Most second-line agents are not considered safe in pregnancy either because of known teratogenicity or inadequate data indicating safety. FQN are best avoided during pregnancy, and breast feeding. The use of injectables (streptomycin, amikacin, kanamycin, and capreomycin) is contraindicated because of the effects on the fetus, including eighth cranial nerve palsies, deafness, and teratogenicity. These drugs should only be considered for use in specific instances after consultation with a TB specialist.

Anti-Tuberculosis Drugs

Anti-TB drugs are divided into two broad groups.

First-line drugs (FLD)

Four drugs are classified as FLD in Canada, because all are effective, can be taken orally and are well tolerated (or at least better tolerated than the second-line drugs).

The **first line anti-TB treatments** for which *M. tuberculosis* is susceptible are the following:

- Isoniazid (INH)
- Rifampin (RMP)
- Pyrazinamide (PZA)
- Ethambutol (EMB)

} Core standard treatment for active TB

The first line drugs are used to treat respiratory and non-respiratory tuberculosis, with several exceptions described in the following sections. FLD are administered orally unless required by means of nasogastric or feeding tube. If oral medication cannot be used, consultation with a TB Specialist is necessary. The tablets can be crushed and mixed with water, or suspensions of the medications can be prepared to make delivery easier.

Isoniazid (INH)

INH was first introduced in 1952 and is still a cornerstone of modern TB therapy. It has very powerful early bactericidal activity, meaning that it is highly effective in rapid killing of bacteria in the first few days. Hence, the drug is important in achieving rapid killing of TB bacilli. It is also effective in preventing the emergence of resistance, although its role in preventing relapse is unclear. If INH is not given for the full duration of therapy, then therapy should be prolonged. If INH is not given at all, therapy should be for at least 12 months. Pyridoxine (vitamin B6) should routinely be added to all INH regimens. A pyridoxine daily dose of 25mg is sufficient; higher doses (50mg) may be used for intermittent therapy.

Rifampin (RMP)

This drug, introduced in 1968, is the most potent anti-TB drug available. Its use allows shortening of the regimen to a total of 9 months (or 6 months if PZA is also used). The drug has good bactericidal activity, prevents acquired drug resistance and is very important in preventing relapse. Current doses are based on studies performed in the 1960s, when the lowest effective dose was used because of the high cost of the drug. If RMP is not given for the full duration of therapy, then therapy should be prolonged. If RMP is not given at all, therapy should be for at least 18 months.

Pyrazinamide (PZA)

This drug is also bactericidal but appears to provide benefit only in the first 2 months of therapy. In randomized trials, use of PZA in the continuation phase did not reduce relapse rates, and the drug appeared to offer no protection against the development of resistance. If PZA is not given for the entire first 2 months, the total duration of therapy should be 9 months.

Ethambutol (EMB)

This is the least effective of the four FLD for bactericidal activity, or prevention of relapse, but it is effective in preventing the emergence of drug resistance. If a previously untreated patient has unrecognized INH resistance and is given only INH, RMP and PZA for the first 2 months then RMP resistance could emerge, given the inability of PZA to protect against the emergence of resistance. Hence, EMB is added in the initial phase empirically while the results of drug susceptibility testing (DST) are pending.

Second-line drugs (SLD)

The SLD include the fluoroquinolones, all injectables and many "older" TB drugs that were used in the 1950s and 1960s but were abandoned because of relatively poor efficacy and/or greater toxicity.

Drug Regime Options

Below are the recommended drug regimen options for the treatment of **fully sensitive TB:**

Table 8.9: Recommended Drug Regime

Standard		
	Initial Phase (first 2 months)	**Continuation Phase**
Regime 1	• INH RMP PZA EMB*† • Daily (or 5 days/week)	• INH RMP for 4–7 months • Daily (or thrice weekly)
Regime 2	• INH RMP EMB*† • Daily (or 5 days/week) • +/- 2nd line agent	• INH RMP for 7 months • Daily (or thrice weekly)
Elderly (>65) or other risk factor for hepatotoxicity		
	• INH RMP EMB*† • Daily (or 5 days/week)	• INH RMP for 7 months • Daily (or thrice weekly)
Pregnant		
	• INH RMP PZA EMB** †, or • INH RMP EMB* • Daily (or 5 days/week)	• INH RMP - for 7 months if PZA not used, and for 4 months if PZA used in first two months • Daily (or thrice weekly)

*EMB can be stopped as soon as the DST are available and if pan sensitive. PZA should continue for the full 2 months of the initial phase.

**Three times weekly preferred over twice weekly for programmatic reasons. If patients miss a single dose while receiving thrice weekly therapy they effectively receive twice weekly therapy, which is still adequate. If they miss a dose of twice weekly therapy they effectively receive once weekly therapy which is inadequate.

† If the patient is smear negative, the TB Specialist or Internal Medicine Specialist may consider thrice weekly for the remainder of the initial phase and all of the continuation phase after the first two weeks of daily dosing (typically thrice weekly treatment is considered after discharge from hospital).

Table 8.10: Recommended Drug Doses for Daily and Intermittent Therapy in Adolescents and Adults

	Daily		Thrice Weekly	
First line drugs	**By weight***	**Max (mg)**	**By weight***	**Max (mg)**
INH	5mg/kg	300	10mg/kg	600
RMP	10mg/kg	600	10mg/kg	600
PZA	20–25mg/kg	2000	30–40mg/kg	4000
EMB	15–20mg/kg†	1600	25–40mg/kg	2400
Second line drugs				
Fluoroquinolones ‡ - Moxifloxacin		400		#
- Levofloxacin		750–1000		#
Injectables: Amikacin♦	15mg/kg as a single dose			#

* For doses for children see **Section 11, Pediatric TB**

† EMB dosing: Optimal dosing is unclear. It is clear that eye toxicity is dose dependant and its risk is higher at 25mg/kg than at 15mg/kg.

‡ Fluoroquinolones: Gatifloxacin is not recommended in Canada because of dysglycemia problems. This drug has been used in recent trials and is still used in some countries.

♦Amikacin: of the injectables, Amikacin is preferred for use in Canada because of the ready availability of the drug, familiarity with its use by clinicians, nurses and pharmacists, and the ability to measure serum drug concentration in many facilities. Streptomycin is not available in Canada, but may be preferred in some low and middle income countries as toxicity is similar and costs may be lower.

#There is inadequate data from randomized trials on use of fluoroquinolones or injectables as part of intermittent regimens. If these drugs are needed, because of intolerance or resistance to first line drugs, daily therapy is suggested.