TUBERCULOSIS PREVENTION

At present, there is no truly effective vaccine available for prevention of tuberculosis. While BCG is licensed in Canada, and is used in selected communities, its real benefit lies preventing the development of **severe** disease. It is known to have limited effect in primary prevention of tuberculosis (estimated at approximately 50%).

Most prevention efforts are therefore directed at ensuring that once an individual is infected with tubercle bacilli, the infection does not progress to disease. This is done with the use of preventive drug therapy. Individuals who are infected but do not have active disease cannot spread the disease to others.

Preventive Drug Therapy

Preventive drug therapy, or treatment of latent tuberculosis infection (LTBI), is the term used to refer to the use of medications to treat TB **after infection** has occurred, but **before active disease** has developed.

The use of single drug preventive therapy is an acceptable practice. This is because TB infection without active disease is the result of a relatively small number of tubercle bacilli. Accordingly the probability of resistant mutants, within an initially susceptible population of bacilli, being selected out by the use of a single drug, is very small.

Some groups of people are more likely to be exposed to, or infected with, *M. tuberculosis* and amongst those infected, some are more likely than others to develop TB disease once infected. People in these groups should receive high priority for preventive therapy if they have a significant TST reaction, and should be referred for assessment. Once active disease has been ruled out they are **candidates for preventive therapy** (see page 5-5). Decisions about which individuals should be offered preventive therapy are based upon assessment of the following 5 factors.

Referrals to TB Control or the TB Clinic should include any significant history identified in these 5 areas.

1. What is the likelihood that the individual has the organism in them? Because significant TST reactions could indicate tuberculous infection, a reaction to previous BCG vaccine **or** nontuberculous mycobacteria, questions should be asked to try to establish the probability of tuberculous infection. For example:

- Has this person lived or travelled extensively in a country with high prevalence of tuberculosis?
- Does this person have a family history of tuberculosis or have known close contact with an infectious individual?

2. What is the likelihood of infection progressing to disease? Medical history can often give indications

of the likelihood that an individual's tuberculous infection will progress to disease. For example:

- Recent infection (indicated by a TST conversion) has a greater likelihood of progression to disease—5 to 10% of individuals recently infected will go on to develop TB disease within 2 years.
- An individual who is co-infected with HIV has a much greater chance (10% per year) of developing active disease than someone without HIV infection.
- Several other medical conditions increase the risk of progression to disease, such as poorly controlled insulin dependent diabetes and end stage renal disease.
- Drugs such as prednisone suppress an individual's immune system, leaving the person at higher risk of progression to disease.

3. What is the likelihood of drug intolerance? The probability of drug intolerance can often be predicted based on history. For example:

- Persons with a history of liver disease or alcohol abuse may have problems tolerating these antituberculous drugs which are potentially hepatotoxic. Other individuals may have developed intolerance to TB medications during previous treatment.
- Individuals who are taking other medications may have difficulty tolerating TB drugs because of interactions between medications.
- Older individuals are more likely to develop adverse reactions to TB medications than are younger ones.

4. What is the likelihood that the individual will comply with the preventive therapy recommendations, and complete treatment once begun? For example:

- Individuals who are transient and are unable to make appropriate arrangements for access to drugs are not likely to complete a course of preventive therapy.
- Short-stay, foreign-born students are often not in the country long enough to complete a course of preventive therapy.

5. What is the anticipated "fallout" if the individual develops disease?

- For example, if a day care worker develops disease the public health implications are greater than if someone living as a hermit were to develop disease.

Referrals for evaluation for a course of preventive therapy should be made to TB Control or the local TB Clinic, using the" TB Referral Form," see page 7-7. A thorough history including symptom inquiry should be conducted and reported on the referral form.

In addition, please ensure:

- ▶ that a recent chest radiograph (i.e. within the past 6 months, in the absence of symptoms) is forwarded to the appropriate area. If no recent radiograph is available or the client has symptoms, use the referral form as a requisition for the x-ray, as it ensures the radiograph is forwarded appropriately.
- ▶ submission of sputum for AFB smear and culture if possible (indicate dates sent).

The TB Referral Form must accompany the radiograph when it is submitted.

Once active disease has been ruled out, a recommendation will be made regarding further need for investigation, follow-up and/or preventive drug therapy.

Candidates for Preventive Therapy

The following individuals should be referred to Tuberculosis Control or the local TB Clinic for consideration for preventive therapy.

Tuberculin Reaction Size	Indication
≥ 5 mm	• recent close contact with infectious TB • HIV infection • presence of lung scar (compatible with old TB but not previously treated)
≥ 10 mm *	• TST converter (previous non-significant TST result within the past 2 years) • immunosupression - organ transplantation - chronic renal failure - prolonged corticosteroid use or other immunosupressive drug therapy - hematologic malignacies--leukemia, lymphoma - silicosis - diabetes mellitus - < 90% of ideal body weight

* Preventative therapy may also be considered in other individuals, particularly if they are under the age of 35, have a TST reaction size ≥ 10 mm and are from one of the following groups: foreign born from TB endemic countries (particularly recent arrivals), Aboriginals, health care workers, and residents in communal care.

In otherwise healthy Canadian-born individuals who are not from an identified risk group and have no known contact with tuberculosis, significant TST results may be due to NTM infection.

Recommendation for Preventive Therapy

If the TB Physician recommends preventive therapy, a copy of the *Recommendation for Preventive Therapy* form (see page 7-14) will be sent to the family physician for signature. The physician will be directed to forward the signed form to the nearest local public health office for the PHN to co-sign. A copy of this form also will be sent to the regional TB program nurse so that she is aware of the recommendation.

Preventive therapy for latent TB infection is not a mandatory program, and the individual has the right to refuse treatment. The recommendation for prevention therefore also provides information about what the follow-up will be if the client refuses therapy.

The Public Health Nurse should consult with the family physician to discuss who will contact the client to discuss this recommendation.

As with treatment for disease, preventive therapy may be lengthy (6 to 9 months). It is often difficult for clients who feel well to understand the need for such a long course of medication. The client must understand that a commitment to completing a course of preventive therapy is necessary to ensure optimal preventive benefits.

In order to make an informed decision, the client needs to have information regarding:

- the reason for the recommendation
- the benefits of preventive therapy
- possible side-effects of the medication and possible drug interaction
- recommended follow-up if medication is refused

Taking the time to provide good education at this point will assist the client to make an informed decision, which should ultimately lead to increased compliance with therapy.

The results of this consultation and discussion will determine whether the client will begin a course of preventive therapy.

If the client agrees to take preventive therapy and the physician concurs:

Before Beginning Treatment

The "Recommendation for Preventive Therapy" form which was sent to the physician must be signed and forwarded to the Public Health Nurse.

Once the Public Health Nurse is confident the client has consented to therapy, the "Recommendation for Preventive Therapy" form should be co-signed and returned to TB Control. As the dose of medication is weight dependent, ensure the client's weight is recorded on the recommendation form.

Either the nurse or the physician can arrange to have baseline bloodwork performed, according to the medication recommended. This will be detailed on the "TB Update form" (see Appendix 14.4) accompanying the recommendation.

If the client is on other medications, check with the pharmacist who fills the prescriptions for those other medications, to ensure drug interactions will not be a concern.

Medication Supply

Drugs for preventive therapy are available through Alberta Health and Wellness TB Control, and they are provided free of charge.

To assist with compliance, directly observed preventive therapy **(DOPT)** is now the standard in all First Nations communities in Alberta and whenever twice weekly, intermittent, preventive therapy is being administered. It should also be very seriously considered:

- whenever DOT is being administered to an active case in the same home
- in very high risk situations or in communal settings (e.g., converters, HIV positive individuals, correctional facilities)
- when treating persons attending Methadone clinics
- when treating persons with a history of depression or other serious psychiatric illness

A 3 month supply of medications will be sent by mail or courier to the local public health office for distribution to the client. Accompanying the medication will be a detailed summary of the monitoring requirements and potential toxicity/drug interactions.

If the client will be taking **daily self-administered preventive therapy**, provide a 1 month supply of medication, and retain the rest at the public health office for distribution monthly.

- Attempt to see the client at weekly intervals over the first month to provide an opportunity to assess compliance with medication, provide education regarding the need for continued medication compliance, and monitor for side-effects to the medication.
- If weekly visits are not possible, phone contact can be a substitute for some of these visits.

If the medication will be DOPT, meet with the client to establish a schedule and meeting place to provide the medication.

Monitoring Compliance

Arrange for regular contact (at least monthly in the case of self-administered medication) to monitor compliance and adverse reactions, and to provide more medication as necessary.

To determine compliance, it is important to know both the number of doses that **should** have been taken since last contact and the **actual** number of doses taken.

- The most accurate way of doing this is by DOPT.
- For those on daily, unsupervised medications, monthly interviews with the client, and pill counts can assist in this determination.

Complete the preventive therapy form, ensuring medication compliance sections are completed, and forward to Tuberculosis Control every second month. Be sure to indicate whether more drugs are needed, as drugs are not sent out automatically.

On the final compliance report, please provide the date medication was stopped. The following will assist you in determining what constitutes adequate treatment:

- daily for 6 months = 180 doses
- daily for 9 months = 270 doses
- twice weekly for 6 months = 52 doses
- twice weekly for 9 months = 78 doses

Brief periods of non-compliance are accepted, but the course of preventive therapy needs to be completed within a specified time period. Such as:

- a 9 month regimen must be completed within 12 months
- a 6 month regimen must be completed within 8 months
- a 4 month regimen must be completed within 6 months

Other Monitoring

Routine monitoring of blood work is age and drug dependent (see Appendix 10), and the TB Update form will detail the recommendations by TB Control for such monitoring as is necessary.

Advise the family physician and TB Control about any adverse reactions to medications.

Notify TB Control promptly if medication is discontinued (even temporarily) because of reactions or if the client moves or is lost to follow-up.

If the client and /or his physician refuses preventive therapy:

Some individuals refuse to take preventive therapy, or their physician does not feel that his or her patient will be able to tolerate it because of age or previous ill health. If this is the case, either the physician or the PHN must notify Tuberculosis Control, and a further recommendation for appropriate follow-up will be made.

- **Tuberculin Skin Test converters** (i.e. those whose TST has converted to a significant reading within the past 2 years) will be followed with symptom inquiry, sputum for AFB smear and culture and radiographs 6 months, 12 months and 24 months following conversion. The highest risk for progression from infection to disease is during the first 2 years following infection.

Preventive Therapy Regimens

Medications used for preventive therapy are the same medications used for treatment of active disease, but protocols for their use differ.

INH is the only drug that has been **proven** effective in large-scale trials for TB preventive therapy, and is the primary drug that is used in Alberta. However, several alternative regimens are currently being used and/or trialed. Protocols in use at present include:

- INH daily or twice weekly for 9 months (270 or 78 doses respectively)
- Rifampin daily for 4 months (120 doses)
- INH and Rifampin twice weekly for 6 months (52 doses)

INH

A 9 month regimen of INH is known to be very effective (over 90% protection), but compliance tends to be a problem for this extended period of time. It has been shown that courses of isoniazid lasting at least 6 months and adhered to provide approximately 65 – 70% protection.

The decision regarding the length of time for treatment is dependent on age and HIV status. The most common prescription will be for 9 months of preventive therapy.

Single drug therapy with INH or rifampin is considered acceptable practice. Other regimens use a combination of drugs.

Rifampin

While rifampin has not been studied as extensively as INH for preventive therapy, in theory it should be equally, if not more effective. It is used routinely in individuals who cannot tolerate INH, or who are contacts of an individual with INH-resistant, rifampin-susceptible organisms.

INH and Rifampin

At times, when preventive therapy is directly observed, 6 months of twice-weekly INH and rifampin is used. Exciting data suggests that it is entirely satisfactory.

This regimen is most often used in First Nations community outbreak situations, or in individuals whose radiographs show lung scars, but activity cannot be confirmed.

Bacille Calmette-Guérin (BCG)

In Canada, Bacille Calmette-Guérin (BCG) vaccine is only given to selected populations where there is greater risk of TB infection and disease.

Although it's effectiveness in preventing pulmonary disease is probably limited, it has been shown to be effective in preventing serious forms of nonrespiratory disease in children. At this time it is still recommended for:

- ▶ First Nations Infants living on reserve. It should be given as soon after birth as possible.
  - Unless the vaccine is given before 6 weeks of age, tuberculin skin testing should be done prior to immunization, as there is no value in immunizing a child who already tests positive.
- ▶ Certain travellers who will be spending extended periods of time in countries with a high incidence of tuberculosis.

About the Vaccine

BCG is a suspension of a live attenuated strain of *M. bovis*—there have been over 3 billion doses administered worldwide since 1948.

Intradermal injection of vaccine that produces an artificial TB infection triggers an immune response that leads to sensitization of the lymphocytes to tuberculosis, without the risk of disease. The vaccine does not prevent a person from being infected. However, if a person does become infected after being vaccinated, their lymphocytes should recognize the organism quickly and hopefully prevent it from multiplying and causing disease.

Contraindications to Vaccine

- ▶ extensive areas of broken or inflamed skin
- ▶ family history of genetically transmitted immune disorders or family history of adverse reaction to BCG
- ▶ immunocompromised state—for any reason
- ▶ infant born to known HIV positive mother
  - As of September 1, 1998, Alberta initiated routine prenatal HIV testing. If the mother is concerned that she is at risk for HIV and was not tested while pregnant, suggest that she have testing before the baby receives BCG.
  - As part of **informed consent**, parents should be given information regarding the concern about immunizing a child who may be HIV positive. They may still consent to BCG immunization in the absence of HIV testing.
  - First Nations and Inuit Health Branch, Alberta Region has developed a consent form to address this issue.

Reactions to Vaccine Administration

Some reactions to BCG vaccine are to be expected, and are in fact an indication that the vaccine is producing the desired results. Parents must be informed about these expected reactions as well as about the possibility of more severe adverse reactions.

Mild (Expected Reaction)

- ▶ small reddened pustule in about 2 weeks which will crust over and may weep
- ▶ scar at this site in about 6 to8 weeks

Note: keep area covered with gauze or a clean cloth (not a band-aid), and keep arm covered with long sleeves to discourage scratching or bumping.

Moderate Adverse Reactions (less than 2 % of cases)

- ▶ skin ulceration which may spread, lasting up to 3 months
- ▶ involvement of lymph glands in the axilla
- ▶ abscess formation (this is the most common of the adverse reactions)

Note: Cover as with mild reactions, but antituberculosis medications may also be prescribed under the direction of a TB specialist.

Severe Adverse Reactions (Frequency <1:1,000,000)

- ▶ disseminated BCG disease may occur in infants who are immunocompromised, and is a life threatening condition.

Note: requires urgent medical attention

Guidelines for the Prevention and/or Detection of Tuberculosis in Travellers

There is little good information on the risk of tuberculosis in travellers to countries with a high prevalence of TB. We know that the annual risk of infection with *M. tuberculosis* in some high prevalence countries is at least 300-fold higher than in non-aboriginal communities in Alberta.

Recommendations for Counselling Prior to Travel

Assess TB risk as part of the routine pre-travel counselling. This means risk of exposure and risk of progression to active TB if infected.

▶ The major determinants of an individual's risk of significant exposure to tuberculosis infection while travelling are thought to be:

- prevalence or transmission rates of TB in the destination country. WHO estimates of cases per 100,000 for the year 2000 are: sub-Saharan Africa, 293; Southeast Asia, 247; Western Pacific, 144; Eastern Mediterranean, 168; Eastern Europe, 120.
- duration of the stay in a high prevalence country
- nature and frequency of contact with local people in a high prevalence country. This is often difficult to quantify. An example would be an individual working in health care in a high prevalence country. This person should be assumed to carry a very high risk of tuberculosis exposure.

▶ Travellers who are immunosuppressed due to HIV, cancer therapy, or other factors are at increased risk of progression to active TB if they are infected.

Inform the client about the possible risk of tuberculosis, based on assessment of the individual and their itinerary.

▶ Immunosuppressed travellers should be informed of the serious risk associated with tuberculosis exposure, the fact that a preventive strategy based on skin testing will have major limitations for them and that BCG is likely to be contraindicated.

▶ Travellers intending to work in a health discipline in a high prevalence country should be informed of the potential high risk of exposure and advised to follow published infection control recommendations for the prevention of TB in health care settings.

Advise all travellers to avoid consumption of unpasteurized milk since it may contain *M. bovis* or other pathogens.

Advise tuberculin skin 2-step testing for travellers to TB endemic countries who anticipate having contact with local residents for any significant amount of time. This is especially important for travellers to high prevalence countries who will be:

- working in a health care setting for any length of time
- travelling or residing in a high prevalence country for more than 3 months
- spending more than 1 month in other circumstances where there is a high risk of exposure

TST screening is not needed for short stay tourists (<3 months) who plan to have little or no contact with local residents.

Reactions to TST

- Individuals with significant reactions should be dealt with according to standard guidelines (see page 2-10). Assessment for the presence of active disease should be carried out immediately, but institution of preventive therapy may need to be deferred until after return from travel depending on the individual's travel schedule.
- Those with no significant reaction should be informed of the following 2 possible strategies for the *prevention* of tuberculosis.

Prevention Strategy Options

Strategy # 1. This is the preferred strategy in most cases.

Repeat TST yearly while in the high-risk country, and 3 months after leaving the high-risk countries, with consideration of preventive therapy for converters.

Disadvantages:

- It is not unusual to see very poor compliance with follow up testing and with preventive therapy, either because of difficulty in having the TST performed while out of the country, or because of the client's mistaken perception of risk.
- Standard preventive therapy may be ineffective against drug-resistant strains prevalent in many TB endemic countries.
- Some infected individuals will progress to active disease in the interval between skin tests.
- Some individuals will be intolerant of preventive therapy.

Note: Travellers opting for Strategy #1 must be very aware of the importance of follow-up testing. In this group, particular effort should be made to encourage and facilitate compliance with post travel TST.

Strategy # 2. This is a less desirable option, but may be warranted in some cases.

BCG vaccination, performed at least 4 weeks prior to departure (when possible).
BCG vaccine is provided by Alberta Health and Wellness only for **selected** travellers, and only when approved by a TB physician in the province.

Disadvantages:

- ▶ modest and uncertain efficacy
- ▶ troublesome ulceration at site of vaccination, particularly when administered to adults
- ▶ may complicate interpretation of subsequent TST

Choosing the Most Appropriate Strategy

The following factors need to be considered when assisting the client to choose the most appropriate strategy.

- ▶ Does the individual qualify for BCG vaccine?
- ▶ How feasible is repeated skin testing and how compliant would this client be with preventive therapy?
- ▶ What is the likelihood of INH intolerance (age, liver disease, alcohol excess)?
- ▶ What is the prevalence of INH or multi-drug resistance in the destination country?
- ▶ What is the individual's preference?
- ▶ Age—BCG may have a greater role in young children, reducing the risk of severe disease.

Recommendation for Follow-up After Return Home

Since no prevention strategy is completely effective, travellers and health care workers must be aware that tuberculosis should be in the differential diagnosis for any persistent, unexplained illness during or following travel.

Travellers who chose strategy # 1 (TST and preventive therapy if necessary) should be followed with annual TST while away. They should be re-tested 3 to 6 months after leaving the high-risk countries.

- ▶ Those with documented conversion should be offered preventive therapy according to standard guidelines.

Travellers who chose strategy # 2 (BCG vaccination) should be tuberculin skin tested 3 months post-vaccination to serve as a "baseline" in interpreting any subsequent TST. Individuals who do not convert their skin test should be re-tested as for those who have chosen strategy # 1.

- ▶ Those whose skin test is read as significant following vaccination should be counselled to report any symptoms of tuberculosis to their physician.

Appendix 8: Flouroquinolone Antibiotics

The floroquinolones are a relatively new class of antibiotics that have shown good in-vitro and in-vivo activity against M. tuberculosis. Amongst second-line anti-tuberculosis drugs, they have emerged as the most important by virtue of the fact that they:

- Are relatively free of hepatotoxicity
- Have high levels of oral bio-availability
- Are found in respiratory secretions in higher concentrations than serum
- Are concentrated inside macrophages
- Are well tolerated
- Have an excellent safety record in long term therapy

For purposes of anti-tuberculosis treatment, the most important members of this class of antibiotics are levofloxacin (Levaquin ®) usually prescribed in a dose of 500 mg P.O. daily, and the newer generation fluoroquinolones, moxifloxacin (Avelox®) and gatifloxocin (Tequin®).

1. Levaquin® is usually taken on an empty stomach with an 8 oz. glass of water. It is recommended that antacids, multivitamins (with minerals), dairy products, calcium fortified juices, sucralfate (Carafate®) or didanosine (Videx®) not be taken 2 hours before or after the administration of Levaquin® (**Videx EC** can be taken at the same time).

2. **Levaquin is contraindicated in persons with a history of hypersensitivity to flouroquinolones. It is also contradindicated in persons with a history of tendonitis or tendon rupture associated with the use of fluoroquinolones.**

3. **The safety and efficacy of Levaquin® in children, adolescents (under the age of 18 years), pregnant women, and nursing mothers who have not been established.**

4. Levaquin® and other floroquinolones should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold.

5. In clinical trials, the most frequently reported adverse events occurring in less than 2% of the study population regardless of drug relationship, were: nausea 6.9%, diarrhea 5.3%, headache 4.9%, constipation 2.7%, dizziness 2.9%, insomnia 3.8%, abdominal pain 2.5% and dyspepsia 2.3%.

6. Dose adjustment is recommended for patients with impaired renal function.

7. The type and dose of fluoroquinolone used to treat active TB or LTBI, should be reviewed with a TB consultant.