DOES EXPOSURE TO FLUOROQUINOLONE ANTIBIOTICS DELAY THE DIAGNOSIS OF PULMONARY TUBERCULOSIS?

by

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ABSTRACT

Tuberculosis (TB) remains a major public health concern, and a delay in its diagnosis leads to continued disease transmission, and at the population level, may result in ineffective TB control programs. This delay may be associated with the inappropriate use of antibiotics, particularly the respiratory fluoroquinolones (FQ). In our study we determined whether the use of fluoroquinolones and other antibiotics results in a delay in the diagnosis of TB.

We used population-based data from the British Columbia Linked Health Databases (BCLHD), which collects longitudinal health care information. Residents who had active pulmonary TB from January 1, 1997 to December 31, 2006 as identified through the provincial TB control database were included and linked with data in BCLHD. Negative binomial regression was used to calculate the relative risk (RR) of *health care delay* (the time between first patient contact with the health care system for a respiratory condition and the initiation of anti-TB medication) and *antibiotic delay* (the time between first patient prescription fill for antibiotics and initiation of anti-TB medication) compared to controls, adjusting for potential confounders.

A total of 2232 patients had active TB diagnosed in BC between 1997 and 2006. Of these, 1544 participants were included in the study with health care contact six months prior to the date of diagnosis. After adjusting for gender, age, foreign-born status, socioeconomic status, prior chest radiograph and physician specialist visit, the health care delay for patients exposed to antibiotics was found to be significant at RR 2.10 (95% CI 1.80-2.44). Gender, age, foreign-born status and socioeconomic status were not found to be significant factors. When categorizing this delay by antibiotic type, all antibiotic categories were at a significantly increased risk for delay. In addition, this delay increased as the antibiotics prescribed also increased for the patient. Delay related to antibiotic exposure was found to be significant for the combination of FQ and non-FQ antibiotics at RR 1.35 (95% CI 1.08-1.70), but not for the FQ or non-FQ only categories.

Our results indicate a delay in TB diagnosis due to previous exposure to any antibiotic and not just fluoroquinolones.

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ABX	antibiotic
AFB	acid-fast bacilli
ATS	American Thoracic Society
BC	British Columbia
BCCDC	British Columbia Centre for Disease Control
BCLHD	British Columbia Linked Health Database
CAP	community-acquired pneumonia
CI	confidence interval
CXR	chest X-ray
DDD	Daily Defined Doses
FQ	fluoroquinolone
HIV	human immunodeficiency virus
ICD	International Classification of Disease
iPHIS	Integrated Public Health Information System
IQR	interquartile range
MDR	multi-drug resistant
MeSH	Medical Search Term
MSP	Medical Services Plan
RR	relative risk
SD	standard deviation
SES	socioeconomic status
TB	tuberculosis

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CO-AUTHORSHIP STATEMENT

The work presented in this thesis was conducted and disseminated by the Master's candidate. The co-authors of the manuscripts that comprise part of this thesis made contributions only as is commensurate with a thesis committee or as experts in a specific area as it pertains to the work. The co-authors provided direction and support. The co-authors reviewed each manuscript prior to submission for publication and offered critical evaluations; however, the candidate was responsible for the writing and the final content of these manuscripts.

CHAPTER 1: INTRODUCTION

1.1 Tuberculosis: burden of disease

Tuberculosis (TB) remains a major public health issue, affecting approximately one-third of the global population.[1] Caused by the pathogen *Mycobacterium tuberculosis*, eight million people become infected with TB annually and as a result two to three million people die from the disease worldwide.[1] These mortality figures have been shown, globally, to account for 25% of total preventable deaths in adults.[2] Although only 5-10% of infected individuals develop active disease, international authorities such as the World Health Organization have nonetheless recognized the significance of this disease by declaring TB a 'global emergency' in 1993.[2] In recent years, due to the increasing prevalence of HIV and the growing emergence of drug-resistant strains, TB continues to be a major public health challenge.

TB was a major cause of morbidity and mortality in Canada in the early 20th century, but with improved living standards and the introduction of anti-TB medications, the incidence of TB disease has declined significantly.[3] However, in recent years the trend has been shown to plateau, with overall incidence rates of TB at 4.8 per 100,000 population corresponding to approximately 1,600 cases per year. In Canada, the highest rate, 149.9 per 100,000 population was reported from the province of Nunavut in 2008 and concerns the Inuit population.[3] In British Columbia, the incidence of TB is the highest among the three most populous Canadian provinces at a rate of 6.8 per 100,000 persons in 2006, translating to approximately 300 cases annually.[3]

1.2 High incidence rates of TB in vulnerable subpopulations in Canada

Although the incidence rate of TB disease within Canada is considered to be relatively low on a global scale, incidence rates in special high-risk groups exceed those

seen in many developing countries. In Canada, foreign-born individuals are the source of the largest single patient group, accounting for approximately two-thirds of the TB cases in the country.[3] Additionally, TB is overrepresented among Aboriginal persons (approximately 15%) and inner-city populations, especially injection drug users and HIV-positive individuals.[4,5,6] As patients infected with HIV are experiencing extended survival due to the use of antiretroviral therapy, increased likelihood of TB co-infection is possible. The emergence of drug-resistant TB strains is also a global threat and a relevant cause for alarm in developed nations such as Canada. In 2001, 18% of the total population was born outside of Canada, with large numbers of immigrants now originating from regions of the world where local TB incidence and prevalence rates are several times greater than those observed in Canada.[1] Citizenship and Immigration Canada is responsible for the immigration process, which states that all people who apply for permanent residency are required to undergo a medical evaluation as TB is considered to be a danger to public health.[1] However, over the last few years, there has been a plateau in the incidence of TB in Canada, which may be related to the failure of strategies to prevent and control TB. Emerging challenges to TB control may include multi-drug resistance, TB/HIV co-infection and lower levels of observation in the private sector. Improvements should be made in regard to geographical and economic access to TB diagnosis, which may be achieved through the participation of communities. In addition, the referral process of TB suspects may lead to increased case detection while better management of TB cases and treatment adherence may improve patient care. Greater emphasis must be placed by healthcare workers to diagnose cases and appropriately treat TB earlier by enhancing surveillance.

1.3 Fluoroquinolones as an anti-TB medication

TB has been treated with combination therapy for almost 50 years, due to the fact that mono-therapy of active disease results in the rapid development of resistance and treatment failure.[1] The treatment for TB is divided into first- and second-line agents. Although these first-line drugs have been shown to be very effective in treating TB, they

can be associated with adverse effects, especially in patients co-infected with HIV or have evidence of liver disease.[6]

Fluoroquinolones (FQ) were introduced in the 1980s and are a class of broad-spectrum antimicrobials that function by inhibiting the activity of the enzyme DNA gyrase, which is essential for bacterial DNA replication.[7] Fluoroquinolone use is increasing throughout the world, with the daily British Columbia consumption surpassing Northern European countries.[8,9] On average, fluoroquinolone use in BC increased from 0.9 to 1.65 Daily Defined Doses (DDD) per 1,000 population per day from 1996 to 2005.[9] Similarly, studies showed that the use of later generation fluoroquinolone (e.g. levofloxacin and moxifloxacin) increased significantly compared to those of earlier generations (e.g. ofloxacin or ciprofloxacin).[9] Guidelines suggest using these agents as second-line treatment for multi-drug resistant TB (MDR-TB), or as a substitute if patients cannot tolerate first-line drugs.[1] Presently, fluoroquinolones are used for prophylaxis of those exposed to MDR-TB, for treatment of proven MDR-TB, for empiric treatment of TB disease in settings of high rates of MDR-TB, and for patients with severe adverse reactions to first-line agents. There is also emerging evidence that isoniazid can be substituted with moxifloxacin as part of first-line treatment for drug-sensitive TB.[10]

1.4 TB (mis)diagnosis as community-acquired pneumonia

Pulmonary TB is the most common form of the disease, with active cases often presenting with clinical features and chest radiology that are indistinguishable from those of pneumonia.[11] Thus, patients may have atypical radiological presentations which may be confused with community-acquired pneumonia (CAP). CAP is defined as pneumonia not acquired in a hospital or long-term care facility.[11] These atypical radiological features can lead to a delayed diagnosis, especially if TB is not considered in the initial differential diagnosis, and if appropriate sputum samples for smear and culture have not been collected.

Including TB in the differential diagnosis of a patient with suspected CAP is complicated by the fact that patients presenting with TB, especially in the early stages, often have non-specific signs and symptoms. Most cases of pneumonia in the community are treated without the submission of sputum samples for culture of organisms or a chest radiograph, the two main ways to diagnose TB. Furthermore, even when the clinician considers the diagnosis of TB and a sputum sample is sent for acid-fast bacilli (AFB) smear examination, this test will only be positive in 50% of cases, with approximately 85% of cases being ultimately culture-positive.[12] Ideally, TB should be part of the differential diagnosis when patients present with signs suggestive of CAP. However, this is often not the case and it is not unusual for clinicians to prescribe a number of courses of antibiotics before the diagnosis of TB is considered, and before either a chest radiograph or sputum sample is collected for bacteriological testing.[12,13]

1.5 Fluoroquinolones as community-acquired pneumonia medication

Although fluoroquinolones, as a class of antibiotics, have excellent *in vitro* activity against TB, new respiratory fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin) also have a broad-spectrum of antimicrobial activity against pulmonary pathogens that cause community-acquired pneumonia.[14-16] Older fluoroquinolones, such as ciprofloxacin and ofloxacin also retain good activity against *M. tuberculosis*.[17] Indeed, respiratory fluoroquinolones are recommended as one of the agents which may be used for the treatment of patients with CAP by the American Thoracic Society and the Infectious Diseases Society of America.[11] This raises the issue of the initial misdiagnosis and subsequent treatment of TB as community-acquired pneumonia, with medications that may have anti-TB activity.

Short courses of fluoroquinolones, as when used for treating community-acquired pneumonia (CAP), do not result in the complete elimination of *M. tuberculosis* and subsequent cure in the case of active TB. Thus, the increasing use of fluoroquinolones may lead to a situation where suspected CAP is in fact TB, which may be partially treated

with a fluoroquinolone. Ultimately this may lead to a delay in TB diagnosis, which could include patients presenting with more severe disease, also increasing the risk of transmission to the general population.

1.6 Significance of fluoroquinolone use in TB

Delays in the diagnosis and treatment of TB have direct consequences on the affected individual as it postpones the initiation of appropriate anti-TB treatment. At the population level, delays promote the continued transmission of *M. tuberculosis* by individuals unaware that they have active TB. In addition to delaying the diagnosis of TB, inadvertent use of fluoroquinolones as mono-therapy for the treatment of TB can also theoretically result in resistance to fluoroquinolones in *M. tuberculosis* isolates.[18]

1.7 Rationale for current study

In this study the evaluation of all antibiotic exposures (including fluoroquinolones) and their associated impact on the time at which TB is diagnosed and the prompt initiation of appropriate treatment of TB will be investigated. Previous research showed antibiotics that were administered up to 6 months prior to initiation of anti-TB treatment had the potential to affect the timeliness of the diagnosis of TB and initiation of proper pharmacotherapy.

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CHAPTER 2: REASONS FOR DELAY IN DIAGNOSIS IN TUBERCULOSIS: A QUALITATIVE SYSTEMATIC REVIEW*

2.1 Introduction

Delays in the diagnosis and treatment of tuberculosis (TB) have direct consequences for the affected individual as it postpones the initiation of appropriate anti-TB treatment. At the population level, delays lead to ineffective TB control programs through continued transmission of *M. tuberculosis* by individuals who are unaware that they have active TB.[1] Effective TB control programs are implemented to stop transmission within the community; however, this goal cannot be fully achieved unless early diagnosis and immediate initiation of treatment occurs. In addition to the delayed diagnosis of TB, inadvertent use of anti-TB medication as mono-therapy for presumed community-acquired pneumonia, when it is in fact a case of active TB, can result in the development of fluoroquinolone resistance.[2]

For these reasons, analysis of the factors leading to delays in TB diagnosis is crucial in combating this global public health danger. These delays may be attributed to patients, as well as to the health care system, or a combination of the two, resulting in an extended (total, or combined) delay. The patients may delay seeking help or individuals within the health care system may delay suspecting and investigating for TB. In addition, patient-specific risk factors may also figure into the ultimate delay in diagnosis of pulmonary TB. Thus, a review of the literature was performed, in an attempt to address this concern.

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2.2 Methods

A primary review of the literature was performed to identify current literature on the subject of delays in diagnosis of pulmonary TB. MEDLINE (1950 to March Week 2 2010) and EMBASE (1980 to Week 10 2010) were searched for articles. Variations of the terms "pulmonary tuberculosis" and "diagnosis delay" were searched, and the closest MeSH subject headings were mapped whenever possible. A subsequent language filter was applied for English-language articles only. References were hand-searched for any relevant articles that may have been omitted in the database searches. Ethical approval was not required for this review.

Included studies were those that either reported a patient, health system or total (combined) delay in the diagnosis of pulmonary TB, or those that described the potential factors that may be responsible for such a delay. All age groups were included in this study. Variability within definitions was expected, and all studies that included data on the aforementioned diagnostic delays were considered for review. Titles and abstracts of studies were examined to exclude studies that did not meet the study inclusion criteria. Studies were excluded if not enough information was provided to assess their methodology, such as brief reports, comments or letters. For the potential studies deemed eligible for inclusion, the full paper was obtained.

2.3 Results

A total of 1291 English-language articles were found from MEDLINE (676 articles) and EMBASE (615 articles) databases. Three hundred and eighty two were non-English articles and were excluded. This left a total of 909 articles (459 from MEDLINE, 450 from EMBASE), which after a non-duplicate filter, left 576 articles for review. From these, 59 review articles were excluded after reviewing the references. Of the 517 articles remaining, another 71 were excluded; 13 for reasons of unascertainable methodology (comments, letters and brief reports which did not specify the study definitions and

therefore arrived at broad conclusions), with the remaining excluded based on the inclusion criteria. Hand-searching of reference lists produced an additional 4 relevant articles. A flow chart of the selection process is presented in Figure 1, with the number of articles remaining after each exclusion stage noted. The final number of studies included was 60.

Within these 60 studies, the inclusion and exclusion criteria among them varied to include incident TB patients, or if more definitive in their patient eligibility criteria, only incident pulmonary TB cases were recruited. Positive sputum smears or bacteriological cultures were often specified in the inclusion criteria, but patient referrals could also have been accepted to define the patient population in studies. Exclusion criteria also varied greatly between the studies, such as the criterion of participants' ages. Many studies excluded children, while few included cases of TB in all ages. In addition, certain studies removed confounding conditions by excluding patients with chronic pulmonary illnesses, while it was not specifically mentioned in others.

Total delay, when measured as an outcome, was often a combination of both a patient delay and a healthcare delay. While some studies presented all three types of delay (patient, health care and total), depending on the nature of the study, others only measured total delay or a combination of two. Thus, it can be noted that much heterogeneity existed within the included 60 studies. Table 2.1 shows the study characteristics for those studies not pertaining to antibiotic use. Data on the primary author, year, country, study design, number of participants and inclusion criteria are presented. The delay time is presented in median time (days) unless otherwise stated.

Storla *et al.* concluded a systematic review in early 2007 on the subject of diagnosis and treatment delays for tuberculosis, which included 58 studies.[2] This present review updated their search as well as focused specifically on the use of antibiotics as a potential risk factor for delays in the diagnosis of TB. For the reasons described previously, antibiotics have antimicrobial activity against pulmonary pathogens including

TB, and as a result, could potentially mask its symptoms. Study characteristics for studies involving antibiotic use in the delay of diagnosis of TB have been presented in Table 2.2.

In addition, Storla *et al*. subcategorized risk factors into categories, some of which this review will also similarly consider: demographic, psychological and socioeconomic factors, clinical characteristics and health care contact.[2] Demographic factors, such as age and gender, have been associated with a delay in the diagnosis of TB and are noted in various studies that have examined the relationship of these specific covariates.[3,4,5] In developing countries, and particularly their rural areas, a strong psychological factor may be present, since the general level of education is low among inhabitants, and social stigma exists surrounding the diagnosis of TB.[6,7] Certain clinical characteristics have been associated with a delay in diagnosis. The presence of co-morbidities and an overall poor state of health may in fact be correlated with this delay seen in patients.[5,8,9] However, this phenomenon may lead to an opposite effect as noted with HIV, where a weakened immune system may prompt patients to actively seek out health care earlier due to general feelings of discomfort and earlier onset of symptoms.[10,11] Health care contact is another issue that arises in ensuring a diagnosis and eventually, treatment, for TB. In a community setting, initial contact may be with a private practitioner, who infrequently encounters TB and is therefore less likely to consider the diagnosis as the presentation overlaps with other respiratory illnesses.[12,13] Socioeconomic factors, such as living in a rural environment rather than urban, can also be limiting in terms of health care accessibility and prevent those with TB from receiving a correct diagnosis.[5,14,15] Table 2.3 shows the different categories of risk factors, with specific examples of the main risk factors found within each in the literature. For each factor, studies are cited (with their corresponding reference number) as to having either found a positive or negative association in the delay in diagnosis of TB, as per the method that was suggested by Storla *et al*. in table format.[2]

2.3.1 Diagnostic delay

A diagnostic delay was either defined as total, patient- or health care-based. Table 2.1 shows the mean or median total, patient- or health care-based delay for the 56 included non-antibiotic studies.[2-58] In eleven studies it is unclear what the patient- or health care-based delays were as they were not specified and instead only a total delay was reported.[4,6,8,15,18,29,33,42-43,46-47] Therefore, in these eleven studies, it cannot be ascertained as to whether the total delay in diagnosis was a result of patient factors, or attributable to the health care system. For the remaining 45 studies, the specified mean and/or median delay has been included in Table 2.1. Eight studies reported a mean time for patient delay that ranged from 9.9 to 73.5 days[9, 17, 20, 34, 37, 39, 47, 48], while the median was reported in 34 studies as being 7-63 days.[3-5, 7, 10-14, 16, 19, 21-26, 30-32, 35-36, 41, 44-45, 50-58] For health care delays, the mean varied between studies, ranging from 5-120 days (from eight studies)[9, 17, 20, 34, 37, 39, 47, 48], with a median of 13-120 days reported in the 31 remaining studies.[5, 10-14, 16, 19, 21, 23-26, 30-32, 35-36, 38, 40-41, 44-45, 50-51, 53-58]

2.3.2 Demographic factors

Demographic factors that were examined in the included studies seemed to indicate an increased risk of delay for the elderly, females and the foreign-born. It was found in twelve of the studies that increasing age (in the majority of the studies, defined as older than 45 years of age) was significantly associated with an increased delay even after adjusting for other covariates.[5, 8-9, 17-18, 28, 33, 40, 42, 51, 56, 58] Likewise, being foreign-born was found in four studies to be associated with increased patient delay.[8, 26, 49, 50] Authors suggested low awareness of TB, stigma, and language and cultural differences as potential reasons for this delay.

Seventeen studies concluded that women were more likely to experience delay in diagnosis.[3-10, 14, 18, 22, 30, 39, 44, 50, 54, 56] In a cross-sectional survey by Karim *et al*. performed in Bangladesh, results revealed that significantly longer delays occurred for women

compared to men, for total delay, total health care system delay and patient delay.[3] It was also found that older women (and also younger men) were less likely to be diagnosed with TB through the existing TB control interventions.[3] Likewise, in another study specifically addressing gender difference in rural Nepal, women had significantly longer delays before the diagnosis of TB was made (median 2.3 months for men, 3.3 months for females).[5] In a third study that examined gender as a primary factor, Needham *et al*. also found that being female was strongly associated with delay, resulting in a mean delay of 8.6 weeks, when adjusting for other potential confounders.[4] However, it was noted by the authors that lower education among women may have been a confounding factor.[4] Similarly, it was also suggested by the authors that the heavy workload of women in rural countries, combined with their lack of mobility, independence and financial resources could potentially explain the female gender as a risk factor.[4]

To contrast, in a study in Estonia females had a significantly shorter patient delay. The authors suggested that it may be possible that females tend to be more concerned about their health and are consequently more active in seeking help for their symptoms.[43] Similarly, in another study performed by Rajeswari *et al.*, men tended to wait somewhat longer than women to seek care (20 days vs. 15 days, p=0.07), however the reasoning for this was found to be attributable to a lack of awareness concerning TB and poor socioeconomic conditions.[45]

2.3.3 Clinical characteristics

Out of the included studies, 14 evaluated clinical characteristics as reasons for a possible delay in diagnosis.[4-5, 8-11, 16, 19, 31, 36, 40, 53, 54, 58] In one study performed in urban Zambia, the authors found that HIV was associated with an increased risk of delay in diagnosis.[4] Surprisingly, in two other studies, researchers arrived at the opposite conclusion.[10,11] In the study by Ngamvithayapong *et al*. conducted in an HIV-endemic mountainous region in Thailand, it was concluded that HIV-positive patients (especially hill tribe people) suffered more symptoms.[11] This caused the requirement for more

intensive care, which increased patients' health-seeking behaviour, resulting in the noted shorter patient delay. Delays in HIV-positive patients, especially married and widowed patients, were significantly shorter than in HIV-negative patients and those whose HIV status was unknown.[11] In addition, almost 75% of the HIV-positive patients regularly sought treatment for other ailments.[11] HIV patients who were married or widowed had particular health concerns because they wanted to prolong their lifespan in order to take care of their family, in particular, young children.[11]

Three studies revealed that negative sputum smears may be a risk factor for increased delay.[36, 40, 54] Ward *et al.* noted that the natural history of the disease is such that cases that are initially sputum-negative may later become sputum-positive so that regular patient review and re-submission of samples may be necessary to make a diagnosis, causing a diagnostic delay.[54] In addition, three studies indicated symptoms or presence of cough as a risk factor for delay in the diagnosis of TB, specifically in regard to patient delay.[16, 52, 58] Van der Werf *et al.* found that patients with an underlying cough (also mentioned by the authors as one of the main symptoms before seeking health care), were at risk for increased patient delay (OR 2.37 95% CI 1.08-5.19)[52], which was also similarly noted by Zerbini *et al*. (OR 0.42 95% CI 0.23-0.77 for those without cough)[58]. Meintjes *et al.* found a significant difference in the median patient delay time for those who reported a cough (14 days, IQR 7-30 days), compared to those who did not (7 days, IQR 4-14 days), suggesting that patients may delay in seeking medical care as per the suggestion of TB public health messages of presence of a cough for two weeks or longer as a sign of TB.[16] Similarly, another reason may be that when patients are presented with more serious symptoms other than those of a cough, earlier health care access may be sought.[16]

2.3.4 Psychological factors

In TB-endemic areas poor education, certain beliefs and societal taboos exist concerning the cause and treatment of TB, leading to a delay in its diagnosis. Seven

studies in total evaluated these factors.[5, 7, 14, 20, 32, 37, 57] In two studies, one conducted in rural South Africa and the other in rural Nepal, it was found that a cause of TB was believed to be an 'evil spirit'.[5,14] When these societal beliefs were considered, they were also identified as potential risk factors for a delay in diagnosis. As a result of this notion, self-treatment was noted among the study participants in these rural areas, producing a patient-based delay in diagnosis of TB. Mesfin *et al.* also noted significant treatment-related factors of a psychological nature, with prior treatment with holy water in some patients.[7]

Patients' own regard for clinical manifestations that cause symptoms was also noted. In a study by Liam *et al.*, which examined symptoms before diagnosis, it was found that the shortest mean patient delays were for those that believed their symptoms were due to lung cancer (delay of 1 week), and the common cold or diabetes (both 1.3 weeks).[32] Two patients in the study correctly attributed their symptoms to TB and had delays of 4 and 21 weeks respectively. Despite this, it was concluded that the patients' lack of understanding of the cause of their symptoms did not significantly affect the delay before their first medical consultation.[32]

2.3.5 Socioeconomic factors

Ten studies found low income and poverty to be significant risk factors for delay in TB diagnosis and treatment.[18, 20, 23, 31, 41-42, 44, 52, 54-55] As in these studies it was often found that a longer delay was associated with lower education levels (in particular for females). It was also noted by the authors that a lack of awareness with regard to TB contributed to a diagnostic delay. For location of residence, it was noted that in fifteen studies total delay was strongly associated with living in a remote or rural region.[5-7, 9, 10, 12, 15, 28, 34, 36, 39, 43, 45, 53, 56] These studies found an association with low access to health care due to geographical location and similarly, an underprivileged environment to first seek health care.

2.3.6 Health care contact

Health care contact in some ways may be limited depending on geographical location, which in turn may be affected by the socioeconomic status of the patients presenting with TB symptoms. Despite the fact that rural residents are likely to have worse access to health care, it was found by Lawn *et al.* that they tended to seek traditional healers more frequently.[10] This, however, was not associated with a patient delay, but instead an increased total delay that could be attributed to doctors (median delay of 3.9 times longer in rural areas).[10]

Likewise, Yimer *et al.* found that those who first visited a health post/clinic or a private medical provider were more likely to have a health system-related delay.[57] Another study by Rojpibulstit *et al.* found that of the patients first presenting to a qualified provider, those whose first visit was to a tertiary hospital or TB centre had a significantly shorter health system delay than those who first visited a lower-level health facility, such as a community hospital, health centre or private clinic or hospital (median 0.7 vs. 3.3–4.7 weeks).[13] In a study conducted in Malaysia, the type of facility that the patients visited for symptoms did not affect the delay before the patients' presentation to the hospital. In addition, it was found that the association between type of facility and delay was weak although significant; however, the number of doctors consulted and the number of consultations the patient made had stronger associations with delay.[32]

Studies varied in terms of levels of care (primary, secondary or tertiary); however there was consensus within the studies that multiple visits potentially lengthened the time to an accurate diagnosis, as the initial facilities were likely to have limited resources for such disease verification or the health care providers themselves lacked the expertise in recognizing and properly associating symptoms with TB. In addition, it was found in eleven studies that an initial visit to a low-level government facility was a risk factor for delay in diagnosis for TB.[4, 6, 10, 13, 16, 22, 28, 41, 45, 51, 57] Similarly, patients who initially visited traditional or private practitioners also experienced a delay, in the thirteen studies

that analyzed this risk factor, the likely reason being that such practitioners had poor knowledge of the disease.[4-6, 12-13, 22, 30, 32, 37, 45, 51, 53, 55]

2.3.7 Antibiotic related delay

In terms of antibiotic related delay, four studies reported specifically the effect of empiric antibiotic therapy resulting in possible delays in the initiation of anti-TB therapy. Dooley *et al.* found that the median time to presentation to hospital and initiation of anti-TB treatment (health care delay) was 21 days among those who were previously exposed to fluoroquinolones, compared to 5 days in those who were not exposed, in 33 patients.[59] Clinicians noted a rapid response to fluoroquinolone treatment (within three days), which led them to believe that the infection had been eliminated. However, the consequences of this premature cessation of antibiotic therapy later manifested as recurrences in signs and symptoms and thus ultimately resulted in a TB diagnostic delay. For patients who received any antibiotic (including fluoroquinolones) prior to their TB diagnosis, the delay from their first health care visit to the time that TB therapy began was significantly longer than those who did not receive antibiotics (39 days versus 15 days, $p < 0.01$).[59]

Similarly, Wang *et al.* performed a retrospective study involving 548 patients with culture-confirmed TB who received fluoroquinolone, another antibiotic or no antibiotic before anti-TB treatment. Results indicated that the empirical use of antibiotics, especially fluoroquinolones prescribed for a bacterial infection, could delay the treatment of TB, especially in patients with smear-negative specimens. Patients who received fluoroquinolones in the study (but not other types of antibiotics) before standard anti-TB treatment were more likely to have a delay in diagnosis (hazard ratio of 6.88, 95% CI of 1.84 to 25.72).[60] Median interval from the initial visit to starting anti-TB in the antibiotic-treated group was longer than those who received no antibiotics (41 days versus 7 days respectively).[60]

A study that assessed specifically the effect of fluoroquinolone therapy on delays in diagnosis, in patients with TB initially misdiagnosed as bacterial pneumonia, was performed by Yoon *et al.* Patients with bacteriologically-confirmed TB, and initially treated for community-acquired pneumonia with fluoroquinolones for more than 5 days, were included in the study.[61] Delay in the initiation of anti-TB medications was longer in the fluoroquinolone group than in the non-fluoroquinolone group (43.1 days versus 18.7 days, $p = 0.04$).[61] This delay, according to the researchers, may have been caused by the higher levels of symptomatic and radiographic improvement shown by fluoroquinolone-treated patients versus non-fluoroquinolone-treated patients (89% versus 42% respectively, $p = 0.04$).[61] However, the study only had nine patients in the fluoroquinolone group and nineteen in the non-fluoroquinolone group.

Golub *et al*. performed a nested case-control study for 85 cases and 73 controls, all patients with culture-confirmed TB.[62] Cases had non-TB-related diagnoses and therefore antibiotics, compared to controls who initially received TB therapy. It was found that there was a significant median health care delay for patients who received antibiotics of 39 days (range 2-519 days) compared to 15 days (range 0-191 days) for patients who did not receive antibiotics ($p<0.01$).[62] When subcategorizing by antibiotic, it was also found that there was no significant difference in antibiotic delay among fluoroquinolones compared to other antibiotics (29 days versus 31 days, $p=0.46$).[62] Researchers commented on this finding suggesting that the inherent wait time for antibiotics may be the reason, rather than the anti-TB effects of fluoroquinolones. Underutilization of chest radiographs was also apparent in the cohort for this study, with patients who had one performed having a delay of 15 days, compared to 69 days for patients who did not receive one at their first visit ($p<0.01$).[62] The authors concluded that from the results, physicians should be recommended to comply more strictly to the guidelines set in place by the American Thoracic Society in ordering chest radiographs before the prescription of antibiotics, in addition to conducting other diagnostic procedures, such as sputum tests, due to the possible health risks that unnecessary delays may pose to both TB patients themselves as well as people coming in contact with them.

2.4 Discussion

From the many risk factors that have been carefully assessed it is evident that certain clinical, demographic, psychological, socioeconomic and health care contact factors leave TB patients prone to diagnostic delays. The general results align with those that were found in the previous systematic review conducted by Storla *et* al.[2] Results from studies indicate that gender (female), immigration status (foreign-born) and age (older than 45 years) are risk factors that result in a delay in diagnosis of TB. Likewise, low income, low education and rural residence also favour a positive risk association, with few studies indicating the opposite. Fewer studies addressed clinical risk factors for the delay in diagnosis of TB, with conflicting results. Co-infection with HIV, negative sputum smear and cough have been identified as potential risk factors that may delay diagnosis. In rural areas, the societal and cultural beliefs and stigmas associated with TB suggested delay potential, in some cases with patients performing self-treatment instead of obtaining proper medical care.

Health care contact is also an important factor, with many studies suggesting that initial visits to private practitioners, traditional practitioners or low-level government healthcare facilities may also delay the diagnosis of TB. This is also apparent in patient-related attributes, such as their beliefs and attitudes toward the disease. Patients' views, or merely their lack of education, affect their health care-seeking behaviour and may increase the number of consultations and visits to doctors and hospitals, creating a potential diagnostic delay.

Although few studies have addressed specifically the use of antibiotics, in particular fluoroquinolones, as a factor in the delay in diagnosis of TB, results show that antibiotics also cause a delay. Large population-based studies which are required to answer this question are infrequent in the literature. The four studies found seem to suggest that antibiotic exposure delays the diagnosis of TB and the initiation of proper long-term TB therapy. As the amount of antibiotics being prescribed is increasing

worldwide, an important health issue arises in their use to treat other pulmonary pathogens, and whether this is associated with a delay in the diagnosis of TB.

Since the studies varied in terms of design and methodology, a wide range of definitions was used that limited their comparability, and made any type of quantitative data analyses unfeasible. Definitions ranged in terms of when symptoms began, first appropriate health care provider, time to diagnosis and start of treatment. It can also be noted that due to the observational nature of the studies, many were limited in the information that was collected and as such, adjustments for potential confounders such as co-morbidities, socioeconomic status and geographical location were not possible for all studies. The range in burden of TB disease between patients in studies may also contribute to study heterogeneity and was not often addressed. Data for TB patients in Canada was limited, with two studies being conducted in the country.[27, 29] For developed countries such as Canada, risk factors such as immigration, low socioeconomic status and antibiotic use may be more relevant due to trends in immigration, as well as vulnerable subpopulations that may be less educated.

To further the understanding of risk factors that may delay the diagnosis of TB, large population-based studies need to be performed, with adequate information for all study participants in terms of potential risk factors assessed. Large populations are required in order to increase the study's power to assess such factors, as the results for smaller studies cannot be met with the same level of confidence. Accurate medical records in terms of underlying symptoms and conditions for TB patients, as well as patient history in their TB progression and health care-seeking patterns are necessary to assess the clinical characteristics and health-seeking behaviour of patients, which have been identified as potential risk factors for delay. For rural areas, thorough understanding of the culture, societial beliefs and stigmas associated with the disease are warranted to gather evidence for differences in seeking health care among this specific subpopulation of TB patients. With this information, knowledge in regard to the factors that could potentially delay diagnosis can be ascertained with greater precision and with fewer study biases, potentially translating to earlier diagnosis in patients with TB.

2.5 Conclusions

As expected, a variety of risk factors may contribute to a delay in the diagnosis of TB, ranging from demographic, psychological, clinical, and health care-related including the use of antibiotics. These may be manifested in the form of patient or health care-related delays, with a combination potentially creating an overall diagnostic delay for TB. Acknowledgement and greater understanding of these risk factors may lead to improved care for TB patients.

Table 2.1: Study characteristics for included non-antibiotic studies on delay in diagnosis of TB

Study	Year	Country	Study type	Number of patients	Inclusion Criteria	Patient Delay‡	Healthcare Delay‡	Total Delay‡
Altet-Gomez	2003	Spain	Cross-sectional interviews	13,038	Patients registered in the TB Control Programme	43 days*	39 days*	82 days*
Asch	1998	US	Prospective cohort	526	Confirmed active TB	-	-	60 days
Basnet	2009	Nepal	Cross-sectional survey	307	Newly diagnosed TB patients registered by National TB Programme	50 days	18 days	60 days
Bassili	2008	Eastern Mediterranean region (7 countries)	Cross-sectional interviews	5,053	Newly diagnosed, adult, smear-positive TB patients	9.9 to 69 days*	5 to 90.7 days*	45-120 days*
Calder	2000	New Zealand	Cross-sectional questionnaires	100	Confirmed active TB	7 days	49 days	84 days
Chang	2007	Malaysia	Cross-sectional	316	New smear-positive TB patients	30 days	-	22 days
Chiang	2005	Taiwan	Cross-sectional interviews	206	Newly diagnosed sputum-positive TB patients	7 days	23 days	44 days
Demissie	2002	Ethiopia	Cross-sectional surveys	700	Newly diagnosed TB patients	60 days	6 days	64 days
Enkhbat	1997	Mongolia	Cross-section interviews	107	Bacteriologically-confirmed TB patients, >16 years old	29 days	35 days	78 days
Farah	2006	Norway	Retrospective cohort	83	Patients registered in National TB Registry	28 days	33 days	63 days
Guneylioglu	2004	Turkey	Retrospective questionnaires	204	Hospitalized patients with smear-positive TB	18 days*	13 days*	64 days*
Kam	2007	Canada	Prospective cohort	23	All TB patients currently treated, ages 13-18 years	-	-	120 days

Study	Year	Country	Study type	Number of patients	Inclusion Criteria	Patient Delay‡	Healthcare Delay‡	Total Delay‡
Karim	2007	Bangladesh	Cross-sectional survey	1000	Newly diagnosed TB patients	50 days (F) 42 days (M)	-	61 days (F) 53 days (M)
Kiwuwa	2005	Uganda	Cross-sectional survey	231	Newly diagnosed smear-positive TB patients	-	-	84 days
Lacroix	2008	Canada	Retrospective cohort	115	Contagious active TB cases declared to Public Health Department	-	-	92.2 days*
Lambert	2005	Bolivia	Cross-sectional interviews	144	Smear-positive patients enrolled in National TB Programme	25.2 days	43.4 days	90.3 days
Lawn	1998	Ghana	Cross-sectional survey	100	Newly diagnosed smear-positive TB	28 days	56 days	120 days
Lewis	2003	UK	Retrospective cohort	93	Confirmed active TB	63 days	35 days	126 days
Liam	1997	Malaysia	Cross-sectional interviews	97	Newly diagnosed TB patients	14 days	49 days	88 days
Lienhardt	2001	The Gambia	Cross-sectional interviews	152	Newly diagnosed TB patients, >15 years	-	-	60 days
Lin	2009	Taiwan	Prospective cohort	78,118	New cases reported using Taiwan enquiry system between 2002-06	-	-	1 day
Long	1999	Vietnam	Cross-sectional interviews	23	All patients aged 15-49 with new smear-positive TB	54 days*	29 days*	93 days*
Lönnroth	1999	Vietnam	Cross-sectional survey	434	Sputum-smear positive patients	7 days	30.1 days	69.3 days

Study	Year	Country	Study type	Number of patients	Inclusion Criteria	Patient Delay‡	Healthcare Delay‡	Total Delay‡
Lorent	2008	Rwanda	Prospective cohort	104	All newly diagnosed TB patients	25 days	28 days	57 days
Maamari	2008	Syrian Arab Republic	Cross-sectional interviews	800	New smear-positive TB cases at observed therapy centres	52.7 days *	24.8 days*	77.6 days*
Mirsaeidi	2007	Iran	Cross-sectional interviews	97	Patients with TB referred to National Research Institute of TB	13 days	75 days	96 days
Mahendradhata	2008	Indonesia	Prospective cohort	421	Smear-positive TB patients	-	-	56 days (U) 84 days (R)
Meintjes	2008	South Africa	Cross-sectional interviews	104	Newly diagnosed TB patients	14 days	30 days	-
Mesfin	2009	Ethiopia	Cross-sectional interviews	924	New TB patients >15 years	30 days	-	-
Mori	1992	Korea	Cross-sectional interviews	630	Newly diagnosed and registered TB patients	54 days*	14 days*	60 days*
Needham	2001	Zambia	Cross-sectional interviews	202	Adults registered with TB centralized Chest Clinic	-	-	60 days
Ngamvithayapong	2001	Thailand	Cross-sectional interviews	557	Patients >15 years with new smear-positive TB	11 days	8 days	-
Odusanya	2004	Nigeria	Prospective cohort	142	Newly diagnosed cases of TB	56 days	7 days	70 days
Okur	2006	Turkey	Cross-sectional questionnaire	151	Newly diagnosed patients with smear-positive TB	30 days	19 days	49 days
Ouedraogo	2006	Burkina Faso	Cross-sectional	61	Newly diagnosed patients with smear-positive TB	-	-	120 days

Study	Year	Country	Study type	Number of patients	Inclusion Criteria	Patient Delay‡	Healthcare Delay‡	Total Delay‡
Pehme	2006	Estonia	Cross-sectional interviews	185	All newly detected symptomatic culture-positive patients, >16 years	-	-	79 days
Pirkis	1996	Australia	Retrospective cohort	142	Active TB patients	-	-	44 days
Pronyk	2001	South Africa	Cross-sectional interviews	298	TB patients, hospitalized and registered in TB services	28 days	7 days	70 days
Qureshi	2008	Pakistan	Cross-sectional questionnaires	301	New smear-positive patients	33 days	60 days	90 days
Rajeswari	2002	South India	Cross-sectional interviews	531	New smear-positive patients	20 days	23 days	60 days
Rodger	2007	UK	Retrospective cohort	853	Smear-positive TB patients	-	-	49 days
Rojpibulstit	2006	Thailand	Cross-sectional interviews	202	Newly diagnosed smear-positive or negative TB patients	31 days	20 days	66 days
Salaponi	2000	Malawi	Cross-sectional interviews	1518	Newly registered patients with smear-positive TB	-	-	56 days
Sanz	2007	Spain	Prospective cohort	296	Immigrants diagnosed with TB, >15 years	15 days*	5 days*	40.5 days*
Sarmiento	2006	US	Cross-sectional survey	39	TB patients within 2 months of enrolment into observed therapy	73.5 days*	52.5 days*	126 days*
Selvam	2003	India	Cross-sectional interviews	601	New smear-positive patients	28 days	28 days	62 days
Sherman	1994	US	Cross-sectional	184	Culture-positive patients without previous treatment for TB	25 days	15 days	57 days

Study	Year	Country	Study type	Number of patients	Inclusion Criteria	Patient Delay‡	Healthcare Delay‡	Total Delay‡
Steen	1998	Botswana	Cross-sectional	212	New and re-treated patients with smear-positive TB	21 days	35 days	84 days
Van der Werf	2006	Ukraine	Cross-sectional interviews	190	Newly diagnosed pulmonary TB patients	30 days	-	-
Wandwalo	2000	Tanzania	Cross-sectional	296	Smear-positive TB patients	15 days	120 days	136 days
Ward	2001	Australia	Retrospective cohort	758	Patients diagnosed through TB database (smear-positive)	30 days	11 days	66 days
Xu	2005	China	Cohort	493	Newly diagnosed TB patients	10 days	39 days	50 days
Yamasaki-Nakagawa	2001	Nepal	Cross-sectional interviews	390	All new patients assigned to observed treatment for TB	23 days	29 days	79 days
Yilmaz	2001	Turkey	Cross-sectional survey	134	Hospitalized patients with smear-positive TB	17.5 days	9 days	3 days
Yimer	2005	Ethiopia	Cross-sectional	384	New smear-positive TB	15 days	61 days	80 days
Zerbini	2008	Argentina	Cross-sectional Survey	243	New smear-positive TB	31 days	12.5 days	62 days

Abbreviations:

‡*Delay - measured in median time; * denotes mean time, instead of median time*

F = female, M = male; U = urban, R = rural

Table 2.2: Study characteristics for included studies on antibiotic use in delay in diagnosis of TB

Author	Year	Sample Size	Study Design	Location	Study Inclusion	Results
Dooley	2002	33	Retrospective Cohort	USA	Culture-confirmed TB; Newly diagnosed	FQ: Median 21 days (IQR 5-32) vs. Non-FQ/No abx: 5 days (IQR 1-16 days), p=0.04
Golub	2005	158	Nested case-control	USA	Cases: abx prior to dx of TB Controls: anti-TB medication	Cases: Median 39 days vs. Controls: 15 days (p<0.01)
Yoon	2005	28	Retrospective Cohort	Korea	Bacteriologically confirmed TB; Newly diagnosed	FQ: Mean days 43.1 +/- 40.0 vs. Non-FQ: Mean days 18.7 +/- 16.9, (p=0.04)
Wang	2006	548	Retrospective Cohort	Taiwan	Newly diagnosed, >14 yrs, culture- confirmed TB	FQ: 41 days Abx: 16 days No abx: 7 days

Abbreviations:

abx = antibiotics; dx = discontinuation

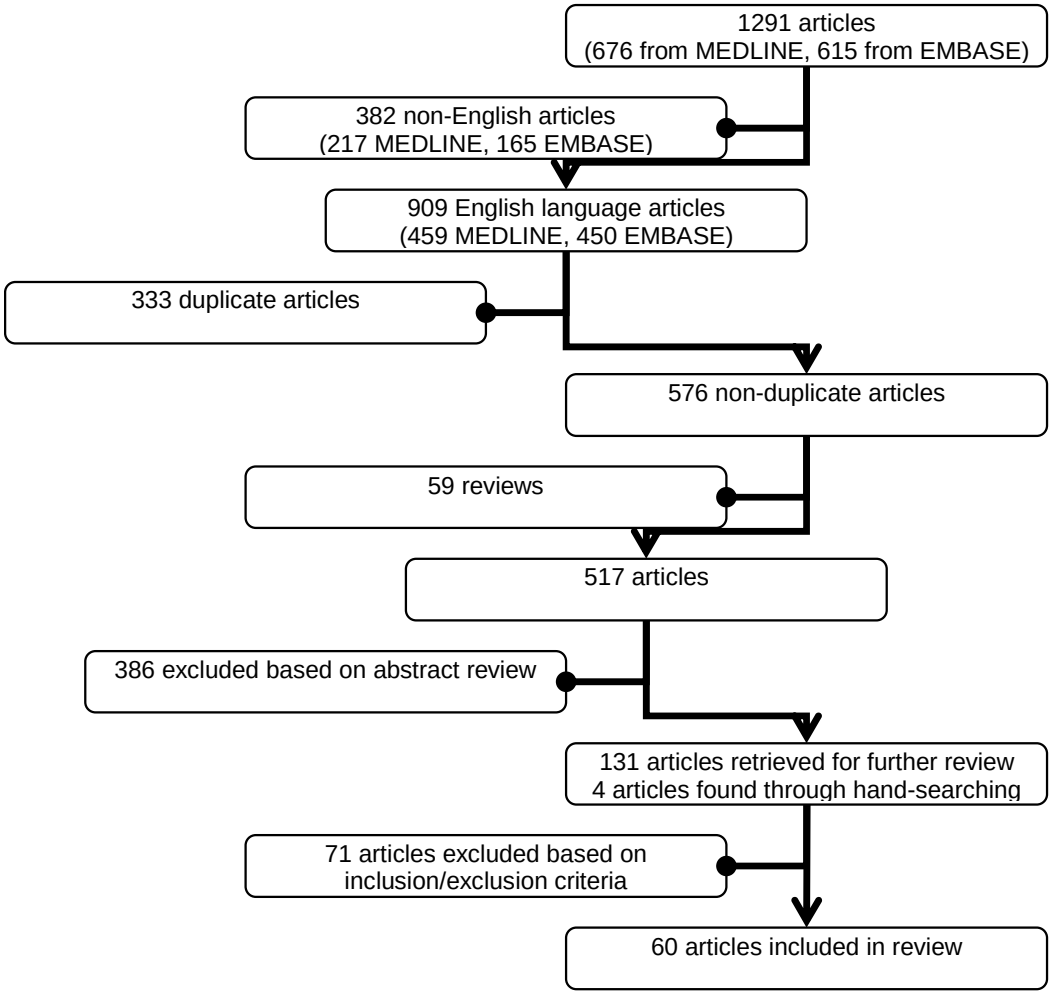
FQ = fluoroquinolone

IQR = interquartile range

Table 2.3: Risk factors for the delay in TB diagnosis

Category	Risk Factor	Positive Risk for Delay (Reference)	Negative Risk for Delay (Reference)
Demographic	Old age	5, 8-9, 17-18, 28, 33, 40, 42, 51, 56, 58	24, 25
	Foreign-born	8, 26, 49, 50	
	Female	3-9, 10, 14, 18, 22, 30, 39, 44, 50, 54, 56	16, 28, 43, 45
Clinical	HIV	4	10, 11
	Negative sputum smears	36, 40, 54	8, 19
	Cough	16, 52, 58	
Psychological	Beliefs and attitudes about TB	5, 14, 20, 37	
	Self-treatment	7, 32, 57	
Socioeconomic	Low income	18, 20, 23, 31, 41-42, 44, 52, 54-55	24
	Low education	7-9, 13, 17, 26, 28, 39, 44-45, 49-50, 52, 54	11
	Rural residence	5-7, 9, 10, 12, 15, 28, 34, 36, 39, 43, 45, 53, 56	
Health care contact	Initial visit to private or traditional practitioner	4-6, 12-13, 22, 30, 32, 37, 45, 51, 53, 55	
	Initial visit to low-level government healthcare facility	4, 6, 10, 13, 16, 22, 28, 41, 45, 51, 57	25
Antibiotics	Antibiotic use	59-62	

Figure 2.1: Flow diagram of studies included in this review



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CHAPTER 3: DOES EXPOSURE TO FLUOROQUINOLONE ANTIBIOTICS DELAY DIAGNOSIS OF PULMONARY TUBERCULOSIS?[†]

3.1 Introduction

Tuberculosis (TB) remains a major public health issue, affecting approximately one-third of the global population.[1] Caused by the pathogen *Mycobacterium tuberculosis*, annually 8.9 million people become infected and over 15 million are prevalent active cases.[1] TB was a major cause of morbidity and mortality in Canada throughout the first half of the 20th century, however rates declined due to improvements in living conditions, control and prevention measures, along with antibiotic therapy in later years.[1] In recent years, due to the increasing prevalence of HIV and the growing emergence of drug-resistant strains, TB continues to thrive, endangering public and population health.

The most common form of TB is pulmonary, accounting for nearly 85% of all cases. Active TB can present features as well as radiological findings that are indistinguishable from those of pneumonia.[2,3] Thus, a significant minority of patients may have atypical radiological presentations which may be confused with community-acquired pneumonia. Initial consideration of TB in the differential diagnosis in a patient with suspected community-acquired pneumonia is obscured by the fact that often patients presenting with TB, especially in the early stages, have non-specific signs and symptoms. Even when the clinician considers the diagnosis of TB and sputum is sent for smear examination, this test will only be positive in 50% of cases with approximately 85% of cases being ultimately culture-positive.[4] Ideally, TB should always be borne in mind when patients present with signs suggestive of community-acquired pneumonia. However, this is often not the case and it is not unusual for clinicians to prescribe a number of courses of antibiotics before the diagnosis of TB is considered, and before either a chest

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radiograph or sputum sample is collected for acid-fast bacilli (AFB) smear and TB culture.[4,5]

As previously mentioned, TB has been treated with combination therapy for almost 50 years, due to the fact that mono-therapy results in the rapid development of resistance and treatment failure. Fluoroquinolones were introduced in the 1980s and are a class of broad-spectrum antimicrobials that function by inhibiting the activity of the enzyme DNA gyrase, which is essential for bacterial DNA replication. Although this class of antibiotics have excellent *in vitro* activity against TB, new respiratory fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin) also have broad-spectrum antimicrobial activity against pulmonary pathogens which cause community-acquired pneumonia.[6-8] Respiratory fluoroquinolones are recommended for the treatment of patients with community-acquired pneumonia by the American Thoracic Society and the Infectious Diseases Society of America.[9] This raises the issue of the potential initial misdiagnosis and subsequent treatment of TB as community-acquired pneumonia. Short courses of fluoroquinolones, as in the case for treating community-acquired pneumonia, do not result in the complete elimination of *M. tuberculosis*, and effective cure of the patient. Despite the potential for initial clinical response, once the fluoroquinolone is discontinued, signs and symptoms of TB recur creating a prolonged course of disease with potentially more complications. Ultimately this could lead to a delay in TB diagnosis, further complicating the disease process.

Delays in the diagnosis and treatment of TB have direct consequences for the affected individual as it postpones the initiation of appropriate long-term anti-TB treatment. It also has the potential to allow ongoing transmission of TB to contacts of such persons. In our study we will evaluate all antibiotic exposures (including fluoroquinolones) and their associated impact on the diagnosis and appropriate treatment of TB. We hypothesize that a relatively short course (fewer than two weeks) of fluoroquinolone therapy or other antibiotics results in a delay in the diagnosis of TB and a delay in initiation of appropriate long-term anti-TB therapy.

The objectives of this study were to determine if use of fluoroquinolones and other antibiotics results in a delay in the diagnosis of TB manifested by:

1. A delay in initiation of anti-TB medications;
2. Increased hospitalization;
3. Increased mortality.

3.2 Methods

3.2.1 British Columbia linked databases

Developed in the early 1990s by researchers at the University of British Columbia (UBC), the BC Ministry of Health and the BC Cancer Agency, the BC Linked Health Database (BCLHD) links longitudinal data across different sources. This database integrates health service records, population health data and census statistics of eligible residents, thereby allowing the possibility of linking administrative records anonymously at the individual level. This is completed through the unique patient identifier (Personal Health Number, or PHN) which permits linkage of data across the various data files and is retained for the lifetime of the individual. Protocols are in place to ensure confidential and accurate linkages, and once this has been completed, randomization of the available PHNs occurred to protect patient confidentiality.

3.2.2 Data collection

For the purposes of this study, we used data from four different data files: three from the BCLHD (PharmaNet, the Medical Services Plan, and the Hospital Separations) and one from the Tuberculosis Control Program, at the British Columbia Centre for Disease Control.

All pharmacies within BC are required to enter drug and dosage information for each prescription into the web-based system called PharmaNet. It captures nearly all dispensing episodes for outpatient residents of BC since January 1997 and contains all drugs dispensed to the individual, any reported drug allergies and clinical conditions and demographic information such as the PHN, name, address and date of birth. Drug information, including dosing and quantity, as well as interaction evaluation data, is also available.

The Medical Services Plan (MSP) data file contains information on patient visits to British Columbian clinicians. Data abstracted included the patient PHN, a single 3-digit diagnostic code (ICD-9) associated with claims, the type of physician and their unique identifier code, fee service codes, and the professional fees paid for each service claim.

Finally, the Hospital Separation data file includes records from all acute-care inpatient separations, day-surgeries, long-term care holding-beds, extended-care beds, rehabilitation beds, and discharge planning units. Patient data includes the individual's PHN, sex, month and year of birth. Four-digit ICD-9 codes are recorded to classify discharge diagnoses.

The other database from which data were extracted is the Integrated Public Health Information System (iPHIS) database within TB Control at the BC Centre for Disease Control. Developed for the surveillance of infectious disease in Canada, it contains information on all patients who have been treated for active TB disease within the province of British Columbia. Access to this information is permitted to designated health care providers and is available through contact with its project coordinator. Data collected from each patient may include PHN, age, sex, ethnicity, HIV and hepatitis status and other chronic conditions, alcohol use, date of presentation to the clinic, symptoms, TB diagnosis and diagnosis site, diagnostic tests performed, treatment regimen, date of initiation, date of prescription fill and refill, changes within that regimen, adverse events, and laboratory tests and results.

3.2.3 Study inclusion criteria

Individuals eligible for inclusion in this study were residents of British Columbia during the study period who had active pulmonary TB as identified through the iPHIS database. The final date for entry into the TB cohort was December 31, 2006 to allow for linkage with the MSP and the Hospital Separations datasets from the BC Linked Health Databases. To permit the examination of data from six months prior to initiation of anti-TB medications, PharmaNet, MSP and Hospital Separations data from January 1, 1997 to December 31, 2006 were examined.

3.2.4 Study exclusion criteria

Excluded from eligibility for health coverage in British Columbia are people whose health care is funded federally, including members of the Royal Canadian Mounted Police and the Canadian Forces, and inmates of federal penitentiaries (accounting for less than 1% of the population). Registered Aboriginals have their hospital and physician services covered under the provincial system, but their prescription drug benefits are covered under a federally-funded program; therefore, no prescription drug information for registered Aboriginals exist in the British Columbia Linked Health Databases.

3.2.5 Study definitions

Initiation of long-term anti-TB therapy: This is the date of initiation of the first anti-TB medication as recorded in the iPHIS database. This typically is a combination regimen of isoniazid, rifampin, pyrazinamide and ethambutol.

Antibiotic exposure: Antibiotic exposure within six months prior to initiation of anti-TB therapy was characterized from PharmaNet records. Antibiotic exposure was classified as

at least one filled prescription for fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin) or non-fluoroquinolone (macrolides, penicillins, sulfonamides, cephalosporins, and others) classes. Exposure groups were classified as no antibiotic prescriptions filled, only fluoroquinolone prescriptions filled, both non-fluoroquinolone and fluoroquinolone antibiotic prescriptions filled, or only non-fluoroquinolone antibiotic prescriptions filled.

Delays were characterized into the following categories:

i) *Health care delay*: This delay was defined as the time interval between the dates that the patient first made contact with the health care system (either physician office visit or hospitalization, or chest radiograph) regarding a respiratory condition and the initiation of anti-TB medication. This outcome was the basis of comparison between antibiotic-exposed individuals (both fluoroquinolone and other antibiotics) and control (those not exposed to antibiotics).

ii) *Antibiotic delay*: This delay was defined as the time interval between the date that the patient filled their prescription for antibiotics (either fluoroquinolones or other antibiotics) and initiation of anti-TB medications. This outcome was the basis of comparison between those exposed to fluoroquinolones, and those exposed to other antibiotics, to determine if fluoroquinolones cause a longer delay due to their intrinsic activity against TB.

Initial health care contact: A period of six months was chosen as the time-window prior to initiation of anti-TB medications as per the literature.[9] The initial health care contact was defined as the date that the patient first made contact with the health care system with a chest radiograph, or through a physician's office as captured by MSP billing codes or hospitalization for the following ICD-9 categories:

i) Acute Respiratory Infections (ICD-9 460-466.1)
ii) Other Diseases of the Respiratory Tract (ICD-9 470-478.9)

iii) Pneumonia and Influenza (ICD-9 480-487.8)
iv) Bronchitis (ICD-9 490, 491)
v) Asthma and Emphysema (ICD-9 492, 493.9)
vi) Bronchiectasis (ICD-9 495)
vii) Other Diseases of the Respiratory System (ICD-9 510 – 519.9)

3.2.6 Data analysis

Patient demographics were matched for all patients with unique Personal Health Numbers (PHNs) in iPHIS and MSP data files who were residents of BC with active pulmonary TB between January 1, 1997 and December 31, 2006. Initial health care contact, initiation of long-term anti-TB therapy and antibiotic exposure within 6 months prior to TB diagnosis was determined for all included patients through the integrated databases, using the aforementioned study definitions as parameters. Sensitivity analyses were performed on all patients in the study cohort (including those patients who were excluded due to an initial health care contact longer than 6 months prior) to assess the robustness of the data. For the excluded patients, for which no initial health care contact date can be determined within 6 months before the diagnosis of TB, a health care delay of 0 was assumed for the analyses.

Relative risks (RR) were calculated with 95% confidence for the time to anti-TB medication by antibiotic exposure (no antibiotic exposure, fluoroquinolone-only, fluoroquinolone and non-fluoroquinolone antibiotics, or only non-fluoroquinolone antibiotics). Separate analyses were performed for both health care and antibiotic delay as described in the study definitions. The mathematical model used was a negative binominal regression to adjust for over-dispersion, with calculated unadjusted and adjusted RRs. The adjusted model factored in the possible confounding factors: age, gender, physician specialty, socioeconomic status, having a chest radiograph and foreign-born status of the patient.[9] All data analyses were performed using SAS version 9.0.

3.3 Results

3.3.1 Patient population

There were 2232 unique patient entries which were found in the linked databases. After patient demographics were matched, 2167 patients remained, of which another 297 patients had to be excluded due to unavailable data regarding treatment start date. Another 326 patients were excluded because they did not have a MSP visit or were hospitalized for a non-respiratory condition, nor had a chest X-ray performed in the six months prior to diagnosis, as per the study inclusion criteria. The final number of patients which were included in the study was 1544. A flowchart of the patient inclusion and exclusion process is shown in Figure 3.1. Patient demographics did not differ between those patients who were included and excluded from the study. The majority of patients were foreign-born (69%) and in the two lowest socioeconomic categories (59%) and included 634 women (41%) and 910 men (59%) (Table 3.1). The mean age for included patients was 51.2 years (SD 21.4).

3.3.2 Delay to initiation of anti-TB medication

Health care delay

The associations for health care delay for the 1544 patients are also shown in Table 3.1. Of the 1544 patients, 414 (27%) received antibiotics, while the remaining 1130 (73%) patients did not. Sex, age (< 35, 35-65, and 65 years and older), foreign-born status and socioeconomic status were not significant factors in health care delay, defined as the time difference between the date the patient first made contact with the health care system regarding a respiratory condition and the initiation of anti-TB medication. However, those who received a chest radiograph were found to be at an increased risk for delay (RR 1.82, 95% CI 1.56-2.13), as well as patients who visited a physician specialist (RR 1.44, 95% CI 1.20-1.74). After adjusting for covariates, it was found that those patients on antibiotics experienced a longer health care delay (adjusted RR 2.10, 95% CI 1.80-2.44) compared to the non-antibiotic group, with a median health care delay of 31.8

days (SD 40.9) for the non-antibiotic group compared to 56.5 days (SD 48.8) for the antibiotic-exposed individuals.

When subdivided by type of antibiotic use for health care delay, it was found that there was no difference between those who received non-fluoroquinolone antibiotics (adjusted RR 1.98, 95% CI of 1.66–2.36), fluoroquinolone-only antibiotics (adjusted RR 2.18, 95% CI 1.43–3.34) and mixed fluoroquinolone and non-fluoroquinolone antibiotics (adjusted RR, 2.36, 95% CI 1.85–3.01) in terms of a delay in diagnosis of TB (Table 3.2).

Furthermore, the delay was seen to increase as the number of antibiotics that were taken by the patient increased. The greatest delay was found in those patients receiving four or more courses of antibiotics (adjusted RR 4.17, 95% CI 2.70-6.44), with a median delay time of 112 days (IQR 53-150). The lowest was in those patients who received only one antibiotic (adjusted RR 1.56, 95% CI 1.30-1.86) with a median delay time of 25 days (IQR 11-57). Accordingly, those who received two (adjusted RR 2.59, 95% CI 1.97-3.41) or three antibiotics (adjusted RR 2.86, 95% CI 1.93-4.24) experienced delays in between, with a median time of 59 days (IQR 36-102) and 67 days (IQR 41-113), respectively (Table 3.2).

To assess the robustness of our data, sensitivity analyses were performed for health care delay (Table 3.4). Included were patients who were initially excluded for the reason that there was not an initial health care contact within the 6 months prior to diagnosis (through MSP or hospitalization visit records), or had a chest radiograph within this time. Therefore, the total number of patients for these analyses was 1870. For the additional 326 patients, a health care delay of zero was assumed. Results of the sensitivity analysis were in accordance with the primary results which indicate fitness of the data. Health care delay was increased in patients exposed to antibiotics (RR 3.53, 95% CI 2.94-4.24) and when subcategorized by antibiotic type, all classes of antibiotics (non-fluoroquinolone only [RR 3.28, 95% CI 2.65-4.07], fluoroquinolone only [RR 4.09, 95% 2.42-6.90]; and mixed fluoroquinolone and non-fluoroquinolone [RR 2.92 95% CI 2.92-5.32]) were found to be significant in delaying diagnosis.

Antibiotic delay

It was found in the linked database that 414 of the 1544 included patients were treated with antibiotics. Of these, 258 patients (62%) received non-fluoroquinolone only antibiotics, while 36 (9%) and 120 (29%) patients received fluoroquinolone-only and mixed fluoroquinolone and non-fluoroquinolone antibiotics respectively (Table 3.5). When adjusting for covariates, results were insignificant for sex, age, foreign-born and socioeconomic status, and physician specialty. Similarly, for antibiotic delay the presence of a chest radiograph was found to be beneficial with regard to earlier diagnosis (RR 0.58, 95% CI 0.46-0.72). Sensitivity analysis for this delay yielded the same results as no additional patients were captured in the database who did not have an initial health contact prior to the investigated 6-month time window for exposure to antibiotics.

3.3.3 Hospitalization and death after treatment

Among patients who did not receive any antibiotics, following the initiation of treatment 96/1130 patients (8.5%) were hospitalized, resulting in 8 deaths (0.71%). In the non-fluoroquinolone group, hospitalization was seen in only 1/258 (0.39%), which did not result in a death. In the fluoroquinolone group, 18/36 patients (50%) of patients were hospitalized following treatment, with three patients dying (8.3%). Finally, in the mixed fluoroquinolone and non-fluoroquinolone group, 9/120 patients (7.5%) were hospitalized following treatment, with two patient deaths (1.7%) (Tables 3.6 and 3.7).

3.4 Discussion

Our results indicate that patients who were prescribed antibiotics prior to the diagnosis of TB experienced a health care delay, as manifested by a delay in the initiation of appropriate anti-TB medication. Furthermore, it was noted that the delay did not only occur among patients prescribed fluoroquinolones, but was seen with any type of antibiotic. Four previous studies have been performed addressing the issue of exposure to

antibiotics prior to the diagnosis of TB and have found similar results to our study.[10-13] While the studies performed by Dooley *et al.* and Yoon *et al.* addressed the use of fluoroquinolones specifically, Wang *et al.* and Golub *et al.* also assessed patients by antibiotic type and found an increased delay that was not specific to the fluoroquinolone class of antibiotics.[10-13] Therefore, as was also the case with our results, it seems to suggest that it is not the anti-tuberculosis effect of fluoroquinolones specifically, as antibiotics where this effect is not seen also resulted in a delay. As suggested by Golub *et al.* the delay may therefore instead be due to the inherent time in taking a course of antibiotics and subsequently waiting for a clinical response.[13] Similarly, a delay was seen in our study when patients saw a specialist or had a chest radiograph. The mean time between the patient's first contact with the health care system and visit to a specialist and/or had a chest radiograph was 45 days (SD 5.2) and 56 days (SD 4.5), respectively. This indicates that the delay may be related to the extra time required for these interventions. When addressing hospitalization and death, similar proportions were seen among the no antibiotic group and the mixed fluoroquinolone and non-fluoroquinolone group. However, a greater proportion of patients who received fluoroquinolones seemed to experience hospitalization and death. One reason could be due to the potential toxic effects of fluoroquinolones, which have been noted to affect the central nervous system and gastrointestinal tract in particular and may be of concern in the elderly population.[14,15] Nevertheless it should be noted that the sample size for this category was the most limited, with only 36 patients, thereby preventing robust conclusions to be drawn.

Compared to the previously conducted studies on this issue, the strengths of our study lie foremost in its large population-based setting with the BC linked database, which has been used in numerous epidemiologic studies of drug use and outcomes.[16] By retrospectively viewing unique patient records in the BC linked database, we were able to include all patients with active TB during our study inclusion period, which resulted in 1544 patients being included based on the defined criteria, the largest sample thus far in regard to assessing the impact of antibiotics on the diagnosis of TB. Furthermore, linkage of the data files allowed us to accurately assess patient demographics, socioeconomic

information from census information as well as hospitalization and physician visits, as categorized by the appropriate and standardized ICD codes. In addition, this allowed us to factor in a number of confounders that have been suggested in the literature to potentially affect the diagnosis of TB, which we were able to adjust for using our mathematical model (sex, age, foreign-born and socioeconomic status, chest radiograph, and physician specialist visit). The large sample size thus provides a more precise effect measure and strengthens the external validity of our study, while the definitions chosen provide a representative clinical situation in the affected population.

However, our study was not without its limitations. The BC linked database does not include prescription information for patients who receive federal health care (although these individuals account for less than 1% of the population in BC). Similarly, registered Aboriginals do not have records in PharmaNet and were therefore excluded as well, although statistics show that they account for 14% of the TB population in BC.[17] In regard to PharmaNet records, information is only present on prescriptions filled and compliance cannot be assessed. However, when analyzing patients who received multiple antibiotics, a positive correlation existed between the number of antibiotics and the increase in delay. Had compliance perhaps been an issue, the results for those patients receiving three or four or more antibiotics would likely have been weaker due to misclassification, which was not seen in our data. Therefore, the increased risk in delay may be due to the increased inherent wait time for the multiple antibiotics.

From the data we were also unable to determine the potential effect of fluoroquinolone mono-therapy and increased resistance, as initial cultures are unfortunately not tested for susceptibility to fluoroquinolones. Of concern is that the development of fluoroquinolone resistance over time may limit the use of this potentially first-line class of anti-TB agents. Such information may have provided further evidence of the harm caused by potentially unnecessary antibiotic prescriptions for patients.

As our study results have shown, delays are associated with the prescription of antibiotics to patients before diagnosis of TB. Such delays also postpone the initiation of

proper treatment and cause unnecessary health risks for not only the patient due to a prolonged disease state, but also the public due to continued transmission by the patient. Bacteriological and histo-pathological tests and chest radiographs should be performed for suspected TB cases by physicians, and the guidelines suggested by the American Thoracic Society should be followed in conducting chest radiographs for community-acquired pneumonia to confirm the diagnosis, before the prescription of antibiotics.[9] Through knowledge translation of these findings, more robust recommendations regarding the prescription of antibiotics in patients with a convergence of lower respiratory chest infection and risks for TB should be considered.

3.5 Conclusion

Our results confirm those of the previous studies that have been performed, however our study is unique in its large Canadian and population-based setting. We found that previous exposure to any type of antibiotic, and not only fluoroquinolones, before diagnosis of TB, causes both a significant health care and antibiotic delay. This delay increases as the number of antibiotics prescribed to the patient increases. From our results, physicians should consider TB in the differential diagnosis in patients presenting with respiratory symptoms, and guidelines for antibiotic use potentially reassessed. Health care professionals should also be educated in the appropriate use of antibiotics in suspect TB cases, as their prescription may delay the diagnosis of TB and therefore appropriate treatment for patients.

Table 3.1: Adjusted health care delay

			Health care delay (days)		Adjusted	
Variable	***n***	***%***	***Median***	***IQR***	***RR***	***95% CI***
ABX						
No	1130	73%	14	3-44	1.00	
Yes	414	27%	41	15–86	2.10	1.80 - 2.44
Sex						
Female	634	41%	23	6–57	1.00	
Male	910	59%	20	6–53	0.91	0.80 - 1.04
Age						
<35 years	404	26%	16	4-51	1.00	
35-65 years	648	42%	18	6-56	0.99	0.84 - 1.16
65+ years	492	32%	25	8-57	1.08	0.92 - 1.28
Foreign-born						
No	478	31%	19	6-50	1.00	
Yes	1066	69%	21	6-57	1.02	0.89 - 1.17
Socioeconomic status						
1st quintile	536	35%	19	5-56	1.00	
2nd quintile	376	24%	21	6-59	1.08	0.91 - 1.27
3rd quintile	226	15%	23	7-55	1.05	0.86 - 1.28
4th quintile	178	12%	18	6-53	1.02	0.83 - 1.26
5th quintile	139	9%	23	5-56	0.95	0.75 - 1.20
Missing	89	6%	19	5-51	0.90	0.68 - 1.20
Chest X-ray performed						
No	409	26%	8	0-42	1.00	
Yes	1135	74%	26	8-57	1.82	1.56 - 2.13
Physician specialist visit						
No	1342	87%	17	4-52	1.00	
Yes	202	13%	39	17-74	1.44	1.20 - 1.74

Table 3.2: Health care delay by antibiotic type

			Health care delay (days)		Unadjusted		Adjusted*	
ABX	***n***	***%***	***Median***	***IQR***	***RR***	***95% CI***	***RR***	***95% CI***
None	1130	73%	14	3-44	1.00		1.00	
Non-FQ only	258	17%	39	16-74	1.68	1.41 – 2.00	1.98	1.66 – 2.36
FQ only	36	2%	35	13-83	1.67	1.10 – 2.55	2.18	1.43 – 3.34
Mixed FQ & non-FQ	120	8%	52	19-105	2.02	1.59 – 2.56	2.36	1.85 – 3.01

** Adjusted for age, sex, socioeconomic status, foreign-born, chest x-ray, physician specialist*

Table 3.3: Health care delay by type and number of antibiotics

			Health care delay (days)		Unadjusted		Adjusted*	
# of ABX	***n***	***%***	***Median***	***IQR***	***RR***	***95% CI***	***RR***	***95% CI***
0	1130	73%	14	3-44	1.00		1.00	
1	254	16%	25	11-57	1.32	1.11 – 1.57	1.56	1.30 – 1.86
2	87	6%	59	36-102	2.24	1.70 – 2.95	2.59	1.97 – 3.41
3	40	3%	67	41-113	2.41	1.62 – 3.59	2.86	1.93 – 4.24
4+	33	2%	112	53-150	3.30	2.13 – 5.10	4.17	2.70 – 6.44

** Adjusted for age, sex, socioeconomic status, foreign-born, chest x-ray, physician specialist*

Table 3.4: Sensitivity analysis for health care delay by antibiotic type

			Health care delay (days)		Unadjusted		Adjusted*	
ABX	***n***	***%***	***Median***	***IQR***	***RR***	***95% CI***	***RR***	***95% CI***
None	1456	78%	7	0-34	1.00		1.00	
Non-FQ only	258	14%	39	16-74	2.16	1.73 – 2.00	3.28	2.65 – 4.07
FQ only	36	2%	35	13-83	2.16	1.24 – 3.75	4.09	2.42 – 6.90
Mixed FQ & non-FQ	120	6%	52	19-105	2.60	1.90 – 3.55	3.94	2.92 – 5.32

** Adjusted for age, sex, socioeconomic status, foreign-born, chest x-ray, physician specialist*

Table 3.5: Adjusted antibiotic delay

			Antibiotic delay (days)		Adjusted	
Variable	***n***	***%***	***Median***	***IQR***	***RR***	***95% CI***
ABX						
Non-FQ only	258	62%	29	10-57	1.00	
FQ only	36	9%	16	4-59	0.75	0.52 – 1.09
Mixed FQ & non-FQ	120	29%	43	13-90	1.27	1.01 – 1.60
Sex						
Female	167	40%	32	9-63	1.00	
Male	247	60%	31	11-65	0.98	0.80 – 1.19
Age (years)						
<35	94	23%	23	8-45	1.00	
35-65	173	42%	26	9-62	1.30	1.00 – 1.95
65+	147	36%	41	14-82	1.48	1.13 – 1.95
Foreign-born						
No	118	29%	30	14-58	1.00	
Yes	296	71%	32	10-68	1.03	0.82 – 1.29
Socioeconomic status						
1st quintile	141	34%	32	11-78	1.00	
2nd quintile	92	22%	37	10-68	0.94	0.72 – 1.23
3rd quintile	64	15%	26	10-62	0.80	0.59 – 1.08
4th quintile	57	14%	23	11-45	0.80	0.58 – 1.10
5th quintile	34	8%	36	8-58	0.95	0.65 – 1.39
Missing	26	6%	27	8-81	0.78	0.50 – 1.21
Chest X-ray performed						
No	115	28%	53	21-98	1.00	
Yes	299	72%	23	8-53	0.58	0.46 – 0.72
Physician specialist visit						
No	341	82%	29	9-62	1.00	
Yes	73	18%	35	20-81	1.14	0.88 – 1.48

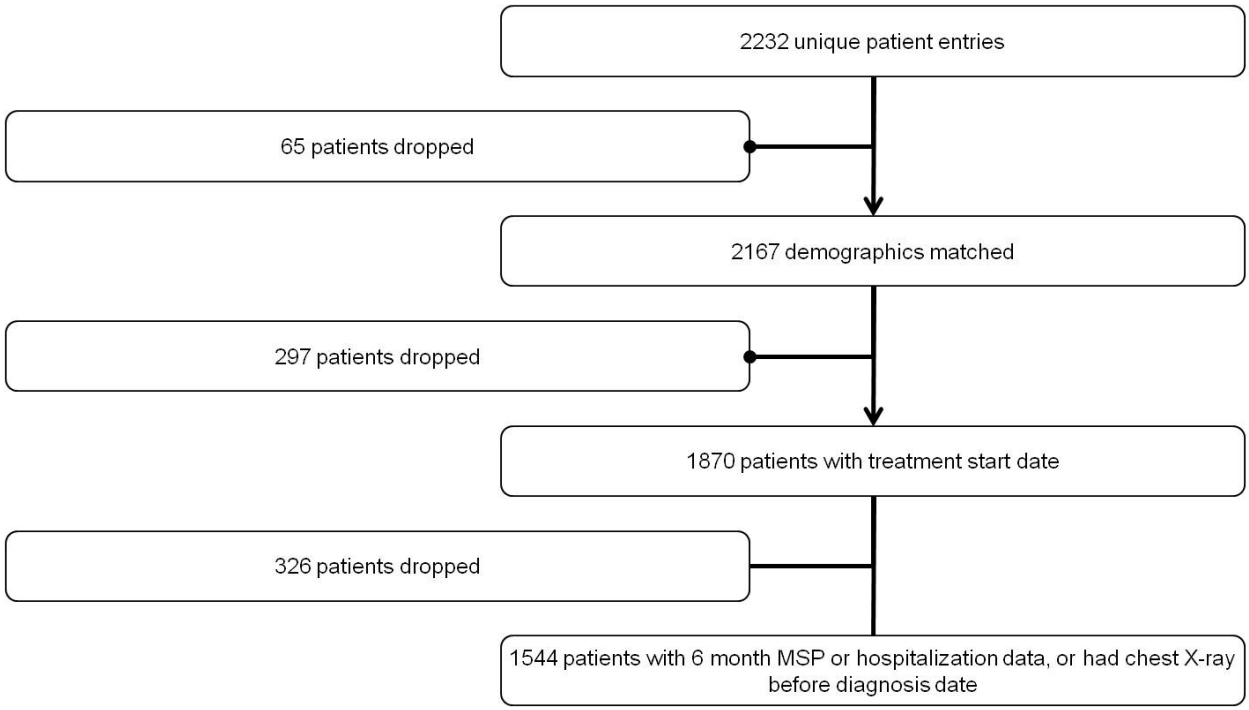
Table 3.6: Hospitalization among patients

			Delay (days)	
ABX	***n***	***%***	***Median***	***IQR***
None	96	8.5%	414	884
Non-FQ only	1	0.39%	1343	1343
FQ only	18	50%	148	877
Mixed FQ & non-FQ	9	7.5%	672	1225

Table 3.7: Death among patients

			Death (days)	
ABX	***n***	***%***	***Median***	***IQR***
None	8	0.71%	62	549
Non-FQ only	0	0%	0	0
FQ only	3	8.3%	23	316
Mixed FQ & non-FQ	2	1.7%	15	969

Figure 3.1: Flowchart of patient inclusion and exclusion process



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CHAPTER 4: SUMMARY, CONTRIBUTION AND RECOMMENDATIONS

4.1 Summary of key research findings

As a major public health issue, the importance of the proper diagnosis of TB and appropriate treatment is central not only to the individual patient, but also to the public, and the control of disease transmission. As established in Chapter 1, TB is primarily a pulmonary disease caused by *Mycobacterium tuberculosis* and is treated with combination antibiotic therapy. Although the incidence of TB has declined in recent years with improved socioeconomic status and the introduction of anti-TB medications, a national rate of 5.2 per 100,000 population is still seen in Canada, with an even higher rate in the province of British Columbia.[1] This thesis aims to address the risk factors in the delay of TB diagnosis, and evaluate the impact of antibiotics, including fluoroquinolones, in this delay.

In Chapter 2, a review was undertaken of the studies that evaluated reasons for delays in diagnosis of TB. An analysis of the risk factors for TB was found to fall into broad categories that ranged from clinical characteristics, demographic, socioeconomic, health care contact and antibiotic-related factors. Being female, elderly, foreign-born, with low education and income, presenting to low-level or traditional health care facilities initially and previous antibiotic exposure have been found to have a role in delaying the diagnosis of TB. Many risk factors are interrelated, or have been suggested by researchers to affect another risk factor in a different category. For example, initial health care contact, which was individually assessed by some researchers, is related to the socioeconomic condition of patients, as those with low education and knowledge will likely present to a traditional healer or to a low-level government health facility, which could also be due to geographical accessibility.[2-4] Likewise, foreign-born status was found to be a signification factor in delay in the majority of studies that included this variable, which could be due to the cultural and language barriers that exist for patients and limit their incentive to seek health care, as well as their accessibility to it. In rural

areas, being female was found to be a risk factor and linked to low education and knowledge of the disease, thereby causing a delay in seeking appropriate health care and delaying diagnosis.[5-6] Furthermore, depending on the severity of initial symptoms of TB, patients differentially presented to health care facilities. The presence of cough was found to be a factor in delay. It was noted by researchers that when patients presented with more debilitating symptoms, a shorter delay in diagnosis was observed, likely due to the more serious implications of those symptoms.[7-9] Aside from the specific risk factors identified as contributing to a delay in the diagnosis of TB, it should be noted that risk factor interactions may also be present, with the potential for creating different underlying incentives to seek medical health care. As such, these risk factors, wherever possible, should be adjusted for in the data analyses to decrease their potential confounding effect on the results of delay.

As mentioned in Chapter 2, previous exposure to antibiotics has been found by other investigators to delay the diagnosis of TB.[10-13] Although TB has been treated with the combination of antibiotics for almost 50 years, the fluoroquinolone class was only introduced in the 1980s. These antibiotics have excellent *in vitro* activity against many pulmonary pathogens, which may lead to the delay of an appropriate TB diagnosis when another differential, such as community-acquired pneumonia, is made initially for patients who in fact have active TB.[14-16] This initial misdiagnosis and subsequent inappropriate treatment (such as single drug prescription for TB) masks symptoms due to the use of a short course of antibiotics, only to have patients present later, thereby causing a delay in the accurate diagnosis of TB. This concern led to our study, in evaluating all antibiotic exposures (including fluoroquinolones) and their associated impact on the diagnosis of TB.

As described in Chapter 3, we designed our study to examine the delay in the diagnosis of TB due to previous antibiotic exposure, addressing the use of fluoroquinolones in particular. For this, the BC Linked Health Database was used, which integrates longitudinal health care data for residents of BC, allowing for the possibility of linking administrative records anonymously at the individual level. Using these data, we

were able to link those patients who were diagnosed with active pulmonary TB during our study period of January 1, 1997 to December 31, 2006 with MSP, hospitalization and PharmaNet dispensing data. Patients were included if they received a chest radiograph or had contact with the health care system, for a pulmonary condition six months prior to the date of the diagnosis of TB. Those patients who have federally-funded health care do not have PharmaNet data within the linked database, and thus were excluded. The exclusion of these subjects is unlikely to be a significant factor in terms of the accuracy of our results as these patients represent less than 1% of study subjects.

We found an increased delay in the initiation of appropriate anti-TB medication among patients who were exposed to antibiotics in general. This delay was not seen for fluoroquinolones specifically. Adjustments were made statistically for sex, age (< 35, 35-65, and 65 years and older), foreign-born status and socioeconomic status, physician specialty and chest radiograph. Furthermore, this delay increased as the patient was prescribed more antibiotics. Sensitivity analyses, with included patients who did not have health care contact or receive a chest radiograph six months prior to diagnosis produced results that aligned with our main analyses. These patients were assumed to have a health care delay of 0, and the similar findings attest to the robustness of our data. This seems to suggest that it is not the anti-tuberculosis effect of fluoroquinolone specifically, as antibiotics where this effect is not seen, also resulted in a delay. Due to access to the provincial administrative database, our study was able to assess this impact on a large scale, which was not performed in the previous studies conducted.

4.2 Study limitations

The limitations of our study were the retrospective nature and our inability to capture those patients with federally-funded health care due to the limitations of administrative data. Therefore, to further elucidate the connection between antibiotics, both fluoroquinolone and non-fluoroquinolone, and their role in the delay of TB diagnosis, large population-based prospective studies need to be performed. As in the

case with retrospective study designs, it may not be possible to infer an association and information may be limited in its presentation due to the lapse in time. Prospective studies of an observational nature will allow for more robust conclusions to be made, and perhaps in a time-dependent manner.

Such as the case for patients included retrospectively, patient recruitment must consider excluding those with underlying respiratory conditions or diseases which may affect their susceptibility to pulmonary pathogens, as that may affect the generalizability of conclusions to be drawn, and ensure a more homogenous study population. Risk factors that fall into the clinical, demographic, socioeconomic and health care contact categories as discussed previously should be noted as these various factors should also be examined in the regression analyses to adjust for their confounding effect. In addition, patient recruitment will allow for investigation of patients' medical records, and interviews and surveys may be conducted with patients to address initial symptoms and verification of medical records. These are not without their biases however, as interviewer and recall bias may be an issue. With multiple interviewers for example, they should be trained beforehand to ensure inter-interviewer consistency in an attempt to minimize this bias. Due to a study's prospective nature, cultures and smears for fluoroquinolone resistance may be possible, as retrospectively information may be inadequate since it is unlikely that all patients will have had these laboratory tests performed. Although researchers found that fluoroquinolone resistance was relatively low in general, exposure for more than 10 days that occurred more than 60 days before the diagnosis of TB was associated with the highest risk for resistance (odds ratio of 17.0; 95% CI 5.1-56.8 compared with no exposure).[17] If similar findings were found, this information could affect the noted antibiotic-related delay, and further attest to the fact that antibiotic use in patients suspected of TB should be carefully considered.

4.3 Knowledge translation

As our study results have shown, increased health care delays are associated with the prescription of antibiotics to patients before the diagnosis of TB. Circulation of this knowledge is imperative as delays in the diagnosis of TB postpones the initiation of proper treatment and causes unnecessary health risks for not only the patient, as a result of a prolonged disease state, but also for the public due to continued transmission by the misdiagnosed and incorrectly treated patient. Within the community, dissemination of information may occur through bulletins and newsletters to health care facilities and research institutions and provincially, through the TB control and surveillance program at the BC Centre for Disease Control. The BC Ministry of Health and likewise Health Canada are also important levels provincially and nationally where information may be conveyed to practicing health care professionals and the public in the form of news releases and advisories.

However, information must be transferred not only to health care professionals in treating patients, but just as importantly to policy makers, researchers and the general public for awareness. The results and conclusions of this study might be properly considered in the assessment and review of the guidelines regarding the use of antibiotics in patients suspected of TB, to form more robust recommendations for the prescription of antibiotics. Policy makers on a national level should have direct contact with both researchers and clinicians in addressing this concern to minimize the potential harm for suspected TB patients as a result of this delay, creating an effective multi-disciplinary environment for discussion and potential implementation.

In terms of the public, particular emphasis should be placed on vulnerable subpopulations, as they are the groups that are most likely to contract TB and therefore potentially be misdiagnosed for another pulmonary disease based on similar symptoms. TB awareness may also be low among these individuals, or certain cultural or linguistic barriers may prevent them from understanding the disease and its implications, as well as

its progression and risk factors. Patients who present with risk factors that are associated with a diagnostic delay should be acutely observed by physicians, with the potential for a differential of TB in mind. Simple, yet accurate knowledge pertaining to TB and antibiotic use should be transferred to these populations in particular, foremost within the city, with the possibility of identifying crucial centres or facilities based on socioeconomic status by region, and continued on the national level in other provinces.

Preliminary results have been presented at the Canadian Association of Population Therapeutics and the American Thoracic Society conferences in poster form, which allowed for not only national and international clinicians to be informed of the results, but also active members of the research community. To further this act of global knowledge translation, study findings will be published academically in a journal of a relevant field of research, such as the International Journal of Tuberculosis and Lung Disease.

4.4 Contributions and impact

As discussed earlier, previous exposure to antibiotics, and fluoroquinolones in particular, has been found by other investigators to delay the diagnosis of TB.[10-13] However, due to their design and approach, these studies were more limited in their patient populations, thereby producing results that are less generalizable and with less power. Due to this, these results may yield less precision and increased bias, as different confounders were addressed by different researchers. Although the design of our study was also retrospective in nature, by using the linked provincial databases, it was possible to capture all diagnosed TB cases at the BC Centre for Disease Control during our study time-frame. Furthermore, adjustments for various confounding factors such as age, sex, socioeconomic status, foreign-born status, physician specialty and chest radiograph were possible due to the linkage of the various data files such as iPHIS and MSP. With PharmaNet, drug dispensing and filled prescription information was available, with data also provided on the types of antibiotics that were taken by each patient. Therefore, it was

possible to additionally examine the contribution of the number of antibiotics taken by the patient in regard to delay in diagnosis of TB, which has not been previously investigated. We found risk of delay to be positively associated, as the number of antibiotics increased. Thus, to the best of our knowledge, our study is the largest of its kind in addressing the concern of previous exposure to antibiotics and its effect on the delay of TB.

As previously discussed, the results and conclusions from our study are not only valuable to health care professionals who treat TB patients directly, but also to the general public and community, researchers and policy makers. Our results further support the evidence in the literature that exposure to antibiotics delays the diagnosis of TB. From our results, it is recommended that bacteriological and histo-pathological tests and chest radiographs be performed for suspected TB cases. Furthermore, physicians should always consider TB as a differential diagnosis when patients present with symptoms that may be related to TB, while being aware of the risk factors associated with the disease. As the initial non-specific symptoms of TB are similar to those of community-acquired pneumonia, another respiratory condition also treatable with fluoroquinolone antibiotics, guidelines suggested by the American Thoracic Society should be followed and a chest radiograph be performed to confirm the diagnosis in the presence of symptoms which might be related to an episode of community-acquired pneumonia or TB, before the prescription of antibiotics.[18] Awareness and knowledge of the delay caused by the prescription of antibiotics, as well as more robust recommendations and guidelines regarding their prescription, are essential in improving health care received by TB patients, by decreasing their risk of a delayed diagnosis, and therefore earlier initiation of appropriate therapy.

4.5 Conclusions

Delays in the diagnosis and treatment of TB have direct consequences in patients as it postpones the initiation of appropriate long-term anti-TB treatment, leading to

continued transmission of disease. A number of factors can lead to a delay in diagnosis of TB. Being female, elderly and foreign-born were found to be risk factors for a delay in diagnosis in the majority of the studies. Likewise, individuals with a low level of education, low income and who lived in rural communities were likely to experience delays. In developing countries, societal beliefs were important and relevant psychologically, as certain stigmas were associated with TB. Clinically, a negative sputum smear and cough symptoms were risk factors, as were initial visits to private, traditional or low-level government healthcare facilities for patients. Few studies addressed antibiotic use, but their results also correlated to increased delay, which provided the rationale behind our study in addressing antibiotic exposure and its effect on TB diagnosis.

Our results align with those of the previous studies that have been performed; however our study is unique in that it uses a large population-based dataset. We found that previous exposure to any type of antibiotic, and not only fluoroquinolones, before the diagnosis of TB, causes a significant health care delay. This delay increases as the number of antibiotics prescribed to the patient increases. From our results, physicians should consider TB as an additional differential in patients presenting with respiratory symptoms, and health care professionals be educated in the appropriate use of antibiotics in suspected TB cases, as their prescription may delay the diagnosis of TB and therefore appropriate treatment for patients.

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