

Delayed tuberculosis treatment in urban and suburban Ontario

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BACKGROUND: Delay in the treatment of patients with tuberculosis (TB) increases the risk of poor clinical outcomes – including death and transmission of disease – and may be reducible.

OBJECTIVE: To estimate delays in TB treatment in a Canadian, multicultural population and to examine factors associated with longer time to treatment.

METHODS: Adult cases of active TB from January 1998 to December 2001 from the Ontario Reportable Disease Information System were included. Time to treatment was defined as the number of days between symptom onset and treatment.

RESULTS: Data from 1753 TB patients (76% of eligible patients) were analyzed. Median time to treatment was 62 days (interquartile range 31 to 114 days). Time periods longer than the median time to treatment were independently associated with middle-aged patients (OR 1.54, 95% CI 1.21 to 1.98), foreign-born patients who had lived in Canada for more than 10 years (OR 1.47, 95% CI 1.02 to 2.12), patients with nonpulmonary disease (OR 1.57, 95% CI 1.28 to 1.92) and patients managed within certain health districts.

CONCLUSION: A time to TB treatment of two months or more is common in Ontario, and associated with several factors. Future studies are needed to build on these findings to decrease delay and improve individual and public health outcomes.

Key Words: Delay; Quality indicator; Treatment; Tuberculosis

Reducing the time that tuberculosis (TB) patients live with and spread their disease, often unknowingly, before starting treatment is an important public health challenge facing low-TB incidence countries today (1). Delayed diagnosis and treatment of TB affects individuals by increasing morbidity and mortality, and society overall by increasing transmission of disease (2-6). Treatment delay in TB patients has not been well characterized, and the reason why it occurs in some patients and not in others is unclear. In one study of TB patients with sputum that was smear-positive for acid-fast bacilli (AFB), a treatment delay of more than 49 days was found to be associated with sex, ethnic group and time since immigration (1). Patients with positive smears, however, represent a minority of patients with TB and delay has still not been well characterized in the rest of patients with TB (7). Therefore, to estimate delay in treatment for all TB patients in

Le délai de traitement de la tuberculose dans les régions urbaines et périurbaines de l'Ontario

HISTORIQUE : Le délai du traitement des patients atteints de tuberculose (TB) augmente le risque d'issue clinique négative, y compris le décès et la transmission de la maladie, et pourrait être réduit.

OBJECTIF : Évaluer les retards de traitement de la TB au sein de la population multiculturelle canadienne et les facteurs associés à un plus long délai avant le traitement.

MÉTHODOLOGIE : Les cas d'adultes atteints de TB active entre janvier 1998 et décembre 2001, tirés du Système d'information sur les maladies à déclaration obligatoire de l'Ontario, ont été inclus dans l'étude. Le délai avant le traitement était défini comme le nombre de jours entre l'apparition des symptômes et le traitement.

RÉSULTATS : Les données portant sur 1 753 patients atteints de TB (76 % des patients admissibles) ont été analysées. Le délai médian avant le traitement était de 62 jours (plage interquartile de 31 à 114 jours). Les délais plus longs que le délai médian avant le traitement s'associaient de manière indépendante aux patients d'âge mûr (RRR 1,54, 95 % IC 1,21 à 1,98), aux patients d'origine étrangère qui habitaient au Canada depuis plus de dix ans (RRR 1,47, 95 % IC 1,02 à 2,12), aux patients atteints d'une maladie non pulmonaire (RRR 1,57, 95 % IC 1,28 à 1,92) et aux patients traités dans certains districts de santé.

CONCLUSION : Il est courant que le délai avant le traitement de la TB soit de deux mois ou plus en Ontario, ce qui s'associe à plusieurs facteurs. Il faudra d'autres études pour tirer parti de ces observations en vue de réduire les délais et d'améliorer les issues individuelles et de santé publique.

a large North American, multicultural population and to further explore factors associated with delay, we conducted the present retrospective database analysis.

METHODS

Ontario is a province of Canada with a population of more than 12 million. It has a large foreign-born population that, like in many other North American provinces and states, is largely concentrated in urban and suburban areas, such as Toronto, Hamilton and Ottawa (8). The Ontario Reportable Disease Information System is a public health database that contains TB surveillance data reported by community health care providers. Permission to use de-identified data from this database was obtained from the Ontario Ministry of Health and Long-Term Care. The validity of mandatory fields in the database has been confirmed in previous studies (9). Patients

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aged 18 years and older who reported having TB from urban and suburban centres between January 1, 1998, and December 31, 2001, were included in the study. Patients were excluded if they did not have an onset of symptoms or treatment date recorded in the database.

The primary outcome of interest was time to TB treatment defined as the number of days between the date of onset of the disease episode and the date of treatment initiation, as reported by their health care provider and/or confirmed by public health providers. The date of treatment initiation was used because disease transmission and progression are expected to cease soon after this time. Because an acceptable time to treatment of TB has not been established, 'delay' was defined, as it has been previously, as a time period longer than the median time to treatment of the entire cohort (1). Covariables extracted from the database and controlled for in the analysis included the following: demographic factors such as age and sex; factors associated with increased suspicion of TB such as country of birth and time living in Canada (10-12), underlying medical conditions that increase the risk of reactivating TB such as known latent TB infection or HIV positivity, and known close contact of active TB; factors that might make a diagnosis of TB more apparent such as pulmonary disease, chest radiograph consistent with TB, positive AFB smear and positive TB culture; and death, a factor that might be associated with more aggressive disease. After exploring the data, it was determined that it would be most suitable to merge country of birth and time living in Canada and then divide the resulting group into three categories: Canadian-born patients, foreign-born patients who have lived in Canada for 10 years or less, and foreign-born patients who have lived in Canada for more than 10 years. Site of disease was the most prominent site as described by the reporting health care provider. Chest radiograph was described as being consistent with TB – eg, displaying upper lobe cavitory disease – or not consistent with TB by the reporting health care provider. Finally, patients were categorized into those who had onset of their symptoms while living inside versus outside of Ontario to account for changes in time to treatment due to superior or inferior health care in the place they lived previously.

Study outcomes were analyzed using the χ^2 test for categorical variables. Variables that were significantly associated with a delay in treatment in univariate analysis ($P \leq 0.10$) were candidates for inclusion in the multivariate model. Variables were retained in the model if they were significant ($P < 0.05$). Multivariate logistic regression was used to analyze the independent effects of covariables. A sensitivity analysis using the Mann-Whitney U test and the Kruskal-Wallis test for comparison of medians, in lieu of the χ^2 test, was performed to determine which variables to use in the logistic regression model. Statistical analyses were performed using SAS System for Windows 8.02 software (SAS Institute Inc, USA).

To characterize delay in patients with the most transmissible form of TB and to produce results that could be compared with previous studies, the analysis was repeated for patients with AFB smear-positive TB only.

RESULTS

A total of 2310 adult subjects were reported to have TB in urban and suburban areas of Ontario between 1998 and 2001. These represented 88% of all adult cases of TB in the province. Of these, 424 subjects did not have an onset of episode date,

89 subjects did not have a treatment date, and 44 subjects had a treatment date that preceded their onset date. These patients were excluded, leaving 1753 subjects (76%) for analysis. Subjects who did and did not have missing data were similar for age, sex, country of birth, comorbidity, AFB smear status and site of disease (data not shown).

Subjects in the final cohort were managed in seven health unit regions across the province. Their median age was 43 years (interquartile range 32 to 65 years), 939 subjects (54%) were men, 1033 subjects (59%) had pulmonary disease, 648 subjects (37%) were AFB smear-positive and 1574 subjects (90%) were foreign-born. Median delays depended on subject characteristics, as described in Table 1.

The overall median time between symptom onset and initiation of treatment was 62 days (interquartile range 31 to 114 days).

Univariate χ^2 analysis revealed that patients of middle age, female sex, foreign-born and living in Canada for more than 10 years, having nonpulmonary TB, not having a chest radiograph consistent with TB, not having an underlying medical condition that increased the risk of TB, and having onset of symptoms while living outside of the province were associated with longer delay ($P \leq 0.10$). In addition, the proportion of patients experiencing delay varied significantly among health units (Table 2). No association between number of patients treated in a health unit and delay was found (data not shown).

The inclusion of covariables in the logistic regression model was also based, in part, on patterns of correlation. Site of disease and chest radiograph status were found to be correlated ($\phi = 0.41$, $P < 0.0001$). Because site of disease had a stronger association with delay, it was used in the adjusted model. In addition, all of the 70 subjects who had symptom onset while living outside of the province were found to also have lived in Canada for less than 10 years. Because variation in country of birth affected many more subjects than onset of symptoms while living outside of the province, it was used in the adjusted model.

In multivariate analysis, a longer than median delay was independently associated with being middle-aged, being foreign born and living in Canada for more than 10 years, and having nonpulmonary TB. The proportion of patients experiencing delay also varied significantly between health units. (Table 3) These results did not differ when comparison of medians was used to determine which variables to use in the logistic regression model (data not shown).

Finally, 648 patients (37%) in the cohort had AFB smear-positive TB. Their median time to treatment was 62 days (interquartile range 30 to 109 days). In these patients, only symptom onset outside Ontario was found to be associated with a longer than median delay in univariate analysis ($P = 0.01$). Multivariate analysis was not performed.

DISCUSSION

The present retrospective study of adult TB patients from urban and suburban areas of Ontario revealed that approximately one-half of TB patients initiated treatment more than two months after symptom onset. It also demonstrated that a time to treatment of more than two months was more likely in middle-aged patients, foreign-born patients who had lived in Canada for more than 10 years, patients with nonpulmonary TB and patients managed within certain health units.

Currently, there is no consensus on the appropriate length of time to TB treatment. Although delays in treatment can

TABLE 1
Characteristics of 1753 patients reported to have tuberculosis (TB) in Ontario between 1998 and 2001*

Characteristic	n (%)	Group median delay, days	Interquartile range, days
Patients	1753 (100)	62	31 to 114
Age, years			
18–34	580 (33)	58	30 to 115
35–64	718 (41)	70	32 to 128
≥65	455 (26)	56	29 to 101
Sex			
Male	939 (54)	59	30 to 107
Female	814 (46)	65	31 to 120
Country of birth			
Born in Canada	161 (9)	50	25 to 103
Lived in Canada 10 years or less	995 (57)	61	31 to 114
Lived in Canada more than 10 years	579 (33)	65	32 to 118
Site of disease			
Pulmonary	1033 (59)	56	28 to 97
Nonpulmonary	720 (41)	73	35 to 150
Acid-fast bacilli smear			
Positive	648 (37)	62	30 to 109
Negative	1105 (63)	61	31 to 116
TB culture			
Positive	1435 (82)	63	31 to 112
Negative	318 (18)	58	27 to 130
Underlying medical condition that increased risk of developing TB			
Yes	343 (20)	52	26 to 95
No	1410 (80)	65	32 to 118
Known close contact of active TB			
Yes	164 (9)	62	31 to 114
No	1589 (91)	62	25 to 123
Chest radiograph consistent with TB			
Yes	670 (38)	55	28 to 98
No	1083 (62)	66	32 to 126
Death due to TB			
Yes	79 (5)	49	20 to 93
No	1674 (95)	63	31 to 115
Onset of symptoms while living outside of the province			
Yes	70 (4)	112	55 to 229
No	1683 (96)	60	30 to 110
Health unit			
A	94 (5)	39	19 to 77
B	124 (7)	53	29 to 90
C	159 (9)	54	26 to 104
D	1215 (69)	64	32 to 117
E	36 (2)	70	32 to 127
F	69 (4)	79	38 to 184
G	56 (3)	90	36 to 167

*Data are missing for country of birth in 18 patients (1%) and site of disease in 12 patients (less than 1%)

lead to progression of disease and subsequent individual morbidity and mortality, the most studied outcome of treatment delay has been increased transmission (2,5,6). Studies have

TABLE 2
Characteristics of subjects who did and did not experience a delay in the treatment of their tuberculosis (TB)*

Characteristic	Delay group†, n (%)	No delay group, n (%)	P
Patients	873 (50)	880 (50)	
Age, years			
18–34	274 (31)	306 (35)	0.0003
35–64	398 (46)	320 (36)	
≥65	201 (23)	254 (29)	
Male sex	450 (52)	489 (56)	0.09
Country of birth			
Born in Canada	69 (8)	92 (11)	0.10
Lived in Canada 10 years or less	493 (57)	502 (58)	
Lived in Canada more than 10 years	303 (35)	276 (32)	
Pulmonary disease	469 (54)	564 (65)	<0.0001
Acid-fast bacilli smear positive	324 (37)	324 (37)	0.90
TB culture positive	718 (82)	717 (81)	0.68
Underlying medical condition that increased risk of developing TB	151 (17)	192 (22)	0.02
Known close contact of active TB	82 (9)	82 (9)	0.96
Chest radiograph consistent with TB	304 (35)	366 (42)	0.004
Death due to TB	33 (4)	46 (5)	0.14
Onset of symptoms while living outside of the province	51 (6)	19 (2)	<0.0001
Health unit			
A	32 (4)	62 (7)	0.004
B	53 (6)	71 (8)	
C	75 (9)	84 (10)	
D	618 (71)	597 (68)	
E	19 (2)	17 (2)	
F	41 (5)	28 (3)	
G	35 (4)	21 (2)	

*Data are missing for country of birth in 18 patients (1%) and site of disease in 12 patients (less than 1%); †Patients experiencing a delay longer than the median of the entire cohort (62 days)

revealed that TB can be spread to casual contacts in just hours (13–15). Thus, any avoidable delay might be considered inappropriate. The challenge is to determine what avoidable delay is, because patient delays are expected to occur while symptomatic people recognize they need medical attention and go to meet with their doctor, and health care system delays are expected to occur while testing is performed. Some experts have proposed that an appropriate total time from symptom onset to treatment should be 30 days or less (16). We propose that, given the results of the present study, a more realistic indicator would be closer to two months; however, further study would be needed to determine what an optimal time should be.

Factors found to be associated with delay in our study were the ones that, in general, elicit a lower suspicion for TB in our province. For example, middle age was associated with

prolonged delay and would elicit a lower suspicion for TB than older age, when TB is known to reactivate, or younger age, when TB is more common than many other respiratory diseases. Similarly, TB in our population is less common in foreign-born people after they have lived in Canada for some time (12). The association between delay and lower suspicion of TB has been noted in previous studies as well (1). Unfortunately, even though TB is generally considered less common in middle-aged patients who are foreign-born and have been in Canada for many years, these lower risk patients still comprise a significant proportion of patients with TB.

We were surprised to note that patients who were in close contact with active cases of TB did not experience less delay compared with those who were not in close contact. This suggests that some individuals might benefit more from contact tracing than others. This is deserving of further study.

A finding of the present study that has not been previously described is the variation in delay among health units. Because the health units studied are similar, the cause of this variation is not apparent. Two possible sources are differences in patient characteristics not captured by the surveillance database or differences in health care provided. In either case, such variation is deserving of further study because it may uncover patient characteristics or health care system characteristics that could be addressed to decrease delay. Indeed, the amount of delay at the health unit with the least delay might indicate an achievable quality standard for the other health units and communities to work toward.

An interesting finding uncovered by the present study was that patients who had onset of symptoms before coming to Ontario experienced more delay. This may have resulted because these patients have been living with their symptoms for a long time before arriving in Ontario, and/or because they were not identified and treated in a timely manner after arriving in Ontario. For example, they might not have had good access to health care services in the country they lived in previously, or they might have experienced cultural and language barriers that prevented them from obtaining care once they came to Ontario. In either case, considering that all of these subjects were foreign-born, it suggests there may be weaknesses in the immigrant screening process, which ideally would ensure that suspicious symptoms are being correctly diagnosed and treated before immigration. Future study of this unique group might reveal ways the immigration screening process could be improved.

As in any retrospective, observational study based on a surveillance database, the present study has limitations in its interpretation that must be acknowledged. To begin, our definition of delay is subject to recall bias because the symptom onset date in the database is self-reported by the patient. However, because TB symptoms are usually insidious and non-specific in onset, it is more likely that patients would not notice mild symptoms or attribute them to more common conditions, like viral illnesses, when they first start. There might also be patient bias in the reporting of symptom onset date, because patients stand to look like more caring members of society if they minimized the time they potentially spread a transmissible infectious disease. For these reasons, the recorded times to treatment were more likely to be underestimated than overestimated.

A second limitation of our study was that potential modifying covariables (eg, socioeconomic status and alcohol use)

TABLE 3
Adjusted ORs for delay in all patients*

Characteristic	Adjusted ORs	
	Value	95% CI
Age, years		
18–34	1.07	0.81 to 1.42
35–64	1.54	1.21 to 1.98
≥65	1	–
Country of birth		
Born in Canada	1	–
Lived in Canada 10 years or less	1.33	0.94 to 1.90
Lived in Canada more than 10 years	1.47	1.02 to 2.12
Site of disease		
Pulmonary	1	–
Nonpulmonary	1.57	1.28 to 1.92
Health unit†		
A	1	–
B	1.39	0.79 to 2.40
C	1.91	1.11 to 3.29
D	2.08	1.33 to 3.27
E	1.97	0.89 to 4.39
F	3.26	1.69 to 6.29
G	2.68	1.33 to 5.41

*Data are missing for country of birth in 18 patients (1%) and site of disease in 12 patients (less than 1%); †Reference health unit defined as the one with the least amount of delay

were not captured by the surveillance database and therefore not included in the analysis. While the absence of these factors limit the scope and interpretation of our study, their absence alone cannot explain the study results. Finally, another limitation is that the date of first contact with the health care system was not available. Without it, one cannot hypothesize the length of delay due to patient factors before that date and health care system factors after that date. However, health care system factors – such as lack of accessibility – might also influence time before first contact, and personal factors – such as not being able to attend follow-up appointments – might influence time after first contact, so that the distinction as to what influences which time period remains a hypothesis even with the added information.

In our secondary analysis, it was interesting to learn that the median delay in AFB smear-positive TB patients was approximately the same as the median delay in all patients. It was also longer than that found in a previous study (1). We were expecting less delay in smear-positive patients because a diagnosis of TB, in general, could be made without having to wait for the results of TB cultures. It is possible, however, that in our population, AFB smear positivity acted as a surrogate marker of patient delay in seeking medical attention (which we were unable to measure), thus giving these patients more time to develop a larger burden of disease that may be detected by the AFB smear test. We also hypothesize that AFB positivity due to a larger burden of disease made the diagnosis of TB less ambiguous, and this was the reason why no other factors appeared to be associated with delayed time to treatment. The only covariable found to be associated with delay in this group was onset of symptoms outside of Ontario, suggesting again, that future study of this unique group would be of interest.

CONCLUSIONS

In our North American, multicultural, community-based TB population, one-half of patients initiated treatment more than two months after symptom onset. Those who were middle-aged, foreign-born and lived in Canada for more than 10 years, who had nonpulmonary TB, and who were treated within certain health units were more likely to experience a longer time to treatment. Although these factors are largely not modifiable, educating people about these findings might bring about improvements. Specifically, education directed toward middle-aged people, long-standing immigrants and health care providers that care for them might be a means to overcoming patient factors and health care system factors

responsible for delay. Thus, directed education that teaches about suspicious TB symptoms and the need for them to be addressed in a timely manner may be an efficient and cost-effective way to decrease transmission, and improve morbidity and mortality from TB. Finally, a program whereby quality indicators are established and routinely monitored would be another way to maintain and improve quality TB management.

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