pregnant women</td>
</tr>
<tr>
<td>Patient’s view on preservatives</td>
<td>Although data is lacking to support negative health effects from thimerosal, there are many single dose or prefilled syringe products that do not contain thimerosal</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Some patients have a needle phobia and may be eligible for nasally administered vaccine</td>
</tr>
<tr>
<td>Quadrivalent influenza strain coverage</td>
<td>Some patients will prefer the influenza vaccine option that provides the largest influenza strain coverage. According to the current NACI influenza statement, the quadrivalent option should be prioritized for young children and adolescents</td>
</tr>
<tr>
<td>NACI recommendations</td>
<td>Each year NACI provides recommendations for specific age groups. Clinicians should consider these recommendations prior to recommending a specific vaccine type</td>
</tr>
<tr>
<td>Cost of the vaccine</td>
<td>In some provinces, the influenza vaccine is provided through a publically funded universal program. In other provinces, some patients will have to pay for the vaccine. Cost can be a consideration for some patients</td>
</tr>
</tbody>
</table>

Revisit our Patient

You explain to Ashley that you feel she is an excellent candidate for the influenza vaccine. You stress that if she becomes ill with influenza she may transmit the virus to her children and her parents. As well, she would likely not be able to provide the care they require while she is ill. She may also not be able to go to her workplace due to work restrictions on those with a febrile respiratory tract infection.

You address many of the myths associated with the vaccine and discuss the overall safety and efficacy. If Ashley is not in one of the categories for the provincial/territorial funded vaccine, or if she has private insurance, or wishes to select and potentially pay for a different influenza vaccine, it would be important to provide her with each of the different vaccine options and allow her to select the vaccine(s) that she feels are the best options for influenza prevention for herself and her family.
Key Learning Points

1. Influenza cases are caused each year by influenza A and influenza B viruses
2. There are two distinct lineages for influenza B and protection against one will not protect against the other
3. Although NACI recommends the influenza vaccine for all high risk patients as a priority, it encourages its use for all Canadians over 6 months of age
4. Only 1 in 3 Canadians were immunized against influenza in 2013
5. There are very few contraindications for patients to receive the inactivated form of the influenza vaccine
6. There are many myths regarding influenza and the vaccine which primary care clinicians can address in practice
7. The newer quadrivalent form of the influenza virus is believed to be able to reduce the hospitalizations and deaths associated with influenza

Discussion Forum

1. There are many myths regarding the influenza vaccine. How do you educate your patients regarding these myths and do you feel this increases influenza vaccine uptake in your patients?
2. As NACI currently includes the quadrivalent influenza vaccine as an immunization option, which patient group do you feel could benefit from protection against 4 influenza strains?
Meet your Patient – Lynn

Lynn (35 yo) was diagnosed with Crohn’s disease approximately 4 years ago. Although she initially responded to oral therapy, her condition has progressed and her gastroenterologist is considering her for biologic therapy.

She was referred to you for testing for tuberculosis (TB) prior to starting her biologic therapy. She was given two testing options. She wants to know your opinion on the two tests. She had been planning to attend a family wedding in the Caribbean in six months. She wondered if being on biologic agents would prevent her from travelling to tropical destinations.

You discuss with her why testing for tuberculosis is important prior to starting biologic therapy. You also review whether her Canadian immunizations are up to date. You also discuss with her whether any additional vaccines for foreign travel would be considered prior to her commencing biologic therapy.

Learning Objectives

Upon successful completion of this continuing education program, you will be better able to:

1. Discuss the epidemiology of tuberculosis and determine patients at risk of infection
2. Review the new 2014 Canadian Tuberculosis recommendations for screening
3. Explore the differences between the tuberculin skin test and the interferon gamma release assay for screening
4. Recommend that if Lynn plans foreign travel, such as her pending trip to the Caribbean, she attend a travel clinic for advice on travel immunizations and other preventive measures for an immunocompromised person
Post-Test

1. All eligible vaccines should ideally be administered prior to initiating a biologic therapy as many vaccines are contraindicated after it is initiated
   a. True
   b. False

2. Both TST and IGRA are acceptable tests for the diagnosis of latent tuberculosis infection
   a. True
   b. False

3. TST is effective for assessing latent tuberculosis infection in patients previously administered the BCG vaccine
   a. True
   b. False

4. IGRA is NOT effective for making a diagnosis of active tuberculosis
   a. True
   b. False

5. Your patient may require immunosuppressive therapy. Which of the following vaccines are contraindicated in immunosuppressed patients?
   a. Live attenuated vaccines
   b. Inactivated vaccines
   c. Polysaccharide vaccines
   d. All of the above

6. You discuss the latent tuberculosis testing options with a patient. Which of the following statements is TRUE?
   a. Tuberculin skin testing and IGRA are both acceptable tools to diagnosis latent tuberculosis
   b. Tuberculin skin testing is preferred in patients that have had BCG immunization
   c. Tuberculin skin testing should be read between 4-5 days
   d. All of the above

Immunization and TB Screening Considerations prior to Initiating Biologics or Immunosuppressant agents

The use of tumor-necrosis factor (TNF) inhibitors (i.e., infliximab, adalimumab) to induce a therapeutic immunosuppression has dramatically improved outcomes in patients with chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease and psoriasis). Use of these agents has been associated with an increased risk of reactivation of latent tuberculosis infection (LTBI). For this reason, current guidelines advise that all patients prior to initiating these therapies be assessed and screened for latent tuberculosis (TB) infection in case they require treatment for TB prior to commencing the immunosuppressant therapy.

Many biologic and immunosuppressant agents also decrease the immune response to some, or all vaccines. Prior to a patient starting on immunosuppressive therapy, it is important to assess whether the patient’s current immunizations are up-to-date including receipt of recently recommended vaccines for Canadians. Depending on future travel plans, consultation with a travel clinic could be
recommended to determine if any additional vaccines might be administered prior to the patient starting immunosuppressive therapy.

Screening for tuberculosis and assessment of immunization status can commonly be done in primary care. This module will focus on providing clinicians some background on these two categories for patients initiating a biologic or other immunosuppressant agent.

**Mycobacterium tuberculosis**

Infection with *M. tuberculosis* is acquired by inhalation of bacilli-containing droplet nuclei small enough (diameter 1-5 microns) to reach the alveoli. In immunocompetent hosts, it is thought that alveolar macrophages ingest the tuberculosis organisms and may or may not destroy them. If bacteria are successfully cleared, then test results will remain negative on the tuberculin skin test (TST or a Mantoux skin test) or interferon-gamma release assay (IGRA).

When innate macrophage activity is inadequate to destroy the initial few bacteria of the droplet nucleus they replicate logarithmically, doubling every 24 hours until the macrophage bursts to release the bacteria. New macrophages attracted to the site engulf these bacilli, and the cycle continues. The bacilli may spread from the initial lesion via the lymphatic and/or circulatory systems to other parts of the body. After a period lasting from 3 to 8 weeks the host develops specific immunity to the bacilli, and individuals typically show positive results on the TST or IGRA.

A small portion of patients (~5%, but much higher in certain populations such as immunocompromised patients) will go on to develop primary disease with the initial infection. With latent tuberculosis infections, *M. tuberculosis* is believed to survive for years in the body. In Canada, most TB is understood to be "reactivation" TB, i.e. occurring 18-24 months or more after the initial infection. It usually presents as adult-type pulmonary disease. This latent tuberculosis infection is usually identified by a positive TST or IGRA in the absence of active disease.

Patients receiving biologics (tumor necrosis factor inhibitors) are at increased risk of reactivation of latent M. tuberculosis infection. In addition, cases of TB occurring in association with TNF-alpha inhibitors have a higher likelihood of involving extrapulmonary sites and of being disseminated at presentation compared with other TB cases. The incubation period from latent infection to active disease also may be shortened.
Tuberculosis in Canada

The World Health Organization estimated that there were 8.8 million incident cases of tuberculosis (TB) worldwide in 2010, for an incidence rate of 128 cases per 100,000 population. In Canada, the reported number of new active and re-treatment TB cases in 2012 was 1686, an increase of 4% from the number of cases in 2011 (1617). The reported incidence rate increased from 4.7 to 4.8 cases per 100,000 population. Foreign-born people continued to account for the majority of reported TB cases. The reported incidence rate per 100,000 population remained highest among Canadian-born Aboriginal peoples.

The outcomes of patients infected with tuberculosis have improved dramatically from the first half of the 20th century, when TB was a major cause of morbidity and mortality in Canada. Of the 1658 cases of active TB disease diagnosed in 2009, 1599 (96%) had treatment outcomes:

- 1,399 (87%) were deemed cured or treatment completed
- 129 (8%) died before or during treatment
- 31 (2%) transferred out of Canada at some point during their treatment and their final outcome was unknown
Between 2000 and 2009, 8.6% of diagnosed cases were reported to have died before or during treatment.  

Individuals at Risk of TB Exposure

With the significant personal and public health consequences of TB infection, screening is used in high-risk groups to identify patients with latent infection. This can allow for appropriate treatment and reduce the potential impact of TB. When selecting patients for TB screening it is important to consider that the benefit of screening programs will be greatest in those with a higher probability of infection and/or significant risk factors for reactivation, coupled with a low risk of toxicity and a high probability of treatment completion. Table 1 reviews the groups with increased risk of TB exposure and latent TB infection.

<table>
<thead>
<tr>
<th>Groups at risk</th>
<th>Prevalence of Positive TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close contacts with active case of pulmonary TB</td>
<td>Variable, higher than the source population</td>
</tr>
<tr>
<td>Immigrants from countries with high TB incidence</td>
<td></td>
</tr>
<tr>
<td>• Children</td>
<td>15-23%</td>
</tr>
<tr>
<td>• Adults (&gt;20 years in country with high TB incidence)</td>
<td>53-61%</td>
</tr>
<tr>
<td>Injection drug user</td>
<td></td>
</tr>
<tr>
<td>• (TST ≥ 10 mm)</td>
<td>66%</td>
</tr>
<tr>
<td>• (TST ≥ 5 mm)</td>
<td>31%</td>
</tr>
<tr>
<td>Homeless</td>
<td>18-51%</td>
</tr>
<tr>
<td>Aboriginal communities</td>
<td></td>
</tr>
<tr>
<td>• Adults</td>
<td>14-30%</td>
</tr>
<tr>
<td>• Children</td>
<td>5-29%</td>
</tr>
<tr>
<td>Healthcare workers</td>
<td>11-46%</td>
</tr>
<tr>
<td>Residents of long-term care facilities</td>
<td>6-25%</td>
</tr>
<tr>
<td>Residents of correctional facilities</td>
<td>12-72%</td>
</tr>
<tr>
<td>Travellers to countries with high TB incidence</td>
<td>Variable</td>
</tr>
</tbody>
</table>

TST- tuberculin skin test

Screening for TB Infection

In most individuals, *M. tuberculosis* infection is contained initially by host defenses, and infection remains latent. However, latent TB infections (LTBI) can develop into active disease at any time. Identification and treatment of LTBI can substantially reduce the risk of development of disease and so have the potential to protect the health of the individual as well as the public by reducing the number of possible sources of future transmission.

There are two tests for identification of LTBI: the TST and the IGRA. Both tests evaluate cell-mediated immunity, and neither test can distinguish between LTBI and active TB disease.

Tuberculin Skin Test (TST)

With the TST a small amount of tuberculin purified protein derivative is injected intradermally. In patients with latent TB infections the cell-mediated immune response, previously acquired through TB
infection, leads to a localized skin reaction. Table 2 and figure 2 review the proper technique for TST administration.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparation</strong></td>
<td><strong>Product</strong>&lt;br&gt;○ Tubersol® 5 tuberculin units (TU) of purified protein derivative is recommended in Canada&lt;br&gt;○ Storage is crucial and the solution should be drawn up just before injecting it&lt;br&gt;○ The solution is light sensitive and should be stored in the dark <strong>Patient</strong>&lt;br&gt;○ Seat the patient comfortably&lt;br&gt;○ Use inner aspect of forearm, preferably the nondominant arm, about 10 cm below the elbow, avoiding abrasion, swelling, visible veins or lesions. If there is a localized rash, a burn or eczema, avoid this area&lt;br&gt;○ If both inner aspects of forearms are not suitable, then use outside of forearm or the upper arm&lt;br&gt;○ Cleanse the area with an alcohol swab and allow it to dry</td>
</tr>
</tbody>
</table>
| **Injecting the purified protein derivative tuberculin solution** | ○ Use a 0.6 to 1.3 cm (¼ to ½ inch), 26 or 27-gauge needle with a disposable plastic tuberculin syringe<br>○ Position the bevel of the needle so that it opens facing up.<br>○ While holding the skin of the inner aspect of the forearm taut<br>  ○ Insert the needle at a 5°-15°angle to the skin without aspirating.<br>  ○ The tip of the needle will be visible just below the surface of the skin.<br>  ○ The needle is inserted until the entire bevel is covered<br>○ Administer the PPD by the slow intradermal injection of 0.1 mL (or 5-TU)<br>○ A discrete, pale elevation of the skin (a wheal) 6-10mm in diameter should appear.<br>  ○ It will typically disappear in 10-15 minutes.<br>  ○ The size of the wheal is not completely reliable, but if a lot of liquid runs out at the time of injection and there is no wheal, then repeat the injection on the opposite forearm, or on the same forearm as before, but at least 5 cm from the previous injection site<br>○ A drop of blood may be seen—this is normal. The person tested should be offered gauze to remove the blood but should be advised not to massage the site in order to avoid squeezing out the PPD and disrupting the test.<br>○ Do not cover the site with a bandage.<br>○ Tell the patient that he or she should not scratch the site but may perform all normal activities, including showering or bathing.<br>○ Place uncapped disposable needles and syringes in appropriate puncture-resistant containers immediately after use.<br>○ If the TST is accidentally given as a subcutaneous or an intramuscular injection, this should not pose a serious problem. It is possible that tuberculin-sensitive people would have localized inflammation, which...
should be self-limited. It would not be possible to take a measurement of or clinically interpret any such reaction, so the TST should be administered again but using proper intradermal technique on the forearm. This should be done immediately (as soon as it is realized that the injection was too deep).

Documentation at administration

- Date of injection
- Dose of PPD (5 TU, 0.1 mL)
- PPD lot number
- Expiration date of the PPD reagent
- Site of injection
- Person administering the TST

**Precautions with TST**

**Table 3 – Precautions with the Tuberculin Skin Test**

**Allergic reaction**

- Acute allergic reactions, including anaphylaxis, angioedema, urticaria rash and/or dyspnea, have been very rarely reported following skin testing
- Epinephrine hydrochloride solution (1:1000) and other appropriate agents should be routinely available for immediate use
- Monitor the patient for immediate reactions over a period of at least 15 minutes after inoculation and for the initial management of anaphylaxis in non-hospital settings

**Patient should NOT receive a TST**

- Those with positive, severe blistering TST reactions in the past or with extensive burns or eczema present over TST testing sites, because of the greater likelihood of adverse reactions or severe reactions.
- Those with documented active TB or a well-documented history of adequate treatment for TB infection or disease in the past.
- Those with current major viral infections (e.g. measles, mumps, varicella).
- Those who have received measles or other live virus vaccine(s) within the past 4 weeks, as this has been shown to increase the likelihood of false-negative TST results.

### Patients who CAN receive a TST
- Those with a history of receiving BCG vaccination(s)
- Those with a common cold
- Those who are pregnant or are breastfeeding
- Those immunized with any vaccine on the same day
- Those immunized within the previous 4 weeks with vaccines other than the ones listed earlier
- Those who give a history of a positive TST reaction (other than blistering) that is not documented
- Those taking low doses of systemic corticosteroids, <15 mg prednisone (or equivalent) daily. It generally takes a steroid dose equivalent to ≥15 mg prednisone daily for 2-4 weeks to suppress tuberculin reactivity

### Measuring the Induration

#### Table 4 – Key Points regarding measurement of Induration with TST[^58]

| Who should measure | • Trained healthcare professional as non-trained individuals may not feel slight induration and score it as 0 mm
|                    | • Self-reading is very inaccurate and is strongly discouraged
| Timing of measurement | • Performed 48-72 hours after administration
|                        | • Maximum induration can take up to 48 hours to develop, but after 72 hours it is difficult to interpret the reaction
|                        | • Reactions may persist for up to 1 week, but for as many as 21% of individuals with a positive reaction at 48 to 72 hours the reaction will be negative after 1 week
|                        | • If the test cannot be read within 72 hours, the test should be repeated at a different injection site
| Measurement | • Forearm should be on a firm surface, slightly flexed at the elbow
|             | • Induration is not always visible and should be palpated with the fingertips
|             | • If there is induration, mark the border of induration by moving the tip of a pen at a 45° angle laterally toward the site of the injection
|             | • The tip will stop at the edge of the induration, if present. Repeat the process on the opposite side of the induration.
|             | • Using a caliper, measure the distance between the pen marks, which reflects the diameter of the induration at its widest transverse diameter
|             | • A caliper is recommended because readings will be more precise and, most important, if the reader has to set the caliper and then read the diameter the rounding error is reduced. If a caliper cannot be found a flexible ruler could be used
|             | • Disregard and do not record erythema (redness)
|             | • Blistering, which can occur in 3% to 4% of subjects with positive tests, should be recorded

[^58]: Reference to specific table or section number
Interpretation of a Positive Tuberculin Skin Test
When interpreting a positive TST, it is important to consider much more than simply the size of the reaction. Three things for the clinician to consider are:

1. Size of induration
2. Positive predictive value
3. Risk of disease if the person is truly infected

There is an online TST/IGRA interpreter (www.tstin3d.com) that can be used to help determine an individual’s risk of active tuberculosis with a positive TST of 5mm or more.

Management of a Positive Skin Test Result
1. If the TST test is considered positive, the patient should be referred for medical evaluation.
2. Medical evaluation should include a full medical history and physical examination with a special focus on:
   a. Symptoms suggestive of possible active TB
   b. Risk factors for TB, such as contact history or other medical illnesses, as well as chest radiography.
3. In the presence of symptoms or signs suggestive of tuberculosis or abnormal chest x-ray, one or more of the following should be taken:
   a. Sputum for demonstration of acid-fast bacilli on smear microscopy and/or
   b. Culture of Mycobacterium tuberculosis
      Or
   c. Amplification and detection of Mycobacterium tuberculosis complex nucleic acids using nucleic acid amplification tests (NAATs)
4. In subjects without evidence of active TB, a recommendation should be made regarding therapy for latent TB infection, based on interpretation of the TST.

Interferon-Gamma Release Assays (IGRAs)
IGRAs are in-vitro blood tests of cell-mediated immune response. They measure T cell release of interferon-gamma (IFN-gamma) following stimulation by antigens specific to Mycobacterium tuberculosis—early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10).

There are several advantages of IGRA testing. The genes encoding these antigens are present in M tuberculosis, but are not found in any BCG vaccine strains or in several of environmental nontuberculous mycobacteria (NTM) strains. These tests are substantially more specific (leading to fewer false positives) than the TST. They are also less subjective with respect to interpretation, have the potential for rapid turnaround time, and require only a single clinic or laboratory visit to complete the testing.
When measured using active TB as a surrogate reference standard, IGRAs have a specificity of >95% in the diagnosis of LTBI. Specificity is not affected by previous BCG vaccination.  

There are also some challenges related to the IGRA. There are two types of assays. The QuantiFERON-TB Gold in Tube (QFT-GIT) assay and the T-SPOT assay are approved by Health Canada. IGRAs require laboratories with adequate equipment and trained personnel to perform the assays. In addition, IGRAs require fresh blood samples: pre-analytical steps and transportation delays can affect test performance. Blood specimens for the QFT assay should be collected and shaken as per the manufacturer’s instructions. They should be placed in an incubator as soon as possible and within 16 hours of blood collection. Test kits should be transported and stored in optimum conditions to prevent exposure to excessive heat.

Like TST the decision to initiate treatment is usually made based on the positive result as well as the patient’s risk of reactivation and adherence to therapy. The online TST/IGRA interpreter can be used to help determine an individual’s risk of active tuberculosis.

**TST or IGRAs?**

The Canadian Standards for Tuberculosis state that both TST and IGRAs are acceptable but imperfect tests for latent TB infection. IGRAs are more specific than the TST in the BCG-vaccinated populations. Neither test can distinguish latent TB infection from TB disease and therefore has no value for active TB detection in adults.

The Canadian standards for recommendations for the screening of latent tuberculosis infection are reviewed in table 5.

<table>
<thead>
<tr>
<th>Table 5 – Canadian Standards for TB on the Diagnosis of Latent TB Infection</th>
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<tbody>
<tr>
<td>1. Both the TST and IGRA are acceptable alternatives for LTBI diagnosis. Either test can be used for LTBI screening in any of the situations in which testing is indicated</td>
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<tr>
<td>- Situations where TST or IGRA should NOT be used include: patients with low risk of infection and a low risk of progression to active TB disease, for the diagnosis of active TB, routine or mass screening of all immigrants, monitoring TB treatment response</td>
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<tr>
<td>2. Situations in which IGRAs are preferred for testing but a TST is acceptable</td>
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<td>- People who received BCG as a vaccine after infancy</td>
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<td>- People from groups that have poor rates of returning for TST reading</td>
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<td>3. Situations in which TST is recommended for testing but IGRA is NOT acceptable</td>
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<tr>
<td>- TST is preferred whenever it is planned to repeat the test later to assess risk of new infection (i.e. conversions), such as repeat testing in a contact investigation, or serial testing of health care or other populations (e.g. corrections staff or prison inmates) with potential for ongoing exposure</td>
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<tr>
<td>4. Situations in which both tests can be used (sequentially, in any order) to enhance sensitivity</td>
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<td>- When the risk of infection, or progression to disease or a poor outcome are high</td>
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<td>- In children (under the age of 10 years) with suspected TB disease</td>
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<td>- TST or repeating IGRA might be useful when the initial IGRA results are inconclusive</td>
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<td>5. IGRA versus TST</td>
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<td>- Current evidence does not clearly suggest that IGRAs are better than TST in identifying individuals with Immune-mediated inflammatory diseases (IMID) who could benefit from LTBI treatment. To date, no studies have been done on the predictive value of IGRAs in</td>
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Among patients receiving biologic therapy, in regions of moderate or high TB prevalence, or in patients with TB risk factors there is some evidence that a dual testing strategy of TST and IGRA improves sensitivity.

The choice of screening test can also be determined by cost per test and access to laboratory facilities for IGRA or qualified healthcare professionals to perform and assess TST results. If they are not going to be performing the test themselves, clinicians should know the different facilities in their communities to refer their patients for appropriate latent TB infection testing. There is no charge to the patient for TST testing in most circumstances. IGRA testing is not funded by all of the provincial/territorial health care plans.

It has been recommended that patients with evidence of LTBI either by a TST $\geq$ 5 mm (without regard to BCG status) or by IGRA be started on treatment for LTBI prior to initiating anti-TNF-alpha therapy.

**Immunization Status in Patients Initiating Biologic Agents**

Prior to patients starting biologic agents, a detailed discussion, and ideally documentation, of their current immunization status should take place. These agents induce immunosuppression and some vaccines are contraindicated. Other vaccines can be given, but the reduced immune response could lead to less than optimal protection against the vaccine preventable disease(s).

With biologic agents commonly being used chronically, it is important to ask patients about future travel plans as this could alter travel recommendations, including using passive, rather than active immunization, to protect against certain diseases (i.e., immune globulin to protect against hepatitis A), or provision of a medical waiver (i.e., in countries where documentation of yellow fever vaccine is required.).

The Canadian Immunization Guide has some recommendations regarding immunization in patients initiating immunosuppressive therapies. These recommendations are reviewed in table 6.

| Prior to starting immunosuppressive therapy | • All appropriate vaccines or boosters should be administered before the initiation of immunosuppressive therapy so that optimal immunogenicity is achieved  

• Although inactivated vaccines can be safely administered at any time before, during or after immunosuppression, inactivated vaccines should be administered at least 14 days before initiation of immunosuppressive therapy to optimize immunogenicity.  

• Live vaccines should be administered at least 4 weeks before immunosuppressive therapy is started to reduce the risk of disease caused by the vaccine strain. |
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<td>During or after immunosuppressive therapy</td>
<td>• If vaccines cannot be given prior to initiation of immunosuppressive therapy, a period of at least 3 months should elapse after immunosuppressive drugs (except high-dose systemic corticosteroids) have been stopped before administration of inactivated vaccines (if possible to ensure immunogenicity) and live vaccines (to reduce the risk...</td>
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of disease caused by the vaccine strain).

- If immunosuppressive therapy cannot be stopped, live vaccines are generally contraindicated, although the risk-to-benefit ratio may favour immunization if only low doses of immunosuppressive drugs are required and there is significant risk of development of disease.

Clinical Practice Tip:
Consider discussing long-term travel plans in patients starting biologic agents. If the patient is considering international travel, consultation with a travel clinic is recommended. Depending on the travel destinations, the patient on tumor necrosis factor biologic agents should also be advised of the risk of tuberculosis transmission in high-prevalence countries.

Revisit our Patient – Lynn
You explain to Lynn the different latent TB infection testing options. You stress the importance of latent TB infection testing prior to the initiation of the biologic therapy so that if she is diagnosed with latent tuberculosis, she can begin treatment for latent tuberculosis prior to starting her biologic therapy. This can reduce her risk of developing active tuberculosis. If she travels to a TB endemic area, she should undergo repeat testing for latent tuberculosis infection ≥ or equal to 8 weeks after return from travel.

You review her Canadian immunization status. Her last immunizations were several years ago. You learn that it will be at least a month prior to her initiating the biologic therapy. She may require a booster dose of some routine vaccine such as tetanus/diphtheria+/- (Td or Tdap), measles, mumps, rubella (MMR) or polio (IPV). For a complete list see http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-02-eng.php. In this manner, she not only has protection against infectious diseases that may be acquired in Canada, but also the primary recommended immunizations for international travel, including her planned trip to the Caribbean. For further immunizations and travel advice, she could be seen at a travel clinic several weeks prior to her departure.
Key Learning Point

1. TB testing and immunization status should be assessed for all patients being considered for biologic therapies.
2. The majority of patients initially infected with TB will go on to develop latent TB infection that could be reactivated in the future.
3. In Canada, the reported number of new active and re-treatment TB cases in 2012 was 1686, an increase of 4% from the number of cases in 2011.
4. Both tuberculin skin testing and IGRA testing are recommended screening tests for patients to assess TB status.
5. TST or IGRA have no value for diagnosing active TB in adults.
6. Immunizations and future travel plans should be discussed prior to initiating a chronic immunosuppressive agent.

Discussion Forum

1. What do you feel is the role of the primary care clinician in assessing and updating a patient’s immunization status prior to initiating biologic therapies?
2. Which latent tuberculosis infection test do you currently use in your practice (TST or IGRA)? What is the primary reason you use this test?

References:


