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Global prevalence of diabetes mellitus in patients with tuberculosis: a systematic review and meta-analysis protocol

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Abstract

Introduction: Diabetes mellitus is an important risk factor for active tuberculosis (TB), which also adversely affect TB treatment outcomes. The escalating global DM epidemic is fueling the burden of TB and should therefore be a major target in the strategy for ending TB. This review aims to estimate the global prevalence of diabetes mellitus in patients with tuberculosis

Methods and analysis: This systematic review will include cross-sectional, case–control or cohort studies of populations including patients diagnosed with tuberculosis that have reported the prevalence of diabetes mellitus using one of the fourth standard recommendations for screening and diagnosis. This protocol is written in accordance with recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Relevant abstracts published in English/French from inception to December 31, 2016 will be searched in PubMed, Excerpta Medica Database, and online journals. Additionally, relevant unpublished papers and conference proceedings will be checked, as well as references of included articles. Two investigators will independently screen, select studies, extract data and assess the risk of bias in each study. The study-specific estimates will be pooled through a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence of diabetes across the studies. Heterogeneity will be assessed, and we will pool studies judged to be clinically homogenous. On the other hand, statistical heterogeneity will be evaluated by the χ^2 test on Cochrane's Q statistic. Funnel-plots analysis and Egger's test will be used to investigate publication bias. Results will be presented by continent or geographic regions.

Ethics and dissemination: The current study is based on published data, and thus ethical approval is not required. This systematic review and meta-analysis is expected to inform health care providers as well as general population on the co-occurrence of these threatening conditions. The final report of this study, in the form of a scientific paper, will be published in a peer-reviewed journal. Findings will further be presented at conferences and submitted to relevant health authorities.

Strengths and limitations of this study

- This will be the first systematic review and meta-analysis aiming to estimate the global prevalence of diabetes mellitus in patients suffering from tuberculosis.
- Methodological and statistical procedures that will be used to derive accurate estimates are powerful and reliable.
- This review would be limited by difficulties related to the accurate diagnosis of tuberculosis infection in some regions.

  Another possible limitation could be the heterogeneity generated by the variability in standards used for diagnosis of diabetes mellitus, especially as the definition of diabetes has changed over time but assessment of heterogeneity will circumvent this limitation

Ethics and dissemination

This study is based on published data, and therefore ethical approval is not a requirement. The final report of this study in the form of a scientific paper will be published in a peer-reviewed journal. Its findings will also be presented at conferences and submitted to relevant health authorities. We also plan to update the review in the future to monitor changes and guide

health service and policy solutions. This protocol is written in accordance with recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement

Introduction

Rationale

Despite the laudable progress registered in the control of tuberculosis, it remains a huge global health threat [1]. In 2014, an estimated 9.6 million people developed new active TB and 1.5 million people died from the disease [2]. Although HIV is still the greatest risk factor for TB, there are several other important determinants of the TB epidemic, among which diabetes mellitus (DM) is of growing interest [3]. Indeed, there is overwhelming evidence that DM represents a major impediment in bending the TB epidemic. DM and poor glycemic control triple the risk of TB and adversely affect TB treatment outcomes such as prolongation of culture conversion, treatment failure, relapse and death. Much more, the world is currently facing a surge in DM prevalence with 1 adult on 11 who has DM and this will increase to 1/10 adults by 2040. The DM epidemic is therefore fueling the TB epidemic [4–6]. The vital need to address the escalating global DM epidemic as part of the strategy for ending TB has led to the creation of Collaborative Framework for Care and Control of Tuberculosis and Diabetes which provides guidance on bidirectional screening and treatment of the two diseases [7–9]. The framework recommends as one major key points the screening and management of DM in patients with TB [3,10]. Systematic screening has shown prevalence rates of DM in TB patients up to 15%, especially in countries with high prevalence of DM at the population level [7–11]. However we are not aware of any previous effort to evaluate the burden of DM in TB patients at the global level. We present here a protocol for a systematic review and meta-

analysis to summarize the existing data on the prevalence of DM in patients with TB, with the aim of providing accurate data for monitoring of future trends.

Objectives

This systematic review aims to determine the global prevalence of DM among patients with TB.

Review question

This review of studies published in the past 30 years, from 1 January 1986 to 31 August 2016, should answer the following question:

What is the global prevalence of DM among patients with TB?

Criteria for considering studies for the review

Inclusion criteria

We will include cross-sectional, case–control or cohort studies conducted in patients suffering from pulmonary or extra-pulmonary, drug-sensitive or resistant TB and reporting on the prevalence of DM or providing enough data to compute this estimate. The diagnosis of diabetes will have to have been made by a physician or defined based on measured fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), or self-report, according to WHO criteria [12]. Tuberculosis cases must have been diagnosed based on WHO criteria [].

Exclusion criteria

We will exclude:

1. Letters, reviews, commentaries and editorials and cases series with less than 50 patients

2. Duplicates: for studies published in more than one paper, the most comprehensive one reporting the largest sample size will be considered.

3. Studies whose key data will not be accessible even after request from the authors.

4. Studies where the diagnosis of DM is not based on standard and validated criteria.

Search strategy for identifying relevant studies

The search strategy will be implemented in two stages:

Bibliographic database searches

A. Relevant abstracts on the prevalence of DM among TB patients will be identified via searching PubMed, Excerpta Medica Database (Embase), Index Medicus and online journals. The search will be limited to studies published from inception to December 31, 2016. Key search terms will include: "tuberculosis", "TB", "mycobacterium", "diabetes", "diabetic patients" and "hyperglycemia". The PubMed search strategy is shown in Table 1, and will be adapted for other databases.

B. Abstracts of all eligible papers will be reviewed and their full articles in the second time. Additionally, references of all relevant articles will be scrutinized for other potential data sources, and their full texts will be accessed in a similar way. Authors whose full text papers will not be accessible by the numerous internet-based sources will be directly contacted to provide them. In case of no feedback from these authors, the corresponding studies will be excluded.

Selection of studies deemed relevant for inclusion in the review

Assessment of eligible papers will be independently run by two authors using an assessment guide to ensure that the selection criteria are reliably applied by them all. They will screen titles and abstracts obtained from the searches and retrieve all full texts of potentially eligible papers. Thereafter, they will independently review the full text of each potentially eligible study, compare their results and resolve any discrepancy by discussion and consensus. If a decision is not reached, a third review author will be consulted for arbitration. Level of agreement between review authors will be measured using the Cohen's Kappa statistic [13].

Assessment of methodological quality and reporting of data

The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses will be used to assess the methodological quality and risk of bias for each study [14]. The STROBE checklist will serve to evaluate the quality of reporting of observational studies [22]. Risk of bias and quality scores will be presented in a table.

Data extraction and management

A data extraction sheet will be used to collect information relating to the country, the region, year of publication, type of study, period of the study, study design, study setting, number of participants, mean/median age or age range of the population, diagnostic criteria for each condition, the presence of another important comorbidity like HIV and the prevalence of DM. Where prevalence rates or information for calculating them (eg, sample size, number of outcomes) are lacking, we will directly contact the corresponding author to request the information. We will conduct a subgroup analysis using comorbidities, different diagnosis criteria and period of the study. The results will be separate to show the population

characteristics and prevalence within individual countries. Where it will not be possible to disaggregate the data by country, the study will be presented as one and the countries in which the study was done will be shown.

Statistical analysis

Data will be analyzed using Stata software (Stata Corp V.14, Texas, USA). A meta-analysis will be conducted for data obtained from studies in which DM will have been diagnosed using the same diagnosis criteria. Standard errors (SEs) for the study-specific estimates will first be determined from the point estimate and the appropriate denominators, assuming a binominal distribution. Then, the study-specific estimates will be pooled through a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence across studies, after stabilizing the variance of individual studies using the Freeman-Tukey double arc-sine transformation [15]. Heterogeneity will be evaluated by the χ^2 test on Cochrane's Q statistic which is quantified by I^2 values, assuming that I^2 values of 25%, 50% and 75% represent low, medium and high heterogeneity respectively [16]. Where substantial heterogeneity will be detected, a subgroup analysis will be performed to detect its possible sources using the following grouping variables: age group, the period of diagnosis (beginning or ending of treatment), positivity of sputum culture at microscopy, relapse or recurrence, association to others comorbid conditions such as HIV, continent or geographical area and study quality. Funnel plots analysis and Egger's test will be performed to detect publication bias. Results will be presented by continent or geographical regions.

Results reporting and presentation

The study selection process will be summarised using a flow diagram. Reasons for studies' exclusion will be described. This will follow the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies [17]. Tables and forest plots will serve to

summarize quantitative data where appropriate. We will examine prevalence by continent, time period of diagnosis, presence of others comorbid conditions, and classification of TB infection depending on available data. We plan to report on quality scores and risk of bias for each eligible study. This may be tabulated and accompanied by narrative summaries.

Conclusion

TB remains a major global health problem. The prevalence of DM which is known as an important risk factor for TB patients is escalating worldwide and is thought to contribute significantly in the burden of TB. According to the rising figures of DM worldwide, we hypothesized that the global prevalence of DM among TB patients is elevated and we are conducting this review to estimate its magnitude. We expect to provide accurate data for effective policies making and for monitoring of future trends.

The major limitation of this study could be the heterogeneity generated by the variability in DM diagnostic criteria for , especially as the definition of DM has changed over time. Despite these potential limitations, this review will be, to the best of our knowledge, the first study aiming to estimate the global prevalence of DM among TB patients.

Protocol and registration

The protocol for this review has been published in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number: CRD42016049901

Authors' Contributions

JJNN, ATT, FTAE and GW conceived and designed the protocol. ATT drafted the manuscript. ATT, JJRB, JRNN, FTAE, GSW, ADK and JJNN critically revised the manuscript for methodological and intellectual content. JJNN is the guarantor of the review. All authors approved the final version of this manuscript.

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Competing interests

None.

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Table 1: Search strategy for PubMed

Search	Search terms
1	"Tuberculosis" OR "TB" OR "Mycobacterium"
2	"Diabetes" OR "diabetes mellitus" OR "hyperglycemia" OR "diabetic patients" OR dysglycemia OR glucose abnormalities OR glucose intolerance
3	# 1 AND # 2
4	Studies published in English/French

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) with pages containing all items of review protocol

Section and topic	Page N° of items	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1	Identify the report as a protocol of a systematic review
Registration	9	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	10	Describe contributions of protocol authors and identify the guarantor of the review
Support:		
Sources	10	Indicate sources of financial or other support for the review
Sponsor		Provide name for the review funder and/or sponsor
INTRODUCTION		
Rationale	4	Describe the rationale for the review in the context of what is already known
Objectives	5	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	5&6	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	12	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	6	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	7	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)

Data collection process	7	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	8	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	8	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	7	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	8&9	Describe criteria under which study data will be quantitatively synthesised
	8	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	8	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	8	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	8	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	8	Describe how the strength of the body of evidence will be assessed (such as GRADE)

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Abstract

Introduction: Diabetes mellitus is an important risk factor for active tuberculosis (TB), which also adversely affect TB treatment outcomes. The escalating global DM epidemic is fueling the burden of TB and should therefore be a major target in the strategy for ending TB. This review aims to estimate the global prevalence of diabetes mellitus in patients with tuberculosis

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Strengths and limitations of this study

- This will be the first systematic review and meta-analysis aiming to estimate the global prevalence of diabetes mellitus in patients suffering from tuberculosis.
- Methodological and statistical procedures that will be used to derive accurate estimates are powerful and reliable.
- This review would be limited by difficulties related to the accurate diagnosis of tuberculosis infection in some regions.
- Since we will only include studies that full-text or abstracts are published in French/English, we could missed some studies published in another language. However, most of paper now are published in English even from researchers in countries where English is not the official language, so, most of the studies on the topic are expected to be in English.
- Another possible limitation could be the heterogeneity generated by the variability in standards used for diagnosis of diabetes mellitus, especially as the definition of diabetes has changed over time but assessment of heterogeneity will circumvent this limitation

Ethics and dissemination

This study is based on published data, and therefore ethical approval is not a requirement. This systematic review and meta-analysis is expected to inform health care providers as well as general population on the co-occurrence of these threatening conditions. The final report of this study in the form of a scientific paper will be published in a peer-reviewed journal. Its findings will also be presented at conferences and submitted to relevant health authorities. We also plan to update the review in the future to monitor changes and guide health service and

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Objectives

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Exclusion criteria

We will exclude:

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condition, the presence of another important comorbidity like HIV and the prevalence of DM. Where prevalence rates or information for calculating them (eg, sample size, number of outcomes) are lacking, we will directly contact the corresponding author to request the information. We will conduct a subgroup analysis using comorbidities, different diagnosis criteria and period of the study. The results will be separate to show the population characteristics and prevalence within individual countries. Where it will not be possible to disaggregate the data by country, the study will be presented as one and the countries in which the study was done will be shown.

Statistical analysis

Data will be analyzed using Stata software (Stata Corp V.14, Texas, USA). A meta-analysis will be conducted for data obtained from studies in which DM will have been diagnosed using the same diagnosis criteria. Standard errors (SEs) for the study-specific estimates will first be determined from the point estimate and the appropriate denominators, assuming a binominal distribution. Then, the study-specific estimates will be pooled through a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence across studies, after stabilizing the variance of individual studies using the Freeman-Tukey double arc-sine transformation [15]. Heterogeneity will be evaluated by the χ^2 test on Cochrane's Q statistic which is quantified by I^2 values, assuming that I^2 values of 25%, 50% and 75% represent low, medium and high heterogeneity respectively [16]. Where substantial heterogeneity will be detected, a subgroup analysis will be performed to detect its possible sources using the following grouping variables: age group, the period of diagnosis (beginning or ending of treatment), positivity of sputum culture at microscopy, relapse or recurrence, association to others comorbid conditions such as HIV, continent or geographical area and study quality. Funnel plots analysis and Egger's test will be performed to detect publication bias. Results will be presented by continent or geographical regions.

Results reporting and presentation

The study selection process will be summarised using a flow diagram. Reasons for studies' exclusion will be described. This will follow the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies [17]. Tables and forest plots will serve to summarize quantitative data where appropriate. We will examine prevalence by continent, time period of diagnosis, presence of others comorbid conditions, and classification of TB infection depending on available data. We plan to report on quality scores and risk of bias for each eligible study. This may be tabulated and accompanied by narrative summaries.

Conclusion

TB remains a major global health problem. The prevalence of DM which is known as an important risk factor for TB patients is escalating worldwide and is thought to contribute significantly in the burden of TB. According to the rising figures of DM worldwide, we hypothesized that the global prevalence of DM among TB patients is elevated and we are conducting this review to estimate its magnitude. We expect to provide accurate data for effective policies making and for monitoring of future trends. Much more, this review may identify the research gaps and remaining challenges that may form the basis of future studies to improve our understanding of the prevalence and impact of DM in TB patients

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The protocol for this review has been published in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number: CRD42016049901

Field Code Changed

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Authors' Contributions

JJNN, ATT, FTAE and GW conceived and designed the protocol. ATT drafted the manuscript. ATT, JJRB, JRNN, FTAE, GSW, ADK and JJNN critically revised the manuscript for methodological and intellectual content. JJNN is the guarantor of the review. All authors approved the final version of this manuscript.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) with pages containing all items of review protocol

Section and topic	Page N° of items	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1	Identify the report as a protocol of a systematic review
Registration	9	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	10	Describe contributions of protocol authors and identify the guarantor of the review
Support:		
Sources	10	Indicate sources of financial or other support for the review
Sponsor		Provide name for the review funder and/or sponsor
INTRODUCTION		
Rationale	4	Describe the rationale for the review in the context of what is already known
Objectives	5	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	5&6	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	12	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	6	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	7	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)

Data collection process	7	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	8	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	8	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	7	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	8&9	Describe criteria under which study data will be quantitatively synthesised
	8	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	8	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	8	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	8	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	8	Describe how the strength of the body of evidence will be assessed (such as GRADE)

BMJ Open

Global prevalence of diabetes mellitus in patients with tuberculosis: a systematic review and meta-analysis protocol

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Global prevalence of diabetes mellitus in patients with tuberculosis: a systematic review and meta-analysis protocol

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Abstract

Introduction: Diabetes mellitus is an important risk factor for active tuberculosis (TB), which also adversely affect TB treatment outcomes. The escalating global DM epidemic is fueling the burden of TB and should therefore be a major target in the strategy for ending TB. This review aims to estimate the global prevalence of diabetes mellitus in patients with tuberculosis

Methods and analysis: This systematic review will include cross-sectional, case–control or cohort studies of populations including patients diagnosed with tuberculosis that have reported the prevalence of diabetes mellitus using one of the fourth standard recommendations for screening and diagnosis. This protocol is written in accordance with recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Relevant abstracts published in English/French from inception to December 31, 2016 will be searched in PubMed, Excerpta Medica Database, and online journals. Two investigators will independently screen, select studies, extract data and assess the risk of bias in each study. The study-specific estimates will be pooled through a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence of diabetes across the studies. Heterogeneity will be assessed, and we will pool studies judged to be clinically homogenous. On the other hand, statistical heterogeneity will be evaluated by the χ^2 test on Cochrane's Q statistic. Funnel-plots analysis and Egger's test will be used to investigate publication bias. Results will be presented by continent or geographic regions.

Ethics and dissemination

This study is based on published data, and therefore ethical approval is not a requirement. This systematic review and meta-analysis is expected to inform health care providers as well as general population on the co-occurrence of these threatening conditions. The final report of this study in the form of a scientific paper will be published in a peer-reviewed journal. Its findings will also be presented at conferences and submitted to relevant health authorities. We also plan to update the review in the future to monitor changes and guide health service and policy solutions.

Protocol and registration

The protocol for this review has been published in the PROSPERO International Prospective Register of systematic reviews, http://www.crd.york.ac.uk/PROSPERO registration number: CRD42016049901

Strengths and limitations of this study

- This will be the first systematic review and meta-analysis aiming to estimate the global prevalence of diabetes mellitus in patients suffering from tuberculosis.
- Methodological and statistical procedures that will be used to derive accurate estimates are powerful and reliable.
- This review would be limited by difficulties related to the accurate diagnosis of tuberculosis infection in some regions.
- Some studies could also be missed due to language restriction
- Another possible limitation could be the heterogeneity

Introduction

Rationale

Despite the laudable progress registered in the control of tuberculosis, it remains a huge global health threat [1]. In 2014, an estimated 9.6 million people developed new active TB and 1.5 million people died from the disease [2]. Although HIV is still the greatest risk factor for TB, there are several other important determinants of the TB epidemic, among which diabetes mellitus (DM) is of growing interest [3]. Indeed, there is overwhelming evidence that DM represents a major impediment in bending the TB epidemic. DM and poor glycemic control triple the risk of TB and adversely affect TB treatment outcomes such as prolongation of culture conversion, treatment failure, relapse and death. Much more, the world is currently facing a surge in DM prevalence with 1 adult on 11 who has DM and this will increase to 1/10 adults by 2040. The DM epidemic is therefore fueling the TB epidemic [4–6]. The vital need to address the escalating global DM epidemic as part of the strategy for ending TB has led to the creation of Collaborative Framework for Care and Control of Tuberculosis and Diabetes which provides guidance on bidirectional screening and treatment of the two diseases [7–9]. The framework recommends as one major key points the screening and management of DM in patients with TB [3,10]. Systematic screening has shown prevalence rates of DM in TB patients up to 15%, especially in countries with high prevalence of DM at the population level [7–11]. However we are not aware of any previous effort to evaluate the burden of DM in TB patients at the global level. We present here a protocol for a systematic review and meta-analysis to summarize the existing data on the prevalence of DM in patients with TB, with the aim of providing accurate data for monitoring of future trends.

Objectives

This systematic review aims to determine the global prevalence of DM among patients with TB.

Review question

This review of studies published in the past 30 years, from 1 January 1986 to 31 August 2016, should answer the following question:

What is the global prevalence of DM among patients with TB?

Criteria for considering studies for the review

Inclusion criteria

We will include cross-sectional, case–control or cohort studies conducted in patients suffering from pulmonary drug-sensitive or resistant TB and reporting on the prevalence of DM or providing enough data to compute this estimate. We will consider extra-pulmonary tuberculosis diagnosed by culture of Mycobacterium tuberculosis and also those which will have been treated as such despite the absence of culture of Mycobacterium Tuberculosis. However, this second group will not be considered for the meta-analysis but will be used for the narrative part review. The diagnosis of diabetes will have to have been made by a physician or defined based on measured fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), or self-report, according to WHO criteria [12]. Tuberculosis cases must have been diagnosed based on WHO criteria [13].

Exclusion criteria

We will exclude:

1- Commentaries, editorials and cases series with less than 50 patients..

2. Duplicates: for studies published in more than one paper, the most comprehensive one reporting the largest sample size will be considered.

3. Studies whose key data will not be accessible even after request from the authors.

Search strategy for identifying relevant studies

The search strategy will be implemented in two stages:

Bibliographic database searches

A. Relevant abstracts on the prevalence of DM among TB patients will be identified via searching PubMed, Excerpta Medica Database (Embase), Index Medicus and African online journals. The search will be limited to studies published from inception to December 31, 2016 Key search terms will include: “tuberculosis”, “TB”, “mycobacterium”, “diabetes”, “diabetic patients” and “hyperglycemia”. The PubMed search strategy is shown in Table 1, and will be adapted for other databases.

B. Abstracts of all eligible papers will be reviewed and their full articles in the second time. Additionally, references of all relevant articles will be scrutinized for other potential data sources, and their full texts will be accessed in a similar way. Authors whose full text papers will not be accessible by the numerous internet-based sources will be directly contacted to provide them. In case of no feedback from these authors, the corresponding studies will be excluded.

Selection of studies deemed relevant for inclusion in the review

Assessment of eligible papers will be independently run by two authors using an assessment guide to ensure that the selection criteria are reliably applied by them all (ATT and JJRB). They will screen titles and abstracts obtained from the searches and retrieve all full texts of potentially eligible papers. Thereafter, they will independently review the full text of each potentially eligible study, compare their results and resolve any discrepancy by discussion and consensus. If a decision is not reached, a third review author will be consulted for arbitration (JJNN). Level of agreement between review authors will be measured using the Cohen's Kappa statistic [14].

Assessment of methodological quality and reporting of data

The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses will be used to assess the methodological quality and risk of bias for each study [15]. Risk of bias and quality scores will be presented in a table.

Data extraction and management

A data extraction sheet will be used to collect information relating to the country, the region, year of publication, type of study, period of the study, study design, study setting, number of participants, mean/median age or age range of the population, diagnostic criteria for each condition, the presence of another important comorbidity like HIV and the prevalence of DM. Where prevalence rates or information for calculating them (eg, sample size, number of outcomes) are lacking, we will directly contact the corresponding author to request the information. We will conduct a subgroup analysis using comorbidities, different diagnosis criteria and period of the study. The results will be separate to show the population

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Authors' Contributions

JJNN, ATT, FTAE and GW conceived and designed the protocol. ATT drafted the manuscript. ATT, JJRB, JRNN, FTAE, GSW, ADK and JJNN critically revised the manuscript for methodological and intellectual content. JJNN is the guarantor of the review. All authors approved the final version of this manuscript.

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Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	**3**
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	**1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	**10**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	/
Support:			
Sources	5a	Indicate sources of financial or other support for the review	**10**
Sponsor	5b	Provide name for the review funder and/or sponsor	**10**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	**10**
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Rationale	6	Describe the rationale for the review in the context of what is already known	**4**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	**5**
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting,	**5+6**

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Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	**13**
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	**7+8**
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	**7**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	**7**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	/
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	/
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	**7**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	**7+8**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	**8**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	**8**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	**8**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication	/

		bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	/

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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