

Improving Latent Tuberculosis Infection Treatment Completion Rates: A Rapid Review of the Evidence

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Table of Contents

<i>Key Take Home Messages</i>	1
<i>Executive Summary</i>	2
<i>1 Issue</i>	4
<i>2 Context</i>	6
<i>3 Conceptual Model</i>	10
<i>4 Literature Review</i>	11
<i>5 Applicability and Transferability</i>	20
<i>6 Recommendations</i>	22
<i>References</i>	23
<i>Appendices</i>	24
<i>Appendix A: Concept Model</i>	25
<i>Appendix B: Literature Search Flowchart</i>	26
<i>Appendix C: Data Extraction Tables</i>	27

Key Take Home Messages

- Latent Tuberculosis Infection (LTBI) treatment completion rates in Peel Region (18.4% in 2010) have been low compared to international rates (60%). Strategies used by Peel Public Health to address this issue have been resource heavy and ineffective.
- Effective physician interventions to increase LTBI treatment completion rates include:
 - Client education,
 - Patient reminder systems,
 - Ongoing education of providers,
 - Patient involvement in treatment decision making,
 - Directly observed therapy (DOT) and
 - Factoring in contextual considerations
- Before any program changes are implemented, a review of the full scope of the issue and the LTBI treatment priority relative to other TB programs must be considered.
- Further investigation of physician and client context within the Region of Peel is required to determine acceptability and capacity prior to the development and implementation of any intervention program.

Executive Summary

The Latent Tuberculosis Infection (LTBI) treatment completion rates in the Region of Peel are lower than the international average. In 2010, of the 717 clients who initiated treatment, only 132 (18.4%) completed treatment. Low LTBI completion rates result in higher risk of developing active TB disease and can contribute to multi-drug resistant TB if active disease has not been adequately ruled out.

In Peel Region, LTBI is diagnosed and treated by primary care physicians within the community. Given their role, they have the most influence on LTBI treatment initiation and completion. This rapid review aims to identify effective strategies that physicians can use to increase LTBI treatment completion rates.

Methods:

Guideline databases and the following bibliographic databases were searched on December 8, 2011 through the Ovid interface: Medline, Medline In-Process & Other Non-Indexed Citations, Healthstar, and the Cochrane Library. The main search concepts were latent tuberculosis and medication adherence. Methodological filters were applied to limit retrieval to English systematic reviews and/or meta-analyses published between 2004 and 2011.

Main findings:

Two guidelines (NICE 2011 & Greenaway et al 2011) and one systematic review (Lutge, 2012) were included in this review. Evidence showed the following interventions were effective in increasing LTBI treatment completion rates:

- *Client education* – including health education counseling, patient centered interview, and health education booklets with the use of a translator if necessary.
- *Patient reminder systems* – including calendar stickers for self-monitoring, phone calls, and letters to increase LTBI treatment adherence.
- *Ongoing education of providers*
- *Patient involvement in treatment decision making* - in immigrant and refugee populations, this may require the use of a translator in order for the client to be able to make an informed decision.
- *Directly observed therapy (DOT)*
- *Contextual considerations*- interventions that address a client’s context has been shown to increase treatment completion rates.

The evidence showed the following interventions not to be effective:

- *Incentives* - for substance users, inmates and adolescents on LTBI treatment, the use of incentives has not increased LTBI treatment completion.

Recommendations

Based on the evidence in this review and the applicability and transferability meeting, the following are recommended:

1. Assess the relative priority of increasing LTBI treatment completion rates with respect to other TB program priorities in order to determine the need for program changes.
2. If changes are needed, collaborate with primary care partners to design interventions that will be effective in increasing LTBI treatment completion rates. Knowledge translation could include sharing with stakeholders what has been learned about interventions identified as effective.

Due to the large number of physicians in Peel Region, utilizing the Region of Peel Healthcare provider website should be considered in the delivery of this knowledge to physicians.

1 Issue

Latent Tuberculosis Infection (LTBI) occurs when a person is infected with *Mycobacterium Tuberculosis* but does not have active disease. During the years of 2009-2011, between 1330-1400 new cases of LTBI have been reported each year in Peel Region. The majority (82%) of LTBI cases in 2010 were identified through routine and immigration screening.

Peel residents are screened for LTBI for a number of reasons, most often because it is required under various federal and provincial legislation. Under these rules, people are screened if they have been exposed to active TB cases, are undergoing medical surveillance, are incarcerated, or intend to participate in school practicum programs such as child care and nursing. People go to primary care providers, their first point of contact in the health care system, to have this screening done. For this reason, LTBI is most commonly diagnosed and treated by family physicians or nurses working in primary care practices. These include detention or student health centres.

Nine months of chemoprophylaxis can provide optimal treatment of LTBI and can prevent active TB by up to 93% (PHAC, 2007). Six months provides 69% protection against developing active TB and is recommended when nine months of treatment is not feasible. LTBI prophylaxis is most effective when over 80% of the prescribed doses are taken (PHAC, 2007, pg 130).

Peel Public Health (PPH) consults with physicians about potential TB cases and collects data regarding clients with LTBI. PPH also provides tuberculosis medication for LTBI free of charge to physicians who then provide the medication and counsel the client. PPH distributes three

months of the nine-month supply at a time of medication to the physician to ensure that the client is routinely monitored for adverse effects.

Internationally, LTBI treatment completion rates are low: current research suggests that the completion rates for six months of Isoniazid therapy is 60% or less (MMWR, 2011). The LTBI treatment completion rates in the Region of Peel are lower than the international average.

Table 1 shows the LTBI treatment outcome for Peel Region during the years of 2009-2011.

Table 1: LTBI treatment completion rates in Peel Region

	Total # of LTBI Clients	# LTBI initiated treatment	# Successfully Completed treatment	# Clients with incomplete treatment	# Unknown¹ treatment status
2009	1330	785 (59.0%)	128 (16.3%)	117 (14.9%)	540 (68.7%)
2010	1330	717 (53.9%)	132 (18.4%)	95 (13.2%)	490 (68.3%)
2011²	1404	634 (45.2%)	102 (16.1%)	47 (7.4%)	485 (76.5%)

Table 1 shows that between 68% and 76% of clients who begin treatment are lost to follow up, and a further 7% to 15% do not complete it. Low LTBI completion rates result in higher risk of developing active TB disease (compared to those who don't take prophylaxis treatment) and can contribute to multi-drug resistant TB if active disease has not been adequately ruled out.

In Peel Region, LTBI is diagnosed and treated by primary care physicians within the community. Given their role, they have the most influence on LTBI treatment initiation and completion. This

¹ Unknown outcome occurs when neither the client nor physician's office notifies PPH that treatment is completed. This category also includes clients with unknown/no reason treatment ended, and "completed as recommended" or "completed-satisfactory" however with no treatment end date. Clients are lost to follow up with PPH; some may also be lost to follow up with their physician.

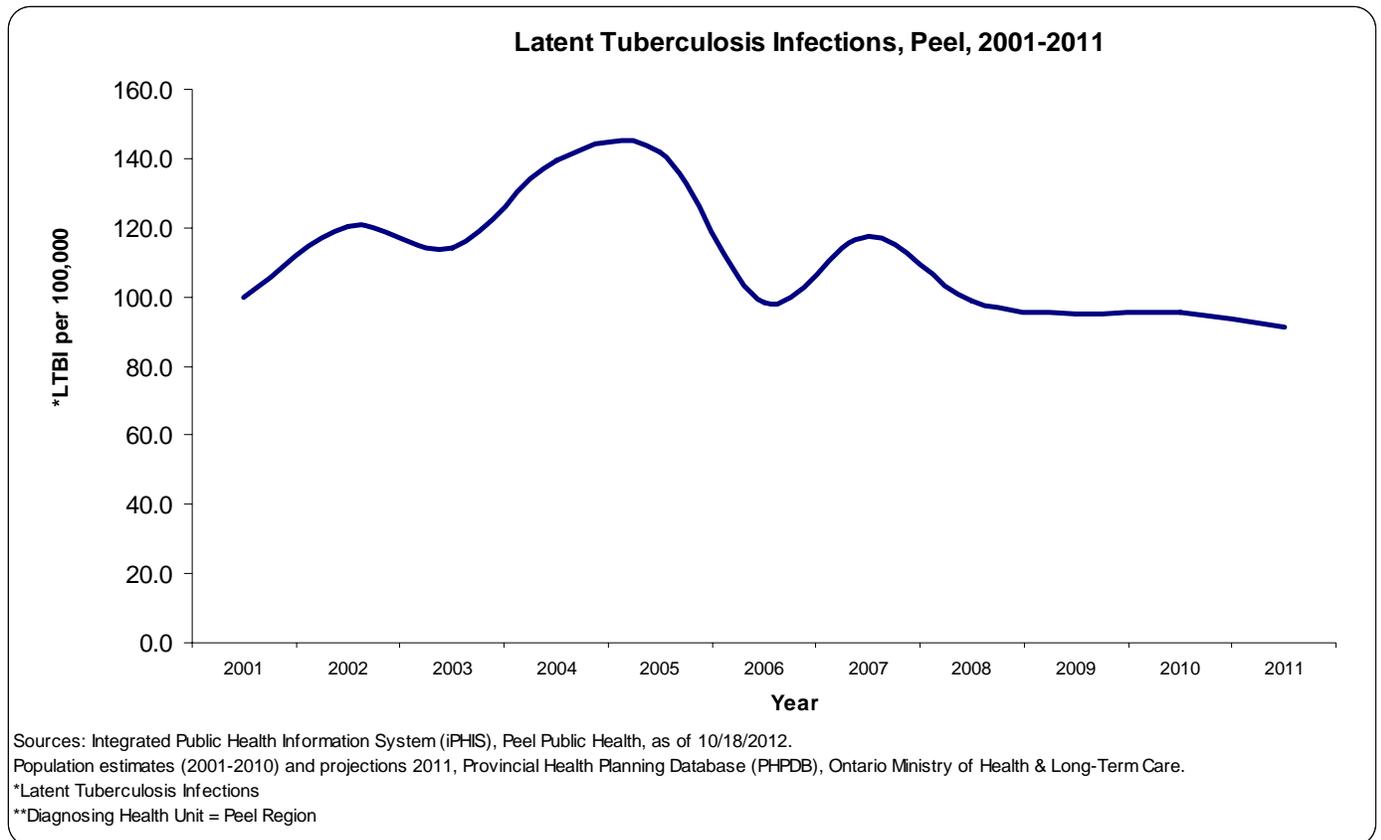
² Accurate as of September 25th, 2012. Due to treatment duration, PPH may not be aware of all treatment outcomes

rapid review aims to find strategies that physicians can use to increase LTBI treatment completion rates.

2 Context

The incidence of LTBI in Peel Region over the past 10 years is shown in Figure 1.

Figure 1: Incidence of Latent Tuberculosis Infections (LTBI), Peel, 2001-2011**



In 2010, more women than men (788 vs. 529, 59% vs. 39.7%³) were diagnosed with LTBI. Both pregnancy and breast feeding may delay treatment for LTBI. Many more women start LTBI treatment than men (457 women vs. 258 men, 64% vs. 36%).

³ In 14 cases (1.3%) the gender is unknown

The age of the LTBI population is predominately within the 19-44 year range (761, 57%) followed by the 45-64 year range (341, 26%). This is the same proportion in the group that started treatment. Older individuals are often not placed on LTBI treatment due to higher risks of hepatotoxicity with increasing age.

Pediatric clients account for 8% (or 110 cases) of the LTBI population in Peel Region⁴. This is significant as children are at greater risk of poorer health outcomes and therefore PPH aims to start as many pediatric clients on prophylaxis treatment as possible. This requires more extensive follow up by PPH which include referring pediatric clients to the Hospital for Sick Children Infectious Disease clinic and telephone follow up with parents and guardians regarding treatment.

From the 2010 data, the most common risk factor for having LTBI was residence in, or travel to, an endemic country (1241, 93.2%)⁵. The top four countries identified were India, the Philippines China and Pakistan (32.2%, 13.0%, 6.2% and 5.9% respectively).

The second most common risk factor was known contact with a confirmed case of active TB (215, 16.2%). The risk of developing active TB disease is highest during the first 2 years after exposure, therefore PPH follow up on treatment more closely by contacting the client regarding the status of their treatment.

⁴ 9% of the population is unknown

⁵ More than one risk factor may have been recorded for each client

Incarcerated individuals make up 6% of the LTBI population⁶. Although correctional facilities are high risk settings due to large number of individuals in a confined space; follow up with these LTBI cases is challenging as time spent in custody varies with individual cases.

Although HIV is the greatest risk factor for LTBI clients to develop active disease, status is not known for this group as the information is not routinely collected by physicians.

For the purposes of this review; four groups (some of the elderly, pediatric, contacts of a confirmed cases and incarcerated individuals) are not considered as PPH follows up with them differently. Removing these groups reduces the LTBI population of interest by around 35%. This is an approximate number as some individuals may have more than one risk factor for exclusion from this review.

There are approximately 840 primary care physicians in Peel region (Gillespie, 2010) working in doctor's offices, walk-in clinics, and community health centres. In 2010, there were 307 physicians who prescribed LTBI treatment to 714 clients. The majority of these physicians (266) prescribed treatment to fewer than five patients. This accounts for over half of the clients on LTBI treatment (400 of the 714). This means that the majority of clients on LTBI treatment are cared for by physicians who infrequently manage LTBI.

The Ontario Public Health Standards (OPHS) outlines PPH's (TB2 Team) role in LTBI management as:

⁶ There are data quality issues due to inconsistent iPHIS entry by referring health units. Anecdotally, we expect that this number is larger.

- to reduce the progression of LTBI to active disease
- identify individuals with LTBI
- offer individuals with LTBI appropriate treatment

PPH role is focused on surveillance and providing medication. With the exception of pediatric and contacts of confirmed cases, PPH have few direct interactions with clients regarding LTBI treatment. Consequently, as in treatment initiation, the decision to continue with treatment is made independently of PPH. The involvement of primary care physicians to improve adherence to TB prophylaxis treatment is recommended by guidelines including *Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and measures for its prevention and control* (NICE, 2011) and the *Tuberculosis: Evidence Review for Newly Arriving Immigrants and refugees* (Canadian Guidelines for immigrant health, 2011).

Low LTBI treatment completion rates can be attributed to a host of reasons: communication barriers, cultural taboos and stigmatization, low client education level, perceived low risk of progression to active disease, belief that a positive TST is due to bacilli Calmette-Guerin, economic factors associated with cost of travel, lack of insurance and missed work days (Greenaway et al, 2011 pg E856).

Recognizing that the prescribing healthcare provider has the most influence on LTBI treatment completion, this rapid review aims to identify strategies that primary care providers can use to increase completion rates. A previous rapid review, “Effectively Communicating with Physicians to Influence Practice” will inform specific strategies to support physicians to increase LTBI treatment completion and ultimately prevent progression of LTBI to active disease.

Anecdote

Filling out three-month drug orders is a day to day activity for the staff of the Tuberculosis Control and Prevention team (TB2). However, in this activity, they are often confronted by a number of scenarios:

- Upon reviewing the client's file, they find that the client already started three months of treatment a couple of years ago, but never finished.
- As they work through the files that have been recalled after three months, they find that no drugs have been reordered for the client
- After calling physicians' offices or clients to follow up on treatment status, they find out that the client stopped prophylaxis treatment months ago, exact date unknown

These situations are frustrating for the TB2 team as they like to take pride in their work in tuberculosis prevention.

3 Conceptual Model

A scoping review identified some of the factors related to long-term medication adherence. The factors were then applied to the LTBI prophylaxis treatment context to develop the foundation for the conceptual model.

The role of primary health care providers in LTBI treatment completion was evident during discussions with the tuberculosis program staff. It was identified that the healthcare provider plays a central role in diagnosing, prescribing, and monitoring during the course of the LTBI treatment. This is presented in the conceptual model that can be found in Appendix A.

4 Literature Review

This review aims to answer the question: “What are the most effective strategies that primary healthcare providers can use to increase latent tuberculosis infection (LTBI) treatment completion rates?”

Applying the PICO framework, our research question is described as:

Population (P) = Primary healthcare providers

Intervention (I) = Activities physicians can do to increase treatment completion

Comparison (C) = Usual practice

Outcome (O) = Increase in LTBI treatment completion rates

Search Strategy

The following grey literature sites were searched: Communicable Disease Control (CDC), World Health Organization, American Thoracic Society, Ministry of Health and Long Term Care, National Institute of Clinical Excellence and the Lung Association. (See Appendix C for more details). Following the review of guideline reference lists to assess publication dates, a search for systematic reviews was conducted to identify more recent and relevant synthesized evidence.

The following bibliographic databases were searched on December 8, 2011 through the Ovid interface: Medline, Medline In-Process & Other Non-Indexed Citations, Healthstar, and the Cochrane Library. Methodological filters were applied to limit retrieval to systematic reviews and/or meta-analyses. Search limits included publications dates between 2004 and 2011 and publications in English. Table 2 shows the search strategy used for this review.

Table 2: Search strategy

1	exp Latent Tuberculosis/ (382)
2	("latent tuberculosis" or "latent TB" or "LTBI").ti,ab. (3084)
3	exp Medication Adherence/ (3795)
4	(complet* or adherence or complian*).ti,ab. (1183020)
5	1 or 2 (3183)
6	meta-analysis.mp,pt. (77469)
7	(search or systematic review or medline).tw. (220399)
8	cochrane database of systematic reviews.jn. (15382)
9	6 or 7 or 8 (260307)
10	exp guideline/ (34846)
11	(practice guideline or guideline).pt. (22050)
12	10 or 11 (34874)
13	9 or 12 (293648)
14	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (1581892)
15	13 not 14 (284352)
16	3 or 4 (1184079)
17	5 and 15 and 16 (34)
18	remove duplicates from 17 (26)

Relevance Assessment

Two reviewers independently assessed the search results for relevance based on title and abstract. The full text of potentially relevant papers was then assessed using the inclusion and exclusion criteria outlined below. Any disagreements were resolved by discussion.

Table 3: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
LTBI Treatment	Active TB treatment
Adult Population	Alternative treatment regime
English language publication	HIV population (if focus of study)
High income country	
Guidelines/Systematic review	
Publication date after 2004	

Search Results

The search yielded 26 results (guidelines and systematic reviews). After the inclusion and exclusion criteria were applied, two guidelines (NICE 2011 & Greenaway et al 2011) were selected for critical appraisal. A recently published systematic review (Lutge, 2012) that was identified following the search was found to be relevant and retrieved for critical appraisal.

Critical Appraisal

Two guidelines and one systematic review were independently appraised for quality by two reviewers. The AGREE II Tool was used to appraise both guidelines and the Health Evidence Quality Assessment Tool (health-evidence.ca, 2010) was used to appraise the systematic review.

Below are the results of the appraisal:

Table 4: Appraisal summary

	Appraisal Tool	Quality
NICE, 2011	AGREE II	Strong
Greenaway et al, 2011	AGREE II	Strong
Lutge et al, 2012	Health Evidence	Strong

All three papers were included in this rapid review.

Included Studies

The focus of this review is to identify effective physician interventions to improve treatment completion. The three included studies assessed a range of interventions and defined treatment completion in a variety of ways. One guideline (NICE) assesses a range of interventions to improve treatment completion of six months of therapy; one guideline (Greenaway et al) assesses a range of interventions to improve treatment adherence, defined as ingestion of 80% of prescribed dosage; and one systematic review (Lutge et al) assesses the effectiveness of incentives to improve treatment completion.

NICE: Clinical Diagnosis and Management of Tuberculosis, and Measures for its Prevention and control

This guideline, developed by the National Institute for Clinical Excellence (NICE), provides guidance to clinicians for all aspects of tuberculosis management, from prevention to diagnosis and the management of active TB disease. The original guideline was developed in 2006; however, the diagnostic section was updated in 2011. The guideline was rated strong in quality by the two reviewers.

The recommendations to improve adherence to LTBI treatment were based on four randomized controlled trials (RCTs) conducted in the United States and on expert opinion. Two focused on adherence counseling interventions that included education sessions, self-esteem coaching, peer counseling and parental contingency contracting within the Latino population in the U.S. Parental contingency contracting involves parents providing incentives to their children for adhering to LTBI treatment. The other two RCTs focused on the use of incentives within the prisoner and the homeless populations in the U.S.

Canadian Guidelines for Immigrant Health: Tuberculosis: Evidence Review for Newly Arriving Immigrants and Refugees

The guideline by Greenaway et al (2011) focused on the burden, treatment and screening of LTBI. The section of interest regarding LTBI treatment adherence strategies was focused on the Canadian immigrant and refugee population. The guideline was rated strong in quality.

The guideline did not make any specific recommendations regarding strategies to improve LTBI adherence, however it did provide a review of the evidence that included one systematic review

and two single studies. This systematic review (Hirsch-Moverman, 2008) was reviewed in greater detail to more clearly describe the interventions. This systematic review included 19 studies assessing the effectiveness of the following interventions: directly observed therapy (DOT), incentives, patient education, professional counseling, peer support and interventions that address contextual circumstances. These contextual circumstances include interventions such as offering methadone treatment and using case managers of the same cultural background as clients.

Cochrane Review: Material Incentives and Enablers in the Management of Tuberculosis

The review by Lutge et al (2012) assessed the effectiveness of different types of incentives and enablers compared to routine care in TB management on the outcome of completed LTBI treatment. The systematic review was rated strong in quality by the two reviewers.

The section focusing on the use of incentives in TB prophylaxis completion was based on three randomized controlled trials (RCTs). All three studies were based in the United States and populations studied included adolescents, substance users or recently released Spanish-speaking inmates.

Synthesis of Findings

Table 5 summarizes the evidence from the two guidelines and one systematic review.

Interventions that have been shown to be effective are indicated with ☑ while interventions that have been identified as ineffective are noted with ☒.

Table 5: Interventions to improve LTBI treatment adherence

	Guidelines		Systematic Review
Title	Nice (2011) Quality: Strong	Greenaway et al (2011) Quality: Strong	Lutge et al (2012) Quality: Strong
Measured Outcome	Treatment completion- 6 months of therapy	Ingestion of 80% of prescribed doses *NOTE: no recommendation grade is given	TB prophylaxis completion: TB cases
Intervention			
Incentives			☑For substance users, inmates and adolescents on LTBI treatment, the use of incentives has not increased LTBI treatment completion. Evidence quality- low ^{1,2}
DOT	☑The use of home visits in LTBI treatment are recommended to improve treatment adherence (Grade D, & expert opinion)	☑ <i>Greenaway</i> - Directly observed therapy is a strategy that can increase adherence to LTBI treatment in immigrant and refugee populations <ul style="list-style-type: none"> ☑<i>HM</i>- Evidence regarding the effectiveness of DOT to improve adherence is mixed. Further research in LTBI treatment context is required 	
Client Education	☑Patient centered interviews and health education provided by healthcare are recommended to improve treatment adherence. (Grade B) Timing of intervention not indicated	☑ <i>Greenaway</i> - ongoing education for clients has increased adherence to LTBI treatment in immigrant and refugee populations <ul style="list-style-type: none"> ☑<i>HM</i>- Education programs reported mixed findings and warrant further investigation in the context of LTBI treatment 	
Patient reminder systems	☑The use of reminder letters in appropriate languages is recommended to improve adherence to LTBI treatment (Grade B)	☑ <i>Greenaway</i> - Calendar stickers for self-monitoring (children) increases adherence to LTBI treatment in the immigrant and refugee population	
	☑Patient diaries (D-GPP) are recommended to improve adherence to LTBI treatment	☑ <i>Greenaway</i> - Phone calls by trained volunteers/health care providers to clients increase adherence to LTBI treatment in immigrant and refugee population	
Ongoing education of providers		☑ <i>Greenaway</i> - Ongoing education of health care providers increased adherence to LTBI treatment in the immigrant and refugee population	
Patient involvement in decision making	☑The involvement of patients in decision making at the onset of treatment is recommended to increase adherence. During the decision making process, there should be an emphasis on the importance of adherence D(GPP)		
Contextual considerations	☑TB services should assess local language and other communication needs and if there is demonstrated need, provide patient information	☑Immigrants & refugees be offered treatment in a culturally sensitive manner and with good access to an interpreter to help improve LTBI treatment adherence	

	accordingly D(GPP)	<input checked="" type="checkbox"/> The use of case managers of the same ethnicity increased treatment completion rates for the immigrant and refugee population	
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NICE classification of recommendations:

Grade B- Based on high quality systematic review or case control or cohort studies. High quality control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal. Directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from high quality meta-analysis, SR of RCTs or RCT with little risk of bias.

Grade D- Based on non-analytic studies (case reports, case series) and expert opinion or formal consensus. It can also be based on extrapolated data from case-control or cohort studies evidence supplemented with health economic modeling.

D(GPP)- A good practice point is a recommendation based on the experience of the Guideline Development Group

GRADE Working Group grades of evidence:

Low quality- Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Other:

¹ Downgraded by 1 for indirectness: These trials were conducted in specific subpopulations from the USA and the result may not be applicable in other settings.

² Downgraded by 1 for inconsistency: Two studies found no suggestion of a benefit with the incentive, and just one study found a clinically and statistically significant benefit in drug users

Two guidelines and one systematic review found the following strategies to be effective in increasing LTBI treatment completion:

Client education

Client education as an intervention to increase LTBI completion rates is recommended by the NICE guideline and discussed in the Greenaway *et al.* guideline. Examples of client education include: health education counseling, patient centered interview, and health education booklets.

Both guidelines emphasize the importance to promote adherence through education in the client’s preferred language (by use of an interpreter if necessary). The evidence rating in the NICE guideline is Grade B and is based on high quality systematic review, case control or cohort studies.

Patient reminder systems

Greenaway *et al.* discusses the use of patient reminder systems such as calendar stickers for self-monitoring, phone calls, and letters to increase LTBI treatment adherence. The NICE guideline

recommends the use of reminder letters in appropriate languages to increase LTBI treatment adherence (GRADE B- based on high quality systematic review, case control or cohort studies).

Ongoing education of providers

This strategy is mentioned by the Greenaway *et al.* guideline. However the details of this intervention are not described in the guideline, the systematic review on which it was based, nor a review of the single studies included in the systematic review.

Patient involvement in treatment decision making

Patient involvement in decision-making regarding treatment initiation is recommended by the NICE guideline. Greenaway et al stresses the need for clients to be informed of the potential benefits and harm of treatment. They emphasize that for the immigrant and refugee populations. This may require the use of a translator in order the client to be able to make an informed decision.

Directly observed therapy (DOT)

The Greenaway *et al.* guideline is based on the Hirsch-Moverman systematic review. However, the evidence found in the Hirsch-Moverman systematic review regarding DOT reports mixed findings on its effectiveness and cautions that further research is required to explore its use to improve LTBI treatment adherence.

Contextual considerations

The following strategies to address contextual circumstances have been found to increase treatment completion:

- providing methadone maintenance among substance users
- using an alias in health charts in clinics serving foreign-born workers in the United States
- using a case manager of the same cultural background

However, the authors of the included Hirsch-Moverman systematic review state that more research is needed to test these strategies for reliability in different settings.

Two guidelines and one systematic review found the following strategies **not** to be effective in increasing LTBI treatment completion:

Incentives

For substance users, inmates and adolescents on LTBI treatment, the use of incentives has not increased LTBI treatment completion. The quality of the evidence used to develop this conclusion was low (Lutge et al, 2012).

Additional Applicability Details from the Literature

- All but one of the studies were American
- The majority of the studies focused on particular high risk groups such as substance users, inmates and underhoused individuals
- The interventions were implemented in the clinic setting and delivered by a range of care providers including physicians, healthcare providers, outreach workers and clinic staff

5 Applicability and Transferability

A meeting was held with the TB program and relevant staff members to discuss the applicability and transferability of the recommendations to improve LTBI treatment completion rates .

Participants included TB program clerical staff, PHNs, supervisors, managers, research and policy analysts, AMOHs, communication specialist and physician outreach specialist.

Applicability (feasibility):

The group felt that the recommended interventions would be viewed favorably within the Region of Peel and by the general public. However, there was less confidence in how this initiative would be perceived by physicians. The current political environment and the ongoing tension between physicians and the provincial government regarding compensation and billing was one of the reasons highlighted. The group noted concerns about motivating physicians to take on an increased workload without additional incentives. This led to discussion about motivational factors and the perceived importance of this issue among physicians and that these factors are unknown to PPH. This gap in knowledge led the group to suggest a needs assessment to determine physician interest and motivation to address LTBI.

Although the interventions were accepted as being effective in increasing LTBI treatment rates, concerns regarding resources, both within Peel region and with physicians and healthcare workers, were raised. Although the recommended interventions could be delivered in a collaborative way with other communicable disease division sections and the physician outreach specialists, there were concerns about front line program staff having the time and capacity to

work with the large number of physicians/HCPs that work with LTBI clients in Peel. However, a member of the group suggested that the initiative might utilize the newly developed healthcare provider website as a vehicle to transfer knowledge related to the identified interventions.

Transferability (Generalizability):

The group agreed that LTBI was a health concern in the Region of Peel as the incidence rates of LTBI are higher than the provincial average. There were expressed concerns regarding how well we actually understand the problem due to issues around reporting treatment completion. The group identified information gaps including reporting issues such as: ‘did physicians and clients know to call in at the end of treatment? How often did they call in at the end of treatment? Was this information captured accurately in our record system?’ They believed that this information was crucial in their understanding of the issue. They also thought that there were a lot of unknown client factors such as the reasons clients completed or discontinued treatment.

The group was concerned about how usable the evidence findings are, given that they focused on a few subgroups that were not representative of Peel’s LTBI population.

Although there were many factors that might support physicians with increasing LTBI treatment completion rates, they wanted more information prior to implementing the effective interventions found in the evidence. The client context was also not fully understood.

The TB program needs to set priorities and assess the relevance and impact of LTBI treatment follow up, since this type of programming has significant workload impact. Capacity within the TB program is currently very limited.

6 Recommendations

Based on the evidence in this review and the applicability and transferability meeting, the following are recommended:

1. Assess the relative priority of increasing LTBI treatment completion rates with respect to other TB program priorities in order to determine the need for program changes.
2. Collaborate with the primary care community to design interventions that will be effective in increasing LTBI treatment completion rates if changes are appropriate. Knowledge translation could include sharing with stakeholders what has been learned about interventions identified as effective.
3. Use and transfer knowledge about effective interventions which include:
 - a. client education through patient centered interviews and health education booklets and if possible, in the appropriate language.
 - b. patient reminder systems to facilitate adherence
 - c. patient involvement in decision making
 - d. interventions that address contextual considerations specific to the patient when providing care
4. Use the Region of Peel Healthcare provider website for the delivery of this knowledge to physicians.

References

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Appendices

Appendix A: Concept Model

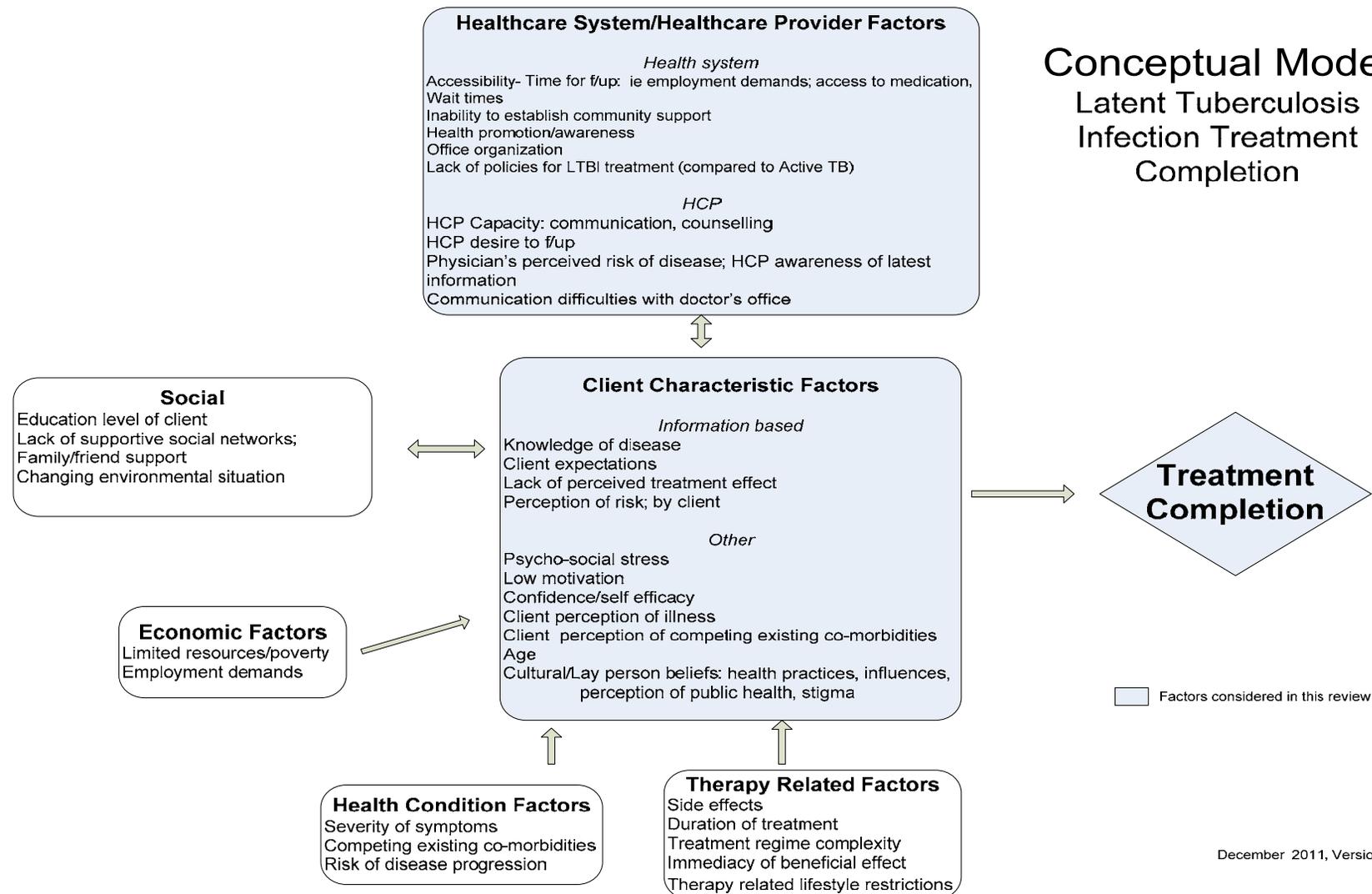
Appendix B: Search Strategy

Appendix C: Literature Search Flowchart

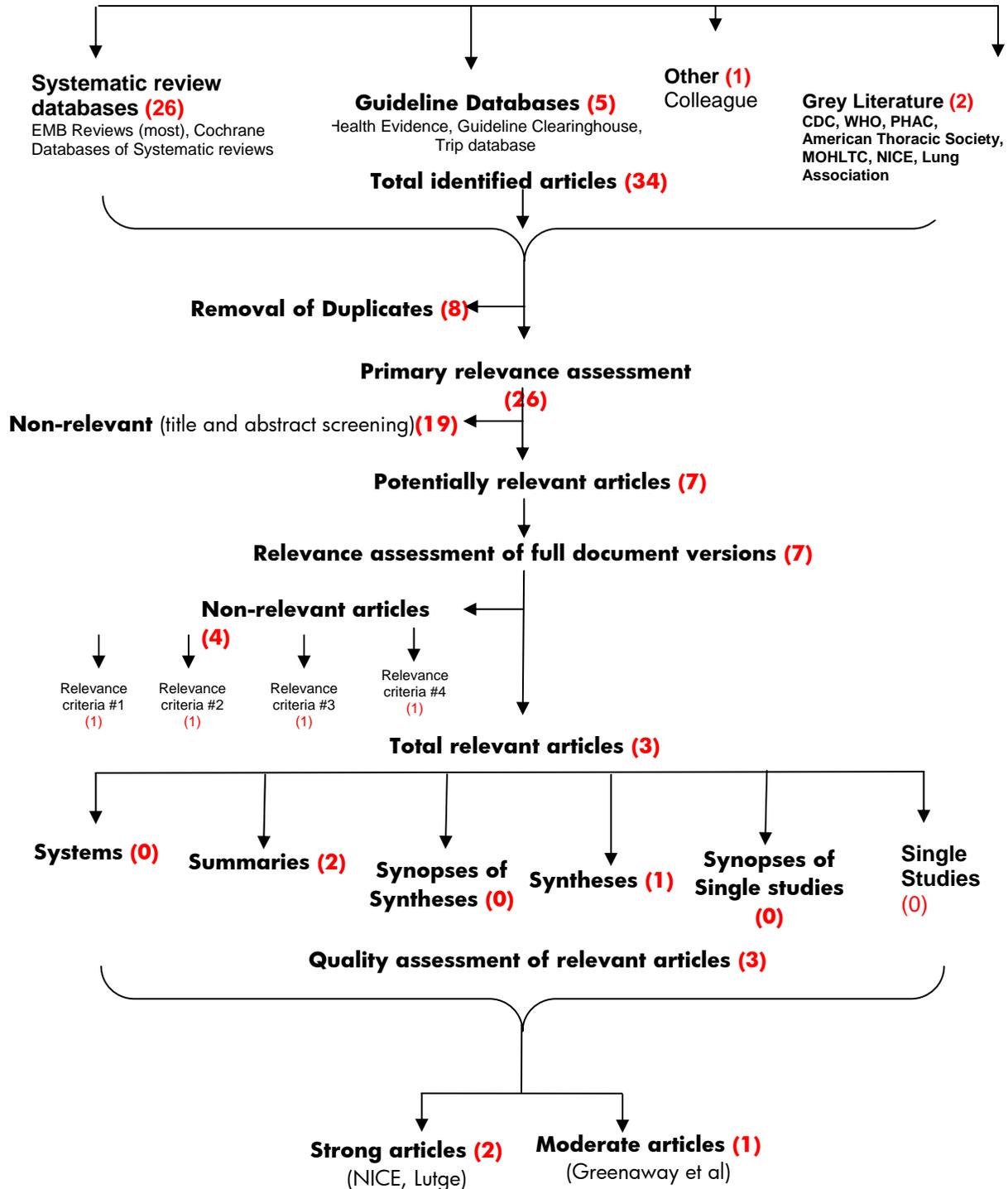
Appendix D: Data Extraction Tables

Appendix A: Concept Model

Conceptual Model Latent Tuberculosis Infection Treatment Completion



Appendix B: Literature Search Flowchart



Relevance criteria: 1. LTBI Treatment 2. Adherence Interventions 3. Post 2007 4. Adult population

Appendix C: Data Extraction Tables

Items Reviewed	Guideline #1 Clinical Diagnosis and Management of Tuberculosis, and Measures for its Prevention and Control (NICE, 2011)
General Information & Quality Rating	
1. Author(s) and Date	National Institute for Health and Clinical Excellence, 2006, updated 2011; however section of interest was not updated
2. Country (individual studies)	USA
3. Quality Rating Using AGREE TOOL	Overall Assessment- Strong Scope & Purpose- 18/21 Stake Holder Involvement- 19/21 Rigour of Development- 46/56 Clarity of Presentation- 16/21 Applicability- 16 /28 Editorial Independence- 12/14
4. Objectives	To identify effective interventions to promote LTBI treatment adherence
Details	
5. Number of primary studies Included for LTBI treatment adherence recommendations	4 Hovell et al, 2003 Morisky et al, 2001 Tulsky et al, 1998 White et al, 2002
6. Types of Studies	RCTs
7. Number of databases searched	7- Medline 1966-2004, Embase 1980-2004, Cochrane (all years), Cinahl 1982-2004, HMIC (all years), PsycINFO 1987-2004, AMED 1987-2004
8. Inclusion and Exclusion Criteria	Inclusion- High methodological quality Exclusion- outcome measure; one study was excluded because the only outcome measure was adherence to first referral. Methodological limitations was another exclusion criteria
Details of Interventions	
9. Description of interventions	Many interventions were examined in the included studies: <ul style="list-style-type: none"> • Hovell et al, 2003- US Latino adolescents living in San Diego on LTBI treatment were assigned to one of the following groups: <ul style="list-style-type: none"> ○ Usual care- Patients had monthly clinic visits for evaluations and prescription renewals or they were provided with 3 months of medication. They could return for refills or if they had experienced symptoms or side effects ○ Usual care with adherence coaching- Bilingual Latino college students or members of the Latino population acted as coaches who provided education sessions about LTBI treatment and assisted with setting adherence goals. These were done through five, 30 minute, in-person sessions (conducted in the patient's home, clinic or other locations) and seven, 15 minute telephone sessions over 6 months. ○ Usual care with self-esteem coaching- Bilingual Latino college students acted as self-esteem counsellors. Counsellors encouraged goal setting and changes in relationships or skills to enhance self-esteem. The self-esteem counsellors

	<p>provided no advice regarding TB counseling</p> <ul style="list-style-type: none"> • Morisky et al, 2001- Adolescents between the ages of 11-19 years living in California were assigned to one of the following groups: <ul style="list-style-type: none"> ○ Usual care- TB clinic staff provided health education assessment of adolescent’s physical health in response to the TB medication. ○ Peer counsellor- Trained adolescents who had completed LTBI treatment provided telephone coaching every 2 weeks to peers who were currently on treatment. Coaching stressed the importance of clinic attendance and medication adherence. ○ Contingency contracting with a parent- With the assistance of clinic staff, parents and adolescents negotiated an incentive plan that the parent would provide to the adolescent if they adhered to treatment. Examples of incentives included: gifts, money and clothes, special meals at home. ○ Combined intervention: Participants in this group received both peer counselling and parental contingency contracting interventions. • Tulskey et al, 2004- Homeless adults living in San Francisco were offered incentives (cash & non-cash) to keep their twice-weekly directly observed therapy (DOT) appointment for 6 months (900mg INH) of treatment or 4 months (600mg Rifampin and 300mg INH) : <ul style="list-style-type: none"> ○ Cash- \$5 cash payment ○ Non-Cash- grocery store coupon, phone cards or bus token, each with face value of \$5 <p>Participants were escorted monthly to a nearby TB satellite clinic for review of symptoms and medication refill. Outreach efforts (letters, phone calls, visits) were initiated if clients missed appointments and stopped after one month of trying to find the client.</p> <ul style="list-style-type: none"> • White et al, 2002- Recently released English/Spanish speaking inmates on LTBI treatment who were encouraged to keep their first follow up appointment were randomized into three groups: <ul style="list-style-type: none"> ○ education every 2 weeks while in jail ○ Incentive- a promise of \$25 equivalent in food or transportation voucher ○ Control group- neither education or incentive provided
10. Intervention provider	Clinic staff (doctors included), nurses, peer counsellors, college students, outreach workers
11. Intervention settings for interested studies	TB clinics in Los Angeles County (Los Angeles County Department of Health, City of Long Beach Department of Health and Human Services), storefront in inner-city San Francisco where the majority of homeless services are provided, TB satellite clinic, San Francisco City and County Jail, participant home
12. Target groups	Latino adolescents living in Los Angeles, USA, adolescents between the ages of 11-19 years, homeless (street and shelter dwelling) and marginally housed (hotel-dwelling) adults, English/Spanish speaking inmates released while still on LTBI treatment
13. Primary Outcomes	Adherence to LTBI treatment
Results	
14. Meta-analysis?	No
15. Main Results (in area of interest-LTBI treatment)	<p>Results of reviewed studies:</p> <ul style="list-style-type: none"> • Hovell et al, 2003- For adolescents of Latino origin on LTBI treatment:

adherence)	<ul style="list-style-type: none"> ○ The adherence coaching group had the highest cumulative mean number of pills consumed and took significantly more pills than members of the usual care and self-esteem groups ($p < 0.05$) ○ No difference in completion rates was detected between the groups that had usual care (37.5%), compared to adherence coaching with usual care (51.1%), or self-esteem coaching with usual care (41.8%). However, the statistical power to detect difference of the observed size was about 0.38, making it unlikely to detect true differences. ● Morisky et al, 2001- <ul style="list-style-type: none"> ○ For adolescents' ages 11-19 years, no differences were found in treatment completion rates for peer counselling, (80.3%) contingency contracting (76.4%), combined peer counselling and contingency contracting (84.8%) and usual care (77.8%). ○ Self efficacy for medication-taking behaviour at post-test correlated strongly with completion of care (correlation $R = 0.367$, $p = 0.002$). Participants randomized to the peer counselling groups demonstrated significantly greater improvements in self-efficacy and mastery than the usual care control group leading to greater medication-taking behaviour. ● Tulsy et al, 2004- There is no difference in LTBI treatment completion rates for the homeless population who received cash incentives (89%) compared to non-cash incentive of the same value (81%) $P = 0.23$ for keeping their twice weekly DOT appointment. ● White et al, 2002- <ul style="list-style-type: none"> ○ Those in the education group were more than twice as likely to complete treatment (adjusted OR 2.2, 95% CI 1.04 - 4.72, $p = 0.04$) than the control group. The treatment completion rates in the incentive group did not significantly differ from the control group (adjusted odds ratio, 1.07; 95% CI 0.47-2.40). <p>NICE Classification of recommendations: B- Based on High quality SR of case-control or cohort studies. High quality case control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal. Directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from high quality meta-analysis, SR of RCTs or RCT with little risk of bias. D(GPP)-A good practice point is a recommendation based on the experience of the Guideline Development Group.</p> <p>In light of lack of evidence regarding LTBI treatment adherence for the general population, the following recommendations to improve active or latent TB infection were made by the NICE Guideline Working Group based on their expertise.</p> <ol style="list-style-type: none"> 1. The patient should be involved in treatment decisions at the outset of treatment. There should be an emphasis on the importance of adherence when discussing treatment initiation- D(GPP) 2. TB services should consider the following interventions to improve adherence for active or latent TB if a patient defaults <ul style="list-style-type: none"> ● Reminder letters in appropriate languages (B)
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	<ul style="list-style-type: none"> • Health education counselling (B) • Patient-centered interview and health education booklet (B) • Home visits D(GPP) • Patient diaries D(GPP) • Urine tests & other monitoring (i.e. pill counts) during visits by a nurse or health visitor D(GPP) • Information about help with paying for prescriptions D(GPP) • Help or advice about where to get social security benefits, housing and social services D(GPP) <p>3. Pharmacies should make liquid preparations of anti-TB drugs readily available to TB patient who may have swallowing difficulties D(GPP)</p> <p>4. TB services should assess local language and other communication needs and, if there is demonstrated need, provide patient information accordingly D(GPP)</p>
17. Comments/Limitations	This guideline was limited to the availability of few high-quality trials. With the studies that were included, the focus has been on the American population raising generalizability concerns. Furthermore, in these studies it is often difficult to assess the contribution of increased attention and motivation from healthcare professional or other individuals, rather than intervention itself, which may have been responsible for the improved outcome.

Items Reviewed	Guideline #2 Canadian Guidelines for Immigrant Health: Tuberculosis: Evidence Review for Newly Arriving Immigrants and Refugees (Greenaway et al, 2011)
General Information & Quality Rating	
1. Author(s) and Date	Greenaway C., Sandoe A., Vissandjee B., Kitai I., Gruner D., Wobeser W., Pottie K., Ueffing E., Menzies D., Schwartzman K., for the Canadian Collaboration for Immigrant and Refugee Health
2. Country	USA & Canada
3. Quality Rating Using AGREE TOOL	<p>Overall Assessment- Strong</p> <p>Scope & Purpose- 19/21</p> <p>Stake Holder Involvement- 20/21</p> <p>Rigour of Development- 40/56</p> <p>Clarity of Presentation- 16/21</p> <p>Applicability- 18 /28</p> <p>Editorial Independence- 14/14</p> <p>This guideline rated poorly in the following criteria:</p> <ul style="list-style-type: none"> • The guideline has been externally reviewed by experts prior to its publication. Recommendations were voted on by the guideline committee & peer reviewed; however it was not reviewed by external experts

	<ul style="list-style-type: none"> No procedure for updating the guideline has been developed to date
4. Objectives of Review (of interest)	<ul style="list-style-type: none"> To identify potential interventions to improve adherence to LTBI treatment in the Canadian Immigrant and Refugee population
Details	
5. Number of included studies	1- Systematic Review by Y. Hirsch-Moverman, A. Daftary, J. Franks, P.W. Colson, 2008 was identified. This systematic review included 19 studies assessing LTBI treatment adherence. An additional 2 single studies (Hovell et al, 2003 & Cass et al, 2004) also assessed completion and adherence.
6. Types of Studies	RCTs and cohort studies
7. Search period of guideline	1950- Dec 17, 2008; Search update-focusing on RCTs and SR Jan 1, 2007-Jan 1, 2010 SR- Jan 1, 1997- December 31 2007
8. Number of databases searched	5 [MEDLINE (Ovid), MEDLINE In-Process, EMBASE, CINAHL, Cochrane Database of Systematic Reviews] <ul style="list-style-type: none"> Searched the following websites: CMA InfoBase, the National Guideline Clearing House, the Canadian Task force on Preventive Health Care, PHAC, Canadian Lung Association, US Preventative Task Force, CDC and Prevention, Infectious Disease Society of America, American Thoracic Society, National Institute for Health and Clinical Excellence, and the WHO SR: 3 [PUBMED, MEDLINE and PsycINFO] Searched reference lists, requested unpublished studies among colleagues, contacted authors of relevant RCTs to request unpublished data on health behaviour variables
9. Inclusion and Exclusion Criteria	<ul style="list-style-type: none"> <u>Inclusion:</u> relevance to immigrant population <u>Exclusion:</u> lack of relevance, poor quality, outdated findings
Details of Interventions	
10. Description of interventions of included studies	<ul style="list-style-type: none"> Hovell et al, 2003- Repeated from previous guideline Cass et al (2004)- Retrospective study of children (14 years and younger and the majority were Hispanic) in San Diego, California on LTBI treatment were assigned to one of the following intervention groups: <ul style="list-style-type: none"> “Treasure chest” program- at the start of treatment, children were provided with a monthly calendar and 30 stickers to put on the calendar each day that medication was taken. When the calendar was completed, the child returned to the clinic and was rewarded with a stuffed animal from the treasure chest. Reminder telephone calls or letters and missed appointment calls or letters. Source case investigation: referrals to public health nurses were made for high-risk patients (children < 5 years of age and/or contacts of active TB cases) who became lost during treatment and who did not respond to missed appointment calls or letters. Completion was considered when the patient attended a minimum of 6 clinic visits <p>Hirsch-Moverman, 2008- This SR reviewed a variety of interventions that included:</p> <ul style="list-style-type: none"> Directly Observed Therapy (DOT), Use of incentives, Education of patients, Interventions that address contextual circumstances,

	<ul style="list-style-type: none"> ○ Professional counselling ○ Peer support for patients.
11. Intervention providers	Prison staff, DOT workers, clinic staff (doctors included) counsellors, nurses, lay person case managers, health care staff, outreach workers, research assistants
12. Intervention settings	Community clinics, jail, pharmacy
13. Target groups	The guideline focused on LTBI in the immigrant and refugee population. The systematic review included: substance users, refugees, Canadian Aboriginals, foreign born factory workers, recently released inmates, jail inmates, homeless and marginally housed populations,
14. Primary Outcomes	LTBI treatment adherence and treatment completion rates
Results	
15. Meta-analysis?	No for LTBI treatment adherence (high heterogeneity on a number of variables across studies, including study designs and outcomes). However, specific recommendations were stated.
16. Main Results	<ul style="list-style-type: none"> ● Hovell et al, 2003- Repeated from previous guideline ● Cass et al, 2005- For children on LTBI children <ul style="list-style-type: none"> ○ Children who received the Treasure Chest intervention were 2.4 more times likely to complete therapy (95% CI 1.68-3.54) ○ No improvement in completion of therapy was seen among patients receiving reminder letters (OR- 0.35 95% CI 0.23-0.52) or calls (OR 0.31 CI 95% 0.22-0.45) ○ Children who received source case investigation were 2.3 times more likely to complete therapy than those who did not (95% CI 1.55-3.50). <p>Hirsch-Moverman SR: No single intervention has shown consistent effectiveness. A ‘one-size-fits-all’ approach to LTBI adherence is not likely to succeed across all settings. Incentives, contextual considerations & professional adherence counselling were successfully applied to improve adherence. However they need to be tested for reliability in diverse settings. DOT, educational programs and peer support reported mixed findings and warrant further exploration in the context of LTBI treatment.</p> <p>The following were identified by the Guideline Development Group as <u>recommended strategies to increase adherence to LTBI treatment</u>:</p> <ul style="list-style-type: none"> ● Patient reminders- Calendar stickers for self-monitoring , phone calls letters & DOT ● Adherence coaches who speak the same language as the patient ● Ongoing education of patient ● Ongoing education of providers ● Cultural case management; adherence to the treatment of latent tuberculosis infection can be increased if delivered in a culturally sensitive manner. <p>NOTE: no recommendation grade is given</p>

17. Comments/Limitations	<ul style="list-style-type: none"> The focus of the guideline was a meta-analysis of the risk of developing active TB, screening for TB in immigrants and refugees. Only a small portion of the guideline was focused on the interventions to increase LTBI treatment adherence. Consideration should be given to developing tuberculosis prevention programs in the context of comprehensive and integrated preventive health care in primary care, where a long-term trusting relationship can be established (Greenaway et al, pg E949)
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Items Reviewed	Cochrane Systematic Review #1 Material Incentives and Enablers in the Management of Tuberculosis (Lutge et al, 2012)
General Information & Quality Rating	
1. Author(s) and Date	Lutge EE., Wiysonge CS, Knight SE, Volmink J
2. Country	USA
3. Quality Rating	Health Evidence Tool -Strong
4. Objective (of interest) of the Review	To assess the effects of material incentives in people undergoing diagnostic testing, or receiving prophylactic or curative therapy, for tuberculosis
Details	
5. Number of primary studies Included	11 studies, 3 individual studies were relevant to this review
6. Types of Studies	RCTs
8. Number of databases searched	3 Cochrane Infectious Disease Group Specialized Register (22 June 2011), Cochrane Central Register of Controlled Trials (CENTRAL: 22 June 2011); MEDLINE (1966 to 22 June 2011); EMBASE (1974 to 22 June 2011); LILACS (1982 to 22 June 2011) ; Science Citation Index (1956 to 22 June 2011), metaRegister of Controlled Trials, WHO International Clinical Trials Registry Platform <ul style="list-style-type: none"> Authors contacted researcher and other experts in the field of TB and adherence research for unpublished and ongoing trials Checked the reference lists of related reviews (Garner 2007; Haynes 2008; Lagarde 2007; Sutherland 2008; Volmink 2000)
9. Inclusion and Exclusion Criteria	Randomized controlled trials of material incentives in patients being investigated for tuberculosis, or on treatment for latent or active disease.
Details of Interventions	
10. Description of interventions	<i>Interventions to encourage the completion of TB prophylaxis: 3 studies (n=869)</i> <ul style="list-style-type: none"> Malotte 2001: Substance users placed on twice weekly DOT were randomized into three different intervention groups: <ul style="list-style-type: none"> DOT by an outreach worker at a location chosen by the client and \$5 incentive per visit Active outreach with no monetary incentive DOT at the study community site and \$5 incentive per visit White 2002: Repeated from previous guideline Morisky 2001: Repeated from previous guideline
11. Intervention Provider	Prison staff, DOT workers, clinic staff (doctors included) counsellors, nurses, health care staff, outreach workers
12. Intervention settings for	<i>Completion of TB prophylaxis:</i> community site, TB clinic, home, telephone

studies of interest	
13. Target groups	People receiving preventative therapy for TB specifically homeless population, recently released prisoners and substance users, adolescents
14. Primary Outcomes	LTBI treatment completion
Results	
15. Meta-analysis?	Yes
16. Main Results of Review	<p><i>Completion of TB Prophylaxis:</i> The quality of the evidence used in synthesis was graded by the GRADE Working Group as low*.</p> <ul style="list-style-type: none"> In 3 trials (869 participants) with substance users, inmates and adolescents on LTBI treatment, the use of incentives had no statistically significant effect on the completion of TB prophylaxis (RR=1.79 95% CI 0.70 - 4.58) compared those who did not receive incentives. <p>*Low Quality- Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate (GRADE Working Group grades of evidence).</p>
17. Comments/Limitations	Few high-quality trials have been completed where there are studies, these are focused on specific populations; raising generalizability concerns.