Molecular clustering of patients with diabetes and pulmonary tuberculosis: A systematic review and meta-analysis

Francés Blanco-Guillot¹, Guadalupe Delgado-Sánchez², Norma Mongua-Rodríguez²,³, Pablo Cruz-Hervert², Leticia Ferreyra-Reyes², Elizabeth Ferreira-Guerrero², Mercedes Yanes-Lane⁴, Rogelio Montero-Campos⁵, Miriam Bobadilla-del-Valle⁶, Pedro Torres-González⁵, Alfredo Ponce-de-León⁶, José Sifuentes-Osornio⁶, Lourdes García-García²*

¹ Doctorado en Ciencias en Enfermedades Infecciosas, Centro de Investigación sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México, ² Centro de Investigación sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública, Cuernavaca, Morelos, México, ³ Maestría en Ciencias Médicas con énfasis en Epidemiología, Facultad de Medicina, Universidad Nacional Autónoma de México, Distrito Federal, México, 4 Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, San Luis Potosí, México, 5 Laboratorio de Microbiología, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”, México, Distrito Federal, México, 6 Dirección Médica, Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”, México, Distrito Federal, México

* garcigarml@gmail.com

Abstract

Introduction

Many studies have explored the relationship between diabetes mellitus (DM) and tuberculosis (TB) demonstrating increased risk of TB among patients with DM and poor prognosis of patients suffering from the association of DM/TB. Owing to a paucity of studies addressing this question, it remains unclear whether patients with DM and TB are more likely than TB patients without DM to be grouped into molecular clusters defined according to the genotype of the infecting Mycobacterium tuberculosis bacillus. That is, whether there is convincing molecular epidemiological evidence for TB transmission among DM patients. Objective: We performed a systematic review and meta-analysis to quantitatively evaluate the propensity for patients with DM and pulmonary tuberculosis (PTB) to cluster according to the genotype of the infecting M. tuberculosis bacillus.

Materials and methods

We conducted a systematic search in MEDLINE and LILACS from 1990 to June, 2016 with the following combinations of key words “tuberculosis AND transmission” OR “tuberculosis diabetes mellitus” OR “Mycobacterium tuberculosis molecular epidemiology” OR “RFLP-IS6110” OR “Spoligotyping” OR “MIRU-VNTR”. Studies were included if they met the following criteria: (i) studies based on populations from defined geographical areas; (ii) use of genotyping by IS6110- restriction fragment length polymorphism (RFLP) analysis and spoligotyping or mycobacterial interspersed repetitive unit-variable number of tandem repeats (MIRU-VNTR) or other amplification methods to identify molecular clustering;
(iii) genotyping and analysis of 50 or more cases of PTB; (iv) study duration of 11 months or more; (v) identification of quantitative risk factors for molecular clustering including DM; (vi) > 60% coverage of the study population; and (vii) patients with PTB confirmed bacteriologically. The exclusion criteria were: (i) Extrapulmonary TB; (ii) TB caused by nontuberculous mycobacteria; (iii) patients with PTB and HIV; (iv) pediatric PTB patients; (v) TB in closed environments (e.g. prisons, elderly homes, etc.); (vi) diabetes insipidus and (vii) outbreak reports. Hartung-Knapp-Sidik-Jonkman method was used to estimate the odds ratio (OR) of the association between DM with molecular clustering of cases with TB. In order to evaluate the degree of heterogeneity a statistical Q test was done. The publication bias was examined with Begg and Egger tests. Review Manager 5.3.5 CMA v.3 and Biostat and Software package R were used.

Results
Selection criteria were met by six articles which included 4076 patients with PTB of which 13% had DM. Twenty seven percent of the cases were clustered. The majority of cases (48%) were reported in a study in China with 31% clustering. The highest incidence of TB occurred in two studies from China. The global OR for molecular clustering was 0.84 (IC 95% 0.40–1.72). The heterogeneity between studies was moderate ($I^2 = 55\%$, $p = 0.05$), although there was no publication bias (Beggs test $p = 0.353$ and Eggers $p = 0.429$).

Conclusion
There were very few studies meeting our selection criteria. The wide confidence interval indicates that there is not enough evidence to draw conclusions about the association. Clustering of patients with DM in TB transmission chains should be investigated in areas where both diseases are prevalent and focus on specific contexts.

Introduction
Tuberculosis (TB) remains one of the main causes of morbidity and mortality in low- and medium-income countries, where the number of individuals with diabetes mellitus (DM) is rapidly increasing.

For more than 30 years genotypic analyses of *Mycobacterium tuberculosis* together with conventional epidemiologic methods have helped to further characterize *M. tuberculosis* strains [1–3] and understand the dynamics of transmission of TB in different regions and populations [4–7]. Patients with identical strains of *M. tuberculosis* are considered to belong to molecular clusters, their disease being due to recent transmission and rapid progression. Unique genetic patterns are likely due to reactivation of latent infection or recent transmission from patients out of the period or area under study [6, 7].

A great variety of individual, biological and social determinants have been associated with clustering of pulmonary TB (PTB) cases. In highly endemic areas for TB some of these factors include being male, young, having been born in an endemic country, resident of an urban area, alcohol or drug consumption, homelessness, HIV infection or having acid-fast bacilli in sputum smear [6, 8–11]. Similar determinants have been described in medium income countries—young age, previous imprisonment and visits to social environments [12]. There are
conflicting results on the association of HIV associated immunodeficiency and increased risk of transmission of *M. tuberculosis* in African countries where both diseases are highly prevalent [13–15]. Fewer studies have investigated if DM increases the likelihood of PTB patients to cluster according to the genotype of the infecting *M. tuberculosis* bacillus.

Owing to a paucity of studies addressing this question, it remains unclear whether patients with DM and TB are more likely than TB patients without DM to be grouped into molecular clusters defined according to the genotype of the infecting *M. tuberculosis* bacillus. That is, whether there is convincing molecular epidemiological evidence for TB transmission among DM patients. This information would contribute to developing effective preventive strategies. We conducted a systematic review and meta-analysis to quantitatively evaluate the propensity of patients with DM and PTB to cluster according to the genotype of the infecting *M. tuberculosis* bacillus.

**Materials and methods**

We conducted this study according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [16] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [17], S1 Table.

**Search strategy**

A systematic search was made in the electronic data bases of MEDLINE and LILACS, from 1990 to June, 2016. The following combinations of key words were used: "tuberculosis AND transmission" OR "tuberculosis AND diabetes mellitus" OR "Mycobacterium tuberculosis" molecular epidemiology" OR "RFLP-IS6110" OR "Spoligotyping" OR "MIRU-VNTR". Two independent reviewers selected potentially relevant articles based on the title and abstracts. We included publications in English or Spanish reporting original data from observational studies in which DM was evaluated among other risk factors for molecular clustering of PTB cases. We contacted the authors of selected articles to clarify methodological aspects and results.

Studies were included if they met the following criteria: (i) studies based on populations from defined geographical areas; (ii) use of genotyping by IS6110- restriction fragment length polymorphism (RFLP) analysis and spoligotyping or mycobacterial interspersed repetitive unit-variable number of tandem repeats (MIRU-VNTR) or other amplification methods to identify molecular clustering; (iii) genotyping and analysis of 50 or more cases of PTB; (iv) study duration of 11 months or more; (v) identification of quantitative risk factors for molecular clustering including DM; (vi) > 60% coverage of the study population; and (vii) patients with PTB confirmed bacteriologically. The exclusion criteria were: (i) Extrapulmonary TB; (ii) TB caused by nontuberculous mycobacteria; (iii) patients with PTB and HIV; (iv) pediatric PTB patients; (v) TB in closed environments (e.g. prisons, elderly homes, etc.); (vi) diabetes insipidus and (vii) outbreak reports. References lists of all included studies were screened to identify further potentially eligible studies.

**Data extraction**

Titles, abstracts, and full-text articles identified from the searches were screened by one reviewer (FBG) to select relevant articles. A second reviewer (GDS) independently screened 10% of titles and abstracts and 30% of full-text articles. Two authors (FBG and GDS) independently extracted data from included studies using previously piloted data extraction forms. The extracted information included: study design, region, period, number of genotyped subjects, sampling fraction, diagnostic criteria for DM, genotyping method, definition of molecular clustering, proportion of cases in the clusters, definition of index case and contact tracing.
If secondary genotyping was used, the combined methods as reported by the authors were reported. When TB rates were not available in the citation, we used data from the World Bank [18]. Disagreements and discrepancies in study selection and data extraction were resolved through discussion.

**Statistical analysis**

The statistical analysis was based on a model of random effects to estimate the odds ratio (OR) (Mantel-Haenszel) of DM associated with molecular clustering of PTB. Pooled OR and 95% Confidence intervals (95% CI) of the association between DM and molecular clustering were estimated using random effect meta-analyses with the Hartung-Knapp-Sidik-Jonkman modification. We used the Hartung-Knapp-Sidik-Jonkman approach since it is a more robust method for meta-analyses with moderate heterogeneity (>50%), few studies (between 5 and 20) and varied sample sizes as compared to DerSimonian and Laird method. [19] Heterogeneity between the studies was assessed using the $I^2$ statistic [20].

Patients with PTB with the same genotype were classified as clustered and those with unique genotypes as not clustered.

**Sensitivity analysis.** To identify the influence of the Borrell et al. [21], we repeated the meta-analysis without this study [22, 23] using the Hartung-Knapp-Sidik-Jonkman test.

**Bias evaluation.** We conducted bias evaluation based on the Cochrane manual [24]. Because evaluation was heterogeneic and, following the manual’s recommendations, we conducted an evaluation of publication bias.

**Evaluation of publication bias.** Because the presence of publication bias can lead to incorrect estimations and false conclusions that affect the validity of the meta-analysis of observational studies, publication bias was analyzed using Beggs tests [25] and Egger [22]. The sample size of each study was compared with the size of the observed effect. A p value of <0.10 was considered statistically significant [23].

Statistical analysis was performed using Review Manager 5.3.5 (Rev Man for Windows, 2015; The Cochrane Collaboration, Oxford, United Kingdom) and Comprehensive Meta-Analysis 3 (CMA v.3, Biostat) [26] and Biostat and Software package R were used.

**Results**

The electronic search produced a total of 13415 articles of which 226 were excluded for duplicity leaving 13189 potentially relevant studies. After a title and abstract revision, 13156 articles were excluded for various reasons: (i) language different to English or Spanish, (ii) had no abstract, (iii) letter to the editor or communication, (iv) outside the scope of this study. After full reading of the 33 articles, 27 were excluded for the following reasons: (i) seven studies [27–33] did not use molecular methods for the characterization, (ii) five studies [34–38] had low coverage of the studied population in regard to the total number of patients with a positive culture for TB, (iii) 13 studies [39–51] did not show the quantification of risk factors for clustering or did not include DM and (iv) two studies [52, 53] reported only the genetic lineages of *M. tuberculosis*. Finally six articles [21, 54–58] met all the inclusion criteria for the quantitative analysis. Fig 1 provides a flow diagram of the systematic selection of the literature.

The literature search for studies on the association between DM and molecular clustering of strains of patients with PTB.

The general characteristics of the selected articles are summarized in Table 1. All six studies were cohort studies, two were conducted in China [57, 58] and one in Spain [21], Canada [55], Mexico [56] and Cuba [54]. Among the 6 studies there were 4076 patients with PTB of which 13% had comorbidity with DM. The total percentage of clustering was 27%. Percentage
clustering was similar among patients with DM (25%) and without DM (28%). The majority of cases (48%) were reported by a Chinese study [58] with 31% clustering. The highest annual incidence of TB was reported by the studies from China (73/100,000 inhabitants).

Diagnosis of DM was obtained from various sources: data collection formats [53, 54], TB control program or statistical center [55, 57] and patient’s medical history [21]. Only one study [56] described diagnostic criteria for DM.

The genotyping methods used in the studies were IS6110-RFLP analysis and spoligotyping and MIRU-VNTR. Therefore, definitions of molecular clustering and method of identification of the index case differed between studies.

The pooled OR for molecular clustering of patients with DM and TB compared to patients with TB was 0.84 (CI 95% 0.40–1.72) with the Hartung-Knapp-Sidik-Jonkman test (Fig 2). There was a moderate heterogeneity [24] between studies (I² = 55%, p = 0.05) (Fig 2).

We did not find a statistically significant publication bias (p<0.1) according to Beggs (p = 0.353) and Egger tests (p = 0.429).

Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% confidence intervals (CIs). Odds ratio (OR) was calculated using the OR, CI and total number of patients with and without DM provided in the paper. Pooled OR and 95% CI of the association between DM and molecular clustering were estimated using random effect meta-analyses with the Hartung-Knapp-Sidik-Jonkman modification.
Table 1. General characteristics of the studies.

| Author and year of publication | Study region | Study period | Design of study | TB annual incidence rate per 100 000 inhabitants | Study duration (months) | Number of genotyped subjects | Sampling fraction (%) | DM diagnosis based on: | Primary genotyping method | Secondary genotyping method | Application of secondary genotyping method | Cluster definition | Index case of the cluster (%) | Subjects in the cluster (%) | Subjects in the cluster (%) | Contact tracing |
|-------------------------------|--------------|--------------|-----------------|-------------------------------------------------|------------------------|-------------------------------|-----------------------|-----------------------|--------------------------|---------------------------|---------------------------------|--------------------------|-------------------------------|-----------------------------|---------------------------|--------------------------|
| Hernández-Garduño et al., 2002 [55] | Greater Vancouver, British Columbia, Canada | 1995–1999 | Cohort | 6.0** | 50 | 793 | 100 | Information obtained from the dataset of the TB division. | RFLP-IS6110 | Spoligotyping | < 6 copies of IS6110 | ≥ 2 strains with identical DNA: (i) ≥ 6 copies with RFLP, or (ii) < 6 copies with spoligotyping | First diagnosed patient | 17.3 | Yes |
| Borrell et al., 2010 [21] * | Barcelona, Spain | 2003–2004 | Cohort | 21.6 | 24 | 115 | 67.4 | Information obtained from TB program database of Barcelona and microbiology areas of hospitals and clinical centers. | RFLP-IS6110 | MIRU-12 loci | < 6 copies of IS6110 or ≥ 6 bands with a different one | ≥ 2 patients: (i) RFLP-IS6110 ≥ 6 bands in the same position; (ii) RFLP-IS6110 < 6 bands in the same position but with identical MIRU-12 loci; (iii) RFLP-IS6110 ≥ 6 bands that differ in 1 band but with identical MIRU-12 loci | Subject with earliest onset of pulmonary symptoms or the one that started treatment first (asymptomatic) | 32 | Unknown |
| Jiménez-Corona et al., 2013 [56] | Orizaba, Veracruz, México | 1995–2010 | Cohort | 21** | 181 | 1013 | 80 | Previous diagnosis from a physician or oral hypoglycemic medication or insulin administration or treatment | RFLP-IS6110 | Spoligotyping | < 6 copies of IS6110 | ≥ 2 two or more isolates from different patients identified within 12 months of each other and with six or more IS6110 bands in an identical pattern, or < 6 bands with identical IS6110 RFLP patterns and a spoligotype with the same spacer oligonucleotides | Not specified | 28.8 | Unknown |
| Wang et al., 2014 [57] | Beijing, China | 2009–2011 | Cohort | 73** | 48 | 115 | 100 | Clinical data obtained from the patient’s medical history | MIRU-VNTR 24 loci (up to 28) | Does not apply | Does not apply | ≥ 2 strains showing identical patterns MIRU-VNTR | Not specified | 17.4 | Unknown |
| González et al., 2015 [54] | La Habana, Cuba | 2009 | Cohort | 8.2 | 12 | 59 | 61 | Clinical information obtained from the national statistics / epidemiology data base of the public health ministry of Cuba | MIRU-VNTR 24 loci | Does not apply | Does not apply | Strains with identical genetic pattern | Not specified | 54.2 | Yes |
| Yang et al., 2015 [58] | China | 2009–2012 | Cohort | 73** | 36 | 1948 | 82 | Clinical information obtained by professional interviewers with standardized questionnaire. | MIRU-VNTR 29 loci | Does not apply | Does not apply | Strains with identical genetic pattern | First patient in the cluster | 31 | Yes |

*We used only information from foreign patients;** Annual rates were taken from World Bank [18]
When we excluded Borrell et al. [21] study, the pooled OR for molecular clustering of patients with DM and TB compared to patients with TB was 0.79 (CI 95% 0.42–1.748), similar to our previous result, (S1 Fig).

Discussion

This systematic review and meta-analysis included 6 cohort studies published between 2002 and 2015 that comprised a total of 4076 patients with PTB of which 13% also had DM. The meta-analysis did not show an association between DM and molecular clustering of PTB in the community. The pooled estimate was 0.84 (CI 95% 0.40–1.72). The wide confidence interval indicates that there is not enough evidence to draw conclusions about the association.

Many studies have explored the relationship between DM and TB, including a recent systematic review demonstrating that the risk of TB among people with DM triples that of people without DM [59] while other studies show poorer outcomes among patients with TB and DM [34, 56, 59–65]. Public health impact of the comorbidity is greater in regions of low and middle income, where 84% of patients with DM live, many of whom are unaware of their condition [66, 67]. In fact, an estimate of incident TB cases attributable to DM increased from 10% to 15% from 2010 to 2013 in the 22 countries with 80% of the global burden of TB [67].

Molecular tools have provided direct evidence for the occurrence of exogenous reinfection among both immunocompetent and immunocompromised individuals [68]. As the present review shows, patients with DM have not been specifically studied [69, 70]. Clinical manifestations among patients with TB and DM such as delayed sputum and culture conversion [56, 63, 71], higher likelihood of pulmonary (versus extra pulmonary) forms [72] and cavitation [56] due to dysfunctional innate and acquired immune system indicate that patients with DM might have an important role in TB transmission. In addition, patients with DM and hyperglycemia have a greater risk of infection and disease [73], which would increase their likelihood of participating in chains of transmission. Furthermore usage of molecular epidemiologic techniques has previously allowed us to show that increased risk of TB among patients with DM is due to both reactivation and recently transmitted infection [62]. More recently, we demonstrated that patients with DM who presented with a subsequent TB episode, were more likely to suffer from infections caused by the same bacteria as the previous episode [56]. However, the occurrence of exogenous reinfection in one-fifth of the cases suggested that exogenous TB reinfection in DM patients might be due to nosocomial TB transmission occurring as a result of DM patients attending clinics where there is a high prevalence of diagnosed and undiagnosed TB, as has been described for HIV infected patients [74]. Patients with DM have been described as index and secondary cases in TB outbreaks [75, 76]. Therefore, there are grounds to hypothesize that patients with DM and TBP may have a greater likelihood of recent transmission than TBP patients without DM.
Recently, a large study of recent transmission in the United States reported substantial geographic heterogeneity in the proportion of cases attributed to recent transmission [77]. Patient characteristics associated to recent transmission differed according to cluster size. Therefore, study of characteristics associated to TB clustering is complex and probably specific to each setting.

The rise in TB incidence in persons with DM seems to have multiple causes. Although the physiopathology of TB susceptibility in patients with DM remains to be clarified, changes in the immune system have been described, including alterations in the complement pathway in patients with DM [78], increase in type 1 innate cytokines [79, 80], a reduction in the activation of alveolar macrophages [81], and increased IL-10 producing ability [82, 83]. Other authors have reported a reduction in Th1 cytokines [84]. Based on murine experiments, it has been suggested that TB susceptibility in DM can cause a delay in the initiation and expression of adaptive immunity [85]. In a recent review, the authors suggested that the interaction between the host and \textit{M. tuberculosis} can be explained by the weakening of innate immunity followed by a hyper-reactive cell response [86]. Therefore, DM deteriorates cell mediated immunity by altering the function and activation of macrophages, monocytes and lymphocytes with possible potential roles for pulmonary microangiopathy, renal dysfunction and vitamin deficiencies [63, 64, 87]. In addition, patients with sustained hyperglycemia seem to be at a higher risk of acquiring TB than those with controlled blood sugar levels suggesting that hyperglycemia is an important determinant in this interaction [63, 64, 87–89].

Association of TB with chronic diseases has been scarcely studied with the exception of TB and HIV/AIDS. Studies have provided conflicting results regarding the association between HIV infection and recent transmission of TB [13–15, 77]. The lack of association could be partially explained by the decreased risk of exposure to TB in patients with HIV in regions where incidence rates of TB have decreased or adequate antiretroviral coverage has been achieved [77, 90], although it has also been reported that antiretroviral treatment does not give protection against TB progression after a recent infection [15]. Clinical characteristics of TB among HIV patients such as degree of immunosuppression, less bacillary load, and decreased frequency of cavitary disease may also impact over infectiousness [14]. In contrast, it has been found that HIV infected patients are more likely to aggregate in molecular clusters suggesting that HIV infection increases an individual’s risk of TB disease due to recent \textit{M. tuberculosis} infection [13].

**Limitations**

This study is limited by the lack of a general agreement over a recognized methodological standard in conducting population-based TB molecular epidemiological studies. Multiple characteristics impact over clustering frequency including TB incidence, study duration, intensity of contact tracing, migration patterns into the study area, size of clusters, sampling fraction, occurrence of endemic strains, frequency of strains with low copy numbers, and age of study populations [66]. We adjusted for some of these factors through our selection criteria (study design, sample fraction, number of participants, and study duration). Our strict inclusion criteria partly explain the small number of studies that were included in the study. There has been extensive discussion in the literature of the validity of estimating pooled effects when the systematic review results in a small number of studies. We agree with Valentine \textit{et. al.} who recommend that doing the meta-analysis with few studies allows the reviewers to compute and interpret confidence intervals and as such add information beyond what is revealed by the individual studies.[91] Furthermore, numbers of studies eligible for meta-analyses are typically very small for all medical areas as was shown in a study of meta-analyses and their component
studies in the Cochrane Database of Systematic Reviews (the median number of studies was 3 (IQR 2–6).[92] Therefore, our study is above the median of number of studies included in meta-analyses in this highly recognized data set. Another possible bias might have occurred if sources of DM diagnosis were different. We consider this unlikely since data sources were clinical or public health datasets. The articles included in this meta-analysis based their genotypic characterization on the two most frequently reported methods—RFLP-IS6110 and MIR-U-VNTR. RFLP and VNTR methods have been widely recognized as tools with similar if not equal power when determining the epidemiologic relationship between M. tuberculosis strains [93–97]. A TB control program pioneer in the use of RFLP-IS6110 in operational conditions, showed an overall concordance in clustering of 79% and highly similar discriminatory power in the two methods when typing 3,978 M. tuberculosis isolates [97]. Our study is also limited by the fact that reviewed studies did not consider the increasing evidence of within patient microdiversity arising both from “de novo” mutations and mixed infections [98, 99]. As a consequence, samples taken from the upper airway (as occurred in the majority of included studies in this review) captured only a fraction of the bacterial population diversity. Future molecular epidemiological studies will need to consider microdiversity and mixed infections since they challenge current understanding of transmission dynamics.

Finally, we excluded studies of patients with PTB and HIV, therefore not considering patients that may have suffered from PTB, HIV and DM and limiting the generalizability of our results particularly to southern Africa where TB and HIV are highly prevalent. The International Diabetes Federation estimates that DM prevalence in Africa is 3.8% (2.6–7.9%) with over two thirds (66.7%) of people with diabetes unaware they have the disease [100]. Moreover, the availability of antiretroviral treatments has extended survival and ageing, with concomitant increase in non-communicable diseases, including DM. However, there is limited knowledge on the association between DM and TB in HIV-infected people from sub-Saharan Africa [101]. Therefore, we would have missed very few molecular epidemiological studies describing the triple morbidity.

Conclusion

Clustering of patients with DM in TB transmission chains should be investigated in areas or countries with high TB and DM rates. Studies with the purpose of better understanding the demographic, clinical, social and geospatial factors associated with TB in regions with a high comorbidity with DM should be conducted to better understand transmission dynamics as has recently been proposed for the association of TB and HIV[102]. Research needs to focus on specific settings investigating if TB transmission is more likely to occur in meeting points such as clinical facilities, clubs, camps, religious gatherings, etc. particularly in countries highly endemic for both diseases.

Supporting information

S1 Table. Prisma checklist.

(S1 Table)

S1 Fig. Molecular clustering risk of patients with PTB and DM compared with patients with PTB excluding Borrell et.al.[21]. Size of the square is proportional to the precision of the study-specific effect estimates, and the bars indicate the corresponding 95% confidence intervals (CIs). Odds ratio (OR) was calculated using the OR, CI and total number of patients with and without DM provided in the paper. Pooled OR and 95% CI of the association between DM and molecular clustering were estimated using random effect meta-analyses with
the Hartung-Knapp-Sidik-Jonkman modification.

Author Contributions

Conceptualization: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Norma Mongua-Rodríguez, Miriam Bobadilla-del-Valle, Pedro Torres-González, Alfredo Ponce-de-León, José Sifuentes-Osornio, Lourdes Garcia-Garcia.

Data curation: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Leticia Ferreyra-Reyes, Elizabeth Ferreira-Guerrero, Mercedes Yanes-Lane.

Formal analysis: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Pablo Cruz-Hervert, Rogelio Montero-Campos, Lourdes Garcia-Garcia.

Funding acquisition: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Elizabeth Ferreira-Guerrero, Pedro Torres-González, Lourdes Garcia-Garcia.

Investigation: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Norma Mongua-Rodríguez, Pablo Cruz-Hervert, Alfredo Ponce-de-León, José Sifuentes-Osornio, Lourdes Garcia-Garcia.

Methodology: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Norma Mongua-Rodriguez, Pablo Cruz-Hervert, Miriam Bobadilla-del-Valle, Pedro Torres-González, Lourdes Garcia-Garcia.

Project administration: Frances Blanco-Guillot, Leticia Ferreyra-Reyes, Elizabeth Ferreira-Guerrero, Rogelio Montero-Campos, Lourdes Garcia-Garcia.

Resources: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Norma Mongua-Rodríguez, Lourdes Garcia-Garcia.

Software: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Norma Mongua-Rodríguez.

Supervision: Mercedes Yanes-Lane, Miriam Bobadilla-del-Valle, Pedro Torres-González, Alfredo Ponce-de-León, José Sifuentes-Osornio, Lourdes Garcia-Garcia.

Validation: Guadalupe Delgado-Sánchez, Norma Mongua-Rodriguez, Alfredo Ponce-de-León, José Sifuentes-Osornio, Lourdes Garcia-Garcia.

Visualization: Frances Blanco-Guillot, Lourdes Garcia-Garcia.

Writing – original draft: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Norma Mongua-Rodríguez, Mercedes Yanes-Lane, Lourdes Garcia-Garcia.

Writing – review & editing: Frances Blanco-Guillot, Guadalupe Delgado-Sánchez, Norma Mongua-Rodríguez, Pablo Cruz-Hervert, Leticia Ferreyra-Reyes, Elizabeth Ferreira-Guerrero, Mercedes Yanes-Lane, Rogelio Montero-Campos, Miriam Bobadilla-del-Valle, Pedro Torres-González, Alfredo Ponce-de-León, José Sifuentes-Osornio, Lourdes Garcia-Garcia.

References

1. Bruday K, Driscoll JR, Rigouts L, Prodinger WM, Gori A, Al-Hajjaj SA, et al. Mycobacterium tuberculosis complex genetic diversity: mining the fourth international spoligotyping database (SpolDB4) for classification, population genetics and epidemiology. BMC microbiology. 2006; 6:23. Epub 2006/03/08. https://doi.org/10.1186/1471-2180-6-23 PMID: 16519816

2. Demay C, Liens B, Burguiere T, Hill V, Couvin D, Millet J, et al. SITVITWEB—a publicly available international multimarker database for studying Mycobacterium tuberculosis genetic diversity and molecular epidemiology. Infection, genetics and evolution: journal of molecular epidemiology and evolutionary...
Molecular clustering of diabetes and pulmonary tuberculosis

3. Small P, van Embden J. Molecular epidemiology of tuberculosis. In: Bloom B, editor. Tuberculosis: Pathogenesis, protection and control. Washington D.C: American Society for Microbiology; 1994. p. 569–82.

4. Gurjav U, Jelfs P, Hill-Cawthorne GA, Marais BJ, Sinchenco V. Genotype heterogeneity of Mycobacterium tuberculosis within geospatial hotspots suggests foci of imported infection in Sydney, Australia. Infection, genetics and evolution: journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2016; 40:346–51. Epub 2015/07/19. https://doi.org/10.1016/j.meegid.2015.07.014 PMID: 26187743.

5. Hoza AS, Mfinanga SG, Moser I, Konig B. Molecular characterization of Mycobacterium tuberculosis isolates from Tanga, Tanzania: First insight of MIRU-VNTR and microarray-based spoligotyping in a high burden country. Tuberculosis. 2016; 98:116–24. Epub 2016/05/10. https://doi.org/10.1016/j.tube.2016.02.002 PMID: 27156627.

6. van Soolingen D, Borgdorff MW, de Haas PE, Sebek MM, Veen J, Dessens M, et al. Molecular epidemiology of tuberculosis in the Netherlands: a nationwide study from 1993 through 1997. The Journal of infectious diseases. 1999; 180(3):726–36. Epub 1999/08/07. https://doi.org/10.1086/314930 PMID: 10438361.

7. Vynnycky E, Nagelkerke N, Borgdorff MW, van Soolingen D, van Embden JD, Fine PE. The effect of age and study duration on the relationship between ‘clustering’ of DNA fingerprint patterns and the proportion of tuberculosis disease attributable to recent transmission. Epidemiology and infection. 2001; 126(1):43–62. Epub 2001/04/11. PMID: 11293682

8. Borgdorff MW, Nagelkerke NJ, de Haas PE, van Soolingen D. Transmission of Mycobacterium tuberculosis depending on the age and sex of source cases. American journal of epidemiology. 2001; 154(10):934–43. Epub 2001/11/09. PMID: 11700248.

9. Heldal E, Dahle UR, Sandven P, Caugant DA, Brattaas N, Waaler HT, et al. Risk factors for recent transmission of Mycobacterium tuberculosis. The European respiratory journal. 2003; 22(4):637–42. Epub 2003/10/30. PMID: 14582917.

10. Inigo J, Garcia de Viedma D, Arce A, Palenque E, Alonso Rodriguez N, Rodriguez E, et al. Analysis of changes in recent tuberculosis transmission patterns after a sharp increase in immigration. Journal of clinical microbiology. 2007; 45(1):63–9. Epub 2006/11/17. https://doi.org/10.1128/JCM.01644-06 PMID: 17108076

11. Small PM, Hopewell PC, Singh SP, Paz A, Parsonnet J, Ruston DC, et al. The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. The New England journal of medicine. 1994; 330(24):1703–9. Epub 1994/06/16. https://doi.org/10.1056/NEJM199406133302402 PMID: 7910661.

12. Garcia-Garcia M, Palacios-Martinez M, Ponce-de-Leon A, Jimenez-Corona ME, Jimenez-Corona A, Balandran-Campos S, et al. The role of core groups in transmitting Mycobacterium tuberculosis in a high prevalence community in Southern Mexico. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2000; 4(1):12–7. Epub 2000/02/02. PMID: 10654638.

13. Houben RM, Crampin AC, Nhlovu R, Sonnenberg P, Godfrey-Faussett P, Haas WH, et al. Human immunodeficiency virus associated tuberculosis more often due to recent infection than reactivation of latent infection. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2011; 15(1):24–31. Epub 2011/02/01. PMID: 21276292.

14. Huang CC, Tchetgen ET, Becerra MC, Cohen T, Hughes KC, Zhang Z, et al. The effect of HIV-related immunosuppression on the risk of tuberculosis transmission to household contacts. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2014; 58(6):785–74. Epub 2013/12/26. https://doi.org/10.1093/cid/cit948 PMID: 24368620

15. Middelkoop K, Mathema B, Myer L, Shashkina E, Whitelaw A, Kaplan G, et al. Transmission of tuberculosis in a South African community with a high prevalence of HIV infection. The Journal of infectious diseases. 2015; 211(1):53–61. Epub 2014/07/24. https://doi.org/10.1093/infdis/jiu405 PMID: 25053739

16. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000; 283(15):2008–12. Epub 2000/05/02. PMID: 10789670.

17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009; 6(7):e1000097. Epub 2009/07/22. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072
18. The World Bank. Incidence of tuberculosis. http://data.worldbank.org/indicator/SH.TBS.INCD. Accessed June, 2016.

19. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014; 14:25. https://doi.org/10.1186/1471-2288-14-25 PMID: 24548571.

20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002; 21(11):1539–58. Epub 2002/07/12. https://doi.org/10.1002/sim.1186 PMID: 12111919.

21. Borrell S, Espanol M, Orcau A, Tudo G, March F, Cayla JA, et al. Tuberculosis transmission patterns among Spanish-born and foreign-born populations in the city of Barcelona. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2010; 16(6):568–74. Epub 2009/08/18. https://doi.org/10.1111/j.1469-0691.2009.02886.x PMID: 19661961.

22. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. Bmj. 1997; 315(7121):1533–7. Epub 1998/02/12. PMID: 9432252

23. Pigott T. Advances in meta-analysis. New York: Springer; 2012.

24. Shabbeer A, Ozcaoglar C, Yener B, Bennett KP. Web tools for molecular epidemiology of tuberculosis. Infection, genetics and evolution: journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2012; 12(4):767–81. Epub 2011/09/10. https://doi.org/10.1016/j.meegid.2011.08.019 PMID: 21903179.

25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50(4):1088–101. Epub 1994/12/01. PMID: 7786990.

26. Varma-Basil M, Kumar S, Arora J, Angrup A, Zozio T, Banavalker JN, et al. Comparison of spoligotyping, mycobacterial interspersed repetitive units typing and IS6110-RFLP in a study of genotypic diversity of Mycobacterium tuberculosis in Delhi, North India. Memorias do Instituto Oswaldo Cruz. 2011; 106(5):524–35. Epub 2011/09/07. PMID: 21894371.

27. Alavi SM, Khoshikh MM, Salmanzadeh S, Eghtesad M. Comparison of epidemiological, clinical, laboratory and radiological features of hospitalized diabetic and non-diabetic patients with pulmonary tuberculosis at razih hospital in ahvaz. Jundishapur journal of microbiology. 2014; 7(9):e12447. Epub 2014/12/09. https://doi.org/10.5812/jjm.12447 PMID: 25485064

28. Coker R, Mc Kee M, Atun R, Dimitrova B, Dodonova E, Kuznetsov S, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. Bmj. 2006; 332(7533):85–7. Epub 2005/12/13. https://doi.org/10.1136/bmj.38684.687940.80 PMID: 16339219

29. Perez A, Brown HS, 3rd, Restrepo BI. Association between tuberculosis and diabetes in the Mexican border and non-border regions of Texas. The American journal of tropical medicine and hygiene. 2006; 74(4):604–11. Epub 2004/12/01. PMID: 16606993

30. Restrepo BI, Camerlin AJ, Rahbar MH, Wang W, Restrepo MA, Zarate I, et al. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. Bulletin of the World Health Organization. 2011; 89(5):352–9. Epub 2011/05/11. https://doi.org/10.2471/BLT.10.085738 PMID: 21556303

31. Suwanpimolkul G, Grinsdale JA, Jarlsberg LG, Higashi J, Osmond DH, Hopewell PC, et al. Association between diabetes mellitus and tuberculosis in United States-born and foreign-born populations in San Francisco. PLoS one. 2014; 9(12):e114442. Epub 2014/12/06. https://doi.org/10.1371/journal.pone.0114442 PMID: 25478954

32. Tian PW, Wang Y, Shen YC, Chen L, Wan C, Liao ZL, et al. Different risk factors of recurrent pulmonary tuberculosis between Tibetan and Han populations in Southwest China. European review for medical and pharmacological sciences. 2014; 18(10):1482–6. Epub 2014/06/06. PMID: 24899606.

33. Chang JT, Dou HY, Yen CL, Wu YH, Huang RM, Lin HJ, et al. Effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary tuberculosis: a potential role in the emergence of multidrug-resistance. Journal of the Formosan Medical Association = Taiwan yi zhi. 2011; 110(6):372–81. Epub 2011/07/12. https://doi.org/10.1016/S0929-6646(11)60055-7 PMID: 21741005.

34. Jagielski T, Brzostek A, van Belkum A, Dziadek J, Augustynowicz-Kopec E, Zwolska Z. A close-up on the epidemiology and transmission of multidrug-resistant tuberculosis in Poland. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology. 2015; 34(1):41–53. Epub 2014/07/20. https://doi.org/10.1007/s10096-014-2202-z PMID: 25037868.
36. Kanamori H, Hatakeyama T, Uchiyama B, Weber DJ, Takeuchi M, Endo S, et al. Clinical and molecular epidemiological features of tuberculosis after the 2011 Japan earthquake and tsunami. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2016; 20(4):505–14. Epub 2016/03/13. https://doi.org/10.1058/ijtld.15.0067 PMID: 26970161.

37. Murase Y, Maeda S, Yamada H, Ohkado A, Chikamatsu K, Mizuno K, et al. Clonal expansion of multi-drug-resistant and extensively drug-resistant tuberculosis, Japan. Emerging infectious diseases. 2010; 16(6):948–54. Epub 2010/05/29. https://doi.org/10.3201/eid1606.091844 PMID: 20507745.

38. Stavrum R, PrayGod G, Range N, Fa hurlot-Jepsen D, Jeremiah K, Fa hurlot-Jepsen M, et al. Increased level of acute phase reactants in patients infected with modern Mycobacterium tuberculosis genotypes in Mwanza, Tanzania. BMC infectious diseases. 2014; 14:309. Epub 2014/06/07. https://doi.org/10.1186/1471-2334-14-309 PMID: 24903071.

39. Chen KS, Liu T, Lin RR, Peng YP, Xiong GC. Tuberculosis transmission and risk factors in a Chinese antimony mining community. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2016; 20(1):57–62. Epub 2015/12/22. https://doi.org/10.1058/ijtld.15.0215 PMID: 26888529.

40. Dawson P, Perri BR, Ahuja SD. High Tuberculosis Strain Diversity Among New York City Public Housing Residents. American journal of public health. 2016; 106(3):563–8. Epub 2015/12/23. https://doi.org/10.2105/AJPH.2015.302910 PMID: 26691125.

41. Devi KR, Bhutia R, Bhowmick S, Mukherjee K, Mahanta J, Narain K. Genetic Diversity of Mycobacterium tuberculosis isolates from Assam, India: Dominance of Beijing Family and Discovery of Two New Clades Related to CAS1_Delhi and EAI Family Based on Spoligotyping and MIRU-VNTR Typing. PLoS one. 2015; 10(12):e0145860. Epub 2015/12/25. https://doi.org/10.1371/journal.pone.0145860 PMID: 26701129.

42. Diab HM, Nakajima C, Kotb SA, Mokhtar NF, Abdelaal AS, et al. First insight into the genetic population structure of Mycobacterium tuberculosis isolated from pulmonary tuberculosis patients in Egypt. Tuberculosis. 2016; 96:13–20. Epub 2016/01/21. https://doi.org/10.1016/j.tube.2015.11.002 PMID: 26786649.

43. Geng E, Kreiswirth B, Driver C, Li J, Burzynski J, DellaLatta P, et al. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. The New England journal of medicine. 2002; 346 (19):1453–8. Epub 2002/05/10. https://doi.org/10.1056/NEJMoa012972 PMID: 12000815.

44. Hu Y, Mathema B, Zhao Q, Zheng X, Li D, Jiang W, et al. Comparison of the socio-demographic and clinical features of pulmonary TB patients infected with sub-lineages within the W-Beijing and non-Beijing Mycobacterium tuberculosis. Tuberculosis. 2016; 97:18–25. Epub 2016/03/17. https://doi.org/10.1016/j.tube.2015.11.007 PMID: 26980491.

45. Kik SV, Verver S, van Soolingen D, de Haas PE, Cobelens FG, Kremer K, et al. Tuberculosis outbreaks predicted by characteristics of first patients in a DNA fingerprint cluster. American journal of respiratory and critical care medicine. 2008; 178(1):96–104. Epub 2008/04/05. https://doi.org/10.1164/rccm.200708-1256OC PMID: 18388352.

46. Kozinska M, Zientek J, Augustynowicz-Kopec E, Zwolska Z, Kozieleski J. Transmission of tuberculosis among people living in the border areas of Poland, the Czech Republic, and Slovakia. Polskie Archiwum Medycyny Wewnetrznej. 2016; 126(1–2):32–40. Epub 2016/02/05. PMID: 26842376.

47. Li Y, Cao X, Li S, Wang H, Wei J, Liu P, et al. Characterization of Mycobacterium tuberculosis isolates from Hebei, China: genotypes and drug susceptibility phenotypes. BMC infectious diseases. 2016; 16 (1):107. Epub 2016/03/05. https://doi.org/10.1186/s12879-016-1441-2 PMID: 26939531.

48. Morcillo N, Zumarraga M, Imperiale B, Di Giulio B, Chirico C, Kuriger A, et al. Tuberculosis transmission of predominant genotypes of Mycobacterium tuberculosis in northern suburbs of Buenos Aires city region. Revista Argentina de microbiologia. 2007; 39(3):145–50. Epub 2007/11/09. PMID: 17987850.

49. Penuelas-Urquides K, Martinez-Rodriguez HG, Enciso-Moreno JA, Molina-Salinas GM, Silva-Ramirez B, Padilla-Rivas GR, et al. Correlations between major risk factors and closely related Mycobacterium tuberculosis isolates grouped by three current genotyping procedures: a population-based study in northeast Mexico. Memorias do Instituto Oswaldo Cruz. 2014; 109(6):814–9. Epub 2014/10/16. https://doi.org/10.1590/0074-0276130550 PMID: 25317710.

50. Perez-Lago L, Herranz M, Comas I, Ruiz-Serrano MJ, Lopez Roa P, Bouza E, et al. UltraFast Assessment of the Presence of a High-Risk Mycobacterium tuberculosis Strain in a Population. Journal of clinical microbiology. 2016; 54(3):779–81. Epub 2016/01/01. https://doi.org/10.1128/JCM.02851-15 PMID: 26719445.

51. Talarico S, Ijaz K, Zhang X, Mukasa LN, Zhang L, Marrs CF, et al. Identification of factors for tuberculosis transmission via an integrated multidisciplinary approach. Tuberculosis. 2011; 91(3):244–9. Epub 2011/03/04. https://doi.org/10.1016/j.tube.2011.01.007 PMID: 21367661.
52. Nogueira CL, Prim RI, Senna SG, Rovaris DB, Maurici R, Rossetti ML, et al. First insight into the molecular epidemiology of Mycobacterium tuberculosis in Santa Catarina, southern Brazil. Tuberculosis. 2016; 97:57–64. Epub 2015/3/17. https://doi.org/10.1016/j.tube.2015.12.005 PMID: 26980497.

53. Outhred AC, Holmes N, Sadsad R, Martinez E, Jelfs P, Hill-Cawthorne GA, et al. Identifying Likely Transmission Pathways within a 10-Year Community Outbreak of Tuberculosis by High-Depth Whole Genome Sequencing. PloS one. 2016; 11(3):e0150550. Epub 2016/03/05. https://doi.org/10.1371/journal.pone.0150550 PMID: 26938641

54. Gonzalez Diaz A, Battaglioni T, Diaz Rodriguez R, Goza Valdes R, Gonzalez Ochoa E, Van der Stuyft P. Molecular epidemiology of tuberculosis in Havana, Cuba, 2009. Tropical medicine & international health: TM & IH. 2015; 20(11):1534–42. Epub 2015/07/28. https://doi.org/10.1111/tmi.12569 PMID: 26214009.

55. Hernandez-Garduno E, Kunimoto D, Wang L, Rodrigues M, Elwood RK, Black W, et al. Predictors of clustering of tuberculosis in Greater Vancouver: a molecular epidemiologic study. CMAJ: Canadian Medical Association journal = journal de l’Association medicale canadienne. 2002; 167(4):349–52. Epub 2002/08/29. https://doi.org/10.1503/cmaj.167.4.0349.

56. Jimenez-Corona ME, Cruz-Hervert LP, Garcia-Garcia L, Ferreyra-Reyes L, Delgado-Sanchez G, Bobadilla-Del-Valle M, et al. Association of diabetes and tuberculosis: impact on treatment and post-treatment outcomes. Thorax. 2013; 68(3):214–20. https://doi.org/10.1136/thoraxjnl-2012-201756 PMID: 23250998

57. Wang G, Lau SK, Liu F, Zhao Y, Li HM, Li BX, et al. Molecular epidemiology and clinical characteristics of drug-resistant Mycobacterium tuberculosis in a tuberculosis referral hospital in China. PloS one. 2014; 9(10):e110209. Epub 2014/10/11. https://doi.org/10.1371/journal.pone.0110209 PMID: 25302501

58. Yang C, Shen X, Peng Y, Lan R, Zhao Y, Long B, et al. Transmission of Mycobacterium tuberculosis in China: a population-based molecular epidemiologic study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2015; 61(2):219–27. Epub 2015/04/02. https://doi.org/10.1093/cid/civ255 PMID: 25829000

59. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS medicine. 2008; 5(7):e152. Epub 2008/07/18. https://doi.org/10.1371/journal.pmed.0050152 PMID: 18630984

60. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff TH, et al. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2007; 45(4):428–35. Epub 2007/02/20. https://doi.org/10.1086/519841 PMID: 17638189.

61. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lonroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC medicine. 2011; 9:81. Epub 2011/07/05. https://doi.org/10.1186/1741-7015-9-81 PMID: 21722362

62. Ponce-De-Leon A, Garcia-Garcia Md Mde L, Garcia-Sancho MC, Gomez-Perez FJ, Valdespin-Gomez JL, Olaza-Fernandez G, et al. Tuberculosis and diabetes in southern Mexico. Diabetes Care. 2004; 27(7):1584–90. PMID: 15220232.

63. Restrepo BI, Schlesinger LS. Impact of diabetes on the natural history of tuberculosis. Diabetes research and clinical practice. 2014; 106(2):191–9. Epub 2014/08/02. https://doi.org/10.1016/j.diabres.2014.06.011 PMID: 25082309

64. Ruslami R, Aarmoutse RE, Alisjahbana B, van der Ven AJ, van Crevel R. Implications of the global increase of diabetes for tuberculosis control and patient care. Tropical medicine & international health: TM & IH. 2010; 15(11):1289–99. Epub 2010/10/20. https://doi.org/10.1111/j.1469-0691.2010.02625.x PMID: 20955495.

65. Singla R, Khan N, Al-Sharif N, Ai-Sayegh MO, Shaikh MA, Osman MM. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2006; 10(1):74–9. Epub 2006/02/10. PMID: 16466041.

66. Borgdorff MW, van Soolingen D. The re-emergence of tuberculosis: what have we learnt from molecular epidemiology? Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2013; 19(10):889–901. Epub 2013/06/05. https://doi.org/10.1111/1469-0691.12253 PMID: 23731470

67. Lonroth K, Roglic G, Harries AD. Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. The lancet Diabetes & endocrinology. 2014; 2(9):730–9. Epub 2014/09/10. https://doi.org/10.1016/S2213-8587(14)70109-3 PMID: 25194886.

68. Mathema B, Kurepina NE, Bifani PJ, Kreiswirth BN. Molecular epidemiology of tuberculosis: current insights. Clinical microbiology reviews. 2006; 19(4):658–85. Epub 2006/10/17. https://doi.org/10.1128/CMR.00061-05 PMID: 17041139
Molecular clustering of diabetes and pulmonary tuberculosis

Fok A, Numata Y, Schulzer M, FitzGerald MJ. Risk factors for clustering of tuberculosis cases: a systematic review of population-based molecular epidemiology studies. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2008; 12(5):480–92. Epub 2008/04/19. PMID: 18419882.

Nava-Aguilera E, Andersson N, Harris E, Mitchell S, Hamel C, Shea B, et al. Risk factors associated with recent transmission of tuberculosis: systematic review and meta-analysis. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2009; 13(1):17–26. Epub 2008/12/25. PMID: 19105874.

Shariff NM, Safian N. Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: A case control study. International journal of mycobacteriology. 2015; 4(4):323–9. Epub 2016/03/12. https://doi.org/10.1016/j.ijmyco.2015.09.003 PMID: 26964816.

Reis-Santos B, Locatelli R, Horta BL, Faerstein E, Sanchez MN, Riley LW, et al. Socio-demographic and clinical differences in subjects with tuberculosis with and without diabetes mellitus in Brazil—a multivariate analysis. PloS one. 2013; 8(4):e62604. Epub 2013/05/03. https://doi.org/10.1371/journal.pone.0062604 PMID: 23638123

Leung CC, Lam TH, Chan WM, Yew WW, Ho KS, Leung GM, et al. Diabetic control and risk of tuberculosis: a cohort study. American journal of epidemiology. 2008; 167(12):1486–94. Epub 2008/04/11. https://doi.org/10.1093/aje/kwn075 PMID: 18400769.

Bock NN, Jensen PA, Miller B, Nardell E. Tuberculosis infection control in resource-limited settings in the era of expanding HIV care and treatment. The Journal of infectious diseases. 2007; 196 Suppl 1: S108–13. Epub 2007/08/30. https://doi.org/10.1086/518661 PMID: 17624819.

Dekhil N, Mftahi N, Mhenni B, Ben Fraj S, Haltiti R, Belhaj S, et al. MDR-TB Outbreak among HIV-Negative Tunisian Patients followed during 11 Years. PloS one. 2016; 11(4):e0153983. Epub 2016/04/29. https://doi.org/10.1371/journal.pone.0153983 PMID: 27124599

Harris TG, Sullivan Meissner J, Proops D. Delay in diagnosis leading to nosocomial transmission of tuberculosis at a New York City health care facility. American journal of infection control. 2013; 41(2):155–60. Epub 2012/07/04. https://doi.org/10.1016/j.ajic.2012.02.015 PMID: 22750037.

Yuen CM, Kammerer JS, Marks K, Navin TR, France AM. Recent Transmission of Tuberculosis—United States, 2011–2014. PloS one. 2016; 11(4):e0153728. Epub 2016/04/16. https://doi.org/10.1371/journal.pone.0153728 PMID: 27082644.

Gomez DI, Twahirwa M, Schlesinger LS, Restrepo BI. Reduced Mycobacterium tuberculosis association with monocytes from diabetes patients that have poor glucose control. Tuberculosis. 2013; 93(2):192–7. Epub 2012/11/08. https://doi.org/10.1016/j.tube.2012.10.003 PMID: 23131496

Gonzalez Y, Herrera MT, Soldevila G, Garcia-Garcia L, Fabian G, Perez-Arredanz EM, et al. High glucose concentrations induce TNF-alpha production through the down-regulation of CD33 in primary human monocytes. BMC immunology. 2012; 13:19. https://doi.org/10.1186/1471-2172-13-19 PMID: 22500980

Restrepo BI, Fisher-Hoch SP, Pino PA, Salinas A, Rahbar MH, Mora F, et al. Tuberculosis in poorly controlled type 2 diabetes: altered cytokine expression in peripheral white blood cells. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2008; 47(5):634–41. Epub 2008/07/26. https://doi.org/10.1086/590565 PMID: 18652554.

Wang CH, Yu CT, Lin HC, Liu CY, Kuo HP. Hypodense alveolar macrophages in patients with diabetes mellitus and active pulmonary tuberculosis. Tuberce and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 1999; 79(4):235–42. Epub 2000/02/29. https://doi.org/10.1086/518661 PMID: 17624819.

Al-Attyah RA, Mustafa AS. Mycobacterial antigen-induced T helper type 1 (Th1) and Th2 reactivity of peripheral blood mononuclear cells from diabetic and non-diabetic tuberculosis patients and Mycobacterium bovis bacilli Calmette-Guerin (BCG)-vaccinated healthy subjects. Clinical and experimental immunology. 2009; 158(1):64–73. Epub 2009/09/10. https://doi.org/10.1111/j.1365-2249.2009.04000.x PMID: 19737232

Kumar NP, Sridhar R, Banurekha VV, Jawahar MS, Nutman TB, Babu S. Expansion of pathogen-specific T-helper 1 and T-helper 17 cells in pulmonary tuberculosis with coincident type 2 diabetes mellitus. The Journal of infectious diseases. 2013; 208(5):739–48. Epub 2013/05/30. https://doi.org/10.1093/infdis/jit241 PMID: 23715661

Tsukaguchi K, Okamura H, Matsuzawa K, Tamura M, Miyazaki R, Tamaki S, et al. [Longitudinal assessment of IFN-gamma production in patients with pulmonary tuberculosis complicated with diabetes mellitus]. Kekkaku: [Tuberculosis]. 2002; 77(5):409–13. Epub 2002/06/21. PMID: 12073618.
Molecular clustering of diabetes and pulmonary tuberculosis

85. Vallerskog T, Martens GW, Kornfeld H. Diabetic mice display a delayed adaptive immune response to Mycobacterium tuberculosis. Journal of immunology. 2010; 184(11):6275–82. Epub 2010/04/28. https://doi.org/10.4049/jimmunol.1000304 PMID: 20421645

86. Restrepo BI, Schlesinger LS. Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus. Tuberculosis. 2013; 93 Suppl:S10–4. Epub 2014/01/07. https://doi.org/10.1016/S1472-9792(13)70004-0 PMID: 24388642

87. Martinez N, Kornfeld H. Diabetes and immunity to tuberculosis. European journal of immunology. 2014; 44(3):617–26. Epub 2014/01/23. https://doi.org/10.1002/eji.201344301 PMID: 24448841

88. Chiang CY, Bai KJ, Lin HH, Chien ST, Lee JJ, Enarson DA, et al. The influence of diabetes, glycemic control, and diabetes-related comorbidities on pulmonary tuberculosis. PloS one. 2015; 10(3):e0121698. Epub 2015/03/31. https://doi.org/10.1371/journal.pone.0121698 PMID: 25822974

89. Harries AD, Lin Y, Satyanarayana S, Lonroth K, Li L, Wilson N, et al. The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2011; 15(11):1436–44. i. Epub 2011/09/10. https://doi.org/10.5588/ijtld.11.0503 PMID: 21902876.

90. Yates TA, Khan PY, Knight GM, Taylor JG, McHugh TD, Lipman M, et al. The transmission of Mycobacterium tuberculosis in high burden settings. The Lancet infectious diseases. 2016; 16(2):227–38. Epub 2016/02/13. https://doi.org/10.1016/S1473-3099(15)00499-5 PMID: 26867464.

91. Valentine JC, Pigott TD, Rothstein HR. How many studies do you need? A primer on statistical power for meta-analysis. Journal of Educational and Behavioral Statistics. 2010; 35(2):215–47.

92. Davey J, Turner RM, Clarke MJ, Higgins JP. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. BMC medical research methodology. 2011; 11(1):160.

93. Surikova OV, Voitech DS, Kuzmicheva G, Tatkov SI, Mokrousov IV, Narvskaya OV, et al. Efficient differentiation of Mycobacterium tuberculosis strains of the W-Beijing family from Russia using highly polymorphic VNTR loci. Eur J Epidemiol. 2005; 20(11):963–74. https://doi.org/10.1007/s10654-005-3636-5 PMID: 16284875.

94. Borgdorff MW, van Soolingen D. The re-emergence of tuberculosis: what have we learnt from molecular epidemiology? Clin Microbiol Infect. 2013; 19(3):893–901. https://doi.org/10.1111/cmi.12253 PMID: 23731470.

95. Jagielski T, van Ingen J, Rastogi N, Dziadek J, Mazur PK, Bielecki J. Current methods in the molecular typing of Mycobacterium tuberculosis and other mycobacteria. Biomed Res Int. 2014; 2014:645802. https://doi.org/10.1155/2014/645802 PMID: 24527454.

96. Varma-Basil M, Kumar S, Arora J, Angrup A, Zozio T, Banavaliker JN, et al. Comparison of spoligotyping, mycobacterial interspersed repetitive units typing and IS6110-RFLP in a study of genotypic diversity of Mycobacterium tuberculosis in Delhi, North India. Mem Inst Oswaldo Cruz. 2011; 106(5):524–35. PMID: 21894371.

97. de Beer JL, van Ingen J, de Vries G, Erkenks C, Sebek M, Mulder A, et al. Comparative study of IS6110 restriction fragment length polymorphism and variable-number tandem-repeat typing of Mycobacterium tuberculosis isolates in the Netherlands, based on a 5-year nationwide survey. J Clin Microbiol. 2013; 51(4):1193–8. https://doi.org/10.1128/JCM.03061-12 PMID: 23363841.

98. Hong MS, Kim Y, Cho EJ, Lee JS, Kwak HK, Kim JH, et al. Comparison of the characteristics of Mycobacterium tuberculosis isolates from sputum and lung lesions in chronic tuberculosis patients. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology. 2017. Epub 2017/06/18. https://doi.org/10.1007/s10096-017-3025-5 PMID: 28620844.

99. Lieberman TD, Wilson D, Misra R, Xiong LL, Moodley P, Cohen T, et al. Genomic diversity in autopsy samples reveals within-host dissemination of HIV-associated Mycobacterium tuberculosis. Nature medicine. 2016; 22(12):1470–4. Epub 2016/11/01. https://doi.org/10.1038/nm.4205 PMID: 27798613.

100. International Diabetes Federation. Diabetes Atlas 7th Edition (2015). https://www.idf.org/e-library/epidemiology-research/diabetes-atlas-13-diabetes-atlas-seventh-edition.html. Accessed July, 2017.

101. Oni T, Stoever K, Wilkinson RJ. Tuberculosis, HIV, and type 2 diabetes mellitus: a neglected priority. The Lancet Respiratory medicine. 2013; 1(5):356–8. Epub 2014/01/17. https://doi.org/10.1016/S2213-2600(13)70116-4 PMID: 24429192.

102. Zetola NM, Modongo C, Moonan PK, Click E, Oeltmann JE, Shepherd J, et al. Protocol for a population-based molecular epidemiology study of tuberculosis transmission in a high HIV-burden setting: the Botswana Kopanyo study. BMJ open. 2016; 6(5):e010046. Epub 2016/05/11. https://doi.org/10.1136/bmjopen-2015-010046 PMID: 27160840