Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature: _____ _____

Catriona Kinane Date

A systematic review of the rates of completion of treatment and activation of disease in patients found to have latent tuberculosis infections after testing and before placement on Anti TNF-Alpha Blockers

By
Catriona Kinane
MPH

Global Health

_____

Kenneth G. Castro MD
Committee Chair

A systematic review of the rates of completion of treatment and activation of disease in patients found to have latent tuberculosis infections after testing and before placement on Anti TNF-Alpha Blockers

By

Catriona Kinane

Bachelor's of Science
Texas A&M University
2016

Thesis Committee Chair: Kenneth G. Castro, MD

An abstract of A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Global Health
2018

Abstract

A systematic review of the rates of completion of treatment and activation of disease in patients found to have latent tuberculosis infections after testing and before placement on Anti TNF-Alpha Blockers

By Catriona Kinane

Background: Before a patient is placed on tumor necrosis factor (TNF)-alpha blockers (TNFAB) for treatment of rheumatoid arthritis (RA) or other autoimmune conditions, they are screened for latent tuberculosis infection (LTBI). If a patient is found to have LTBI, they are to receive treatment with drugs shown to be effective in preventing progression to TB disease, often given under directly observed therapy. These recommendations by health agencies and professional organizations are meant to protect persons who receive immunosuppressive therapy with TNFAB from the underlying risk of developing active TB disease.

Methods: A systematic review of the literature was done using PubMed to identify English publications with data for completion of LTBI therapy and for TB disease progression in patients who received TNFAB for treatment of their autoimmune diseases. After these publications were identified, the risk ratios activation of TB disease and proportion of completion of treatment were determined using Open Epi software. These results were entered into Stata software, and an overall probability of completion of LTBI therapy and of disease activation was calculated using the formula for risk ratio.

Results: There were high rates of completion of treatment for LTBI. The overall risk ratio of activation of TB if a patient was found to have LTBI was 3.299 with a 95% confidence interval (CI) of 1.195 to 9.105. Patients who were placed on TNFAB and had a positive test for LTBI where at a higher risk of developing TB than those who had a negative baseline LTBI test. However, the overall risk of TB disease, given a person had completed treatment for LTBI was 1.094 (CI 0.402, 2.979).

Conclusions: Those patients prescribed LTBI treatment after a positive screening test (before placement on TNFAB) are likely to complete the treatment regimen. In addition, being treated for LTBI was not associated with a statistically significant risk of progression to active TB, suggesting a protective effect of treatment for LTBI. Results could have underestimated the benefit of LTBI therapy in persons with false-negative tests for LTBI, possibly related to immunosuppression.

A systematic review of the rates of completion of treatment and activation of disease in patients found to have latent tuberculosis infections after testing and before placement on TNF-Alpha Blockers

By

Catriona Kinane

Bachelor's of Science
Texas A&M University
2016

Thesis Committee Chair: Kenneth G. Castro, MD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health in Global Health
2018

Acknowledgements

I would like to thank my family for their constant support throughout my educational career. I would also, like to thank my thesis chair Dr. Castro for his feedback and motivation during this process, Dr. Goodman for his help in Stata analysis and feedback on tables and figures, and Dr. Bednarczyk for his statistics advise. Finally I would like to thank Amelia Jazma for explaining systematic reviews and the process in which to effectively perform one.

Table of contents

Background 1
Methods 5
Results 10
Discussion 12
Conclusion 16
Figures 17
Figure 1: Systematic review flow chart 17
Figure 2 Calculated risk of developing TB in patients treated for LTBI in publications that provided activation data 18
Figure 3 Publication bias for all publications that provided activation data 19
Figure 4 Calculated risk of developing TB in patients treated for LTBI in publications that provided completion data 20
Figure 5 publication bias for developing TB in patients treated for LTBI in publications that provided completion data 21
Tables 22
Table 1A Publications that provide data for disease activation in patients that were found to have LTBI infection compared to those that were found to be negative duration 22
Table 1B Publications that provide data for disease completion for patients found to have LTBI and were placed on treatment 23
Table 1C Publications that provide data for disease completion and activation of disease in patients that were found to have LTBI and were placed on treatment 24
Table 2: risk of reactivation given a person is found to be positive for LTBI with Stata provided statistical test values 25
Table 3: Publication Bias table for Activation of TB disease when comparing Activation in Patients found with LTBI and no LTBI with Stata provided statistical test values 25
Table 4: Filled model of Publication Bias for Activation of TB disease when Comparing Activation in patients found with LTBI and no LTBI with Stata provided statistical test values 25
Table 5: Risk of Activation given a person is Found to be Positive for LTBI with Stata provided statistical test values 26
Table 6: Publication Bias Table for Activation of TB Disease when Comparing Activation in Patients found with LTBI and no LTBI with Stata provided statistical test values 26
Table 7: Filled model of Publication Bias for Activation of TB Disease when Comparing Activation in Patients found with LTBI and no LTBI with STATA provided statistical test values 26

Table 8: Percentile of Completion and Weight of Importance per paper for LTBI Treatment with Stata provided statistical test values 27
References 28
Appendix 1: Open epi outputs 33
Appendix 2: Stata code 39

Abbreviations:

FDA	---------->	Food and Drug Administration
IGRA	---------->	Interferon gamma release assays
LTBI	---------->	Latent tuberculosis infection
TB	---------->	Tuberculosis
TNF	---------->	Tumor Necrosis Factor
TNFAB	---------->	TNF-alpha Blocker
RA	---------->	Rheumatoid Arthritis
WHO	---------->	World Health Organization

Background

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (1). These bacteria can cause human infections and are transmitted from person-to-person through the airborne route. Most commonly TB is transmitted when a person with TB disease of the respiratory system coughs or sneezes, causing these bacteria to become aerosolized. Once aerosolized, the bacteria can spread via airborne droplet nuclei inhaled by susceptible persons during prolonged contact and/or in close proximity. Once infection occurs, most people develop asymptomatic latent TB. Latent TB infection (LTBI) can progress to TB disease (or active TB). This risk of progression is enhanced in individuals who have known risk factors and conditions that result in impairment of the immune system. Immune defects can be congenital, where they are present from birth, or can be acquired or induced by medications that are used to treat other diseases. Most persons with TB disease are treatable with a course of four first line drugs consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol. However, when resistance to these drugs has developed, patients require prolonged treatment with second-line drug regimens (1).

TB is not considered as contagious as other infectious diseases such as measles or varicella zoster; on average a patient who is infectious with TB will infect 3-10 people within one year, with relatively few of these new second generation infections progressing to active tuberculosis (1). According to the World Health Organization (WHO), TB disease is ranked as the 9th leading cause of death, just above HIV infection. It is the leading infectious cause of death in young adults (2). TB can be fatal, even in the absence of complications or the presence of other co-morbid conditions. This global situation has resulted in TB being included as one of the diseases in need of sustained attention and targeted for elimination by 2030 in the United Nations' Sustainable Development Goals (SDGs) (3). Most countries track and report persons

with active TB, the contagious form of this disease. In 2016, there were 9,272 total TB cases reported in all 50 states, giving an estimated incidence of about 2.9 cases for every 100,000 people (4). In contrast, WHO reported 10.4 million persons with TB disease in 2016 (2).The WHO region in the Americas accounted for only 3% of the world's TB incident cases, whereas five countries (India, Indonesia, China, Pakistan, and the Philippines) accounted for 56% of the burden of global TB.

Globally, it is estimated that 1.7 billion persons had latent TB in 2014 (5). This population has the potential to become future cases of TB disease, as a result of the progression from latent TB to active TB. By definition, people with latent TB infection (LTBI) do not have clinical symptoms and cannot spread TB (1). Persons with LTBI can be identified using the tuberculin skin test or approved blood assays (i.e., interferon gamma release assays [IGRA]) (6). In persons at risk for TB, and with a relatively high pre-test probability, a positive result from either test has been accepted as appropriate to determine if a person has LTBI and to guide recommendations for targeted treatment. Persons latently infected with *Mycobacterium tuberculosis*, carry a 5-15% lifetime risk of disease progression to active TB. Underlying co-morbid conditions, such as HIV and diabetes mellitus, have been associated with accelerated disease progression from latent to active TB disease (1). In addition, some drugs which decrease a person's immunity can render them susceptible to opportunistic infections and diseases. One class of these drugs includes the tumor necrosis factor (TNF) alpha-blocking agents (TNFAB). TNF is a cytokine that regulates the immune system (7). TNF mediates its effects by binding to two receptors, TNFR1 (TNF receptor type 1) and TNFR2 (TNF receptor type 2). Although TNF was originally identified as a cytokine that had the potential to induce the death of cancer cells, this effect is considered modest. More recently, it is accepted that its main role is the control of

infections. TNF mediates its effects by activation of macrophages and recruitment of this cell type to the site of the site of infection. Also, it is the cytokine that coordinates granuloma formation, which is an important response by the body to control infections such as TB. Thus, neutralization of this cytokine inhibits the body's ability of control disease progression after initial latent TB infection. In patients treated with TNFAB there is an increased susceptibility to TB (7). These TNFAB class of medications are effective treatments for a variety of autoimmune diseases, but they also induce immunosuppression, and the Food and Drug Administration (FDA) has warranted giving these drugs a black box warning with three alerts: one that it could increase a patient's risk of developing serious infections such as TB, two that the patient has an increased risk of developing lymphoma and other malignancies, and third that there have been a few post market cases of fatal hepato-splenic T-cell lymphoma (7; 8).

TNFABs have been approved for the treatment of rheumatoid arthritis (RA) and other immune-mediated diseases (7). These include a variety of diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and ankylosing spondylitis (9). Some of these drugs include rituximab, etanercept, and certolizumab pegol. Other drugs, such as adalimumab and infliximab, have been approved for treatment in pediatric Crohn's disease patients (7). As prescription of these drugs has become popular, monitoring for side effects is essential (7).

People who receive treatment with TNFABs, and have latent infection due to *Mycobacterium tuberculosis* (LTBI) are at risk of disease progression due to drug-induced immune suppression (10). Compared to the general population, patients with RA in Spain have a 4- fold higher risk for developing TB; the authors were able to define "the magnitude of the problem attributable to the introduction of new therapies in RA" (11; 12). The risk of disease progression, despite being relatively uncommon in the United States, has led to the

recommendations to test for LTBI and, if positive, to treat persons with isoniazid, rifampin, or isoniazid and rifapentine for 3-9 months, before initiating treatment with TNFAB (13; 14). Most of TB disease in RA patients comes from activation of LTBI, not from new TB infection (12). One TNFAB, infliximab, is commonly used; it has been estimated that in the United States 45,000 patients take this drug to treat RA and another 76,000 take it from Crohn's disease (15). Thus 121,000 Americans are potentially at risk of opportunistic diseases.

By testing for LTBI and providing preventive therapy before treatment with TNFABs, it has been estimated that activation TB cases have been reduced by up to 85% (12). Existing guidelines seek to balance the risks associated with TB disease progression against the benefits of receiving immunosuppressive therapy with TNFAB for underlying inflammatory conditions.

Methods

The purpose of this systematic review is to answer, what evidence do we have that people with LTBI would complete recommended treatment for this infection and thus potentially benefit from treatment before placement on TNFABs? A systematic review as performed to answer this question. The focus of this research was to determine the likelihood of completion of LTBI treatment in patients who are being prescribed TNFABs. The following PICO statement was formed. The population (P) are patients being placed on TNF-alpha blockers, the intervention (I) testing for latent TB and then treatment of LTBI before placement on the a full TNFAB regimen, the comparison (C) is with those who did not receive treatment for their latent TB, and the outcome of interest (O) is the occurrence of TB disease in those who received treatment. The lack of occurrence of TB in persons treated for LTBI is interpreted to imply protection against TB disease progression.

Scientific publications in English were searched on PubMed using the EndNote X8.2 interface (Clarivate Analytics) with the terms "tuberculosis and treatment and latent". The entire PubMed library was searched. Also a further search was performed where the order of the terms was changed in order to ensure that no publications were missed; reordering the search words did not have an effect on the output of publications. These terms were chosen to limit the publications to those which included tuberculosis, treatment, and latent tuberculosis infections. The list of publications generated from this search were automatically entered in EndNote X8.2 software using the search portion of the End Note application selecting the PubMed (U.S. National Library of Medicine, National Institutes of Health) search tool in the EndNote (Microsoft® Endnote® x8.2 2006-2013).

These research results were subject to successive reviews (Figure 1). The initial publications were kept if their title included terms related to TB treatment, this includes the words tuberculosis, treatment, name of a drug used to treat TB, or the type of study being done or reviewed. If the title included these terms and contained key words connected to TNF-alpha therapy, such as TNF-alpha, RA, and inflammatory bowel disease, they proceeded to the next step. If the title was a focused on one type of testing such as TST and IGRA but excluded treatment of persons with LTBI, or if a publication is about TB vaccination or if the publication focused on cost, they were excluded from this review.

Abstracts of selected publications were reviewed to determine if the publication addressed treatment of LTBI. If a publication did not state that it tested for LTBI or include patients treated for TB treatment or had some patients with latent TB, the publication was excluded. Once the abstract was read, publications that were case studies or letters to the editor were excluded. Only publications that included data collection or findings in the abstract continued onto the next step.

The final step of the initial view was a full reading of the publication. Published reports were read to determine if they linked treatment with TNF-alpha blockers to testing and treatment for latent TB. If a publication mentioned the link but did not provide data (or a number comparison such as a risk ratio), it was excluded. Other systematic reviews were kept, in order to compare publications used in the analysis and also served to identify other useful references.

After the first search was completed, an additional search was performed with the words TNF alpha blocker therapy and tuberculosis was performed using the End Note interface to search PubMed. An additional 25 publications were found; all 25 proceeded to a full review. After a full review 7 publications were retained based on including data from multiple patients

being placed on TNFABs and being tested and treated for LTBI. One publication was a duplicate from the previous review and was excluded. From this review an additional 6 publications were included with the kept publications to extract data from. After completing both systematic reviews, there were a total of 50 publications. These reports were then divided into two groups, one group consisting of all the cohort studies and clinical trials from which data was extracted and a second group of similar systematic reviews to be used as references. There were a total of 4 systematic reviews and 46 cohort studies and clinical trials.

After reviewing the data provided in the publications, the focus of the research was narrowed to focus on LTBI completion and occurrence of TB disease (interpreted as disease progression). The 50 remaining publications were reviewed; after an analysis for the presence of numerical data (crude numbers) for patients who had developed active TB and/or if there was crude number of patients who completed treatment, only 14 publications were retained. From these publications data were extracted and entered into Table 1.

To calculate completion of treatment, data were extracted from publications into an Excel spreadsheet (Microsoft® Excel®2016). The number of people who completed treatment, the number of people placed onto treatment, and the first authors name were noted. In the excel sheet standard error was calculated. This excel sheet was entered into Stata and a code to calculate the overall completion proportion based off the weight of each study; these data were run by Stata to calculate weighted treatment outcomes (Code Provided in appendix 2).

After the data were extracted and ratios calculated, a meta-analysis was performed to combine the results of the various studies, using pooled results of individual studies, the data from each study was used to calculate the risk ratio, these ratios were put into an excel sheet and run through Stata. In Stata the overall risk ratio along with a 95% confidence interval (CI) was

calculated. Stata calculates the overall confidence interval by providing a weight to each publication based on sample size and study characteristics, and recalculates the weighted 95% CI for each study and a composite estimate with its corresponding 95% CI for pooled studies. Two by two tables were used based on the data provided in the publications. The tables compared screened patients by LTBI status (i.e., infected, not infected) and whether they were diagnosed with TB disease (i.e., TB disease, no TB disease). In cases where there were cells indicating 0 patients in either group had developed TB, that zero value was consistently transformed by a continuity correction of 0.1. The two by two tables were entered into OpenEpi, and risk ratios with confidence intervals were extracted. (Data outputs in appendix 1). OpenEpi calculates a risk ratio and its confidence interval by running formulas coded into the software, that calculate the weight of each paper based on its risk ratio and upper limit of the 95% confidence interval. Based on this ratio, a percentage of overall weight is given to the data in each publication. The overall weighted risk ratio and confidence intervals are then calculated by combining all the risk ratios, confidence intervals, and weights in the various publications. Risk ratios were calculated by dividing the prevalence of TB disease in those with LTBI and treated, divided by the prevalence of TB disease in the group without LTBI (and not treated). Statistical tests included Fischer and mid-p exact tests, Chi squares, and maximum likelihood odds ratio estimates.

The calculated risk ratios were entered into an Excel spreadsheet, and included the authors of the cited reference, and the upper limit of the 95% confidence interval. The excel sheet was entered into Stata/MP™ software (Release 15), and run to calculate an overall 95% confidence interval (Code provided in appendix 2). Stata runs the confidence intervals to determine the weight to assign to each of the studies to determine an overall risk ratio and

confidence interval for the pooled data. The process was repeated limited only to publications that included both completion and activation of disease. These publications were entered into a new excel sheet and the same code was run to determine risk ratios.

In order to calculate publication bias, the excel sheet used for reaction was entered into Stata. To calculate the publication bias random effect and a fixed effect model was run for both a filled and non-filled model (Code provided in appendix 2). Stata runs this code to calculate a filled model to predict if papers were missing due to lack of publication. This is determined if there is a difference in numbers between the non-filled and filled model. This process was run for both the activation and the combination completion activation data sets.

Results

Table 1 shows all 14 publications that were included in this systematic review. These publications came from various counties. There were 5 publications from South Korea, and one publication from each of the following countries: United States, France, Turkey, and Italy. Most publications reported using isoniazid and rifampicin for treatment of LTBI, however there were some differences in the use of LTBI treatment regimens. All LTBI treatment regimens were consistent with existing recommendations.

Overall, the LTBI treatment completion ratio was 0.822, which corresponds to 82.2%. The individual completion rates for individual studies range from 0.177 to 0.966. In four of the studies (Bray, Byun, Hou, and Kurt), all 95% confidence intervals included the value of 1. The lowest completion rate was reported Jo, et al. with a completion proportion of 0.177, with a 95% confidence interval of 0.082 to 0.273. The highest completion rate was reported by Kurt, et al., with a treatment completion ratio of 0.966, and 95% confidence interval of 0.919 to 1.012. Other detailed results are listed in table 5.

The risk ratio for developing TB when comparing people found to have LTBI to those who were found to be negative for LTBI and not placed on treatment was 3.299 with a 95% confidence interval of 1.195 to 9.105. Only three publications (Hou, Jauregul-Amezage, and Kim) did not have the null value of 1 in their confidence interval. The publication by Hou and colleagues had the widest confidence interval, 2.853 to 909655.44. Four of the publications (Bruy, Hou, Jo, and Kurt) had wide intervals of over 100 units in length.

The publication bias test for publication of studies with TB disease progression was established. Table 3 shows what the pooled risk would be for a fix and random effects mode. Fix was found to be 1.365 with a confidence interval of 0.828 to 1.902 and random had a 1.194 with

an interval of 0.178 to 2.209. The filled mode was run, to determine if publications could be missing from the data due to lack of publication. The fix and random effects models stayed the same as the non-filled model. The plot is shown to be symmetric (Figure 3).

When papers that included both completion of therapy and activation of disease were analyzed, the risk of disease progression changed. The risk ratio of disease progression in those patients who completed therapy was 1.094 with a 95% confidence interval of 0.40 to 2.98. This ratio represents the risk that disease activation will happen in a patent that completed LTBI therapy compared to a patient that did not complete treatment or did not have LTBI infection. The publication bias test did not change in the filled and non-filled model. The random effect value was 0.090 with a confidence interval of -0.912 to 1.092 and the fixed effect value was also 0.090 with a confidence interval of -0.912 to 1.092.

Discussion

Present recommendations suggest screening patients for LTBI and treatment, if positive, before being prescribed TNFABs for autoimmune diseases. During the review of the publications, it became evident that the majority of the research has occurred in upper-middle income countries where TNFABs are likely to be used, as these are expensive medications. This systematic review of English language publications suggests that there is a paucity of information from countries where TB is common, and the risk of disease progression associated with TNFAB medications could represent a higher risk of TB disease among those with underlying LTBI. For instance, four publications were from South Korea, and these provided information both on treatment completion for LTBI and reactivation of TB disease. This could reflect a relatively higher prevalence of TB in that country, combined with healthcare resources for TNFAB medications. It is also plausible that this relatively high publication rate reflects interest in TB and access to research funds. The patients in these 4 studies were found either directly through work done by rheumatologists or through patient records; thus patients are derived from populations that seek healthcare. These populations are likely to adhere with LTBI therapy recommendations, as suggested by the published reports.

If the tuberculin skin test is positive, then treatment is recommended with therapy that has been previously shown to protect from TB disease progression (1; 5; 6). A number of studies confirm the appropriateness of this recommendation. However, in two of these studies relatively few persons completed the recommended treatment regimens for LTBI (3.1% and 38.4%). It is unclear why LTBI treatment completion rates were so low in these two studies; both suggest very poor adherence and possibly no added efforts or incentives provided to ensure that patients adhere to the recommended treatment. When the completion rates are low, the personal and

public health benefits of screening and treatment of persons with LTBI prior to being started on TNABs are suboptimal. However, in all the other publications that were evaluated as part of this systematic review, completion of LTBI therapy rates were much more favorable, and ranged from 72.1% to 100%. Future studies should identify what factors promote or limit completion of LTBI therapy. Intuitively, it would appear that reliance on shorter treatment regimens, coupled with either directly observed therapy or other adherence promotion tools, are likely to improve treatment completion, but we were unable to discern these from the published reports.

Our review of the published literature showed that patients who were placed on TNFAB and had a positive test for LTBI were at a higher risk of developing TB than those who had a negative baseline test, as suggested by the risk ratio for developing TB of 3.299 (95% CI 1.195, 9.105. This observation confirms the risk of TB disease progression previously described by other authors in the setting of immunosuppressive treatment with TNFABs. This disease progression could be related to activation of remote latent TB infection or to new LTBI infections with rapid disease progression in high-TB burden country settings. In our systematic review, the specific reasons for TB disease progression are not explained. However, when only reviewing publications that have risk and completion data, patients who had completed LTBI treatment had a risk of 1.09, but the 95% confidence intervals often included 1, the null value. This suggests that, once the treatment is completed, the risk of developing TB is not statistically different from that observed in the uninfected population. The benefit of treatment is suggestive, but not conclusive. Previous publications have demonstrated that for LTBI therapy to be fully effective, the complete course of treatment should be administered and taken by the patient. This report must clarify that the observed excess risk of TB disease in persons with LTBI is not seen in those who complete treatment for LTBI. Based on the pooled 95% CI, the observed risk of

developing TB in persons with LTBI who completed the recommended therapy became indistinguishable from the risk observed in someone who did not have underlying LTBI.

On a societal basis, it is beneficial to patients and their community to limit TB disease progression that is associated with the use of TNFAB therapy. Efforts to design and implement uniform recommended guidelines are warranted. Presently available recommendations should reduce the suffering and disease burden in these patients, and the risk of TB disease progression. Efforts to facilitate and monitor adherence to therapy are also essential.

There are limitations to this systematic review. A major factor that can affect the observed results is that we limited our review to English language publications. Exclusion of non-English language publications introduces observation bias, because any published reports in language other than English were omitted from this systematic review. This is especially concerning when we take into consideration that the largest burden of TB disease in the globe occurs in countries where the main language is other than English. Also, a more objective approach to systematic review requires a number of different data reviewers. A single reviewer may be introduce bias during inclusion and exclusion of published reports.

A strength of this meta-analysis is the identification of the need for better designed studies. In such clinical trials, interferon-gamma release assays (IGRAs) would be used to establish LTBI in settings where BCG vaccination and cross-reactivity with non-tuberculosis mycobacteria could yield false-positive tuberculin skin tests. A prospectively designed study could also compare the risk of disease progression in persons who have a negative IGRA result and thus provide an estimate of risk of TB disease in the population studied. In the absence of a gold standard, it is impossible to ascertain the false negative LTBI results that could occur as patients with rheumatological and inflammatory bowel disease are treated with a variety of

immunosuppressive therapies. Knowing the difference between true and false positive results is important to understand the accurate rates of TB disease progression. In high burden TB countries, others with true negative IGRAs could become subsequently infected with LTBI and remain at risk of TB disease progression in the absence of effective preventive therapy. As stated previously, the added specificity provided by IGRAs could help reduce the numbers needed to screen for beneficial LTBI therapy before starting TNFAB treatment regimens in future studies.

Conclusion

Ethically, doctors take an oath to do no harm. In this case when it comes to treatment of LTBI, the focus is on finding and treating persons with these infections to prevent long term harm. In settings where the risk of disease progression is high as occurs with TNFAB-mediated immunosuppression, finding and treating persons with LTBI is warranted. Recommended treatments have some known side effects. Based on this systematic review, it was observed that most patients who are found to have LTBI and prescribed treatment, are likely to complete the recommended treatment regimens – as evidenced by the calculated statistically high completion proportions. However, data about diagnosis of LTBI and overall disease progression is inconclusive and limited. In the end it is better to protect the patient and treat the preexisting LTBI. This treatment appeared to be useful and accepted, but does not eliminate all risk of disease progression.

Figures

Figure 1: Systematic review flow chart

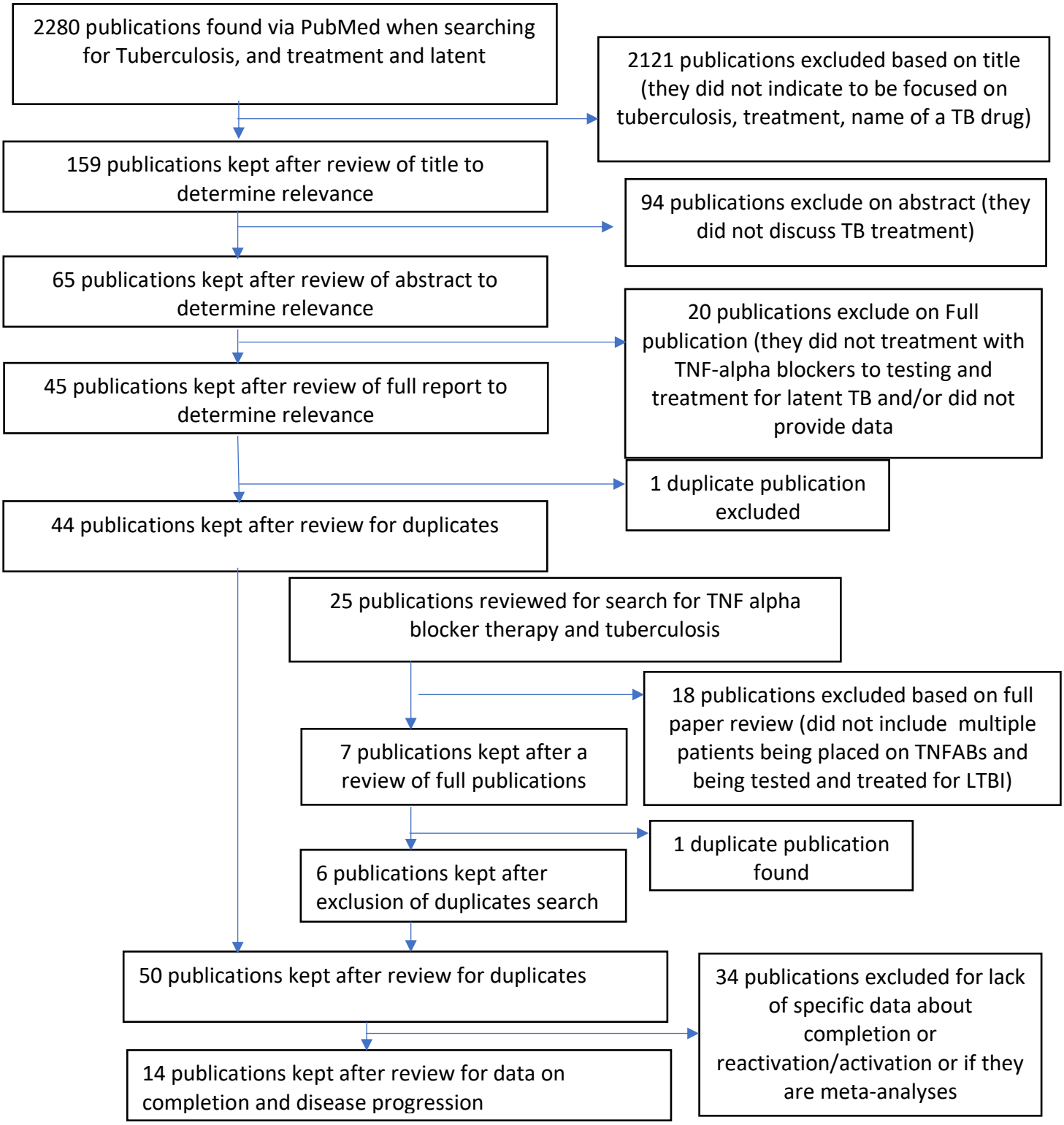
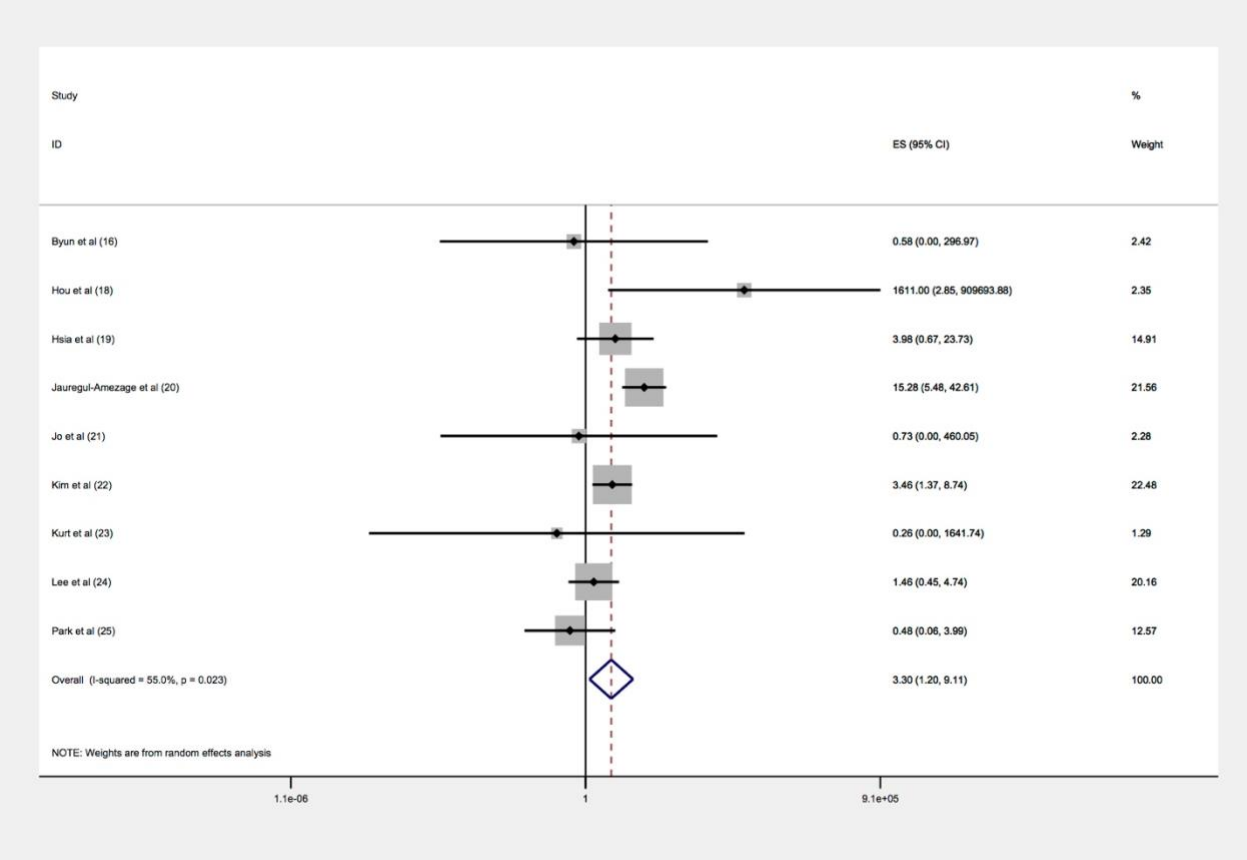


Figure 2 Calculated risk of developing TB in patients treated for LTBI in publications that provided activation data



The x-axis for this graph is the risk ratio.
ES stands for effect size, which in this case is presenting a risk ratio

Figure 3 Publication bias for all publications that provided activation data

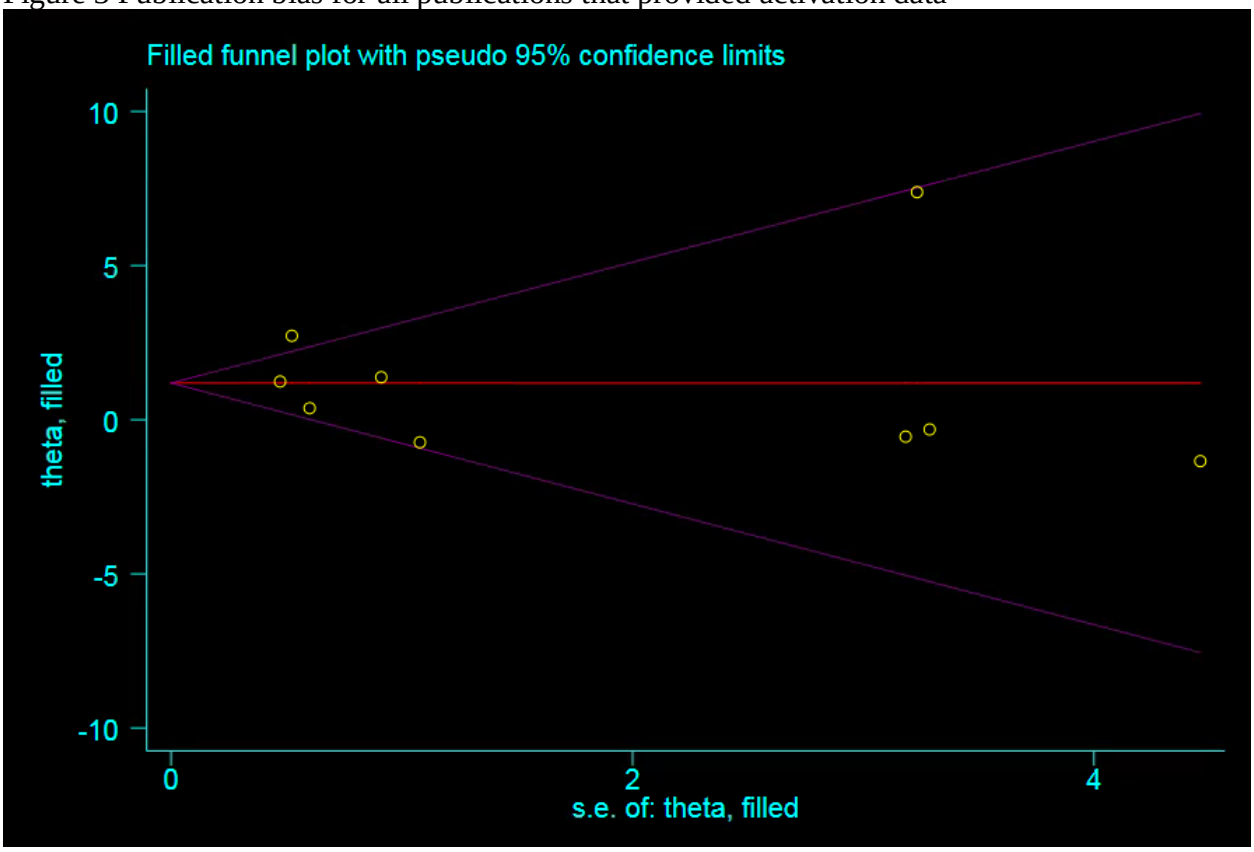
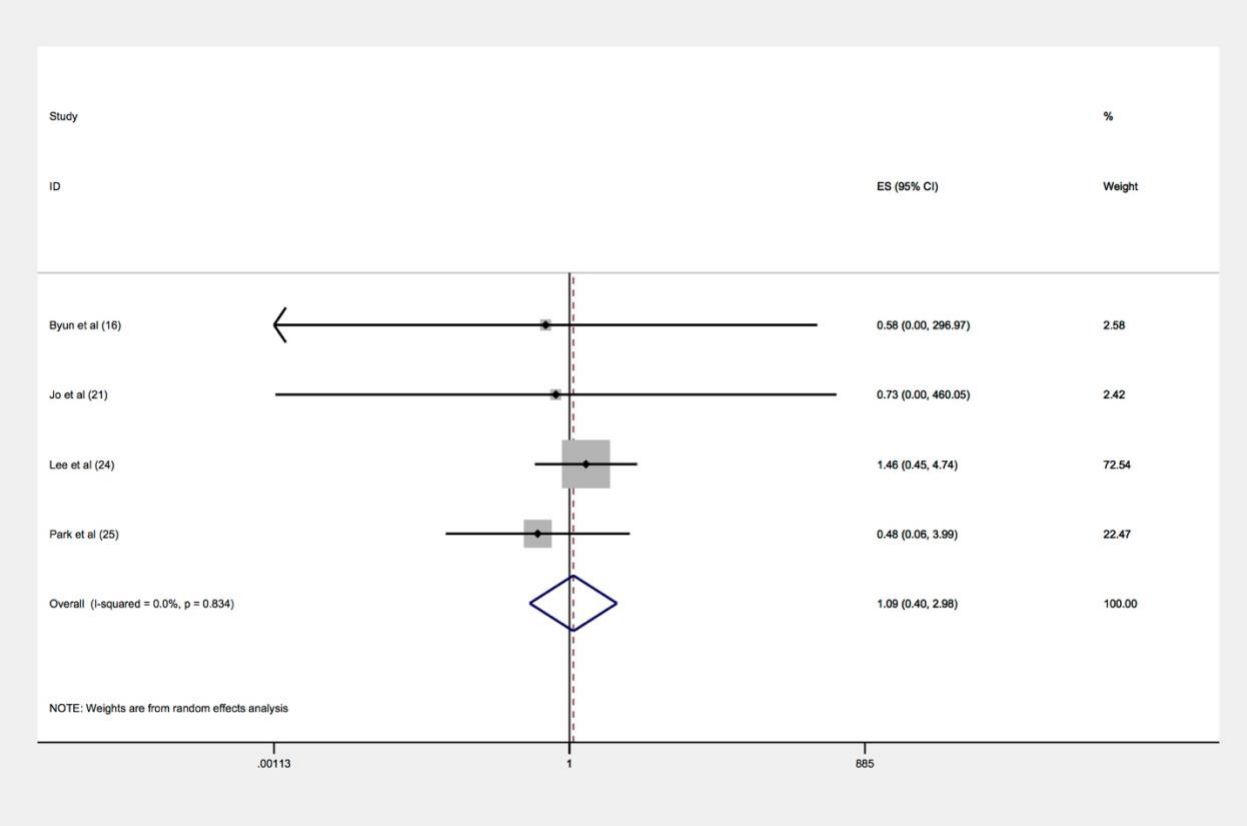
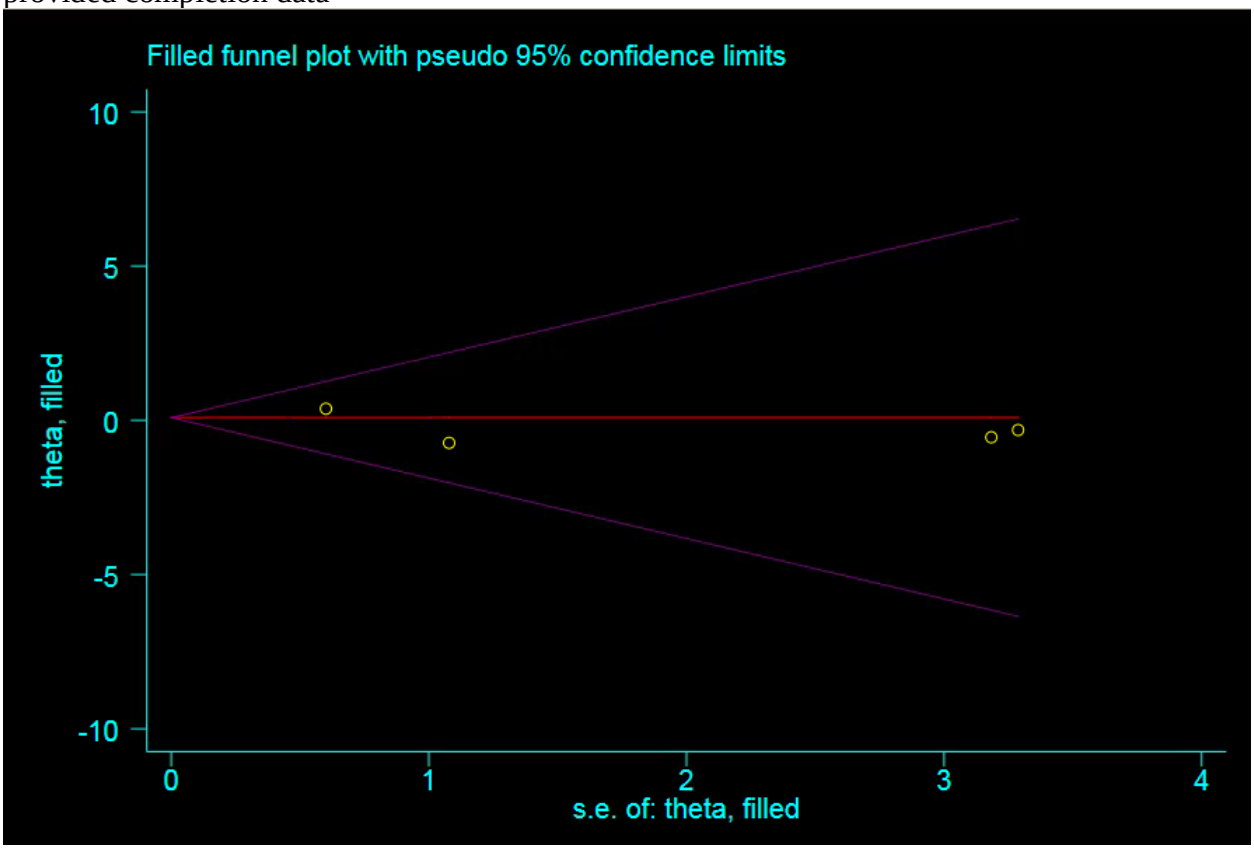


Figure 4 Calculated risk of developing TB in patients treated for LTBI in publications that provided completion data



The x-axis for this graph is the risk ratio.
ES stands for effect size, which in this case is presenting a risk ratio

Figure 5 publication bias for developing TB in patients treated for LTBI in publications that provided completion data



Tables

Table 1A Publications that provide data for disease activation in patients that were found to have LTBI infection compared to those that were found to be negative duration

Authors	Location	Year published	Sample Size	Number of patients with LTBI	Length of LTBI treatment	Number that completed LTBI treatment	Number of cases with TB disease progression (Found to have LTBI and treated/ found not to have LTBI and not treated))
Byun et al (16)	South Korea	2015	525	17	INH	9 months	0 / 5
Cantini et al (17)	Italy	2016	39353	N/A *	INH/RIF	3-9 months	192
Hou et al (18)	United states	2017	3357	43	Isoniazid	6-9 months	2/0
Hsia et al (19)	Global studies; evaluated using US guidelines	2013	2210	317	isoniazid	At least 6 months	2 / 3
Jauregul-Amezage et al (20)	Spain	2013	423	30	INH/RIF, INH	4-6 months	7 / 6
Jo et al (21)	South Korea	2013	101	11	Rif, INH/RIF, INH	3-9 months	0 / 1
Kim et al (22)	South Korea	2015	376	16	Rif, INH/RIF, INH	3-9 months	4 / 26
Kurt et al (23)	Turkey	2013	73	58			0
Lee et al (24)	South Korea	2017	702	219	INH	9 months	5
				27	INH/RIF	3 months	0
				Total: 255			5 / 6
Park et al (25)	South Korea	2015	1589	61	INH	9 months	N/A
				139	Rif	4 months	1
				208	INH/RIF	3 mounts	0
				Total 408			1 /6

Table 1B Publications that provide data for disease completion for patients found to have LTBI and were placed on treatment

Authors	Location	Year published	Sample Size	Number of patients with LTBI	Drugs for treatment of LTBI	Length of LTBI treatment	Number that completed LTBI treatment
Bray et al (26)	France	2010	1028	216	INH/RIF	3-months	83 (38.4%)
Byun et al (16)	South Korea	2015	525	17	INH	9 months	16 (94.1%)
Cantini et al ** (17)	Italy	2016	39353	N/A *	INH/RIF	3-9 months	317 (N/A**)
Jo et al (21)	South Korea	2013	101	11	RIF, INH/RIF, INH	3-9 months	11 (100%)
Lee et al (24)	South Korea	2017	702	219	INH	9 months	186 (84.9%)
				27	INH/RIF	3 months	26 (96.3%)
				Total: 255			246 (96.5%)
Lopes et al (27)	Brazil	2011	68	45	INH	6 months	41 (89.1%)
Munoz et al (28)	Spain	2015	726	237	INH	9 months	221 (93.2%)
				6	RIF	4 months	6 (100%)
Park et al (25)	South Korea	2015	1589	61	INH	9 months	44 (72.1%)
				139	RIF	4 months	112 (80.6%)
				208	INH/RIF	3 mounts	176 (84.6%)
				Total 408			362 (88.7%)
Vallis et al (29)	Spain	2015	78	69	INH/RIF	3 months	60 (87.0)

* Provides percentage of Rheumatologist that screen but not number of patients found to have infection

**this study was a questionnaire of 449 rheumatologists, the percent of patients who completed treatment could not be calculated since the denominator of number of patients with LTBI was not provided in the publication.

Table 1C Publications that provide data for disease completion and activation of disease in patients that were found to have LTBI and were placed on treatment

Authors	Location	Year published	Sample Size	Number of patients with LTBI	Drugs for treatment of LTBI	Length of LTBI treatment	Number that completed LTBI treatment	Number of cases with TB disease progression (Found to have LTBI and treated/ found not to have LTBI and not treated)
Byun et al (16)	South Korea	2015	525	17	INH	9 months	16 (3.05%)	0 / 5
Jo et al (21)	South Korea	2013	101	11	RIF, INH/RIF, INH	3-9 months	11 (100%)	0 / 1
Lee et al (24)	South Korea	2017	702	219	INH	9 months	186 (84.9%)	5
				27	INH/RIF	3 months	26 (96.3%)	0
				Total: 255			246 (96.5%)	5
Park et al (25)	South Korea	2015	1589	61	INH	9 months	44 (72.1%)	N/A
				139	RIF	4 months	112 (80.6%)	1
				208	INH/RIF	3 mounts	176 (84.6%)	0
				Total 408			362 (88.7%)	1

Table 2: risk of reactivation given a person is found to be positive for LTBI with Stata provided statistical test values

Study	ES	95% confidence interval		% Weight
Byun et al (16)	0.579	0.001	296.966	2.42
Hou et al (18)	1611.000	2.853	9.1 E+05	2.35
Hsia et al (19)	3.982	0.668	23.728	14.91
Jauregul-Amezage et al (20)	15.280	5.483	42.609	21.56
Jo et al (21)	0.732	0.001	460.046	2.28
Kim et al (22)	3.661	1.048	12.790	22.48
Kurt et al (23)	0.262	0.000	1641.736	1.29
Lee et al (24)	1.461	0.451	4.738	20.16
Park et al (25)	0.482	0.058	3.995	12.57
D+L pooled ES	3.299	1.195	9.105	100.000

Heterogeneity chi-squared = 17.76 (d.f. = 8) p = 0.023
I-squared (variation in ES attributable to heterogeneity) = 55.0 %
Estimate of between-study variance Tau-squared = 0.9707
Test of ES=1 : z= 2.30 p = 0.021

*ES stands for effect size, which in this case is presenting a risk ratio
**D+L stands for random effect

Table 3: Publication Bias table for Activation of TB disease when comparing Activation in Patients found with LTBI and no LTBI with Stata provided statistical test values

Method	Pooled Est	95% CI		Asymptotic Z value	Asymptotic o value	No. of Studies
Fixed	1.365	0.828	1.902	4.981	0.000	9
Random	1.194	0.178	2.209	2.304	0.021	

Test for heterogeneity: Q= 17.761 on 8 degrees of freedom (p= 0.023)
Moment-based estimate of between studies variance = 0.971

Table 4: Filled model of Publication Bias for Activation of TB disease when Comparing Activation in patients found with LTBI and no LTBI with Stata provided statistical test values

Method	Pooled Est	95% CI		Asymptotic Z value	Asymptotic o value	No. of Studies
Fixed	1.365	0.828	1.902	4.981	0.000	9
Random	1.194	0.178	2.209	2.304	0.021	

Test for heterogeneity: Q= 17.761 on 8 degrees of freedom (p= 0.023)
Moment-based estimate of between studies variance = 0.971

Table 5: Risk of Activation given a person is Found to be Positive for LTBI with Stata provided statistical test values

Study	ES *	95% confidence interval		% Weight
Byun et al (16)	0.579	0.001	296.966	2.58
Jo et al (21)	0.732	0.001	460.046	2.42
Lee et al (24)	1.461	0.451	4.738	72.54
Park et al (25)	0.482	0.058	3.995	22.47
D+L pooled ES	1.094	0.402	2.979	100.000

Heterogeneity chi-squared = 0.86(d.f. = 3) p = 0.834
I-squared (variation in ES attributable to heterogeneity) = 0.0 %
Estimate of between-study variance Tau-squared = 0.0000

Test of ES=1 : z= 0.18 p = 0.861

*ES stands for effect size, which in this case is presenting a risk ratio
**D+L stands for random effect

Table 6: Publication Bias Table for Activation of TB Disease when Comparing Activation in Patients found with LTBI and no LTBI with Stata provided statistical test values

Method	Pooled Est	95% CI		Asymptotic Z value	Asymptotic p value	No. of Studies
Fixed	0.090	-0.912	1.092	0.175	0.861	4
Random	1	-0.912	1.092	0.175	0.861	

Test for heterogeneity: Q= 0.863 on 3 degrees of freedom (p=0.834)
Moment-based estimate of between studies variance = 0.000

Table 7: Filled model of Publication Bias for Activation of TB Disease when Comparing Activation in Patients found with LTBI and no LTBI with STATA provided statistical test values

Method	Pooled Est	95% CI		Asymptotic Z value	Asymptotic p value	No. of Studies
Fixed	0.090	-0.912	1.092	0.175	0.861	4
Random	1	-0.912	1.092	0.175	0.861	

Test for heterogeneity: Q= 0.863 on 3 degrees of freedom (p=0.834)
Moment-based estimate of between studies variance = 0.000

Table 8: Percentile of Completion and Weight of Importance per paper for LTBI Treatment with Stata provided statistical test values

Study	ES *	95% confidence interval		% Weight
Bray et al (26)	0.892	0.2663	1.522	1.58
Byun, et al (16)	0.882	0.729	1.036	8.09
Hou et al (18)	0.957	0.898	1.015	10.40
Jo et al (21)	0.177	0.082	0.273	9.64
Kim et al (22)	0.533	0.353	0.713	7.36
Kurt et al (23)	0.966	0.919	1.012	10.59
Lee et al (24)	0.961	0.937	0.985	10.85
Lopes et al (27)	0.911	0.828	0.994	9.91
Munoz et al (28)	0.934	0.903	0.965	10.79
Park et al (25)	0.887	0.857	0.918	10.79
Vallis et al (29)	0.870	0.790	0.949	10.00
D+L **pooled ES	0.822	0.736	0.907	100.000

Heterogeneity chi-squared = 274.95 (d.f. = 10) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 96.4%
Estimate of between-study variance Tau-squared = 0.0174

Test of ES=0 : z= 18.85 p = 0.000
*ES stands for effect size, which in this case is presenting a proportion of completion
**D+L stands for random effect

References

1. Pai M, Behr MA, Dowdy D, et al. Tuberculosis. Nature Reviews Disease Primers **2016**; 2:16076. DOI: 10.1038/nrdp.2016.76.
2. WHO. Global Tuberculosis Report **2017**; WHO/HTM/TB/2017.23. Available at http://www.who.int/tb/publications/global_report/en/
3. Raviglione M, Maher D. Ending Infectious Diseases in the Era of Sustainable Development Goals. Port Biomedical Journal **2017**;2:140-142. Available at https://www.sciencedirect.com/science/article/pii/S2444866417303008
4. CDC. Reported Tuberculosis in the United States **2016**; CDC/TB/2017. Available at https://www.cdc.gov/tb/statistics/reports/2016/pdfs/2016_Surveillance_FullReport.pdf
5. Houben R , Dodd P, The Global Burden of Latent Tuberculosis Infection: a Re-estimation using Mathematical Modelling. PLoS medicine **2016**; 13(10) Available at http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002152
6. Lewinsohn D, Leonard M, LoBue P, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: Diagnosis of Tuberculosis in Adults and Children. Clinical Infectious Diseases **2017**;64(2):1-33.
7.Lis K, Kuzawińska O , Bałkowiec-Iskra E, Tumor necrosis factor inhibitors–state of knowledge. Archives of medical science: AMS, **2014**; 10(6): 1175.Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4296073/
8. FDA. Information on Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi). FDA, **2015**; Available at https://www.fda.gov/Drugs/DrugSafety/ucm109340.htm.
9. FDA Drug Safety Communication: Drug labels for the Tumor Necrosis Factor-alpha (TNFα) blockers now include warnings about infection with Legionella and Listeria bacteria. FDA, **2011**; Available at https://www.fda.gov/Drugs/DrugSafety/ucm270849.htm
10.Keystone E.C., Papp K.A., Wobeser W., Challenges in diagnosing latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. The Journal of rheumatology, **2011**; 38(7):1234-1243. Available at https://doi.org/10.3899/jrheum.100623
11. Carmona L., Hernández-García C., Vadillo C., et al, Increased risk of tuberculosis in patients with rheumatoid arthritis. The Journal of rheumatology **2003**; 30(7): 1436-1439.
12. Mehta, B., Zapantis, E., Petryna, O., Efthimiou P, Screening optimization of latent tuberculosis infection in rheumatoid arthritis patients. Arthritis **2015**; Available at http://dx.doi.org/10.1155/2015/569620
13. Mariette X., Salmon D., R Group, French guidelines for diagnosis and treating latent and active tuberculosis in patients with RA treated with TNF blockers. Annals of the Rheumatic Diseases **2003**; 62(8): 791. DOI: 10.1136/ard.62.8.791
14. Soare A., Gheorghiu A.M., Aramă V., et al., Risk of active tuberculosis in patients with inflammatory arthritis receiving TNF inhibitors: a look beyond the baseline tuberculosis screening protocol. Clinical rheumatology **2017**; 1-7.
15. Keane J, Gershon S, Wise R, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α–neutralizing agent. New England Journal of Medicine **2001**;345(15):1098-10. DOI: 10.1056/NEJMoa011110
16. Byun JM, Lee CK, Rhee SY, et al. The risk of tuberculosis in Korean patients with inflammatory bowel disease receiving tumor necrosis factor-α blockers. Journal of Korean medical science **2015**;30(2):173-9.. Available at https://doi.org/10.3346/jkms.2015.30.2.173

17. Cantini F, Lubrano E, Marchesoni A, et al. Latent tuberculosis infection detection and active tuberculosis prevention in patients receiving anti-TNF therapy: an Italian nationwide survey. International journal of rheumatic diseases. **2016**; 19(8):799-805.Available at https://doi.org/10.1111/1756-185X.12708
18Hou J, Kramer J, Richardson P, et al., Tuberculosis screening and reactivation among a national cohort of patients with inflammatory bowel disease treated with tumor necrosis factor alpha antagonists. Inflammatory bowel diseases **2016**; 23(2):254-60. Available https://doi.org/10.1097/MIB.0000000000001003
19. Hsia E, Cush J, Matteson E, et al., Comprehensive tuberculosis screening program in patients with inflammatory arthritides treated with golimumab, a human anti–tumor necrosis factor antibody, in phase III clinical trials. Arthritis care & research **2013**;65(2):309-13. Available at https://doi.org/10.1002/acr.21788
20. Jauregui-Amezaga A, Turon F, Ordás I, et al., Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. Journal of Crohn's and Colitis **2013**;7(3):208-12. Available at https://doi.org/10.1016/j.crohns.2012.05.012
21. Jo K, Hong Y, Jung Y, et al., Incidence of tuberculosis among anti-tumor necrosis factor users in patients with a previous history of tuberculosis. Respiratory medicine **2013**;107(11):1797-802. Available at https://doi.org/10.1016/j.rmed.2013.08.011
22. Kim E, Am Song G, Cho K, et al., Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. World Journal of Gastroenterology: WJG **2015**;21(11):3308. DOI: 10.3748/wjg.v21.i11.3308
23. Kurt O, Kurt B, Talay F, et al. Intermediate to long-term follow-up results of INH chemoprophylaxis prior to anti-TNF-alpha therapy in a high-risk area for tuberculosis. Wiener klinische Wochenschrift **2013**;125(19-20):616-20.
24. Lee E, Kang YA, Leem AY, et al., Active Tuberculosis Incidence and Characteristics in Patients Treated with Tumor Necrosis Factor Antagonists According to Latent Tuberculosis Infection. Scientific reports **2017**;7(1):6473. DOI:10.1038/s41598-017-06899-1
25. Park S, Jo K, Yoo B, et al., Comparison of LTBI treatment regimens for patients receiving anti-tumour necrosis factor therapy. The International Journal of Tuberculosis and Lung Disease **2015**;19(3):342-8. Available at https://doi.org/10.5588/ijtld.14.0554
26. Bray MG, Poulain C, Dougados M, Gossec L. Frequency and tolerance of antituberculosis treatment according to national guidelines for prevention of risk of tuberculosis due to tumor necrosis factor blocker treatment. Joint Bone Spine **2010**; 77(2):135-41. Available at https://doi.org/10.1016/j.jbspin.2009.10.012
27. Lopes D, Pinheiro V, Monteiro H, Queiros J, Madeira Ldos S, Lopes M, Diagnosis and treatment of latent tuberculosis in patients with chronic inflammatory diseases: use of TNF-alpha-targeting biological products. J Bras Pneumol **2011**; 37: 308-16.
28. Muñoz L, Casas S, Juanola X, Borda X, Martinez C, Santin M, Prevention of Anti–Tumor Necrosis Factor–Associated Tuberculosis: A 10-Year Longitudinal Cohort Study. Clinical Infectious Diseases **2014**;60(3):349-56. Available at https://doi.org/10.1093/cid/ciu796
29. Valls V, Ena J. Short-course treatment of latent tuberculosis infection in patients with rheumatic conditions proposed for anti-TNF therapy. Clinical rheumatology **2015**;34(1):29-34.
30. Winthrop KL, Siegel JN, Jereb J, Taylor Z, Iademarck M, Tuberculosis associated with therapy against tumor necrosis factor α. Arthritis & Rheumatology **2005**; 52(10):2968-74..Available at https://doi.org/10.1002/art.21382

31.Shinnick D, Lewinsohn M, Leonard P, et al., Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clinical Infectious Diseases **2017**;64(2):e1-33.
32. Abreu C, Magro F, Santos-Antunes J, et al., Tuberculosis in anti-TNF-α treated patients remains a problem in countries with an intermediate incidence: Analysis of 25 patients matched with a control population. Journal of Crohn's and Colitis. **2013**;7(10):e486-92.
33. Ai J, Zhang S, Ruan Q, et al., The risk of tuberculosis in patients with rheumatoid arthritis treated with tumor necrosis factor-α antagonist: a metaanalysis of both randomized controlled trials and registry/cohort studies. The Journal of rheumatology **2015**;42(12):2229-37.
34. Bernal J, Andres M, Jovani V, Garcia Sevila R, Begazo A, Vela P, Primary tuberculosis infection in patients treated with tumor necrosis factor-alpha antagonists and a negative initial screening. Reumatología Clínica (English Edition) **2016**;12(2):81-4.
35. Bonfiglioli K, Ribeiro A, Moraes J, et al, LTBI screening in rheumatoid arthritis patients prior to anti-TNF treatment in an endemic area. The International Journal of Tuberculosis and Lung Disease **2014**;18(8):905-11.
36. Brunelli J, Bonfiglioli K, Silva C. et al., Latent tuberculosis infection screening in juvenile idiopathic arthritis patients preceding anti-TNF therapy in a tuberculosis high-risk country Revista brasileira de reumatologia **2017**;57(5):392-6
37. Busquets-Perez N, Ponce A, Ortiz-Santamaria V, et al., How many patients with rheumatic diseases and TNF inhibitors treatment have latent tuberculosis? Reumatología Clínica (English Edition) **2017**; 13(5):282-6.
38. Byun J, Lee C, Rhee S. et al., Risks for opportunistic tuberculosis infection in a cohort of 873 patients with inflammatory bowel disease receiving a tumor necrosis factor-alpha inhibitor. Scandinavian journal of gastroenterology **2015**;50(3):312-20.
39. Calzada-Hernandez J, Anton-Lopez J, Bou-Torrent R, et al., Tuberculosis in pediatric patients treated with anti-TNFalpha drugs: a cohort study. Pediatric Rheumatology **2015**;13(1):54.
40. Cekic C, Aslan F, Vatansever S, et al., Latent tuberculosis screening tests and active tuberculosis infection rates in Turkish inflammatory bowel disease patients under anti-tumor necrosis factor therapy. Annals of Gastroenterology: Quarterly Publication of the Hellenic Society of Gastroenterology **2015**;28(2):241.
41. Chan M, Huang Y, Wen Y, et al., Compliance with risk management plan recommendations on laboratory monitoring of antitumor necrosis factor-alpha therapy in clinical practice. Journal of the Formosan Medical Association **2016**;115(2):83-93.
42. Denis B, Lefort A, Flipo R, et al., Long-term follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)-alpha antagonist therapy: safe re-initiation of TNF-alpha blockers after appropriate anti-tuberculous treatment. Clinical Microbiology and Infection **2008**;14(2):183-6.
43. Hazlewood G, Naimark D, Gardam M, Bykerk V, Bombardier C, Prophylaxis for latent tuberculosis infection prior to anti-tumor necrosis factor therapy in low-risk elderly patients with rheumatoid arthritis: a decision analysis. Arthritis care & research. **2013**;65(11):1722-31.
44. Kim E, Uhm W, Bae S, Yoo D, Kim T, Incidence of tuberculosis among korean patients with ankylosing spondylitis who are taking tumor necrosis factor blockers. The Journal of rheumatology **2011**;38(10):2218-23.

45. Kisacik B, Pamuk O, Onat A, et al., Characteristics Predicting Tuberculosis Risk under Tumor Necrosis Factor-alpha Inhibitors: Report from a Large Multicenter Cohort with High Background Prevalence. The Journal of rheumatology **2016**; 43(3):524-9.
46. Lee H, Park H, Jeon K, et al., QuantiFERON-TB Gold In-Tube assay for screening arthritis patients for latent tuberculosis infection before starting anti-tumor necrosis factor treatment. PLoS One **2015**; 10(3):e-119260.
47. Lee J, Choi C, Park J, et al., Clinical features of active tuberculosis that developed during anti-tumor necrosis factor therapy in patients with inflammatory bowel disease. Intestinal Research **2016**; 14(2):146-51.
48. Lee S, Kim S, Kim E, et al., Mycobacterial infections in patients treated with tumor necrosis factor antagonists in South Korea. Lung **2013**; 191(5):565-71.
49. Li C, Mao Q, Chen M, et al., Acquired latent tuberculosis infection in psoriasis patients treated with etanercept in the People's Republic of China. Drug design, development and therapy **2015**;9:5591.
50. Papay P, Eser A, Winkler S, et al., Factors impacting the results of interferon-gamma release assay and tuberculin skin test in routine screening for latent tuberculosis in patients with inflammatory bowel diseases. Inflammatory bowel diseases **2010**;17(1):84-90.
51. Papay P, Primas C, Eser A, et al., Retesting for latent tuberculosis in patients with inflammatory bowel disease treated with TNF-alpha inhibitors. Alimentary Pharmacology & Therapeutics **2012**; 36(9):858-65.
52. Park D, Hisamatsu T, Chen M, et al., Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: management. Journal of Gastroenterology and Hepatology **2017**; doi:10.1111.
53. Qumseya B, Ananthakrishnan A, Skaros S, et al., QuantiFERON TB gold testing for tuberculosis screening in an inflammatory bowel disease cohort in the United States. Inflammatory bowel diseases **2010**;17(1):77-83.
54. Ringrose J, Sanche S, Taylor-Gjevre R, Detecting latent tuberculosis infection during anti-tumor necrosis factor therapy. Clinical and Experimental Rheumatology **2011**;29(5):790.
55. Saraceno R, Specchio F, Chiricozzi A, et al., Usefulness of QuantiFERON(R)-TB Gold test in psoriatic patients under treatment with tumour necrosis factor blockers. Expert Opinion on Biological Therapy **2014**; 14(2):151-6.
56. Sauzullo I, Mengoni F, Marocco R, et al., Interferon-gamma release assay for tuberculosis in patients with psoriasis treated with tumour necrosis factor antagonists: in vivo and in vitro analysis. British Journal of Dermatology **2013**; 169(5):1130-40.
57. Sfikakis P, The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. Current Directions in Autoimmunity **2010**; 11:180-210
58. Singanayagam A, Manalan K, Sridhar S, et al., Evaluation of screening methods for identification of patients with chronic rheumatological disease requiring tuberculosis chemoprophylaxis prior to commencement of TNF-alpha antagonist therapy. Thorax **2013**; 68(10):955-61.
59. Sung Y, Cho S, Kim D, et al., Isoniazid treatment for latent tuberculosis infection is tolerable for rheumatoid arthritis patients receiving tumor necrosis factor inhibitor therapy. The Korean Journal of Internal Medicine **2017**; doi: 10.3904/kjim.2016.214
60. Tong Q, Cai Q, de Mooij T, et al., Adverse events of anti-tumor necrosis factor alpha therapy in ankylosing spondylitis. PLoS One **2015**;10(3): e0119897

61. Vaughn B, Doherty G, Gautam S, Moss A, Cheifetz A, Screening for tuberculosis and hepatitis B prior to the initiation of anti-tumor necrosis therapy. Inflammatory Bowel Diseases **2012**; 18(6):1057-63.
62. Wong S, Gao Q, Tsoi K, et al., Effect of immunosuppressive therapy on interferon gamma release assay for latent tuberculosis screening in patients with autoimmune diseases: a systematic review and meta-analysis. Thorax **2015**; 71(1):64-72.
63. Xie X,Li F, Chen J, Wang J, Risk of tuberculosis infection in anti-TNF-alpha biological therapy: from bench to bedside. Journal of Microbiology, Immunology, and Infection **2014**; 47(4):268-74.
64. Yang J, Jo K,Hong S, et al., Adequacy of initiating TNF antagonists within 3 weeks of starting latent tuberculosis infection treatment in patients with immune-mediated inflammatory diseases. Infectious Diseases **2016**; 48(4): 293-298.
65. Yonekura C, Oliveira R, Titton D, et al., Incidence of tuberculosis among patients with rheumatoid arthritis using TNF blockers in Brazil: data from the Brazilian Registry of Biological Therapies in Rheumatic Diseases (Registro Brasileiro de Monitoracao de Terapias Biologicas - BiobadaBrasil). Revista Brasileira De Reumatologia **2017**; 57 Suppl 2: 477-483

Appendix 1: Open epi outputs

Open epi outputs for activation

Risk of TB progression by LTBI status for Byun et al ** (16)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	0.1	17.1
	No	5.1	503.1

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates		**Confidence Limits**	
Type	**Value**	**Lower, Upper**	**Type**
Risk in Exposed	0.5814%	0.0, 22.19	Taylor series
Risk in Unexposed	1.004%	0.3639, 2.378	Taylor series
Overall Risk	0.9897%	0.3639, 2.327	Taylor series
Risk Ratio	0.5793	0.00113, 297[1]	Taylor series
Risk Difference	-0.4221%	-4.118, 3.274°	Taylor series
Prevented fraction in pop.(pfp)	1.377%	-12.09, 11.96	
Prevented fraction in exposed(pfe)	42.07%	-29600, 99.89	

Risk of TB progression by LTBI status for Hou et al ** (18)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	2.1	41.1
	No	0.1	3314.1

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates	**Confidence Limits**

Type	Value	Lower, Upper	Type
Risk in Exposed	4.861%	0.5579, 16.54	Taylor series
Risk in Unexposed	0.003017%	0.0, 0.1448	Taylor series
Overall Risk	0.06553%	0.004303, 0.2409	Taylor series
Risk Ratio	1611	2.853, 909800[1]	Taylor series
Risk Difference	4.858%	-1.554, 11.27°	Taylor series
Etiologic fraction in pop.(EFp)	95.4%	67.51, 100	
Etiologic fraction in exposed(EFe)	99.94%	64.95, 100	

Risk of TB progression by LTBI status for Hsia et al (18)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	2	315
	No	3	1890

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates		**Confidence Limits**	
Type	**Value**	**Lower, Upper**	**Type**
Risk in Exposed	0.6309%	0.01987, 2.424	Taylor series
Risk in Unexposed	0.1585%	0.03051, 0.4883	Taylor series
Overall Risk	0.2262%	0.08008, 0.5451	Taylor series
Risk Ratio	3.981	0.6679, 23.73[1]	Taylor series
Risk Difference	0.4724%	-0.4174, 1.362°	Taylor series
Etiologic fraction in pop.(EFp)	29.95%	-20.11, 80.02	
Etiologic fraction in exposed(EFe)	74.88%	-49.72, 95.79	

Risk of TB progression by LTBI status for Jauregul-Amezage et al (19)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	7	23
	No	6	387

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates		**Confidence Limits**	
Type	**Value**	**Lower, Upper**	**Type**
Risk in Exposed	23.33%	11.52, 41.2	Taylor series
Risk in Unexposed	1.527%	0.6199, 3.372	Taylor series
Overall Risk	3.073%	1.753, 5.238	Taylor series
Risk Ratio	15.28	5.482, 42.61[1]	Taylor series
Risk Difference	21.81%	6.624, 36.99°	Taylor series
Etiologic fraction in pop.(EFp)	50.32%	21.58, 79.07	
Etiologic fraction in exposed(EFe)	93.46%	81.76, 97.65	

Risk of TB progression by LTBI status for Jo et al ** (20)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	0.1	11.1
	No	1.1	89.1

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates		**Confidence Limits**	
Type	**Value**	**Lower, Upper**	**Type**
Risk in Exposed	0.8929%	0.0, 30.67	Taylor series
Risk in Unexposed	1.22%	0.0, 6.775	Taylor series
Overall Risk	1.183%	0.0, 6.206	Taylor series
Risk Ratio	0.7321	0.001165, 460.1[1]	Taylor series
Risk Difference	-0.3267%	-6.283, 5.63°	Taylor series
Prevented fraction in pop.(pfp)	2.959%	-109.7, 36.87	
Prevented fraction in exposed(pfe)	26.79%	-45910, 99.88	

Risk of TB progression by LTBI status for Kim et al (21)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	4	12
	No	26	334

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates		**Confidence Limits**	
Type	**Value**	**Lower, Upper**	**Type**
Risk in Exposed	25%	9.708, 49.97	Taylor series
Risk in Unexposed	7.222%	4.939, 10.41	Taylor series
Overall Risk	7.979%	5.614, 11.19	Taylor series
Risk Ratio	3.462	1.371, 8.737[1]	Taylor series
Risk Difference	17.78%	-3.606, 39.16°	Taylor series
Etiologic fraction in pop.(EFp)	9.481%	-2.427, 21.39	
Etiologic fraction in exposed(EFe)	71.11%	27.08, 88.55	

Risk of TB progression by LTBI status for Kurt et al ** (22)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	0.1	58.1
	No	0.1	15.1

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates		**Confidence Limits**	
Type	**Value**	**Lower, Upper**	**Type**
Risk in Exposed	0.1718%	0.0, 7.673	Taylor series

Risk in Unexposed	0.6579%	0.0, 24.44	Taylor series
Overall Risk	0.2725%	0.0, 6.389	Taylor series
Risk Ratio	0.2612	0.00004153, 1642[1]	Taylor series
Risk Difference	-0.4861%	-4.687, 3.715°	Taylor series
Prevented fraction in pop.(pfp)	58.58%	'undefined', 50	
Prevented fraction in exposed(pfe)	73.88%	-164100, 100	

Risk of TB progression by LTBI status for Lee et al (23)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	5	250
	No	6	441

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates		**Confidence Limits**	
Type	**Value**	**Lower, Upper**	**Type**
Risk in Exposed	1.961%	0.7086, 4.639	Taylor series
Risk in Unexposed	1.342%	0.5442, 2.969	Taylor series
Overall Risk	1.567%	0.8416, 2.819	Taylor series
Risk Ratio	1.461	0.4503, 4.738[1]	Taylor series
Risk Difference	0.6185%	-1.39, 2.627°	Taylor series
Etiologic fraction in pop.(EFp)	14.34%	-31.5, 60.17	
Etiologic fraction in exposed(EFe)	31.54%	-100, 78.9	

Risk of TB progression by LTBI status for Park et al (24)

		Developed active TB	
		Yes	No
Found to have LTBI and placed on treatment	Yes	1	407
	No	6	1175

Risk-Based* Estimates and 95% Confidence Intervals
(Not valid for Case-Control studies)

Point Estimates		Confidence Limits	
Type	**Value**	**Lower, Upper**	**Type**
Risk in Exposed	0.2451%	0.0, 1.519	Taylor series
Risk in Unexposed	0.508%	0.2045, 1.132	Taylor series
Overall Risk	0.4405%	0.1936, 0.9265	Taylor series
Risk Ratio	0.4824	0.05826, 3.995[1]	Taylor series
Risk Difference	-0.2629%	-0.8911, 0.3652°	Taylor series
Prevented fraction in pop.(pfp)	13.29%	-24.27, 33.41	
Prevented fraction in exposed(pfe)	51.76%	-299.5, 94.17	

*Conditional maximum likelihood estimate of Odds Ratio
** These tables are adjusted by a 0.1 factor per cell, due to a 0 being present in an experimental value

Appendix 2: Stata code

The code below has been adapted from notes provided in Dr. Michael Goodman's Epidemiology 590R: Systematic Review And Meta-Analysis, at Emory University Fall semester 2017.

First install mais software

net from http://www.stata-press.com/data/mais
net install mais
spinst_mais

To get 95% confident internal of ratios

metan ln_risk se_lnrisk , eform random label(namevar=study)

For publication bias

metatrim ln_risk se_lnrisk, reffect funnel

for completion

metan prop Se_prop, random label(namevar=study)