SYSTEMATIC REVIEW AND META-ANALYSIS

Diabetes mellitus comorbidity in patients enrolled in tuberculosis drug efficacy trials around the world: A systematic review

Nurul Cholifah Lutfiana[1,2] | Job F.M. van Boven[1] | Muhammad Asim Masoom Zubair[1,3] | Michelle J. Pena[1] | Jan-Willem C. Alffenaar[1,4,5]

[1] Department of Clinical Pharmacy & Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2] Faculty of Medicine, Department of Biomedicine, Brawijaya University, Malang, Indonesia

[3] Department of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan

[4] Faculty of Medicine and Health, School of Pharmacy, University of Sydney, Sydney, Australia

[5] Westmead Hospital, Sydney, Australia

Correspondence
Dr Jan-Willem C. Alffenaar, Department of Clinical Pharmacy & Pharmacology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands.
Email: j.w.c.alffenaar@umcg.nl

Aims: With a prevalence of 16%, diabetes mellitus (DM) is one of the most frequent non-communicable comorbidities of tuberculosis (TB). DM is a major risk factor for adverse TB outcomes and may require personalized TB drug dosing regimens. However, information on the inclusion of DM in TB drug trials is lacking. We aimed to assess the percentage of recent TB drug efficacy trials that included DM patients.

Methods: A systematic review was performed and reported according to PRISMA guidelines. PubMed, Science Direct, and ClinicalTrials.gov databases were systematically searched for TB drug trials published between 1 January 2012 and 12 September 2017. Primary outcome was the percentage of TB drug trials performed around the world that included DM patients.

Results: Out of the included 41 TB drug trials, 12 (29.3%) reported DM comorbidity among the study participants. Nine trials (21.9%) excluded all patients with DM comorbidity, ten (24.4%) excluded only insulin-dependent or uncontrolled DM, and 10 (24.4%) did not mention whether DM was included or excluded. Of the 12 trials that included DM comorbidity, the majority did not report the diagnostic criteria for DM and none reported outcomes in the DM subpopulation. Inclusion of DM was higher in drug-resistant-TB trials (67%, $P = .003$, *vs* drug-susceptible) and trials performed in Asia (60%, $P = .006$, *vs* Africa).

Conclusions: Fewer than 1/3 recent TB drug trials reported the inclusion of DM. To better reflect real-world DM prevalence and differential TB drug effectiveness, inclusion of DM patients requires increased attention for future TB drug trials.

KEYWORDS

diabetes, drug trials, review, tuberculosis

Authors contributed equally, shared first authors.

1 | INTRODUCTION

The dual burden of tuberculosis (TB) and diabetes mellitus (DM) is a major global public health problem.[1] In 2017, the World Health Organization reported 10 million cases of TB and 1.3 million TB-related deaths.[2] Approximately 415 million people worldwide live with DM and another 318 million people have impaired glucose tolerance—a marker for future diabetes.[3] By 2040, these numbers are likely to grow to 642 million and 481 million, respectively.[4]

The global burden of TB-DM overlap is high, with a prevalence of 16% globally, 17% in Asia, 7% in Africa, 24% in North America, 23% in Oceania, 11% in South America, and 6% in Europe.[1] The International Diabetes Federation (IDF) estimates that 46% of diabetes cases worldwide (around 175 million) are not diagnosed, with the highest proportions concentrated in Africa (62%) and southeast Asia (54%), coinciding with the greatest TB burden. Globally, 84% of all people with undiagnosed diabetes live in low-income and middle-income countries where the management of these people is rarely optimal.[5] DM could severely threaten TB control and may become most profound in resource-poor areas where TB thrives.[6]

A systematic review and meta-analysis of studies published between 1980–2010 reported that DM is associated with 69% higher risk of death and increased risk of TB relapse than TB patients without DM.[7] Since 2010, several large cohort studies reported unfavourable effects of DM on TB outcomes. DM was associated with more severe clinical manifestations of TB such as higher frequency of cavities on chest X-ray and higher hospitalization rates.[8-10] Patients with DM were more likely to have up to 2 times higher TB reactivation, recurrence, and relapse.[8-11] TB-DM patients were more likely to have delayed sputum conversion and higher probability of treatment failure.[8,9,12] A recent systematic review showed that glycaemic control has a favourable effect on TB treatment outcomes and, conversely, uncontrolled DM or poor glycaemic control (i.e. HbA1c > 7%) was associated with delayed sputum conversion.[13,14]

Early screening for TB-DM comorbidity can help clinicians to act promptly, thereby resulting in improved TB treatment outcomes.[15] Notably, given the profound impact of DM comorbidity on TB treatment outcomes and the call for intensified precision drug therapy, this comorbidity should receive higher priority in prospective randomized clinical TB drug efficacy trials. However, an overview of current data on TB-DM comorbidity in recent TB drugs trials is lacking. This overview may help to raise awareness on the inclusion of DM comorbidity and could benefit the design of future TB drug trials. We therefore aimed to systematically review the inclusion of DM comorbidity in recent TB drug efficacy trials, with specific emphasis on differential outcomes of TB-DM overlap patients.

2 | METHODS

2.1 | Study design

A systematic review was performed and reported according to the Preferred Reporting Items for Systematic review and Meta-Analyses

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What is already known about this subject

- Globally, around 16% of tuberculosis (TB) patients suffer from comorbid diabetes mellitus
- Diabetes is a risk factor for TB, altered pharmacokinetics and can thus impact pharmacological TB treatment outcomes
- In recent years, multiple TB drug trials have been performed, yet a systematic overview of the inclusion of diabetes comorbidity and potential differential outcomes within these trials is lacking.

What this study adds

- This systematic review provides an overview of diabetes inclusion in recent TB drug trials performed around the world
- Of the 41 studies included, <1/3 TB drug trials reported the inclusion of patients with diabetes
- A total of 12 studies (29%) reported the inclusion of patients with diabetes, yet the vast majority of TB drug trials did not report the diagnostic criteria for diabetes
- None of the studies reported differential outcomes for the TB–diabetes overlap subpopulation, warranting increased attention on the design and analyses of future TB drug trials

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(PRISMA) statement (Supporting information Appendix S1). The review was registered at PROSPERO (registration number: 71203) and is available online on https://www.crd.york.ac.uk/prospero/display_record.php? RecordID = 71203.

2.2 | Information sources and search strategy

In this review, the PubMed, Science Direct and ClinicalTrials.gov databases were systematically searched (in September 2017) for TB drug trials published between 1 January 2012 and 12 September 2017 using combinations of the keywords "tuberculosis", AND "drug" AND "trial". Full search criteria can be found in Supporting information Appendix S2.

2.3 | Inclusion criteria

The following eligibility criteria were applied for studies to be considered for inclusion: (i) published in peer-reviewed journals; (ii) clinical trials or interventional studies of TB drug efficacy in TB confirmed (i.e. sputum smear or culture positive) patients that have been completed and published; and (iii) in English[16] and reflecting an original study. All criteria were required to be met for inclusion.

2.4 | Exclusion criteria

Exclusion criteria were: (i) studies only assessing risk factors, biomarkers (and not drugs) in the TB trials; (ii) reviews, comments, conference abstracts, case reports or editorials; and (iii) study designs other than clinical trials.

2.5 | Study selection

Study screening based on title and abstract and selection based on full-text assessment was first performed by one researcher (N.L.) and checked by a second researcher (M.Z.). Any discrepancies were solved by consensus and/or consultation of a third researcher if needed.

2.6 | Data extraction and data items

Data extracted included the studies' first author, the year of publication, study design, study sample size, number and percentage of comorbid DM patients, diagnostic criteria for DM, type of TB population, drug(s) studied, and country where the trial was performed. Again, data extraction was first performed by one researcher (N.L.) and subsequently checked by a second researcher (M.Z.). Any discrepancies were solved by consensus and/or consultation of a third researcher if needed.

2.7 | Study measures and outcomes

The primary outcome of interest was the percentage of TB drug trials performed around the world that included DM patients. Additionally, results were assessed per continent. Exploratory, more descriptive outcomes included differential outcomes of TB-DM patients (if reported). Chi-square tests were performed to assess potential statistical differences in inclusion (yes/no) of DM comorbidity across subgroups (e.g. type of TB and continent were trials were performed). A P-value <.05 was considered statistically significant.

2.8 | Assessment of reporting bias

To assess potential reporting bias, we searched for study protocols of each study to check recruitment criteria of DM patients in the eligible trials against reported population characteristics. If unclear, we contacted the study authors to get more information about the DM criteria and reported outcomes.

3 | RESULTS

3.1 | Study selection

After duplicates were removed, a total of 1177 records were screened based on abstract and title. We identified 54 potentially eligible full-text papers of which 13 studies were excluded after detailed review (10 studies were noninterventional, and 3 assessed a diagnostic tool or the pharmacokinetics of TB drugs and not the efficacy of the TB drug itself). A flow diagram is presented in Figure 1 and study characteristics of the final selection of 41 trials are presented in Table 1. Eligibility decisions for in- and excluded studies have been provided in Supporting information Appendix S3. Of note, compared to our initial study protocol we did not apply the full-text being available as an inclusion criterion, given that we did not restrict ourselves to online available full-texts only but also contacted study authors to retrieve full-texts.

3.2 | Study characteristics

The vast majority of TB drug trials was exclusively performed in Asia (n = 15; 37%) and Africa (n = 13; 32%). North America (USA) and South America (Brazil) contributed only one trial each, while others were performed in Europe (n = 2, both in Georgia) or in multiple sites around the world (n = 9). Study size varied between 31 patients for a TB trial performed in Georgia[25] and 1931 for a multicentre trial with moxifloxacin.[47] Drugs mostly studied were isoniazid, rifampicin, pyrazinamide and ethambutol.

3.3 | Overview of DM comorbidity in TB drug trials

Out of the included 41 trials, 12 (29.3%) reported DM comorbidity among the study participants (Figure 2).

Nine trials (21.9%) clearly excluded patients with any DM comorbidity, 10 (24.4%) excluded only insulin-dependent or uncontrolled DM but did not report data of noninsulin dependent DM patients, and 10 (24.3%) did not mention whether DM was included or excluded. DM was included in 9 of the 15 (60%) trials performed in Asia and in both European trials (Figure 2). In 12 of the 13 (92.3%) African TB trials, patients with DM comorbidity were excluded. There was a significant difference (P = .006) between DM inclusion in Asian and African TB drug trials. Of the 12 trials that included patients with DM comorbidity regardless of severity, 5 studies did not report the diagnostic criteria for DM. Three studies used random blood glucose.[36,37,54] One study used fasting plasma glucose and 2-hour oral glucose tolerance test[23] and 3 studies obtained DM comorbidity from patients' history.[38,39,48] The prevalence of DM among TB patients in the 12 trials ranged from 0.7% in Mongolia and Ukraine[54] to 36% in South Korea[19] with overall median DM prevalence of 12.3%. Naturally, in the study that specifically focused on TB-DM overlap, this was 100%.[23] Three out of 12 trials reporting DM comorbidity showed that DM was the most common comorbidity.[37-39] Of the 12 trials reporting DM comorbidity, none of the studies assessed any potential effects of DM on anti-TB drugs outcomes. Of note, 6 out of 9 (67%) drug trials for drug-resistant TB included DM comorbidity in their baseline characteristics, while only 4 out of the 32 (12.5%) drug-susceptible TB trials included DM comorbidity in their baseline characteristics, and this differed significantly (P = .003).
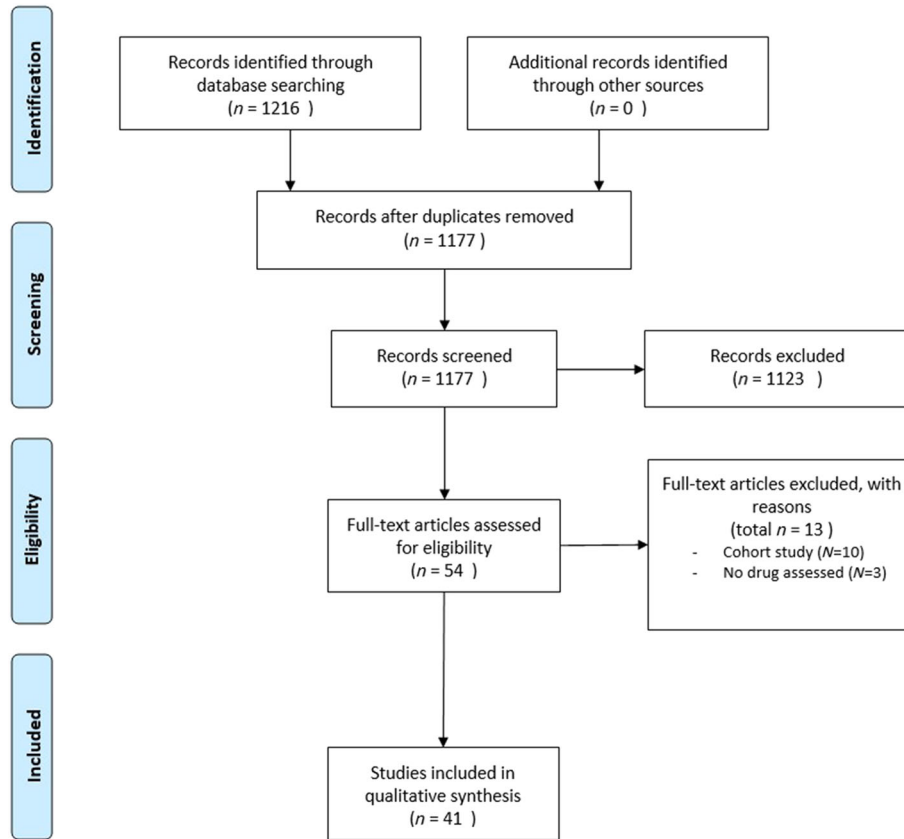
FIGURE 1 PRISMA flow diagram

4 | DISCUSSION

Data from this systematic review indicate that <1/3 recent TB drug efficacy trials reported the inclusion of patients with DM comorbidity regardless of DM severity. If included, diagnostic criteria for DM were often unclear. Notably, inclusion of DM was relatively higher in MDR-TB drug trials and trials performed in Asia. Although DM patients were included in some studies, no differential outcomes for DM-TB overlap patients were reported.

Asia has high DM prevalence among TB patients; therefore, it is not surprising that most trials that included DM comorbidity were conducted in Asia, mainly China. China and India are 2 leading countries that have piloted the TB-DM collaborative framework and have demonstrated bidirectional screening for both diseases.[57-59] Although India is one of the pilot countries, most drug trials conducted in India had unclear criteria for DM comorbidity, and one Indian trial even excluded DM patients. Most trials that excluded DM comorbidity were conducted in Africa. Notably, South Africa has high prevalence of TB, and TB ranks third in diseases that causes life-years lost,[60] but none of the TB drug trials conducted in South Africa screened for DM comorbidity. For South Africa, this omission may be related to the relatively low comorbid DM rates compared with, for example, comorbid human immunodeficiency virus/acquired immune deficiency syndrome. However, the few TB drug trials conducted in America also did not assess DM comorbidity, while DM rates in these continents are relatively

high.[1] In particular, multidrug-resistant TB (MDR-TB) continues to be a public health crisis and in MDR-TB the importance of DM comorbidity seems more widely acknowledged. Indeed, in a meta-analysis it was shown that DM was an independent risk factor for MDR-TB and, in most drug-resistant TB trials, DM comorbidity was more often included.[61] Regarding the effect of DM comorbidity to unfavourable treatment of TB, none of the TB trials that included DM comorbidity reported specific outcomes related to the TB-DM subpopulation. A systematic review suggested a phase III clinical trial to ensure the safe use of new TB drugs in diabetes patients.[62] Indeed, there is still a lack of sufficient data regarding pharmacokinetic and clinical data of TB drugs in DM patients, despite the continuous growth of DM patients in the future that will cause a further threat to TB control.

Some TB drug trials excluded insulin-dependent DM patients. Insulin-dependent diabetes will usually reflect uncontrolled DM.[63] As TB patients with uncontrolled DM are more likely to fail on treatment, trials that are specifically designed to show efficacy of a new TB drug usually exclude those patients as they could compromise trial results.[64]

Several underlying mechanisms to understand adverse treatment outcomes of TB due to hyperglycaemia have been suggested.[65,66] One mechanism is related to an altered immunological response[67-69] which is important, but difficult to account for in TB treatment decisions. Another factor that explains unfavourable treatment outcomes are the drug–drug and drug–disease interactions. A systematic

TABLE 1 Study characteristics of randomized clinical trials of anti-tuberculosis (TB) drugs (n = 41)

Author[ref]	Year	Type of study	Sample size	DM patients (n, %)	Diagnostic criteria for DM	Type of TB	Drugs	Country
Diacon et al.[17]	2012	Phase 2 RCT	85	DM insulin dependent were excluded	Judge by the investigator	PTB	Proteomanid, pyrazinamide, bedaquiline, rifafour, moxifloxacin	South Africa
Diacon et al.[18]	2012	Phase 2 RCT	89	DM insulin dependent were excluded	Judge by the investigator	PTB	Proteomanid, rifafour	South Africa
Lee et al.[19]	2012	Phase 2 RCT	39	14 (36%)	Unexplained, medical history and blood examination performed	XDR PTB	Linezolid	South Korea
Gler et al.[20]	2012	Phase 2 RCT	481	Evidence of clinically significant metabolic, endocrine diseases were excluded	unexplained	MDR-PTB	Delamanid	Philippines, Peru, Latvia, Estonia, China, Japan, Korea, Egypt and USA
Zhang et al.[21]	2013	Phase 2 RCT	38	5 (13.2%)	Unexplained, blood biochemistry performed	MDR-TB	Delamanid	China
Jawahar et al.[22]	2013	Phase 3 RCT	416	Excluded		PTB	Moxifloxacin, gatifloxacin	India
Wang et al.[23]	2013	Phase 2 RCT	100%	100%	Fasting blood glucose and oral glucose tolerance test	PTB	Retinol, vitamin D	China
Jindani et al.[24]	2014	Phase 3 RCT 3	827	Unclear		PTB	Rifapentine, moxifloxacin	Zimbabwe, Botswana, Zambia, South Africa
Diacon et al.[25]	2014	Phase 2 RCT	160	Unclear		MDR-PTB	Bedaquiline	Brazil, India, Philippines, Latvia, Peru, South Africa, Thailand
Gillespie et al.[26]	2014	Phase 3 RCT	1931	Excluded	Unexplained	PTB	Moxifloxacin	South Africa, India, Tanzania, Kenya Thailand, Malaysia, Zambia, China, Mexico
Nunn et al.[27]	2014	Phase 3 RCT	1348	Unclear		PTB	Isoniazid, rifampicin, pyrazinamide, ethambutol, prothionamide	Africa, Asia, Latin America

(Continues)

TABLE 1 (Continued)

Author[ref]	Year	Type of study	Sample size	DM patients (n, %)	Diagnostic criteria for DM	Type of TB	Drugs	Country
Luangchosiri et al.[28]	2015	Phase 4 RCT	55	Unclear		PTB	Silymarin	Thailand
Diacon et al.[29]	2015	Phase 2 RCT	105	DM insulin dependent were excluded	Unexplained	PTB	Bedaquiline, proteomanid, pyrazinamide, clofazimine, rifafour	South Africa
Daley et al.[30]	2015	Phase 3 RCT	247	Unclear		PTB	Vitamin D	India
Dawson et al.[31]	2015	Phase 2 RCT	207	Excluded	History of DM	PTB	Moxifloxacin, proteomanid, pyraziamide	South Africa, Tanzania
Dorman et al.[32]	2015	Phase 2 RCT	334	Unclear		PTB	Rifapentine	USA, Brazil, Uganda, Canada, South Africa, Spain
Heinrich et al.[33]	2015	Phase 2 RCT	90	DM insulin dependent were excluded	Random blood glucose	PTB	SQ109, rifampicin	South Africa
Merle et al.[34]	2015	Phase 3 RCT	1836	Excluded		PTB	Gatifloxacin	Benin, Guinea, Kenya, Senegal and South Africa
Mily et al.[35]	2015	Phase 2 RCT	288	Excluded	History of DM	PTB	Vitamin D3	Bangladesh
Dawson et al.[31]	2015	Phase 2 RCT	153	Evidence of clinically significant metabolic endocrine diseases, DM insulin dependent were excluded	Random blood glucose	PTB	Rifapentine	Tanzania, South Africa
Wu et al.[36]	2015	Phase 4 RCT	161	24 (14.9%)	Random blood glucose	PTB	Isoniazid, rifampicin, pyrazinamide, ethambuthol (FDC compared to separate formulation)	Taiwan
Tang et al.[37]	2015	Phase 4 RCT	65	13 (20%)	Random blood glucose	XDR-TB	Linezolid	China
Tang et al.[38]	2015	Phase 4 RCT	105	21 (20%)	History of DM	MDR PTB	Clofazimin	China
Tukvadze et al.[39]	2015	Phase 2 RCT	199	10 (5%)	History of DM	PTB	Vitamin D	Georgia
Aseffa et al.[40]	2016	Phase 4 RCT	1000	Excluded	Fasting blood glucose	PTB	Isoniazid, rifampicin, pyrazinamide, ethambuthol: FDC vs loose regimen	Ethiopia, Nigeria

(Continues)

TABLE 1 (Continued)

Author[ref]	Year	Type of study	Sample size	DM patients (n, %)	Diagnostic criteria for DM	Type of TB	Drugs	Country
Conde et al.[41]	2016	Phase 2 RCT	121	HbA1c >8 g/dl were excluded	HbA1c	PTB	Rifapentine, moixifloxacin, pyrazinamide, isoniazid	Brazil
Furin et al.[42]	2016	Phase 2 RCT	75	Excluded	Random blood glucose	PTB	Azd5847	South Africa
Heemskerk et al.[43]	2016	Phase 4 RCT	817	Unclear	Unclear	Meningitis TB	Rifampicin, levofloxacin, isoniazid, pyrazinamide, ethambutol, streptomycin	Vietnam
Kang et al.[44]	2016	Phase 3 RCT	151	5 (3.3%)	Unexplained	MDR-TB	Levofloxacin, moxifloxacin	South Korea
Milstein et al.[45]	2016	Phase 2 RCT	180	Uncontrolled DM HbA1c >7.5 excluded	HbA1c	PTB	Higher dose rifampin	Peru, USA, UK
Pym et al.[46]	2016	Phase 2 RCT	233	Unclear		MDR-PTB and XDR-PTB	Bedaquiline	China, Estonia, Kenya, Korea, Latvia, Peru, Philippines, Russia, South Africa, Thailand, Turkey, Ukraine
Chesdachai et al.[47]	2016	Phase 2 RCT	31	3 (9.7%)	History of DM	PTB	Vitamin D3	Georgia
Zhang et al.[48]	2016	Phase 4 RCT	370	34 (9.2%)	Unexplained	Unspecified	Silybum marianum capsule as hepatoprotectant	China
Aarnoutse et al.[49]	2017	Phase 2 RCT	150	Excluded	Medical History	PTB	Rifampicin	Tanzania
Alsultan et al.[50]	2017	Phase 2 RCT	60	Excluded	Random blood glucose > 150 mg/dL excluded	PTB	AZD-5847 Rifafour	South Africa
Boeree et al.[51]	2017	Phase 2 RCT	365	Uncontrolled or DM insulin dependent were excluded	History of DM	PTB	Rifampicin, moxifloxacin, SQ109	Tanzania, South Africa
Boutoun et al.[52]	2017	Phase 2 RCT	111	Poorly controlled DM (HbA1c >9%) were excluded	HbA1c	MDR-PTB	Levofloxacin	Peru, South Africa
Batbold et al.[53]	2017	Phase 3 RCT	269	2 (0.7%)	Random blood glucose	PTB	Imunoxel honey lozenges	Mongolia, Ukraine
Lee et al.[54]	2017	Phase 2 RCT	429	Unclear		PTB	Linezolid, ethambutol	South Korea

(Continues)

TABLE 1 (Continued)

Author[ref]	Year	Type of study	Sample size	DM patients (n, %)	Diagnostic criteria for DM	Type of TB	Drugs	Country
Sigal et al.[55]	2017	Phase 2 RCT	389	Unclear		PTB	Rifapentine, isoniazid, pyrazinamide, ethambutol	USA
Ganmaa et al.[56]	2017	Phase 4 RCT	380	19 (5%)	Unexplained	PTB	Vitamin D3	Mongolia

DM: diabetes mellitus; RCT: randomised controlled trial; PTB: pulmonary tuberculosis; MDR: multidrug resistant; XDR: extensively drug resistant; FDC: fixed drug combination.

review that assessed the pharmacokinetics of first-line TB drugs showed that age, sex, malnutrition, food intake, genetic factors and comorbidities (mainly human immunodeficiency virus and diabetes) could all play a role.[70]

Altered pharmacokinetics of anti-TB drugs may warrant a need for routine monitoring and modification of the regimens in patients with DM. American Thoracic Society, Center for Disease Control and Prevention, and Infectious Diseases Society of America guidelines suggest early identification of patients at increased risk of relapse such as those with DM[71] as well as therapeutic drug monitoring (TDM). TDM does allow for timely, informed decisions regarding the need for dose adjustment when necessary. TDM is considered to be helpful in situations in which clinicians are confronted with drug malabsorption, drug under-dosing, or clinically important drug–drug or drug–disease interactions, such as diabetes comorbidity.[72]

To our knowledge, this is the first systematic review specifically focusing on the inclusion of DM in TB drug trials. Major strengths are the search within 3 different databases, double checking of inclusion and data extraction and reporting according to the standardized PRISMA statement. Also, some limitations need to be mentioned. First, given the focus on English language manuscripts and our own restricted language knowledge, we had to exclude the few trials that were only published in a local language. These trials could potentially be informative but may often be less generalizable as the larger multicountry trials. Second, the studies included in this review used different diagnostic criteria for DM that could induce the risk of over- or under representation of DM patients among studies. Also, we should consider that if studies did not explicitly listed DM as an exclusion criterion, it may well be that DM patients were eligible but were not included in the trial. Third, no meta-analysis was performed because we felt that simply combining all rates would be less informative than providing separate DM inclusion rates by region/continent. Fourth, in the PubMed search, we applied a *full-text available filter* (see Supporting information Appendix S2). This could have excluded some full manuscripts that only had an abstract available in PubMed. Retrospectively, we have checked the impact of this filter. In the search without the filter, 21 additional hits (equalling 3.7% more hits) were found, although, after inspection, none were eligible. Finally, we could not assess reporting bias as clinical trials around the world can be registered in many different databases and we received little response from contacting the study authors. Therefore, comparing published trials with registered trials was not feasible.

Regarding future research and policies, it is important for TB drug trials to screen for DM comorbidity, aim for a representative, real-life, DM percentage according to the location and appropriately diagnose DM. Alternatively, a separate multicentre trial in diabetic patients could be considered where also more emphasis can be placed on diabetes-specific outcomes such as hypoglycaemias. Intensified research and development of TB drugs, particularly in the context of comorbidities such as DM, play a crucial role to improve TB control and contribute to reductions in TB incidence and mortality required to reach global TB targets by 2035, one of the pillars of World Health Organization's Post-2015 Global TB Strategy.[16]
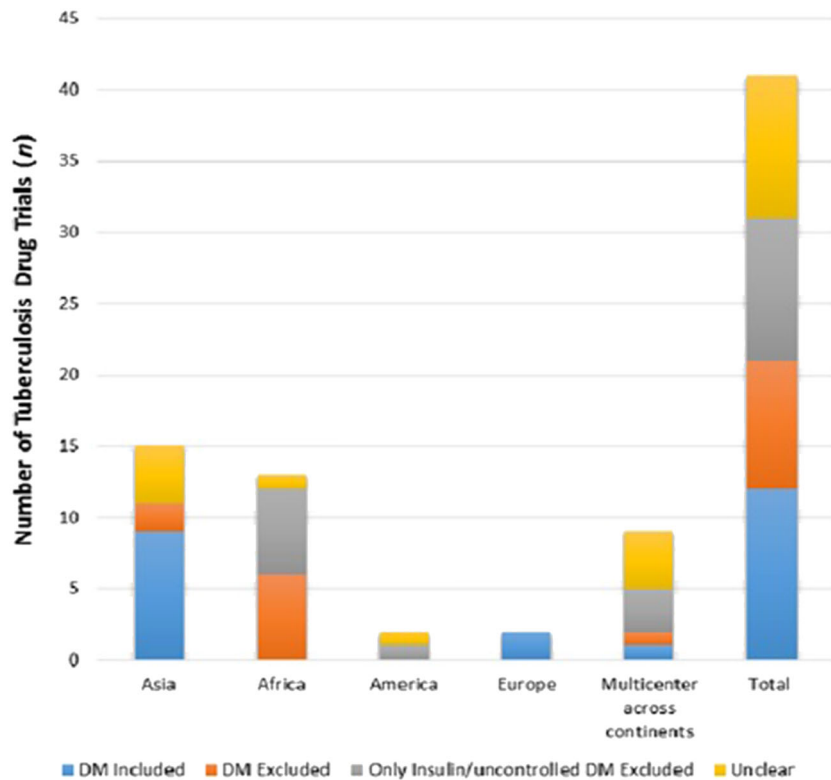
FIGURE 2 Inclusion status of diabetes mellitus (DM) in tuberculosis drug trials 2012–2017 (total *n* = 41)

Including DM comorbidity in TB drug trials will allow for the study of possible DM-TB drug–drug and drug–disease interactions that can alter the pharmacokinetics, safety and clinical effects of the TB drugs. Eventually, these findings will enable us to assess TB-DM patients' individual need for personalize treatment options and lead to better real-world TB-DM outcomes and possibly lower resistance rates.

5 | CONCLUSION

To conclude, current inclusion of DM comorbidity in recent TB drug efficacy trials is suboptimal compared with its increasing prevalence and significance. Considering the considerable prevalence and impact of DM comorbidity, the inclusion of patients with DM in future TB efficacy drug trials warrants increased attention and requires a joint effort of trialists, clinicians and policy makers alike.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.[73]

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COMPETING INTERESTS

The authors declare no competing interests.

CONTRIBUTORS

The study was designed by J.B. and J.A. Data collection was done by N.L. and M.Z. The initial manuscript was drafted by J.B. and N.L. All other authors helped with data interpretation and commented on the study design and the first draft. All authors helped with completing the final manuscript. J.A. is the guarantor of the study.

ORCID

Job F.M. van Boven https://orcid.org/0000-0003-2368-2262
Jan-Willem C. Alffenaar http://orcid.org/0000-0001-6703-0288

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.