Completion Rates of Treatment for Latent Tuberculosis Infection in Quebec, Canada From 2006 to 2010

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ABSTRACT

Objective: Treatment of latent TB infection (LTBI) in high-risk populations has been identified as a priority activity for reducing TB incidence. Treatment completion rates are usually far from the 80% target. The objective of this study was to evaluate the proportion of individuals who obtained enough medication for standard LTBI treatment.

Methods: Using the *Régie de l'assurance maladie du Québec* database, we extracted data on all prescriptions filled as part of the free anti-tuberculosis medication program. We calculated the proportion of patients who had obtained at least 270 doses among patients who had started treatment with isoniazid (INH), and the proportion of patients who had obtained at least 120 doses among patients who had started treatment with rifampin (RMP).

Results: Among the 2,895 patients who had started INH, 907 (31.3%) obtained at least 270 doses. Among the 373 patients who had started RMP, 242 (64.9%) obtained at least 120 doses. Women were more likely to stop INH treatment before acquiring 270 doses of the medication than men (hazard ratio [HR] = 1.08; 95% confidence interval [CI]: 1.01-1.17).

Conclusion: Only 31.3% of patients who started treatment with INH had procured at least 270 doses. Completion rates are far below target values.

Key words: Tuberculosis; isoniazid; treatment; compliance; adherence

La traduction du résumé se trouve à la fin de l'article.

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In 2010, 1,575 tuberculosis (TB) cases (4.6 per 100,000) were reported to the Canadian Tuberculosis Reporting System.¹ The disease remains a significant health problem among Aboriginal persons and immigrants, with incidence rates of 26.3 and 13.3 per 100,000, respectively. In comparison, the incidence rate for non-Aboriginal Canadian-born individuals is 1.9 per 100,000.¹ For the same year, 208 TB cases (2.6 per 100,000) were reported in Quebec. Among these cases, 61.5% were reported in Montréal residents.

Screening for and treatment of latent TB infection (LTBI) in high-risk populations (e.g., close contacts of individuals with active TB, persons with HIV infection, foreign-born persons referred for medical surveillance by Citizenship and Immigration Canada, urban homeless and the under-housed, including staff at homeless shelters) have been identified as priority activities for reducing the TB incidence in Canada.²

A 300 milligram (mg) daily dose of isoniazid (INH) for nine months is the current standard LTBI treatment for adults.³ INH daily for six months is acceptable when nine months daily treatment is not accepted by the patient. Rifampin (RMP) 600 mg daily for four months is an acceptable alternative when INH cannot be used.³ However, convincing patients with LTBI to take medication for nine months has always been challenging: asymptomatic patients often perceive LTBI as a non-contagious infection that progresses to active TB in only 10% of cases, and patients may fear developing adverse effects from treatment lasting nine months.⁴

Many studies have shown variable treatment completion rates in developed countries, usually far from the Canadian program performance standard of 80% for LTBI treatment.³ In a US study examining contact investigations in 24 states, 4 large cities, and Puerto Rico in 1999, of 13,083 contacts exposed to pulmonary TB cases and found to have LTBI, 5,746 (44.5%) completed treatment to prevent TB.⁵ In another study in five health departments in the US, among 398 contacts of pulmonary TB cases who initiated LTBI treatment, 203 (51%) were documented to have completed a six-month treatment. However, these contacts represented less than one third of all contacts with newly detected LTBI.⁶ In a more recent retrospective cohort study in New York City, from 1997 to 2003, 30,561 contacts were identified during investigation of 5,182 pulmonary TB cases. Of 6,001 infected contacts who initiated LTBI treatment, 3,642 (60.7%) completed the treatment.⁷

Among 2,484 foreign-born who screened positive for TB at county health departments for public health services in Tennessee, 1,416 (57%) completed LTBI treatment.⁸ With a cultural case manage-

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Figure 1. Flowchart for patients treated for latent tuberculosis infection

* tab=tablet.

ment approach established for finding and treating LTBI among former Soviet Union, former Yugoslavia, and Somalia refugees, a completion rate of 72% was obtained from July 1999 through December 2000 in the Seattle & King County TB Clinic.⁹

In other settings, a systematic review of studies on adherence to LTBI treatment has found that completion rates varied from 32% to 61% within correctional facilities, and from 39% to 70% among injection drug users.⁴ A four-month regimen with RMP seemed to be associated with better completion rates, ranging from 72% to 91%.¹⁰⁻¹²

The aim of this study was to evaluate the proportion of adult patients who started LTBI treatment and completed it within 12 months of first prescription.

METHODS

Data source

We used a database administered by the *Régie de l'assurance maladie du Québec* (RAMQ),* established in 1969 for the purpose of setting up and managing the public Health Insurance Plan. Most residents

* Québec's health insurance board.

of the province (7.9 million in 2011) are eligible for the plan, which covers many health-related services, including medical services. Since 1997, prescription drug insurance coverage has been compulsory for all citizens. It is a mixed system, where those who have access to private plans must join them (most often available through employment); all others must register for the public plan, administered by the RAMQ. However, provision of medication for the treatment of sexually transmitted diseases and active TB or LTBI is covered for all under the Health Insurance Plan. This is to ensure that anyone needing these prescription drugs has access to them at no cost, regardless of insurance coverage (public or private plan). Therefore, data collected by the RAMQ likely reflects the use of anti-TB therapy for the whole population.

Data relative to drug dispensation by pharmacists are collected in a central database. Any medication covered by the Health Insurance Plan and dispensed to insured persons is automatically entered into the database by the pharmacist via an interactive communications network. Information collected includes patient identifiers, patient characteristics (sex, age group, and region of residence), medication, quantity dispensed, length of treatment, and pharmacist identifiers.

Table 1. Completion Rates of LTBI Treatment With INH*

Characteristic	LTBI Treatment With INH 300 mg Daily				
	Patients n (%)†	≥270 Doses n (%)‡	95% CI of Row Percent	≥180 Doses n (%)‡	95% CI of Row Percent
Sex					
Female	1686 (58.2)	487 (28.9)	(26.7-31.1)	905 (53.7)	(51.3-56.1)
Male	1209 (41.8)	420 (34.7)	(32.0-37.4)¶	720 (59.6)	(56.8-62.4)**
Age group (years)					
20-34	1210 (41.8)	365 (30.2)	(27.6-32.8)	672 (55.5)	(52.7-58.3)
35-64	1558 (53.8)	511 (32.8)	(30.5-35.1)	894 (57.4)	(54.9-59.9)
≥65	127 (4.4)	31 (24.4)	(16.9-31.9)	59 (46.5)	(37.8-55.2)
Residence region§					
Greater Montréal	2226 (76.9)	700 (31.5)	(28.7-34.3)	1271 (57.1)	(55.0-59.2)
Other regions	652 (22.5)	202 (31.0)	(27.4-34.6)	342 (52.5)	(48.7-56.3)
Year of prescription					
2006	460 (15.9)	138 (30.0)	(25.8-34.2)	257 (62.8)	(58.4-67.2)
2007	1004 (34.7)	327 (32.6)	(29.7-35.5)	579 (61.5)	(58.5-64.5)
2008	838 (28.9)	260 (31.0)	(27.9-34.1)	476 (68.6)	(65.5-71.7)
2009	593 (20.5)	182 (30.7)	(27.0-34.4)	313 (52.8)	(48.8-56.8)
Total	2895 (100)	907 (31.3)	(29.6-33.0)	1625 (56.1)	(54.3-57.9)

* LTBI: latent tuberculosis infection; INH: isoniazid.

† Column percent.

‡ Row percent.

§ Data missing for 17 cases.

|| July 1st to December 31st.

¶ p=0.001.

** p=0.002.

We extracted data on all prescriptions for active TB or LTBI treatment reimbursed through the Health Insurance Plan from January 1, 2006 to December 31, 2010. No personal information was included except a unique encrypted identifier number for each patient. The data set was organized as a line list of prescriptions. Any medication dispensed to an insured patient on a specific date is entered in the data set as one prescription, even if the original prescription written by the physician included more than one medication. Lines were aggregated by patient, and aggregate variables for each individual included treatment regimen received and the length of treatment.

Cohort construction

The cohort is made up of adult patients who were prescribed LTBI treatment and obtained medication within a 12 month-period following the date of first prescription. A prescription is defined as a “first prescription” when no other prescription for the same medication has been dispensed in the previous six months. For 2006, the first year of observation, patients who had received a prescription on June 30, 2006 or before were excluded. The last cases included in the cohort had to have received a first prescription by December 31, 2009 at the latest, to enable verification of treatment adherence for the 12 months after the prescription was issued. Patients who had obtained drugs other than INH or RMP were excluded. Patients who had received INH and RMP simultaneously at first prescription were also excluded to avoid inclusion of active TB cases. Because we wanted to limit our analysis to adults receiving standard LTBI treatment, patients under 20 years of age were excluded, as were patients who had prescriptions for INH 100 mg tablets, INH syrup (50 mg/5 ml) or RMP 150 mg tablets. Also excluded were patients who had initiated treatment with INH 300 mg tablets and continued treatment with RMP 300 mg tablets.

Patients were observed for 12 months following the date of the first prescription. We analyzed medications procured every month as well as duration of treatment indicated on the prescription for each patient in the cohort. To calculate the total number of days of

treatment, we added the number of days indicated on each prescription for the 12 months following first prescription.

Data analysis

The data were analyzed using the Stata Data Analysis and Statistical software version 10.0 (StataCorp LP). We calculated the proportion of patients who had obtained at least 270 doses or at least 180 doses for daily INH 300 mg treatment, and the proportion of patients who had obtained at least 120 doses for daily RMP 300 mg treatment. Proportions are displayed by type of regimen, sex, age group and region of residence (Greater Montréal [Montréal Island, Laval Island and Montréal South Shore] vs. all other regions of Quebec). Pearson's χ^2 significance test was applied to calculate p-values for cross-tabulated variables. P-values were considered significant if <0.05. Kaplan-Meier survival analysis was used to estimate the probability of acquiring INH or RMP each month for 12 months following the date of the first prescription. Follow-up began at the time the patient filled out his or her first LTBI prescription and the outcome event was the filling out of the last LTBI prescription during the study period (referred to as “cessation”). We used Cox proportional hazards regressions to further test the association between the independent variables and INH and RMP adherence. Graph plots and tests for each covariate (results not shown) indicate no violation of the proportional hazards assumption. Hazard ratios (HR) larger than 1 indicate a higher rate of cessation in the exposed category and therefore a shorter average length of treatment. Ethics approval was not required for this study.

RESULTS

Figure 1 shows the study cohort flowchart, from all the LTBI treatments prescribed down to the patients meeting all eligibility criteria. Thus, from July 1, 2006 to December 31, 2009, 2,895 patients were given a first prescription for 30 days of INH 300 mg tablets (Table 1). Among them, 907 (31.3%) procured at least 270 doses of medication (nine months), and 1,625 (56.1%) at least 180 doses (six months). Figure 2 shows how the risk of cessation evolved over time in all subjects. The Cox regression analysis of the survival data

Figure 2. Kaplan-Meier estimates for LTBI cessation, in days

shows that, after controlling for age, region of residence and year of prescription, women were more likely to stop INH treatment before acquiring 270 doses of the medication than men (hazards ratio [HR] = 1.08; 95% confidence interval [CI]: 1.01-1.17). Consequently, the proportion of patients who had obtained at least 270 doses of medication was higher among men than among women (34.7 vs. 28.9, $p=0.001$), and the proportion of patients who had obtained at least 270 doses of treatment did not vary significantly by age, place of residence, or year of prescription.

For the same period, 373 individuals began LTBI treatment with RMP (Table 2 and Figure 2), 242 (64.9%) of whom obtained at least 120 doses of treatment (four months). The proportion of patients who had obtained at least 120 doses of medication did not vary significantly by sex, age, place of residence, or year of prescription.

DISCUSSION

Our results indicate that only 31.3% of patients who initiated INH for preventive LTBI treatment obtained at least 270 doses, which corresponds to nine months of treatment. This figure rises to 56.1% when we consider patients who procured at least 180 doses. These results are comparable to those from two recently published studies. In one retrospective cross-sectional study of 68 clinics in 19 regions in the United States and Canada, only 57.1% of patients who had been prescribed nine months of INH treatment had taken it for at least six months.¹³ In a study that used RAMQ data to assess adverse effects associated with LTBI treatment from 1998 to 2003, 54.1% of patients had completed six months of INH treatment; in this study, 56.2% of patients had completed four months of RMP treatment.¹⁴ The corresponding figure in our study is 64.9%.

Based on Kaplan-Meier curves, 17.4% of patients did not renew their INH prescription after the first month of treatment. From the second to the ninth month, an average of 7.3% of patients (range:

5.0-9.5) stopped treatment each month. The step at one month being higher than the others suggests that some patients never renew their prescription, possibly because of adverse reactions or fear of these. Afterwards, the risk of cessation remains constant until completion. The absence of a large step after six months means that the majority of patients probably received a nine-month prescription of INH.

Our study has several limitations. We cannot be sure that the RAMQ database captures all patients who were prescribed and obtained a LTBI treatment. However, it is unlikely that a patient chooses to pay a monthly deductible and a co-insurance fee when he or she can get his or her medication totally free of charge. Moreover, there is no reason to believe that patients getting INH or RMP through private insurance would have higher or lower completion rates than those we obtained in our study.

From a database such as the one we used, we cannot determine whether patients who purchase LTBI medication actually take the number of doses prescribed. Moreover, our results did not take into account the number of patients who were prescribed LTBI medication but declined all treatment. Usually, a significant proportion of patients for whom LTBI treatment is offered decline. In the New York City study cited previously, of 7,597 infected contacts, 1,596 (21.0%) never initiated treatment.⁷ In 32 US and Canadian clinics that performed skin testing and offered treatment, of 720 infected patients, 123 (17.1%) declined initiation of treatment; employees at a health-care facility were more likely to refuse treatment, whereas contacts of a case of TB were less likely to decline.¹³

Results indicate that usual completion rates obtained in the field leave much to be desired and are considerably lower than the objective of 80% established by the Canadian Tuberculosis Standards.³ Effectiveness of LTBI treatment with INH is a function of adherence and duration of treatment. In persons taking >80% of doses,

Table 2. Completion of Treatment for LTBI With RMP*

Characteristic	LTBI Treatment With RMP 600 mg Daily		
	Patients n (%)†	≥120 Doses n (%)‡	95% CI
Sex			
Female	182 (48.8)	118 (64.8)	(57.9-71.7)
Male	191 (51.2)	124 (64.9)	(58.1-71.7)
Age group (years)			
20-34	184 (49.3)	116 (63.0)	(56.0-70.0)
35-64	171 (45.8)	117 (68.4)	(61.4-75.4)
≥65	18 (4.8)	9 (50.0)	(26.9-73.1)
Residence region§			
Greater Montréal	334 (89.6)	220 (65.9)	(60.8-71.0)
Other regions	35 (9.4)	20 (57.1)	(40.7-73.5)
Year of prescription			
2006	63 (16.9)	44 (30.0)	(58.5-81.1)
2007	97 (26.5)	61 (62.9)	(51.3-70.7)
2008	99 (26.0)	61 (61.6)	(52.0-71.2)
2009	114 (30.6)	76 (66.7)	(58.1-75.4)
Total	373 (100)	242 (64.9)	(60.1-69.7)

* LTBI: latent tuberculosis infection; RMP: rifampine.

† Column percent.

‡ Row percent.

§ Data missing for 4 cases.

|| July 1st to December 31st.

daily INH for one year provided 93% protection, and daily INH for six months provided 69% protection.³ Incomplete LTBI treatment is probably better than no treatment at all. In the New York study, not only LTBI treatment completion in infected contacts was associated with a lower risk of incident tuberculosis compared with no treatment (adjusted Hazard Ratio, 0.16) but also initiation without completion (adjusted Hazard Ratio, 0.24). Despite completion rates around 50%, offering LTBI treatment to infected contacts or to persons at high risk for TB exposure or progression to active TB seems to be an effective intervention and may reduce TB rates over time.^{7,8}

Completion rates with four months of RMP treatment are better than completion rates with six months of INH but are still far from the recommended targets. This suggests that successful LTBI treatment may depend on the availability of effective regimens shorter than the six- or nine-month INH schedule. Recently, treatment based on weekly doses of INH and rifapentine (RPT) for three months has shown promising results: 82% completion rate, efficacy comparable to nine months of INH treatment, and similar toxicity profile.¹⁵ These results have prompted the US Centers for Disease Control to recommend the new INH-RPT treatment as an equivalent alternative to the nine-month INH regimen for healthy patients aged ≥12 years who have LTBI and have factors predictive of developing active TB.¹⁶ Unfortunately, until RPT is approved in Canada, this regimen will not be available for LTBI treatment.

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RÉSUMÉ

Objectif : Traiter l'infection tuberculeuse latente (ITL) dans les populations à haut risque représente une activité importante pour réduire le fardeau d'incidence de la tuberculose. Les taux d'achèvement du traitement demeurent en deçà de l'objectif habituel de 80 %. Le but de cette étude était d'évaluer la proportion des personnes qui se sont procuré suffisamment de médicaments pour le traitement de l'ITL.

Méthode : À partir du fichier de données de la Régie de l'assurance maladie du Québec, nous avons obtenu toutes les ordonnances remplies dans le cadre du Programme de gratuité des médicaments pour la tuberculose. Nous avons calculé, parmi des patients qui ont été traités avec isoniazide (INH), la proportion de ceux qui se sont procuré au moins 270 doses. Nous avons également calculé, parmi des patients qui ont été traités avec rifampine (RMP), la proportion de ceux qui se sont procuré au moins 120 doses.

Résultats : Parmi les 2 895 patients qui ont été traités avec l'INH, 907 (31,3 %) se sont procuré au moins 270 doses. Parmi les 373 patients qui ont commencé un traitement préventif à la RMP, 242 (64,9 %) se sont procuré au moins 120 doses. Les femmes avaient plus de chances d'abandonner le traitement avant de s'être procuré au moins 270 doses d'INH que les hommes (Ratio de taux [RT] = 1,08; Intervalle de confiance [IC] à 95 % : 1,01-1,17).

Conclusion : Seulement 31,3 % des patients qui ont été traités avec l'INH se sont procuré au moins 270 doses. Les taux d'achèvement sont bien en deçà des taux habituellement visés.

Mots clés : tuberculose; isoniazide; traitement; observance; fidélité au traitement