# Treatment with isoniazid or rifampin for latent tuberculosis infection: population-based study of hepatotoxicity, completion and costs

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**The use of 4 months rifampin (4R) instead of 9 months of isoniazid (9H) for treatment of latent tuberculosis infection is supported by our findings of lower risk of severe hepatotoxicity, better completion and lower adjusted direct costs with 4R** http://bit.ly/3agWLh9

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ABSTRACT Clinical trials suggest less hepatotoxicity and better adherence with 4 months rifampin (4R) *versus* 9 months isoniazid (9H) for treating latent tuberculosis infection (LTBI). Our objectives were to compare frequencies of severe hepatic adverse events and treatment completion, and direct health system costs of LTBI regimens 4R and 9H, in the general population of the province of Quebec, Canada, using provincial health administrative data.

Our retrospective cohort included all patients starting rifampin or isoniazid regimens between 2003 and 2007. We estimated hepatotoxicity from hospitalisation records, treatment completion from community pharmacy records and direct costs from billing records and fee schedules. We compared rifampin to isoniazid using logistic (hepatotoxicity), log-binomial (completion), and gamma (costs) regression, with adjustment for age, co-morbidities and other confounders.

10 559 individuals started LTBI treatment (9684 isoniazid; 875 rifampin). Rifampin patients were older with more baseline co-morbidities. Severe hepatotoxicity risk was higher with isoniazid (n=15) than rifampin (n=1), adjusted OR=2.3 (95% CI: 0.3–16.1); there were two liver transplants and one death with isoniazid and none with rifampin. Overall, patients without co-morbidities had lower hepatotoxicity risk (0.1% *versus* 1.0%). 4R completion (53.5%) was higher than 9H (36.9%), adjusted RR=1.5 (95% CI: 1.3–1.7). Mean costs per patient were lower for rifampin than isoniazid: adjusted cost ratio=0.7 (95% CI: 0.5–0.9).

Risk of severe hepatotoxicity and direct costs were lower, and completion was higher, for 4R than 9H, after adjustment for age and co-morbidities. Severe hepatotoxicity resulted in death or liver transplant in three patients receiving 9H, compared with no patients receiving 4R.

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## Introduction

Treatment for latent tuberculosis infection (LTBI) is a key component of TB prevention, particularly in low-TB incidence countries [1]. The recommended LTBI treatment regimen is 9 months daily isoniazid (9H) in the US [2] and Canada [3], and 6–9 months isoniazid in the European Union [4]. However, hepatotoxicity concerns and low completion with isoniazid have prompted trials of shorter duration regimens.

A randomised controlled trial of 4 months rifampin (4R) reported comparable efficacy to 9H, but with fewer adverse events and higher adherence [5–7]. However, while the drug cost of rifampin is often higher than isoniazid, costs of monthly monitoring and unplanned visits to manage drug-related adverse events are higher with the 9H than the 4R regimen [8]. Further, most studies of 4R have been randomised trials [5–7] or single-clinic observational studies [9–13]. These studies may overestimate adherence and underestimate drug-related adverse event rates and costs occurring in "real-world" settings with more diverse provider types and patient populations, including older patients and those with co-morbidities [14].

In Quebec, Canada, approximately 99% of permanent residents are beneficiaries of the provincial health insurance plan, and since 1997, all TB drugs have been paid for by this plan for all Quebec residents [15]. This means that information from this provincial health insurance plan is essentially complete for all persons receiving TB drugs in the province. Our objectives were to use this population-wide data to compare frequencies of severe hepatic adverse events, treatment completion and direct health system costs of 4R and 9H, in all persons receiving these two regimens in Quebec between 2003 and 2007.

## Methods

### *Data source and population*

A retrospective cohort was identified of all individuals starting LTBI treatment with isoniazid or rifampin between 2003 and 2007 in Quebec. During these years, 9H was considered the primary LTBI regimen, and 4R was considered an alternative regimen. The cohort was extracted from the provincial public health insurance (*Régie de l'assurance maladie du Québec* (RAMQ)) database, including physician billing records, hospitalisations, drug plan coverage, and drugs dispensed.

The first RAMQ drug dispensation record for isoniazid or rifampin was identified as a patient's "index date". We extracted data starting 3 years before, and ending 3 years after, the index date, or ending earlier with death or study period end (October 18, 2009). We excluded rifampin patients from the cohort when prescribed for other known indications (table S1).

### *Definitions of exposure and outcome*

We defined the "LTBI treatment period" as starting on each patient's index date and ending 30 days after the last TB drug was dispensed (*i.e.* date last drug dispensed+number of days dispensed+30 days). The main exposure variable was the LTBI regimen the patient initially started (isoniazid or rifampin). We identified LTBI regimen switches when a change in regimen occurred ⩾7 days after the initial regimen dispensation date, with permanent discontinuation of the initial regimen. When patients switched from one regimen to another, we calculated the number of doses dispensed for the first regimen only and ended the LTBI treatment period window at 30 days after the last dispensation of the initial drug. Patients dispensed isoniazid and rifampin concurrently, when not identified as a regimen switch, were excluded from the cohort definition (n=81).

We defined "LTBI treatment completion" as 120 doses dispensed within 6 months (4R), and 270 doses within 12 months (9H) [2]. We identified a "severe hepatic adverse event" as any hospital admission occurring within the LTBI treatment period, with an incident International Classification of Diseases (ICD) 9/10 diagnostic code or procedure code indicating a hepatotoxic event [16] followed by permanent drug discontinuation (table S1). If any of the same codes for liver disease also occurred in the year before start of LTBI treatment, we did not count this patient as having a severe hepatic adverse event related to LTBI treatment.

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Health service events included emergency department visits, hospitalisations, hospital day procedures, physician visits and drugs dispensed. Health service costs were tabulated to the end of LTBI treatment or to the recommended time limit for each regimen (*i.e.* 12 months (9H) and 6 months (4R)), whichever was earliest. Among patients whose LTBI treatment ended due to a severe hepatotoxic adverse event or regimen switch, costs were included up to 30 days after the last dispensation date of the initial drug (*i.e.* if a regimen was switched on January 1, costs were tabulated to January 30). Costs were estimated using 2011 Canadian dollars, representing the final follow-up year. Direct costs were estimated using fees paid by RAMQ (as reported in the RAMQ database), or where not available (*e.g.*, hospitalisations, emergency department visits and day procedures), fee schedules were used [17, 18] (table S2).

### *Definitions of confounders*

Potential confounder variables were identified based on *a priori* hypotheses about factors associated with LTBI treatment outcomes [10, 19–21]. Variables were extracted at each patient's index date, including treatment initiation year, age group (0–19, 20–34, 35–49, 50–64, 65–74 and ⩾80 years), sex, pre-treatment co-morbidities and treating physician type.

We measured co-morbidities in multiple ways. First, we identified when a cohort member was hospitalised for any reason in the year before treatment start (considered as a general indicator of baseline co-morbidity). Secondly, we calculated the Charlson–Deyo co-morbidity score for each patient in the year before treatment start as an indicator of general co-morbidity severity [22]. The Charlson–Deyo score is a validated risk predictor of one-year mortality often used as an indicator of co-morbidity severity, and is calculated using diagnostic codes in hospital discharge records. Thirdly, we identified when individuals had specific TB-related medical risk factors (HIV/AIDS, diabetes, cancer, renal disease, solid organ transplant, silicosis and treatment with tumour necrosis factor-α inhibitors) [3], liver disease or a psychiatric diagnosis when there were one or more relevant ICD 9/10 diagnostic codes or procedure codes from hospital discharge abstracts, or at least two ICD 9/10 codes from physician billing records, in the 2 years before the index date. We used validated algorithms to identify co-morbidities, when available (tables S1 and S3). Lastly, we identified if the initial TB drug prescription prescriber was licensed as a family physician or another specialist physician.

### *Statistical analysis*

We estimated treatment completion (with 95% confidence intervals) as the number of patients completing treatment divided by the number starting treatment. Patients who switched drugs were not considered to have completed treatment. We used Kaplan–Meier curves to plot the proportion of people still receiving LTBI treatment across increasing number of doses dispensed, with curves stratified by LTBI regimen and co-morbidity at treatment start. We estimated severe hepatic adverse event frequency as the proportion of people who started LTBI treatment who had an adverse event during LTBI treatment. Among patients switching regimens, if an adverse event occurred within 30 days after the switch date, it was attributed to the initial regimen.

We calculated descriptive statistics of health system costs during LTBI treatment, in total and stratified by event type, including mean±SD and median (IQR) of costs per patient starting treatment, percentage of patients with any event, and mean±SD and median (IQR) number of events per patient. We estimated descriptive statistics of total mean direct costs occurring before, during and after LTBI treatment start, with total costs calculated for each 30-day period up to 3 years before and after the index. We considered costs incurred in the months before the index as baseline co-morbidity markers. To examine whether outcomes differed by LTBI regimen, co-morbidity and age, we stratified treatment completion, severe hepatic adverse events and mean costs by these factors.

Next, we performed uni- and multi-variable log-binomial regression to compare rifampin and isoniazid treatment completion, since the main outcome variable was binary and a non-rare event [23]. We used generalised estimating equation (GEE) methods with a compound symmetric working correlation structure and robust standard errors to account for patients clustering by treating physicians. We selected variables for inclusion in final multivariable models using backward selection, first including all variables and then removing variables that were not statistically significant at a level of $p<0.2$. We then performed logistic regression with similar GEE methods to compare severe hepatic adverse event risk. Finally, we performed gamma regression to compare direct costs during LTBI treatment. The gamma distribution is appropriate for skewed cost data, while the log-link guarantees non-negative outcomes and retains the original (arithmetic mean) scale of the data [24]. We used similar GEE methods and backward selection to select final multivariable models.

Sensitivity analyses included expanding the definition of LTBI treatment to include events and costs occurring up to 90 days after the last drug dispensation, calculating treatment completion assuming all

days in-hospital had LTBI drugs dispensed (since inpatient drug dispensation data were missing in the RAMQ database), and excluding TB drug costs from direct cost calculations (since Quebec TB drug costs may not be generalisable to other settings given a higher cost ratio of rifampin to isoniazid compared to Global Drug Fund pricing).

All analyses were completed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). This study was funded by a grant through the Canadian Institutes of Health Research. The funder had no role in the study conduct. This study received ethics approval from the McGill University Institutional Review Board (IRB# A06-M 88-09 A).

## Results

In total, 9684 (93%) patients started isoniazid and 864 (7%) started rifampin between 2003 and 2007 (table 1). There was a slight decrease in the proportion of patients started on isoniazid and a corresponding increase in patients starting rifampin over the time period of the study, though this trend was not statistically significant (p=0.058). LTBI treatment was initiated by a total of 1857 physicians within all 18 health regions in the province (1721 physicians started one or more patients on isoniazid, 263 physicians started one or more patients on rifampin), with a median (range) of 1 (1–916) patient per treating physician (data not shown).

Rifampin patients were more likely than isoniazid patients to have had a hospitalisation in the previous year, be male, older, have more co-morbidities at baseline, including cancer, diabetes, renal failure,

TABLE 1 Characteristics of patients initiating treatment for latent tuberculosis infection (LTBI) in Quebec, stratified by initial regimen (isoniazid (H) or rifampin (R)) and start year of treatment, 2003–2007 (n=10 559)

| Patient characteristics at index date | R (n=875) | H (n=9684) | p-value |
|---|---|---|---|
| **Sex male** | 421 (48.1) | 4155 (42.9) | 0.003 |
| **Age group years** | | | <0.001 |
| 0–19 | 63 (7.2) | 2296 (23.7) | |
| 20–34 | 309 (35.3) | 3005 (31.0) | |
| 35–49 | 220 (25.1) | 2557 (26.4) | |
| 50–64 | 147 (16.8) | 1233 (12.7) | |
| ⩾65 | 136 (15.5) | 593 (6.1) | |
| **Hospital admission in year before index date** | | | |
| Patients | 221 (25.4) | 899 (9.3) | <0.001 |
| Median (IQR) days spent in-hospital | 20 (9–41) | 5 (2–12) | |
| **Charlson–Deyo co-morbidity level** | | | <0.001 |
| High (score ⩾3) | 41 (4.7) | 172 (1.8) | |
| Moderate (score 1–2) | 50 (5.7) | 122 (1.3) | |
| **TB-related co-morbidities** | | | |
| HIV/AIDS | 5 (0.6) | 103 (1.1) | 0.166 |
| Cancer | 50 (5.7) | 301 (3.1) | <0.001 |
| Diabetes | 73 (8.3) | 383 (4.0) | <0.001 |
| Renal disease | 40 (4.6) | 240 (2.5) | 0.002 |
| Solid organ transplant | 11 (1.3) | 30 (0.3) | <0.001 |
| Silicosis | 2 (0.2) | 22 (0.2) | 0.993 |
| TNF-α inhibitors | 1 (0.1) | 31 (0.3) | 0.289 |
| **Any psychiatric diagnosis** | | | |
| Yes | 112 (12.8) | 789 (8.2) | <0.001 |
| **Liver disease** | | | |
| Yes | 46 (5.3) | 129 (1.3) | <0.001 |
| **LTBI treatment started by non-family physician#** | | | |
| Yes | 720 (83.2) | 7570 (78.7) | <0.001 |
| **Year of treatment start** | | | |
| 2007 | 141 (16.1) | 1893 (19.6) | <0.001 |
| 2006 | 215 (24.6) | 1783 (18.4) | |
| 2005 | 194 (22.2) | 1963 (20.3) | |
| 2004 | 185 (21.1) | 1961 (20.3) | |
| 2003 | 140 (16.0) | 2084 (21.5) | |

Data are presented as n (%), unless otherwise stated. #: 73% R and 63% H patients treated by specialist in respiratory medicine or infectious diseases. p-values obtained using chi-squared tests.

transplant, and be treated by a physician licensed in a specialty other than Family Medicine (table 1). Almost one-third (32%) of rifampin patients were 50 years and older, compared with only 18% of isoniazid patients (table 1).

### *Severe hepatic adverse events*

In all age groups, the severe hepatotoxic event risk was lower in rifampin than isoniazid patients (table 2). In total, 15 isoniazid patients (0.2%, 95% CI: 0.1–0.3) had an incident severe hepatic adverse event during LTBI treatment (table 2), of whom one died, and two received liver transplants (table S4). The five-year age ranges of the two patients who underwent transplants were 20–24 years and 50–54 years, and the patient who died had an age range of 45–49 years. By contrast, only one rifampin patient (0.1%, 95% CI: 0.02–0.6) had a severe hepatic adverse event and did not die nor require liver transplant. This person was aged >65 years and had co-morbidities (table 2). The median (IQR) length of hospital stay for a severe hepatic adverse event was 11 (5–21) days (table 2). In adjusted models, the risk of severe hepatotoxic event was higher in 9H patients than 4R patients, though not statistically significant (OR=2.3, 95% CI: 0.3–16.1) (data not shown).

### *LTBI treatment completion*

A total of 392 isoniazid (4.0%, 95% CI: 3.7–4.5) and 13 rifampin (1.5%, 95% CI: 0.8–2.5) patients switched regimens during the LTBI treatment period (data not shown). Overall an estimated 53.5% (95% CI: 50.2–56.8) of patients completed 4R and 36.9% (95% CI: 35.9–37.8) completed 9H (figure 1). Completion was lowest in rifampin-treated patients with co-morbidities (21.9%, 95% CI: 15.8–26.9), *versus* 29.9% (95% CI: 21.9–32.9) in isoniazid-treated patients with co-morbidities (figure 1). The proportion of patients stopping treatment was highest in the first month for both regimens (12% of those started on isoniazid, 20% of those started on rifampin), followed by a lower but consistent dropout proportion each subsequent month (with exception of rifampin-treated patients with co-morbidities where monthly dropout frequency was higher). An estimated 59.5% (95% CI: 58.5–60.5) completed 6 months of isoniazid (figure 1).

Rifampin patients aged 65 years and older not completing treatment tended to be those with more co-morbidities and greater healthcare utilisation, including 82% having had a hospitalisation in the past year and 65% a hospitalisation during LTBI treatment (data not shown). In multivariable models (table 3), 4R completion was significantly higher than 9H (adjusted RR=1.5, 95% CI: 1.3–1.7) after adjustment for age, co-morbidities and other confounders. Sensitivity analyses using different completion definitions and

TABLE 2 Frequencies of latent tuberculosis infection (LTBI) treatment completion and severe hepatic events, and mean direct health system costs during LTBI treatment[#], stratified by patient age group and co-morbidity[¶,+,§]

| | With co-morbidity by age years | | | | No co-morbidity by age years | | | | All patients |
|---|---|---|---|---|---|---|---|---|---|
| | 0–19 | 20–34 | 35–64 | ⩾65 | 0–19 | 20–34 | 35–64 | ⩾65 | |
| **Number of people n** | | | | | | | | | |
| R | 8 | 20 | 87 | 106 | 55 | 289 | 280 | 30 | 875 |
| H | 132 | 228 | 356 | 183 | 2164 | 2777 | 3434 | 410 | 9684 |
| **Treatment completion %** | | | | | | | | | |
| R | 28.6 | 30.0 | 18.7 | 16.4 | 61.6 | 66.8 | 63.5 | 39.4 | 53.5 |
| H | 19.4 | 22.1 | 28.2 | 27.7 | 33.8 | 25.3 | 28.3 | 34.0 | 36.9 |
| **Severe adverse events hepatic n (%)** [f] | | | | | | | | | |
| R | 0 | 0 | 0 | 1 (0.9) | 0 | 0 | 0 | 0 | 1 (0.1) |
| H | 0 | 1 (0.4) | 2 (0.6) | 2 (1.1) | 2 (0.09) | 2 (0.07) | 5 (0.2) | 1 (0.2) | 15 (0.2) |
| **TB drug costs mean CAD** | | | | | | | | | |
| R | 212 | 170 | 225 | 265 | 252 | 257 | 267 | 281 | 256 |
| H | 152 | 74 | 80 | 68 | 182 | 75 | 80 | 77 | 102 |
| **Other costs mean CAD** | | | | | | | | | |
| R | 12089 | 4571 | 9651 | 8587 | 341 | 223 | 591 | 8558 | 2793 |
| H | 2540 | 5813 | 13090 | 25280 | 556 | 660 | 2227 | 8491 | 2593 |

[#]: patients starting LTBI treatment with H or R in Quebec between 2003 and 2007 (N=10559). [¶]: Co-morbidity defined as having one or more hospitalisations in the year before LTBI treatment start. [+]: Treatment completion for 9H was 270 doses dispensed in 12 months and for 4R was 120 doses dispensed in 6 months. [§]: Costs during LTBI treatment period (from first date with a TB drug dispensed to 30 days after the last TB drug dispensed, limited to a period of up to 12 months for H and 6 months for R). Costs reported in 2011 Canadian dollars (CAD; rounded to the nearest dollar). "Other costs" include all *Régie de l'assurance maladie du Québec*-paid costs, except those for TB drugs (*i.e.* sum of hospitalisations, emergency department visits, hospital day procedures, physician billing, and non-TB drugs dispensed). [f]: Included liver transplants (n=2) and hospitalisations ending in death (n=1), all occurring in H patients.

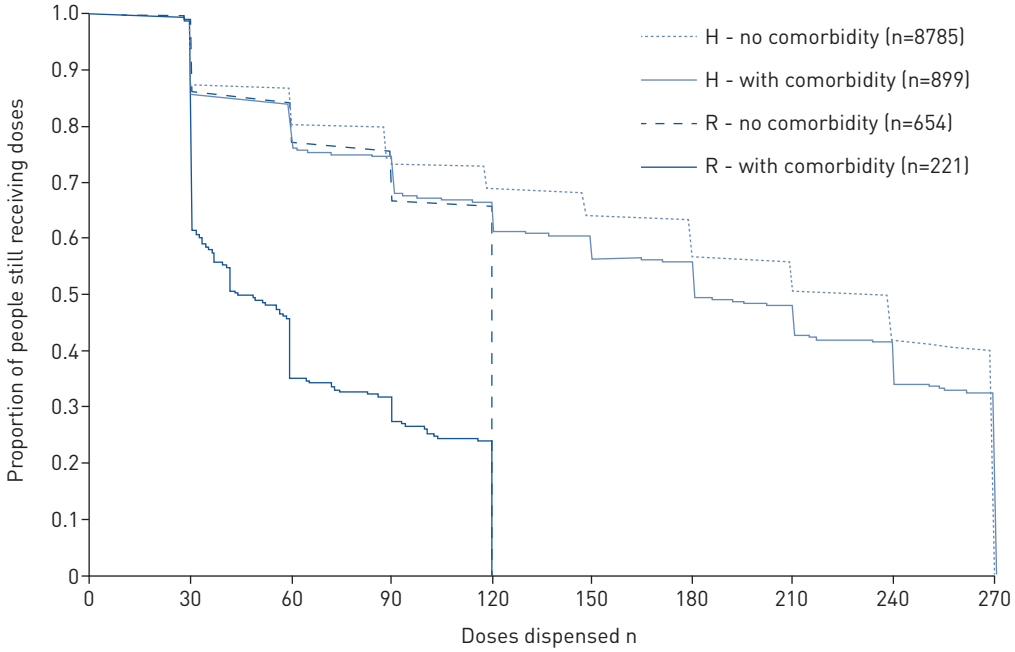


FIGURE 1 Number of latent tuberculosis infection (LTBI) doses dispensed in Quebec, stratified by starting regimen (H *versus* R) and co-morbidity (co-morbidity defined as having one or more hospitalisations in the year before LTBI treatment start). H: isoniazid; R: rifampin.

of potential bias due to missing inpatient drug exposure data had a negligible impact on effect estimates (table S5).

### *Direct health service use costs*

Hospitalisations accounted for the highest mean direct costs per-person starting LTBI treatment (table 4). When stratified by age and co-morbidities, the trend was towards higher mean and median costs of health service use during LTBI treatment in patients with co-morbidities compared to patients without co-morbidities within the same age group (table 2). Median (IQR) health service costs during LTBI treatment were CAD 397 (194–793) for isoniazid patients starting treatment and CAD 524 (380–998) for rifampin patients. Median (IQR) health service costs excluding TB drugs were CAD 284 (122–640) and CAD 234 (112–803) for patients starting isoniazid and rifampin, respectively (data not shown). Rifampin-treated patients with co-morbidities also had higher health service costs in the months leading up to treatment start (figure 2). In multivariable models (table 3), 4R costs for direct health service use during LTBI treatment were lower than 9H (adjusted cost ratio=0.7, 95% CI: 0.5–0.9) after adjustment for age, co-morbidities and other confounders. A sensitivity analysis with TB drug costs excluded led to a larger effect estimate for the adjusted cost ratio of rifampin *versus* isoniazid (0.6, 95% CI: 0.4–0.8).

## Discussion

This study found that the severe hepatic adverse event risk was higher for isoniazid than rifampin across all age groups, and was highest in patients with co-morbidities. Treatment completion was higher for 4R (54%) than 9H (37%), with the lowest completion frequency among people with co-morbidities. Direct health service costs during LTBI treatment were lower for 4R than 9H patients after age and co-morbidities adjustment.

The proportions of people completing treatment for both regimens in our study were lower than reported in other studies [5, 7, 9–13, 25–27]. Much higher completion rates have been reported in randomised clinical trials: Menzies *et al.* [7] reported 71% completion for 4R and 58% completion for 9H among adults in a phase III trial. But, in contrast to our general population cohort, trial participants may be more likely to exhibit "healthier" behaviours (*e.g.* following treatment recommendations), and also are likely to be monitored more closely throughout the treatment follow-up period. Completion rates in our study were more comparable to other observational studies comparing the two regimens: Horsburgh *et al.* [27], for example, in a retrospective observational study of 68 clinics in both the USA and Canada found a 55% completion rate for 4R and 31% completion for 9H. Despite differences in completion rates across studies, however, all studies have found 4R completion to be substantially higher than 9H [5, 7, 9–13, 25–27].

TABLE 3 Predictors of latent tuberculosis infection (LTBI) treatment completion and *Régie de l'assurance maladie du Québec* (RAMQ)-paid costs for health service use during LTBI treatment period (n=10 559)

| Patient and physician characteristics | LTBI treatment completion[#] | | | Mean RAMQ-paid costs[¶] | | |
|---|---|---|---|---|---|---|
| | n (%) completing | Univariable RR (95% CI) | Multivariable RR (95% CI) [+] | Mean±SD costs CAD | Univariable cost ratio (95% CI) | Multivariable cost ratio (95% CI) [+] |
| **Starting LTBI regimen** | | | | | | |
| Rifampin | 468 (53.5) | 1.4 (1.2–1.7) | 1.5 (1.3–1.7) | 3048±10 505 | 1.1 (0.7, 1.8) | 0.7 (0.5, 0.9) |
| Isoniazid | 3570 (36.9) | 1.0 | 1.0 | 2694±13 539 | 1.0 | 1.0 |
| **Sex** | | | | | | |
| Male | 1859 (40.6) | 1.1 (1.1–1.2) | 1.1 (1.0–1.1) | 3574±16 989 | 1.7 (1.4, 2.1) | 1.2 (0.9, 1.4) |
| Female | 2179 (36.4) | 1.0 | 1.0 | 2073±9547 | 1.0 | 1.0 |
| **Age group years** | | | | | | |
| 0–19 | 975 (41.3) | 1.2 (1.1–1.3) | 1.2 (1.1–1.3) | 883±6707 | 0.8 (0.5, 1.2) | 0.96 (0.7, 1.3) |
| 20–34 | 1162 (35.1) | 1.0 | 1.0 | 1091±8765 | 1.0 | 1.0 |
| 35–64 | 1629 (39.2) | 1.2 (1.1–1.3) | 1.2 (1.1–1.3) | 3297±14 188 | 3.1 (2.2, 4.2) | 2.3 (1.7, 3.1) |
| ⩾65 | 272 (37.3) | 1.2 (1.1–1.4) | 1.2 (1.0–1.4) | 12 832±28 269 | 11.7 (8.5, 16.1) | 6.3 (4.3, 9.2) |
| **Any hospitalisation in year before index** | | | | | | |
| Yes | 316 (28.2) | 0.7 (0.7–0.8) | 0.7 (0.6–0.8) | 11 621±31 892 | 6.9 (5.7, 8.5) | 2.8 (2.2, 3.7) |
| No | 3722 (39.4) | 1.0 | 1.0 | 1668±8198 | 1.0 | 1.0 |
| **Any Charlson co-morbidities** | | | | | | |
| Yes | 100 (26.0) | 0.7 (0.6–0.9) | 0.8 (0.6, 0.9) | 20 641±43 686 | 10.1 (7.8,13.0) | - |
| No | 3938 (38.7) | 1.0 | 1.0 | 2046±99 806 | 1.0 | |
| **HIV/AIDS** | | | | | | |
| Yes | 55 (50.9) | 1.5 (1.2–1.8) | 1.5 (1.3–1.9) | 17 334±46 256 | 6.7 (3.9,1 1.7) | 5.5 (3.6, 8.6) |
| No | 3983 (38.1) | 1.0 | 1.0 | 2573±12 448 | 1.0 | 1.0 |
| **Cancer** | | | | | | |
| Yes | 106 (30.2) | 0.9 (0.7–1.0) | | 19 245±43 269 | 8.9 (6.7,11.8) | 3.1 (2.1, 4.6) |
| No | 3932 (38.5) | 1.0 | | 2156±10 462 | 1.0 | 1.0 |
| **Diabetes** | | | | | | |
| Yes | 172 (37.7) | 1.0 (0.9–1.2) | | 12 220±33 187 | 5.3 (4.0,7.0) | 1.6 (1.2, 2.0) |
| No | 3866 (38.3) | 1.0 | | 2295±11 464 | 1.0 | 1.0 |
| **Renal failure** | | | | | | |
| Yes | 108 (38.6) | 1.1 (0.9–1.4) | 1.2 (0.96, 1.4) | 18 853±30 224 | 8.2 (6.3,10.6) | 3.8 (2.9, 4.9) |
| No | 3930 (38.2) | 1.0 | 1.0 | 2285±12 248 | 1.0 | 1.0 |
| **Solid organ transplant** | | | | | | |
| Yes | 18 (43.9) | 1.2 (0.9–1.7) | | 22 594±69 369 | 8.5 (3.3,21.8) | - |
| No | 4020 (38.2) | 1.0 | | 2646±12 575 | 1.0 | |
| **Silicosis** | | | | | | |
| Yes | 11 (45.8) | 1.3 (0.8–2.2) | | 5951±12 657 | 2.2 (0.9,5.5) | - |
| No | 4027 (38.2) | 1.0 | | 2716±13 316 | 1.0 | |
| **Tumour necrosis factor-α inhibitors** | | | | | | |
| Yes | 12 (37.5) | 1.1 (0.7–1.7) | | 13 866±7921 | 5.2 (3.9,6.8) | 5.3 (3.7, 7.8) |
| No | 4026 (38.2) | 1.0 | | 2690±13 313 | 1.0 | 1.0 |
| **Any psychiatric diagnosis** | | | | | | |
| Yes | 305 (33.9) | 0.9 (0.8–1.0) | | 7949±24 198 | 3.6 (2.8,4.6) | 2.5 (1.8, 3.5) |
| No | 3733 (38.7) | 1.0 | | 2237±11 682 | 1.0 | 1.0 |

Continued

TABLE 3 Continued

| Patient and physician characteristics | LTBI treatment completion[#] | | | Mean RAMQ-paid costs[¶] | | |
|---|---|---|---|---|---|---|
| | n (%) completing | Univariable RR (95% CI) | Multivariable RR (95% CI) [+] | Mean±SD costs CAD | Univariable cost ratio (95% CI) | Multivariable cost ratio (95% CI) [+] |
| **Physician licensing** | | | | | | |
| Other specialist | 1361 (42.2) | 1.1 (1.0–1.2) | 1.1 (0.98, 1.2) | 2714±13 104 | 0.98 (0.7,1.4) | 1.3 (1.0, 1.7) |
| Family physician | 712 (32.5) | 1.0 | 1.0 | 2765±14 239 | 1.0 | 1.0 |
| **Year of treatment start** | | | | | | |
| 2007 | 782 (38.5) | 1.1 (0.96–1.2) | 1.1 (0.99–1.2) | 2559±14 225 | 1.0 (0.8,1.5) | - |
| 2006 | 775 (38.8) | 1.1 (0.99–1.2) | 1.1 (0.99–1.2) | 3031±11 741 | 1.2 (0.8,1.6) | |
| 2005 | 873 (40.5) | 1.2 (1.1–1.3) | 1.1 (1.0–1.3) | 2832±14 448 | 1.1 (0.9,1.7) | |
| 2004 | 814 (37.9) | 1.1 (0.96–1.2) | 1.1 (0.97–1.2) | 2712±12 230 | 1.1 (0.7,1.4) | |
| 2003 | 794 (35.7) | 1.0 | 1.0 | 2505±13 649 | 1.0 | |

Missing: treating physician (n=78). [#]: Treatment completion for 9H was 270 doses dispensed in 12 months and for 4R was 120 doses dispensed in 6 months. [¶]: costs during LTBI treatment period (from first date with a TB drug dispensed to 30 days after the last TB drug dispensed), limited to a period of up to 1 year for H and 6 months for R. Costs reported in 2011 Canadian dollars (CAD). RAMQ-paid costs are sum of hospitalisations, emergency department visits, hospital day procedures,physician billingand drugs dispensed (TB and non-TB drugs). [+]: Adjusted models including all variables with p<0.2 in multivariable models.

TABLE 4 Patterns and direct costs of health service use by latent tuberculosis infection (LTBI) patients in Quebec (2003–2007) during LTBI treatment period[#,¶]

| Health service utilisation and estimated RAMQ paid costs, per component | Rifampin (n=875) | Isoniazid (n=9684) |
|---|---|---|
| **Hospitalisations** | | |
| Total number of hospitalisations n | 76 | 725 |
| Patients with any event n (%) | 59 (6.7) | 493 (5.1) |
| Events per patient n [¶] | 1.3±0.7 | 1.5±0.9 |
| Median (IQR), max [¶] | 1 (1–2), 5 | 1 (1–2), 6 |
| Days in-hospital per stay n[¶] | 12.3±13.3 | 12.2±24.0 |
| Days in-hospital per stay n [¶] | 9 (4–19) | 5 (2–12) |
| Cost per patient starting treatment CAD | 1687±9079 | 1276±11 775 |
| **Emergency department visits** | | |
| Total number of visits n | 210 | 2977 |
| Patients with any event n (%) | 131 (15.0) | 1853 (19.1) |
| Events per patient n [¶] | 1.6±1.7 | 1.6±1.3 |
| Median (IQR), max [¶] | 1 (1–2), 16 | 1 (1–2), 26 |
| Cost per patient starting treatment CAD | 44±158 | 56±156 |
| **Hospital day procedures** | | |
| Total number of procedures n | 14 | 311 |
| Patients with any event n (%) | 13 (1.5) | 259 (2.7) |
| Events per patient n [¶] | 1.1±0.3 | 1.2±0.5 |
| Median (IQR), max [¶] | 1 (1–1), 2 | 1 (1–2), 6 |
| Cost per patient starting treatment CAD | 3±25 | 6±39 |
| **Physician billing** | | |
| Total number of physician contacts n | 6535 | 86 904 |
| Patients with any event n (%) | 820 (93.7) | 8986 (92.8) |
| Events per patient n [¶] | 8.0±12.3 | 9.6±18.8 |
| Median (IQR), max [¶] | 5 (3–8), 109 | 5 (3–10), 314 |
| Cost per patient starting treatment CAD | 426±1186 | 466±1271 |
| **Other drug dispensations[+]** | | |
| Total number of other drug dispensations n | 2950 | 57 522 |
| Patients with any event n (%) | 381 (43.5) | 6146 (63.4) |
| Events per patient n [¶] | 7.7±7.1 | 9.3±12.5 |
| Median (IQR), max [¶] | 6 (2–11), 54 | 6 (2–10), 34 |
| Cost per patient starting treatment CAD | 668±1865 | 793±3128 |
| **First-line TB drug dispensations** | | |
| Total number of TB drug dispensations n | 2755 | 60 876 |
| Patients with any event n (%) | 875 (100) | 9684 (100) |
| Events per patient n [¶] | 3.1±1.6 | 6.3±3.7 |
| Median (IQR), max [¶] | 4 (2–4), 9 | 7 (3–9), 50 |
| Cost per patient starting treatment CAD | 221±118 | 99±128 |
| **Total RAMQ-paid costs per patient starting treatment CAD** | | |
| Mean±SD | 3049±10 505 | 2695±13 540 |
| Median (IQR) | 524 (380–998) | 397 (194–793) |

[#]: Total costs during LTBI treatment period (from first date with a TB drug dispensed to 30 days after the last TB drug dispensed, limited to a period of up to 365 days for H and 180 days for R). Costs reported in 2011 Canadian dollars (CAD; rounded to the nearest dollar). [¶]: Among patients with one or more events. [+]: Other drugs most frequently dispensed, by AHFS drug class: anti-inflammatory agents (acetylsalicylic acid, cox-2 inhibitors), benzodiazapenes, proton-pump inhibitors.

As we observed and as has also been previously reported, dropout rates were highest in the first month [10, 25, 27], followed by steady drop-off rate observed with each subsequent month.

Our study adds to evidence comparing hepatotoxicity risk between isoniazid and rifampin regimens. Similar to findings of a network meta-analysis [28] and clinical trial results [6, 7], we found lower severe hepatotoxicity risk in rifampin than isoniazid patients. Our estimates of hepatotoxicity risk were, however, lower than other published studies comparing the two regimens [6, 7, 9–13, 25]. This likely is because we only included severe hepatotoxicity, defined as a hospitalisation directly related to acute hepatotoxicity. Most other published studies have included less severe hepatotoxicity, such as elevated liver enzyme levels or other clinical signs of hepatitis. Menzies and colleagues [6, 7] reported grade 3/4 hepatotoxicity rates of

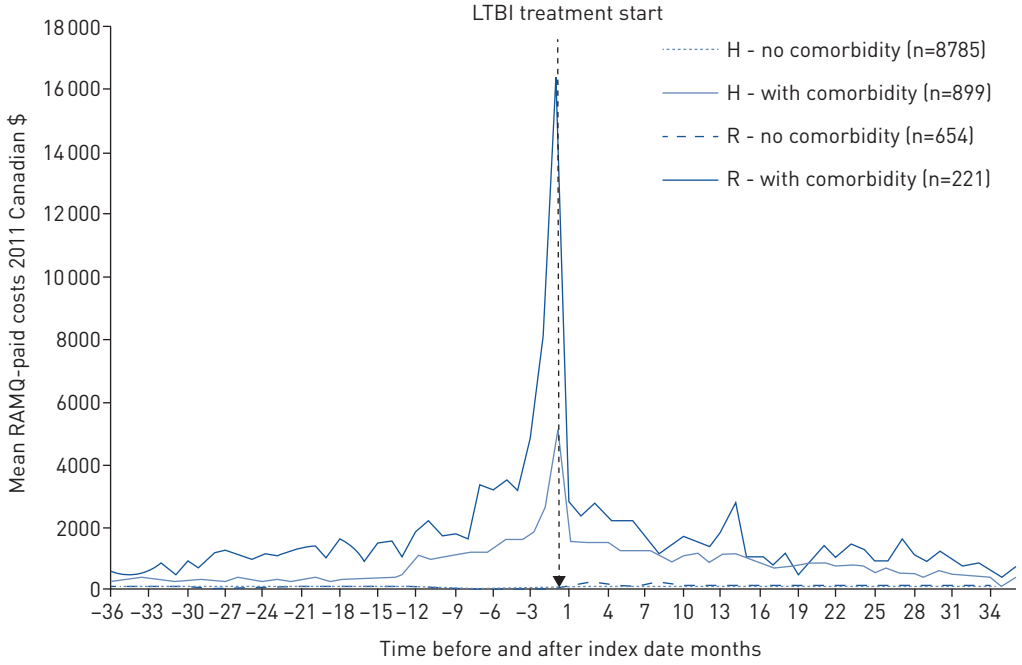


FIGURE 2 Estimated mean direct health service use costs for latent tuberculosis infection (LTBI) patients (patients starting LTBI treatment in Quebec with isoniazid (H) or rifampin (R) between 2003 and 2007), stratified by number of months before and after LTBI treatment start and comorbidity (co-morbidity defined as one or more hospitalisations in year before LTBI treatment start; costs reported in 2011 Canadian dollars (rounded to the nearest dollar)). Estimated total *Régie de l'assurance maladie du Québec* (RAMQ)-paid costs=sum of hospitalisations+emergency department (ED) visits+hospital day procedures+physician billing+drugs dispensed (tuberculosis (TB) and non-TB drugs).

1.8% and 3.8% for 9H, and 0.3% and 0.7% for 4R in two randomised trials in adults. Other observational clinic studies have reported hepatotoxicity rates ranging from 1.4% to 2.2% for 9H, and from 0% to 0.7% for 4R [9–11, 13, 25]. However, the frequency of deaths related to INH-associated hepatitis in our study was comparable to older series reported by Snider *et al.* [29] and Kopanoff *et al.* [30].

Also, similar to systematic review results [31] we found higher hepatotoxicity risk overall in older-aged patients; however, this trend was primarily observed among patients with co-morbidities. Among patients without co-morbidities, hepatotoxicity risk with isoniazid was low and there were no hepatotoxic events in patients taking rifampin. Given that concern about isoniazid hepatotoxicity is a barrier in deciding to treat patients for LTBI [31], the findings of low hepatotoxicity risk with rifampin should help increase treatment uptake and completion. Further, our results support previous findings that LTBI treatment for people aged 35 years and older without co-morbidities may be safe with appropriate liver function and symptom monitoring [31].

Contrasting clinical trial results, crude costs were higher for rifampin patients, before and during LTBI treatment. Given that LTBI is asymptomatic and diagnostic work-up would be similar between the regimens, it is unlikely the cost increase observed before the index date was attributable to LTBI. Rather, it is more likely that rifampin patients were more frequently diagnosed with other co-morbidities which were also risk factors for TB reactivation (and LTBI treatment subsequently initiated). Costs associated with other co-morbidities also likely accounted for some of the non-TB drug costs observed during the LTBI treatment period for the two regimens. Notably, however, after adjustment for numerous co-morbidities as well as older age within the multivariable model for total cost, the cost associated with the rifampin treatment regimen was lower than the cost associated with the isoniazid regimen.

A major strength of our study is that we had complete information on virtually every person in the entire Quebec population who received either isoniazid or rifampin from community pharmacies in the five-year study period. To our knowledge this is the only study to describe use of these two drugs in an entire population, since over 99% of those receiving TB drugs in Quebec were registered in the administrative datasets used. This complete population coverage should have eliminated many of the selection and reporting biases that severely limit the value of many observational studies. And, the inclusion of all persons treated should have overcome the greatest limitation of randomised trials which typically exclude

the very young, very old, pregnant women, and persons with important co-morbidities. Hence, we believe this data strongly complements evidence from randomised trials; the similar results confirm the critically important safety advantage of rifampin compared with isoniazid-based treatment. In addition, the study documents outcomes with hundreds of different providers, many of whom treated few patients, and thus likely less familiar with LTBI management. As well, the large number treated provided greater power to detect rare events, such as liver failure resulting in transplant or death, which are otherwise noted as case reports, making risk estimation difficult.

There are also limitations. Inpatient drug dispensation data were missing and were only available from community-based pharmacies when paid for by RAMQ (*i.e.* data for non-TB drugs were missing when paid for by private insurance). This could have led to some underestimation of drug costs and LTBI treatment completion, particularly among rifampin patients since a higher proportion were hospitalised during treatment. We relied on hospitalisation data to identify patients with severe hepatotoxicity; milder toxicity that did not result in hospitalisation may have been much more common, but could not be accurately identified with the administrative health data available. We also limited our analysis of adverse events to hepatotoxicity, thus we would not have captured other potential adverse events associated with these regimens. We recommend that future analyses should also focus on less serious hepatotoxic and other types of adverse events to capture the full adverse event profiles of these drug regimens. We only had drugs dispensed data thus were unable to determine whether all doses were ingested. A further limitation is that rifampin may be prescribed for other conditions. We excluded rifampin prescriptions when given for other known indications, but it is possible that we inadvertently included a few patients for whom rifampin was prescribed for other conditions. This may have underestimated completion since most other conditions require rifampin for less than 4 months, and overestimated costs since these conditions more likely require close follow-up and hospitalisation.

Confounding by indication was a further potential bias. We found (similar to other studies [10]) that rifampin patients were more seriously ill at treatment start compared to isoniazid patients, with more co-morbidities, higher hospitalisation rates, and higher pre-treatment health service costs. We adjusted for pre-treatment co-morbidities through use of multiple co-morbidity measures. However, residual confounding is still possible, which would underestimate the advantages of 4R. As this was a province-wide study which included all providers in all settings in the province, incentives and reminder programmes may have differed between providers and settings. However, we did not have access to this type of data and so do not know if any interventions were in place or if completion rates were higher with specific providers or settings. Lastly, as typical with administrative database studies, misclassification error due to inaccurate data is also possible.

In conclusion, this study found that compared to the 9H regimen, completion was substantially higher with 4R, costs were significantly lower, and severe hepatotoxicity risk, including liver transplant and death was also lower with the 4R regimen. Our findings support use of 4R in preference to 9H for treatment of LTBI.

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