Over the last 30 years, the epidemiology of tuberculosis (TB) infection and disease has changed dramatically in Canada. We now have one of the world’s lowest reported rates of active TB, with less than six cases per 100,000 people. This low rate, however, masks the fact that certain populations in Canada remain at a high risk for active TB. Primary-care physicians need to be aware of these risk groups—primarily so they can prevent TB through targeted testing and treatment of latent TB infection (LTBI), and also for earlier diagnosis of active TB, if it occurs.

Over two-thirds of all active TB cases now occur among foreign-born Canadians, who may have a high prevalence of infection if they are from Asia, Africa or Latin America—regions that still have very high rates of TB disease. People co-infected with human immunodeficiency virus (HIV) and Mycobacterium TB constitute an emerging group with an extremely high risk of...
developing TB disease. Finally, Aboriginal Canadians remain a high-prevalence group, despite efforts in TB control (Table 1).1

In this article, the term “treatment of LTBI” has replaced the previous expressions “chemoprophylaxis” and “preventive treatment” to minimize patients’ confusion regarding the purpose of therapy. As well, the term “tuberculin skin testing” (TST) is used in place of older terms, such as “Siebert purified protein derivative of tuberculin” (PPD), which refers to the material used, or “Mantoux,” which refers to the technique used.

**Diagnosis of LTBI**

**How to test for LTBI.** The TST is the only method to identify latent infection with M. TB. The chest radiograph will be normal in more than 90% of individuals with LTBI. The term PPD refers to the purified protein derivative, which is the antigenic material used in the TST. A person with prior mycobacterial infection and an intact cell-mediated immunity will develop a delayed-type hypersensitivity reaction after 48 to 72 hours at the site of the TST.

The recommended method is the Mantoux method, which consists of an intradermal injection of 0.1 mL (five tuberculin units) of PPD on the volar aspect of the forearm. After 48 to 72 hours, the transverse diameter of the skin induration—not the redness—should be measured by a trained health professional and recorded in millimeters. The reaction may last up to one week. The multiple puncture method (also known as Tine method) or other tuberculin strengths (i.e., 1-TU or 250-TU) should not be used due to a lack of standardization. Self reading and reporting is not recommended.

Although anergy testing was commonly done in the past with the TST, it is no longer routinely recommended.

**Who to test.** The TST should be targeted for people who are at high risk for M. TB infection and who would benefit from treatment of LTBI.2 As summarized in Table 2, high-risk people include those recently infected with M. TB and those with a medical condition associated with an increased risk of developing active TB disease.
Within the first two years after infection with M. TB, there is a 15-fold increased risk to develop active TB, and over one-half of cases will occur during that period. Those most likely to have had a recent infection include: people in close contact with recent active pulmonary TB; recent immigrants from endemic countries within five years of their arrival; homeless people; intravenous drug users; and institutional residents and workers (i.e., those in nursing homes, and health care and correctional facilities).

**Who not to test.** A TST should not be performed in the following situations:
- Previous severe reaction to a TST (e.g., a history of blistering), extensive burns or eczema; in these situations the TST may cause serious adverse reactions;
- During major viral infections or within one month of live-virus vaccinations (measles or mumps), as these cause transient anergy and, therefore, false-negative TSTs;
- A documented history of active TB, treatment for LTBI, or documented prior positive TST; in these situations the TST will be of no clinical use;
- Low-risk populations; screening of persons who have a low risk of development of active disease, even if they have LTBI, is not recommended because they often will not be treated anyway; and
- Suspected active TB disease in adults, because as many as 20% to 50% of adults will have a negative TST at the time of initial diagnosis.

The TST may be given if the patient has a common cold, is pregnant, has been vaccinated recently (but not with a live virus), has received bacille Calmette-Guérin (BCG) vaccination or

### Table 2

**Conditions That Increase The Risk of Developing Active TB**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>Annual Risk of Developing Active TB (%)</th>
<th>Cumulative Lifetime Risk (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>90-170</td>
<td>8-17</td>
<td>100</td>
</tr>
<tr>
<td>HIV infection</td>
<td>40-113</td>
<td>4-11.3</td>
<td>100</td>
</tr>
<tr>
<td>Transplantiation</td>
<td>20-74</td>
<td>2-7.4</td>
<td>100</td>
</tr>
<tr>
<td>Pulmonary silicosis</td>
<td>30</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Chronic renal failure/hemodialysis</td>
<td>10-25</td>
<td>1-2.5</td>
<td>50-100</td>
</tr>
<tr>
<td>Recent infection within 2 years</td>
<td>15</td>
<td>1.5</td>
<td>75</td>
</tr>
<tr>
<td>Carcinoma of head and neck</td>
<td>16</td>
<td>1.6</td>
<td>80</td>
</tr>
<tr>
<td>Fibronodular disease on chest radiograph</td>
<td>6-19</td>
<td>0.6-1.9</td>
<td>30-95</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2-3.6</td>
<td>0.2-0.36</td>
<td>10-18</td>
</tr>
<tr>
<td>Granuloma on chest radiograph</td>
<td>2</td>
<td>0.2</td>
<td>10</td>
</tr>
<tr>
<td>No known risk factor</td>
<td>1</td>
<td>0.1</td>
<td>5</td>
</tr>
</tbody>
</table>

† Estimates for young adults
**The tuberculin skin test is the only method to diagnose latent TB infection, and should target high-risk populations.**

Tuberculosis Infection

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How to interpret results. Although the TST is a simple test, its interpretation often is more difficult. The following three steps are recommended:

**Step 1.** The first step is to determine whether a TST is “positive,” based on the size of the skin reaction. If the TST is positive, then no further tuberculin testing should be done (ever). The patients should undergo medical evaluation to assess the likelihood this is a true positive test, (Step 2), to rule out active TB disease, and to evaluate the risk of developing active TB in the future (Step 3).

**Criteria for considering a tuberculin reaction as positive:**

- Higher than 5 mm. This includes: very high-risk subjects, namely in HIV infection; close contacts of an active contagious case of TB; and subjects with evidence of fibronodular disease (“inactive TB”) on chest radiographs.
- Higher than 10 mm for all others. The 15 mm cut-off proposed for low-risk populations in the United States is not appropriate for Canadian practice.

**Step 2.** Once the test is read as “positive,” one needs to determine whether it is a “true positive” or not. False-positive results are defined as a positive TST (as defined above), but do not mean the person has M. TB infection. This can be seen after BCG vaccination or after exposure and infection with non-tuberculous mycobacteria (NTM).

The BCG vaccine is given in most developing countries, and many European countries. In Canada, BCG vaccination has been commonly given to Aboriginal populations and most individuals born in Quebec and Newfoundland between 1940 and 1980. The size of reaction does not help to distinguish a false-positive TST due to BCG vaccination from a true positive TST from TB infection. As summarized in Table 3, however, a history of BCG vaccination can be ignored in a number of situations.

Infection with NTM may cause false-positive responses due to cross-reactivity between the tuberculin (from M. TB) and NTM antigens. Fortunately, this is not a major problem in Canada because the prevalence of NTM in Canadian populations is very low (less than 5%). In endemic areas, such as the southeastern United States, over 70% of adults have been exposed
and infected with NTM. This means that false-positive reactions are common, which is why, in the United States, the criterion for a positive TST may be 15 mm.

The subject must also have a medical evaluation to assess his/her risk factors for LTBI and to rule out active TB disease. In particular, contact and immigration history, occupational exposure, and HIV risk factors and status are particularly important. A chest radiograph (posterior-anterior) should be performed to assess for evidence of old, healed TB or active disease. Finally, treatment of a LTBI should be considered, but should not begin until active disease has been excluded. People with respiratory symptoms and a chest radiograph suggestive of old, healed TB should have three spontaneous or induced sputum samples sent for acid-fast bacillus (AFB) smear and culture.

*Step 3.* The final step in the evaluation of a positive TST is to identify those who would benefit from LTBI treatment. As a general rule, all people at increased risk of active TB disease, as outlined in Table 3, should be treated regardless of age. In particular, treatment is crucial in HIV-infected cases and in those in recent contact of an active case. The risk of toxicity certainly increases with age and certain medical conditions, such as liver disease, and should be weighed against the cumulative risk of active TB disease.

In cases of pregnancy, it is generally recommended to postpone treatment of LTBI until after delivery, with the exception of HIV-infected women and those with a recent M. TB infection. Treatment is safe during lactation.

**The Booster phenomenon, two-step testing, and conversion.** In a number of situations, individuals may have repeated TSTs. The most common reason is because of potential exposure, such as with health-care workers or travellers. On repeated testing, reactions size may increase. Small increases of less than 6 mm may occur because of biologic variation, or technical differences in administration and reading. Larger increases may reflect new infection (conversion) or boosting. Boosting happens when the first TST is negative, but stimulates the immune system to “recall” prior mycobacterial exposure. This is common in people who received BCG, or had exposure to NTM or a remote M. TB infection.

The best way to identify boosting is to perform
a second TST one to four weeks later, if the first TST is negative (i.e., two-step testing). This second TST is performed with the same method and material (i.e., 5-TU using the Mantoux method), but on the opposite arm. Boosting is defined as a TST greater than 10 mm, with an increase of 6 mm or more from the first TST as long as there has not been any recent exposure. If both tests are negative, and then a third TST months to years later is positive, then conversion is said to have occurred.

Certain populations, such as those with HIV infection, pulmonary silicosis, organ transplantation and other medical illnesses, are at very high risk for active TB when infected with M. TB.

Table 4
Treatment Options of LTBI For Daily Self-administered Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration (in months)</th>
<th>Dose (mg)</th>
<th>Total number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9</td>
<td>300</td>
<td>270</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6</td>
<td>300</td>
<td>180</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4</td>
<td>600</td>
<td>120</td>
</tr>
<tr>
<td>Rifampin</td>
<td>2</td>
<td>600</td>
<td>60</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td>1,500</td>
<td></td>
</tr>
</tbody>
</table>

The use of rifampin allows for shorter regimens. Rifampin monotherapy for four months is likely as effective as the nine-month INH regimen. In HIV-infected patients, the two-month regimen of rifampin plus pyrazinamide has provided comparable protection as the six- or 12-month INH regimens. Recent reports, however, suggest an increased risk of hepatitis and even death. Therefore, until further information is available, this regimen should only be given with extreme caution, and in situations where the associated risks are clearly warranted.

Regular clinic visits, reinforcement of the importance of therapy, advice to minimize drug side effects, prescriptions for a short duration (generally one month) and flexible clinic hours are all critical to optimize patients’ compliance. Directly observed therapy (DOT) may improve compliance, but should be reserved for high-risk individuals in unusual situations, such as homeless
people, methadone clinic patients, etc. All intermittent regimens must be directly observed. When treatment is interrupted, the total duration of therapy and number of doses are more important than continuity. Therapy can be restarted to achieve the total number of doses desired.

Treatment of LTBI in contacts of active cases whose isolates were resistant to INH and/or rifampin should be referred to a TB specialist.

*About the medications.* The regimen of choice is nine months of daily INH. Patients’ preferences regarding the duration and complexity of the regimen, likelihood of compliance and/or side effects, including drug interactions, should be taken into account when choosing alternative regimens.

The most important toxicity with INH is hepatotoxicity. Incidence is age related—negligible in persons less than 35 years old, 1.5% if aged 35 to 50, 2.4% if aged 50 to 64, and 5% if older than 65. Other risk factors include alcohol consumption, Asian origin and underlying liver disease. Drug-induced hepatitis is almost always reversible if the INH is stopped soon after the development of symptoms of hepatitis, or when the allergy serum transfer (AST) exceeds five times the normal value. Death is extremely rare (1/100,000) when patients are closely monitored. A common side effect of INH is gastrointestinal upset, with poor appetite, nausea, vomiting or abdominal pains. These side effects will usually be improved if INH is taken with meals, which has a minor effect on absorption. Rash and drug fever can occur, as can fatigue and headache. Vitamin B6 (pyridoxine) should be added to prevent neuropathy if there are predisposing factors, such as malnutrition, alcoholism, pregnancy, diabetes or uremia.

Rifampin causes an orange discoloration of body fluids, including tears, and can cause gastrointestinal upset or rash. Hepatitis is less common than with INH. The main problem is potential drug interactions, as rifampin induces the hepatic cytochrome p450, which results in accelerated clearance of drugs, such as estrogens (oral contraceptive), cyclosporins, warfarin, glucocorticoids and sulfonylureas. An alternative method of contraception is required when oral contraceptives are used. In HIV patients, it should not be used in conjunction with protease inhibitors or non-nucleotide reverse transcriptase inhibitors (NNRTIs).

The rifampin-pyrazinamide regimen causes more skin rash, intolerance due to nausea and vomiting, and may be associated with a high risk of hepatotoxicity. It should only be given with extremely close monitoring and is not recommended as a first-line treatment at this time.

Baseline liver function tests (alanine aminotransferase [ALT] and AST) should be obtained in all patients. Regular monitoring of side effects, including liver function tests, is recommended for patients who are older than 35, or who have a history of alcohol abuse or underlying liver disease.

**Conclusion**

Identifying and treating LTBI in high-risk people reduces the risk of developing active TB, and benefits general public health by reducing future transmission. Primary-care physicians can play a pivotal role in this effort by identifying patients at high risk of developing active TB. These people should be screened with TST, and results should be interpreted in a step-wise fashion. Those with true positive TSTs should be considered for treatment with one of several alternative regimens now available.

**References**