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Delay on pulmonary tuberculosis diagnosis in low-incidence countries: a systematic review

25th Master's in Public Health Edition

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This dissertation is delivered and presented to comply with the necessary requisites for obtaining the Master's degree in Public Health, performed under the tutelage of Professor João Almeida Santos and Professor Andreia Leite.

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Resumo

Introdução: A redução da mortalidade e morbilidade por tuberculose requer uma demora mínima entre início de sintomas e diagnóstico (demora total), e das suas duas subcomponentes (demora do doente e dos cuidados de saúde). Esta revisão sistemática visa identificar fatores associados à demora no diagnóstico de tuberculose pulmonar em países de baixa incidência.

Métodos: Foram incluídos estudos que avaliaram os fatores associados a demora entre 2009 e 2019 em países de baixa incidência (<20 casos/100.000 habitantes). Foram realizadas pesquisas em *Web of Science, Scopus, Medline* e *The Cochrane Library*. Foi realizada seleção dupla dos artigos, seguida de extração por um investigador com validação. O risco de viés foi avaliado usando as ferramentas do *Joanna Briggs Institute.* Caso existam dados em cinco estudos será realizada uma meta-análise (mínimo pré-estabelecido), caso contrário será realizada uma síntese qualitativa. A qualidade da evidência de cada resultado foi avaliada usando metodologia GRADE.

Resultados: Dos 2623 artigos extraídos, 18 cumpriram os critérios de seleção. Devido a falta de dados, não foi realizada meta-análise. A síntese qualitativa mostrou que foram encontradas demoras totais e de doente mais longas em imigrantes, enquanto o acesso a tecnologia de diagnóstico associou-se a menor demora dos cuidados de saúde.

Discussão: Em diferentes artigos, foram identificadas demoras superiores ao recomendado, sendo o país de origem um fator importante para a ocorrência destas demoras. Foram identificadas qualidades muito baixas de evidência global. Mais estudos serão necessários para avaliar a robustez destes achados.

Palavras-chave: Tuberculose pulmonar, demora do doente, demora dos cuidados de saúde, demora total, países de baixa incidência

Abstract

Background: Reducing tuberculosis (TB) mortality and morbidity requires minimal delay from onset of symptoms to diagnosis (total delay), and its two subcomponents (patient and healthcare delays). This systematic review aims to study pulmonary TB diagnosis delay associated factors in low-incidence countries.

Methods: Articles assessing TB delay associated factors from 2009 to 2019 in low-incidence countries (<20 cases/100,000 inhabitants) were included. Web of Science, Scopus, Medline and The Cochrane Library were searched. Double screening was performed, followed by single article extraction with validation. Risk of bias was assessed using Joanna Briggs Institute Tools. Meta-analysis was planned whenever 5 studies were available, otherwise a qualitative synthesis would be conducted. Each outcome's quality of evidence was evaluated using GRADE methodology.

Results: From 2,623 articles extracted, 18 articles met the selection criteria. Due to lack of data, no meta-analysis was performed. Qualitative synthesis showed that longer total and patient delays were found among foreigners, while access to diagnostic technology was associated with shorter healthcare delay.

Discussion: Longer delays than recommended were found, and country of origin is an important factor for it. Very low overall quality of evidence was found for all outcomes. Further studies are required to assess the robustness of these findings.

Keywords: Pulmonary tuberculosis, Patient delay, Healthcare delay, Total delay, Low-incidence countries

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Abbreviations

CI: Confidence Interval

GBD: Global Burden of Disease

GP: General Practitioner

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HIV: Human immunodeficiency virus

HR: Hazard Ratio

IHME: Institute Health Metrics and Evaluation

JBI: Joanna Briggs Institute

NAT: Nucleic acid test

OR: Odds Ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO: International Prospective Register of Systematic Reviews

RoB: Risk of Bias

RR: Relative Risk

SDG3: Sustainable Development Goal 3

TB: Tuberculosis

TR: Time Ratio

UK: United Kingdom

WHO: World Health Organization

Study Global Introduction

Tuberculosis (TB) is an infectious disease mainly caused by *Mycobacterium tuberculosis* and is estimated to already have been transmitted to a quarter of the world's population, representing 2.3% of the total burden of disease (1–3). Incidence is also rising, having 7,5 million individuals been infected in 2022 alone, a 16% increase in the number of new cases since the previous year (4). Both incidence and prevalence differ between countries and world regions, with the European region (currently reporting 25 new cases per 100,000 inhabitants) experiencing a constant drop in TB cases since 2000, the fastest decline of any region on the globe (3,5). These differences led to the classification of nations according to incidence rates into high TB incidence countries (more than 20 new tuberculosis cases per 100,000 inhabitants) and low TB incidence countries (less than 20 new tuberculosis cases per 100,000 inhabitants) (4). These low TB incidence countries are characterized by TB transmission taking place in vulnerable populations, such as migrants, people co-infected with Human Immunodeficiency Virus (HIV) and prison inmates (6). Additionally, the world's TB mortality rate is 16.4 per 100,000 inhabitants per year, however, considerable differences between countries and regions of the globe can be found. For example, the African Region recorded 26 non-HIV coinfected TB deaths per 100,000 inhabitants, while the European Region reported 1.9 non-HIV coinfected TB deaths per 100,000 inhabitants (7). An analogous difference is also observed among HIV coinfected TB deaths (7). These statistics are seen by the World Health Organization as reasons for applying actions to reduce TB's burden. Additionally, the United Nations sustainable development goal 3 (SDG3), focused on ensuring healthy lives and promoting well-being for all at all ages, includes a target for ending several epidemics worldwide, including tuberculosis. An ambitious goal met with mixed progress, because, despite estimates pointing to a drop in incidence and mortality, there is still a long way to go before we reach TB eradication (8). More effective action is needed, and, in this regard, early TB diagnosis, and prompt initiation of treatment are paramount to effectively control transmission and its fatal consequences. This concern is further increased for pulmonary TB (PTB) because of its higher capacity to spread among populations (9–11).

PTB has two forms: an asymptomatic form (latent TB) which can persist for a long time and, in some cases, be followed by an activation into a symptomatic form (active TB). Diagnosing asymptomatic cases often depends on passive case finding, while for PTB, clinical suspicion is paramount. Identification of a PTB case is frequently based in observing a persistent cough (for more than two weeks), regularly in combination with one of the following: fever, night sweats, unintentional weight loss, dyspnea, hemoptysis,

or chest pain (12). Report of exposure to an already infected patient increases diagnostic suspicion, however, sharing so many symptoms with other respiratory diseases makes TB a very difficult disease to diagnose in low-incidence countries (12). Therefore, early TB diagnosis is not always possible, and delays may occur. Because of its importance for treatment outcomes, the occurrence of delays has been studied in literature as total delay, and as its two subcomponents - patient delay and healthcare delay (10,13). Patient delay is defined as the gap between symptom onset and first contact with a healthcare provider (11). This gap is expected not to be longer than two to three weeks (13). However, because patient delay may be influenced by several factors (such as country of origin or health literacy) other periods have been discussed (14). Healthcare delay, also described as provider delay, is the time between a patient's first consultation with a healthcare provider and TB diagnosis (11). The combination of these two delays (total delay) is expected to take no more than 3 to 4 weeks, with some studies using a thirty-day cutoff point (10,13). These delays are common, having previous studies detected an average of ten-week patient delays (15). These findings highlight the importance of understanding the factors that influence timely TB diagnosis in low-incidence countries, where the majority of cases occur within specific population subgroups that face unique diagnostic challenges. (6).

Reviews have been conducted to identify barriers to diagnosis in low-income countries, but as of the time of submission, none specifically focused on low-incidence countries have been identified (10,16,17).

In high TB incidence countries, associations have been found between longer patient delays and factors such as: rural residence, illiteracy, poor knowledge on PTB signs and symptoms and TB cause and treatment, superstition, traditional healing consulting, social stigmatization, fear of HIV coinfection, limited access to health facilities, lack of TB detection equipment, and proportionally high out-of-pocket costs for diagnostic techniques (X-ray, for instance) (10). However, it is expected that low TB incidence countries may show different barriers than those found in high TB incidence countries. Additionally, worldwide efforts to follow the World Health Organization (WHO) End TB Program, which strives for a 90% reduction in world incidence and a 95% drop in deaths, will consequently lead to increasing numbers of low TB incidence countries (18). Thus, it is critical to identify modifiable factors associated with delay in TB diagnosis in countries with low TB incidence in order to maintain the decreasing trend of disease cases and eventually end the TB epidemic in these countries.

Thus, to contribute to the goal of SDG3 centered on the elimination of several global epidemics, such as tuberculosis, the objective of this systematic review was to

characterize the association between several factors and three outcomes: total delay, patient delay and, and healthcare delay, in order to answer the question: “What factors are associated with delayed diagnosis of PTB in low-incidence countries?”.

The following document is a manuscript of a paper addressing this question and objectives for submission in a peer-review scientific journal.

Background

Tuberculosis (TB) is an infectious disease mainly caused by *Mycobacterium tuberculosis* which represents 2.3% of the total burden of disease (1–3). Countries can be classified as high TB incidence countries (>20 new TB cases per 100,000 inhabitants) and low TB incidence countries (≤20 new TB cases per 100,000 inhabitants) (19). Low TB incidence countries are characterized by transmission taking place in vulnerable populations such as migrants, people co-infected with Human Immunodeficiency Virus (HIV) and prison inmates (6).

Prompt TB diagnosis is paramount to reduce transmission and incidence, however, delays can occur. Literature describes three delays: total, patient and healthcare (10,13). Patient delay (defined as the time interval between symptom onset and first contact with a healthcare provider) is expected not to be longer than two to three weeks (11,13). However, because patient delay may be influenced by factors such as country of origin or health literacy, other periods have been discussed (14,15). On the other hand, healthcare delay (the time interval between a patient's first consultation with a healthcare provider and TB diagnosis) is dependent on diagnostic technology, clinician activity or health human resources (11). The combination of these two delays (total delay) is expected to take no more than 3 to 4 weeks, with some studies using a thirty-day cutoff point (10,13). Achieving the World Health Organization (WHO) End TB Program goals, which include a 90% reduction in worldwide TB incidence and a 95% drop in deaths, will consequently lead to increasing numbers of low TB incidence countries (18). To sustain the decline in TB cases in low-incidence countries, it is crucial to identify the barriers to a timely TB diagnosis in these countries. This will allow for the implementation of targeted strategies aimed at eradicating the disease (6).

Hence, the aim of this systematic review was to characterize the association between several variables and three outcomes: total delay, patient delay and healthcare delay, and answering the question: "What factors are associated with delayed diagnosis of pulmonary TB in low-incidence countries?".

Methods

In conducting this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist was used (20). This systematic review's protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Registration Number CRD42023449784), where it will be available after the study's publication. Ethical issues regarding disclosure and use of information were covered by this review's use of data from previously published articles.

Inclusion/exclusion criteria

Both observational studies and mixed-method studies with peer-reviewed full text articles, and assessing, at least, one low-incidence TB country (with less than 20 new TB cases per 100,000 inhabitants (Supplementary Data, Table S1[1])) were included. The included studies, published in English, Portuguese, Spanish, or French, examined the associations between total delay, patient delay, or healthcare delay in PTB diagnosis (outcome variables) and various independent factors. The analysis period of these studies spanned from 2009 to 2019. Reviews, ecologic studies, or studies not complying with the abovementioned criteria were excluded.

Search and data extraction strategy

Searches were conducted in natural language for the search engines (Web of Science and Scopus) and in a combination of natural language and controlled language for databases (Medline, and The Cochrane Library) in accordance with our search strategy (Supplementary Data, Table S2). Article's title and abstract selection was performed independently on Rayyan website by two investigators (NDA, HP) (21). Full text screening followed suit in an Excel sheet by the same investigators (excluded articles on Supplementary Data, Table S3). All conflicts were resolved by a third investigator in both phases (JAS). Selected articles and main descriptive data are gathered in Supplementary Data, Table S4, S5 and S6. Extraction was performed by one investigator (NDA) with further validation by another (HP). Studies' information was extracted to a pilot form that included: title, authors, year of publication, study design, study period beginning, study period end, total delay, patient delay, healthcare delay,

[1] TB incidence data for each country was obtained on December 2022 from the Global Burden of Disease (GBD) Compared web software, from the Institute for Health Metrics and Evaluation (IHME).

country TB incidence, inclusion of risk group patients, type of risk group, mean age, gender, presence/absence of healthcare access barriers, previous knowledge/suspicion of TB. For each outcome and exposure assessed, measures of effect (odds ratio – OR, risk ratio – RR, time ratio - TR, or hazard ratio – HR) were looked for and measures of effect missing data was excluded from further analysis (Supplementary Data, Table S7).

Data analysis

Regarding data analysis, as stated in the study protocol, we intend to synthesize the data as a meta-analysis, using the most frequently reported measures of effect, followed by a description of the most relevant findings. For the purposes of analysis, we attempted to identify a common definition of the association assessed. Whenever comparable data was found among at least five articles, a meta-analysis would be performed. If applicable, heterogeneity would be assessed *in visu* and by calculation (using I^2), and, for publication bias analysis, a funnel plot plus a Begg and Egger test would be performed. Regarding modeling, a fixed-effect model would be used if low heterogeneity between studies (less and equal to 50%) was found, while a random-effect model would be used otherwise. If meta-analysis was not feasible, a qualitative synthesis was performed.

Quality assessment

For each article, Risk of Bias (RoB) was assessed using three *Joanna Briggs Institute* (JBI) *Critical Appraisal Tools*, in accordance with study design (Checklist for Cross Section Analytical Studies and Checklist for Cohort Studies), which may be consulted in Supplementary Data Tables S8, S9 and S10 (22,23).

Each objective's quality of evidence was classified using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and organized as a table presenting RoB, inconsistency, indirectness, imprecision, publication bias, and overall certainty of the evidence (Supplementary Data, Table S11).

Results

From our search in July 2023, a total of 2,643 studies were identified. After duplicate removal, 2,558 articles were screened for title and abstract, 61 were selected for full text screening, and 18 met our inclusion criteria (Figure 1). Of those, 12 were cross-sectional studies (24–35) and six were cohort studies (36–41) (Supplementary Data, Table S4). This review's included articles that were published between 2012 and 2023 and were conducted in: Portugal (24,39), Qatar (25), France (26), Italy (27), United Kingdom (36,37,41), Iran (28,33), United States of America (29), Switzerland (30), Tunisia (31,32), Australia (38,40), and Ireland (34,35). Therefore, in total, six European countries, one American, one in Oceania, one African and two Asian countries were analyzed. The 2019 mean TB incidence of all these countries was lower than 10 cases/100,000 inhabitants.

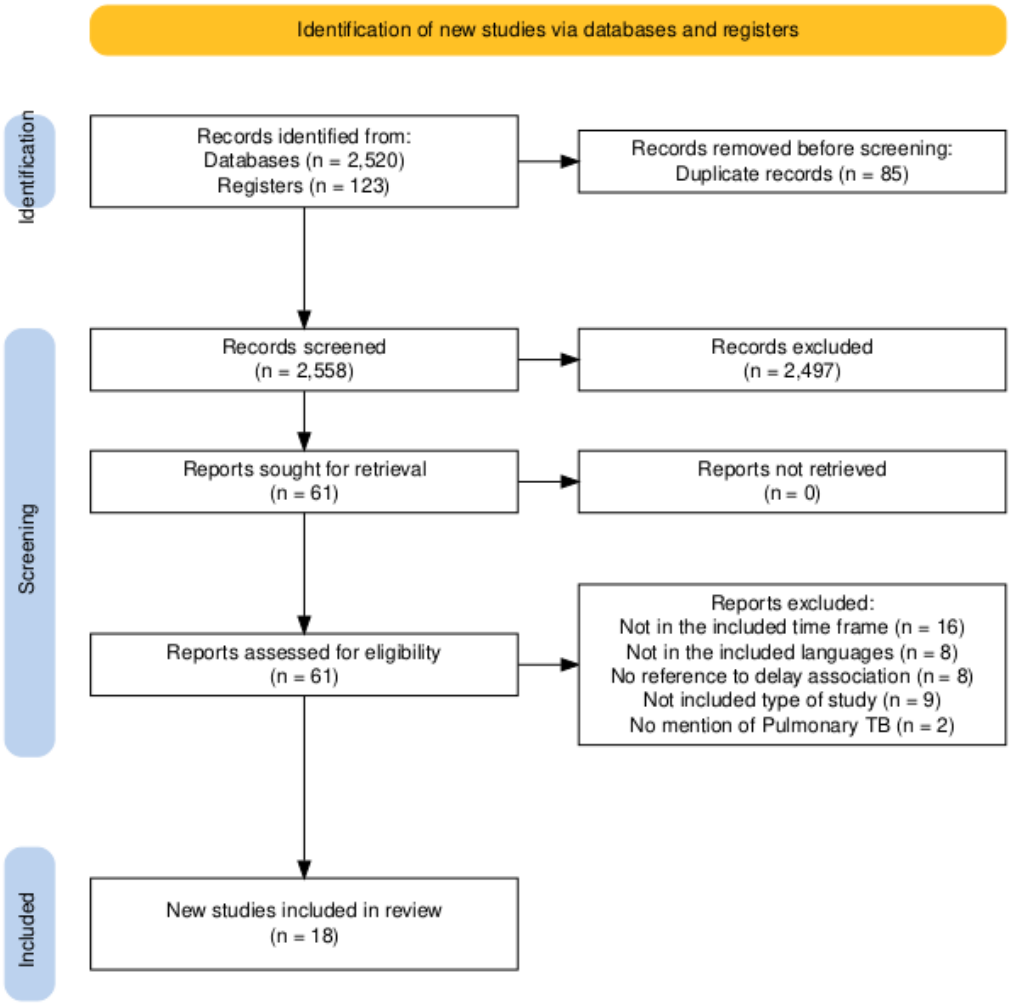

Fig. 1. PRISMA Study Flow Diagram

The mean age ranged from 33.8 (25) to 55.6 (28) years old, while the median ranged from (30,38) to 45 (40) years old. Only two articles did not report how many patients with PTB were enrolled. Sample sizes ranged from 19 (35) to 8461 (36) individuals. All studies

had a masculinity ratio bigger than 1 with a mean of 1.8 man for each woman. Also, 15 studies reported some sort of risk group patients in their sample (Supplementary Data, Table S5).

Seven articles studied total delay associated factors (24,26,32,33,38–40) (Table 1 and Supplementary Data, Table S7). Two articles found an association between foreign nationality and longer total delay, however one of them without statistical significance (33,39). Nunes, et al. (2016) pointed out that being male is associated with shorter total delay (39). One article (26) found a significant association between longer total delay and the total number of healthcare contact visits (OR 2.29), and absence of HIV coinfection (39), but also found an association between shorter total delay and having a first healthcare contact in a hospital (OR 0.32), having medical insurance (OR 0.24), and having been previously diagnosed with TB (OR 0.28).

Table 1. List of study associations with total delay outcome with respective measure of effect and confidence interval.

Exposure	**Studies**	**Measure of effect**	**CI 95%**
Being an older patient	Yazdani-Charati 2017	HR 0.997	0.994-0.999
Smear-negative result at first admission	Yazdani-Charati 2017	HR 1.116	0.992-1.255
First healthcare contact in hospital setting	Tattevin 2012	OR 0.320	Not reported
Several healthcare contacts	Tattevin 2012	OR 2.290	1.410-3.730
Medical Insurance	Tattevin 2012	OR 0.240	0.080-0.750
Previously having TB	Tattevin 2012	OR 0.280	0.080-1.000
Being a Foreigner	Yazdani-Charati 2017 Nunes 2016	HR 0.812 RR 0.870 (Lisbon), 1.010 (Oporto)	0.593-1.113; 0.800-0.960 (Lisbon), 0.780-1.290 (Oporto)
Unknown HIV status	Yazdani-Charati 2017	HR 1.286	1.131-1.463
Unknown contact history	Yazdani-Charati 2017	HR 0.668	0.599-0.746
Being a male patient	Yazdani-Charati 2017 Nunes 2016	HR 0.975 RR 1.190 (Lisbon), 1.180 (Oporto	0.877-1.084; 1.090-1.290 (Lisbon), 1.070-1.300 (Oporto)
Absence of Alcohol misuse	Nunes 2016	RR 1.030 (Lisbon), 1.020 (Oporto)	0.910-1.180 (Lisbon), 0.880-1.180 (Oporto)
Absence of HIV infection	Nunes 2016	RR 0.850 (Lisbon), 0.810 (Oporto)	0.760-0.950 (Lisbon), 0.690-0.990 (Oporto)
CI - confidence interval, OR – odds ratio, RR - risk ratio, HR - hazard ratio,			

Mean total delay ranged from 79,5 (39) to 97 days (26) while the median ranged from 30 days (25) to 90 (40). However, it is important to mention that due to a different definition of healthcare delay, total delay was not calculated in eight articles (24,28,30,32,34–36,41).

Zão et al. (2019) and Williams et al. (2018 showed an association between being a foreigner and having longer patient delay (Table 2 and Supplementary Data, Table S7). Zão et al. (2019) showed an association between having longer patient delay and having an alcohol or drug addiction (24). Roberts et al. (2020) identified a significantly shorter patient delay in younger age groups (1 to 14 years old). One study pointed to association between patient delay and being male (OR 2.28) (28). Having a chronic disease was significantly associated with having longer delay in two studies (27,38). Quattrocchi et al. (2018) identified living at a longer distance from a healthcare provider was associated with longer patient delay (OR 2.3) while the opposite was found in Zão et al. (2019) (24). Also, being employed was reported as being associated with longer patient delay (OR 5.86) (28).

Mean patient delay ranged from 14 days (30) to 109 days (34) and median ranged from 13 (28) to 60 (35).

Williams et al. (2018) found an association between being an older patient and longer healthcare delay (Table 3 and Supplementary Data, Table S7). Misdiagnosis was also reported as being associated with longer delay in one study (28), with an OR of 2.61 for diagnosing cold or other viral infection instead of TB. Also, a positive association with having longer healthcare delay was found for medical consultation in outpatient setting (OR 7.67) (38). An association with shorter delay was found between healthcare delay and low socioeconomic status (OR 0.974) (24), Chest X-ray showing a cavity (OR 0.25) (38), and nucleic acid test (NAT) for TB in sputum with positive result (OR 0.14) (38). Coughing (38) was reported as having an association with shorter healthcare delay.

Table 2. List of study associations with patient delay outcome with respective measure of effect and confidence interval.

Exposure	**Studies**	**Measure of effect**	**CI 95%**
Being a Foreigner	Zão 2019; Quattrocchi 2018; Williams 2018	TR[2] 1.777; OR 1.670; OR 0.300	1.091-1.270; 0.960-2.890; 0.120-0.740
Alcohol misuse	Zão 2019	TR 1.169	1.072-1.276
Drug addition	Zão 2019	TR 1.153	1.027-1.295
Being a younger patient	Roberts 2020	TR 0.230	0.090-0.590
Having non-pulmonary comorbidities	Zão 2019	TR 0.935	0.878-0.996
Resident in moderately urban areas	Zão 2019	TR 0.955	0.791-0.946
Long distance from a healthcare service	Zão 2019; Quattrocchi 2018	TR 0.961; OR 2.300	0.942-0.979; 1.150-4.620
Medical Insurance	Tattevin 2012	OR 0.360	Not described
Being followed by a GP	Tattevin 2012	OR 0.220	0.080-0.610
Fever at symptom onset	Tattevin 2012	OR 0.420	0.190-0.920
Stigma towards TB infection	Quattrocchi 2018	OR 2.640	1.510-4.610
Low economic capacity	Kalan 2018	OR 0.540	0.290-1.010
Presence of chest pain	Quattrocchi 2018	OR 1.970	1.080-3.610
Presence of weight loss	Quattrocchi 2018; Williams 2018	OR 4.410; OR 2.230	2.480-7.830; 1.000-4.960
Need to pay for transportation	Quattrocchi 2018	OR 3.180	1.770-5.730
Presence of chronic Disease	Quattrocchi 2018; Williams 2018	OR 2.170; OR 3.020	1.210-3.900; 1.040-8.780
Being Employed	Kalan 2018	OR 5.860	1.590-21.640
Attendance to a public hospital or clinic	Kalan 2018	OR 2.640	1.010-6.860
Being a male patient	Kalan 2018	OR 2.280	1.290-4.390
Having language barriers	Roberts 2020	TR 1.400	1.010-1.940
Having mental health barriers	Roberts 2020	TR 2.060	1.220-3.500
Being a smoker	Williams 2018	OR 2.270	0.990-5.180
Having fatigue	Williams 2018	OR 0.410	0.160-0.990
CI – confidence interval, OR – odds ratio, TR - time ratio			

The mean healthcare delay was 48 days (26), the median ranged from 7 (27) and 25 days (26). Because in eight articles (24,28,30,32–36) healthcare delay was based on a different definition than the one selected for our study, this outcome was not considered for our review.

[2] In Zão, et al. (2019), measure of effect expressed as “time ratio” (TR) here defined as the change in the time to the outcome event/delay per unit increase of the independent variable.

Table 3. List of study associations with healthcare system delay outcome with respective measure of effect and confidence interval.

Exposure	Studies	Measure of effect	CI 95%
Being an older patient	Williams 2018	OR 4.290	1.550-11.890
Presence of Coinfection	Zão 2019	TR 0.900	0.790-1.025
Low economic capacity	Zão 2019	TR 0.974	0.958-0.991
Presence of Cough	Williams 2018	OR 0.090	0.010-0.790
Having fatigue	Williams 2018	OR 0.430	0.180-1.010
Outpatient review	Williams 2018	OR 7.670	3.510-16.770
Emergency department review	Williams 2018	OR 0.430	0.170-1.070
Hospital admission	Williams 2018	OR 0.280	0.090-0.920
Chest X-ray showing cavity	Williams 2018	OR 0.250	0.090-0.670
Sputum NAT positive	Williams 2018	OR 0.140	0.030-0.620
Misdiagnosis with viral infection or cold	Kalan 2018	OR 2.610	1.400-4.910
Misdiagnosis with Asthma	Kalan 2018	OR 0.580	0.180-1.840
Misdiagnosis with Chronic Obstructive Pulmonary Disease	Kalan 2018	OR 0.960	0.260-3.450
CI – confidence interval, OR – odds ratio, TR – time ratio			

Using JBI Critical Appraisal Tools for RoB assessment, three cross-sectional studies (25,29,31) and one cohort study (37) were excluded from data synthesis because of high RoB. Besides, after counting the number of studies assessing each variable for every outcome, patient delay was the only one which had an independent variable (being a foreigner) close (with two comparable studies) in reaching the five-article threshold, defined in our protocol, for meta-analysis. For this reason, no quantitative component was added to data synthesis, which implied that heterogeneity tests, funnel plots and *Begg and Egger* tests were not performed. Publication bias was evaluated considering solely qualitative criteria for each of the three outcomes of the study, and was based on the types of reported outcomes, their measures of effect, search for grey literature in online academic repositories and scientific or institutional webpages, and each study's protocol search. Because of the qualitative nature of the synthesis, statistical sensitivity analysis was also not performed, however, several factors (such as study quality, study design, sample size or region of the globe where the study was carried) were considered while assessing the impact of the results.

GRADE was also applied for each outcome variable to assess the evidence quality (Supplementary Data, Table S11). No large effect size, dose-response relationship, or negative impact of confounding on the outcome was observed in this study, for this reason no rating up in evidence level was performed.

For total delay, global study RoB was low, inconsistency of results was rated as moderate (from all independent variables only one showed contradictory information between studies), and indirectness of evidence was low (all studies were measuring the outcome at hand). Imprecision was rated moderate because several articles had sample

sizes no higher than 100 individuals, and large confidence intervals (several crossing the no-effect line).

Most of the grey literature reviewed on this topic primarily focused on high TB incidence countries, making it challenging to assess publication bias. Additionally, no study protocols were identified for the aforementioned articles (42–44). Despite these findings, based on significance of results and their outcomes, no evidence of article selection for publishing was identified. Consequently, the risk of publication bias was rated as moderate.

For patient delay, RoB was rated low, inconsistency of results was rated high (seven out of thirty-two variables had different directionality of results), and, for the same reason as for total delay, indirectness was low. Imprecision was rated as moderate (with several CI crossing the no-effect threshold). For the same reason as for total delay, publication bias was rated moderate.

For healthcare systems delay, RoB was rated low, inconsistency was rated moderate (with one variable, out of twenty-one, having contradictory results) indirectness of evidence was low and imprecision was moderate (for the same reason as for the previous two delays).

Discussion

This systematic review was intended to cover a knowledge gap regarding TB delay in low-incidence countries. Prior to this study, it was assumed that in these countries, the association of TB with low income and homelessness would naturally point to these conditions or their consequences as contributing factors to delays in treatment. However, this review identified many additional factors, revealing a more complex phenomenon than previously anticipated (18).

For total delay, despite only one article showing statistical significance, being a foreigner appeared to be associated with longer delay in being diagnosed (33,39). Socioeconomic status also seems to have an impact on total delay, with patients having medical insurance experiencing shorter delays (26). Additionally, shorter total delays in men might be attributed to the fact that PTB is generally more prevalent in men than in women. This higher prevalence may lead to greater clinical suspicion of TB in male patients presenting with suggestive symptoms, potentially resulting in earlier diagnosis (45). Moreover, shorter total delays for patients previously diagnosed with TB may result from the similarity of symptoms plus previous clinical record of the disease. This familiarity can heighten clinical suspicion, leading to quicker identification and diagnosis of the disease.

However, shorter delays were found for unknown HIV status, unknown contact history with TB patients, and having a smear-negative test. These findings conflicted with our theoretical assumptions because those status would, in theory, reduce clinician's suspicion of TB or their need for additional testing. On the other hand, having a first healthcare contact in a hospital setting, possibly due to technology access unavailable elsewhere, correlates to shorter delays.

Studies pointed to an association between being a foreigner and longer patient delay, which would be congruent with reports on latency on going to a health facility due to language barriers, stigma towards TB symptoms, and fear of immigration authorities (24,27). However, these findings were not matched by our shorter delay results of low income on patient delay (46). Many different factors may be in play here, from a health system that covers a large part of the diagnosis costs, to higher care for PTB symptoms regardless of economic capacity, to knowledge of contact with PTB cases. On the other hand, being employed seemed to be associated with longer patient delay, but the opposite relation was found if the patient had insurance, which would lead us to postulate that different work conditions, and salaries may have different associations with delay. Being male was associated to longer patient delays, which may be due to a reduced seeking behavior among men to go to health services (47). Additionally, the age group

from 1 to 14 years old was found to have shorter delays, which may be due to parents' concern, leading to earlier medical consultation, for instance. On the other hand, chronic diseases being associated with longer delay may suggest that patients may take TB symptoms as resulting from their underlying disease or treatment. However, it seems that not all symptoms contribute the same on health seeking behavior because non-pulmonary comorbidities and having fever and fatigue were linked to shorter delay, while chest pain and weight loss were linked to longer delay. In contrast, having an addiction (alcohol, smoking or drugs) is associated with longer delays, possibly, by patients postponing a health consultation (48,49). Living in rural settings was linked to shorter latencies despite the apparent role of transportation in this issue, because it was reported that, especially for women, in some of the studied countries, the need for a male driver, to get them to health care facilities is a requirement and paying for transportation was associated to longer patient delay (27). In contrast, shorter latencies found by patients followed by a general practitioner (GP) may be due to more easiness of access to healthcare.

Our study showed that, despite being theoretically possible for a less than three-week delay to be achieved, total delay exceeded the recommended three to four weeks suggested in literature, which stresses once again the importance on knowing which modifying factors exist, and on exploring ways to address low-incidence counties' barriers on diagnosis (10,13).

Despite all previous remarks regarding our findings, it is important to notice that, after performing GRADE to all three outcome variables, evidence was very low confidence, which means that all these findings must be taken with caution when making recommendations (50).

Additionally, one of this study's main limitations is not being able to perform a meta-analysis of the data without risking incurring in methodological errors. One reason for this fact was the low comparability between studies, contrary to what was expected in the beginning of this study, when the concern was not to find enough studies to be reviewed. Despite exploratory searches prior to the start of this study (mostly with Portuguese sources), which pointed to the usefulness of using time to diagnosis as the concept of delay, many international studies focus on time to treatment. This fact led eleven studies not to be suited to study this specific outcome. Different measuring units for each of these variables were also an obstacle because delay, for instance, may be summarized both in mean and median, and different studies report it in different ways. The same may be said about age, which was divided by age groups in several studies.

The use of different time units in several studies for delay classification (time in days, and time in weeks) reduced comparability because of differences in granularity.

Initially there was also the intention of using additional databases for analysis. However, lack of access to them limited the scope of this review. Additionally, defining a 10-year filter for the analysis period in the search strategy, to include a decade of data, led to the removal of many studies that would increase our chances of being able to meta-analyze the data.

The use of GRADE in this study allowed us to assess the quality of the evidence. However, because most studies in this subject are not clinical trials, being rather observational studies, our outcomes' certainty of evidence started as low, making it more difficult to reach higher confidence levels upon completing evaluation. For these reasons, more robust studies should be performed on this subject, with uniform delay definitions, that, in our perspective, should include time between symptom onset and first contact with a healthcare professional, time between first contact with healthcare professionals and diagnosis, and time that encompasses these two timeframes. For higher comparability the reporting would benefit to be counted as days (including both mean and median).

Despite the abovementioned limitations, this article addresses TB diagnostic delay in a group of countries that lacks study in the form of systematic reviews, allowing us to gather knowledge on this subject, and constituting a steppingstone into further understanding this phenomenon.

Conclusion

Our review points to a possible association between being a foreigner and having longer total and patient delay, while shorter delay seems to be found where access to higher diagnostic technology is present. However, it is important to stress that it was not possible to quantitatively synthesize our data, and GRADE quality of evidence was rated as very low.

The scarce congruence between definitions and metrics implies that more studies in this area are required to allow for further exploration of these associations. Nonetheless, this review may be a steppingstone in starting to better understand this phenomenon in low TB incidence countries, and, ultimately, to contribute for improvements in health systems in tackling this socioeconomic, access and diagnostic issues, which will be more prevalent with our continuous fight of TB infection.

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Supplementary Data

Table S1. Countries' TB incidence in 2009 and 2019

Country	2009 TB Incidence	2019 TB Incidence
Australia	5.83	5.59
New Zealand	9.67	10.87
Japan	15.5	11.98
Iran	14.31	12.4
Oman	19.54	13.14
Qatar	18.4	12.46
Jordan	5.84	4.13
Israel	4.61	3.1
Lebanon	16.74	12.19
Syria	10.53	9.27
Egypt	15.93	12.58
Libya	15.59	15.12
Tunisia	19.1	14.78
Algeria	19.56	16.54
Mauritius	14.26	12.18
Canada	5.19	4.89
USA	3.44	2.47
Mexico	14.86	16.03
Bahamas	13.86	12.6
Cuba	8.35	5.9
Jamaica	5.42	3.89
Saint Lucia	15.41	13.59
Saint Vincent and the Grenadines	18.93	16.41
Barbados	8.62	6.8
Grenada	15.74	11.75
Guatemala	16.68	14.8
El Salvador	13.44	12.13
Costa Rica	11.12	8.16
Suriname	12.6	11.09
Trinidad and Tobago	12.45	10.96
Chile	13.44	11.43
Argentina	12.28	12.41
Uruguay	16.86	18.87
Iceland	6.79	5.32
Ireland	7.9	5.64
UK	15.39	9.24
Portugal	16.71	13.04
Spain	9.72	7.13
France	7.88	6.62
Italy	9.71	7.29
Malta	8.25	7.99
Cyprus	4.05	3.02
Switzerland	6.57	5.68
Belgium	8.45	7.24
Netherlands	5.71	4.55
Luxembourg	7.11	6.08
Germany	5.6	5.84
Denmark	6.44	4.81
Sweden	8.73	8.57
Norway	8.6	5.55
Finland	6.39	4.71
Slovakia	7.44	5.37
Czechia	7.42	5.01
Austria	7.7	5.97
Hungary	12.39	6.88
Serbia	14.15	10.22
Slovenia	9.14	6.00
Croatia	15.89	9.62
Bosnia and Herzegovina	19.88	17.14
Montenegro	8.8	6.9

Albania	4.3	3.52
Greece	5.47	5.35
North Macedonia	15.88	12.81

Table S2. Search Strategy for article gathering

Search Strategy
#1 "Tuberculosis, pulmonary"[Mesh]
#2 "Pulmonary Tuberculosis"[tiab]
#3 "Pulmonary TB"[tiab]
#4 #1 OR #2 OR #3
#5 "developed countries"[Mesh]
#6 "Low Incidence"[tiab]
#7 Australia[Mesh]
#8 Australia[tiab]
#9 "New Zeland"[Mesh]
#10 "New Zeland"[tiab]
#11 Japan[Mesh]
#12 Japan[tiab]
#13 Iran[Mesh]
#14 Iran[tiab]
#15 Oman[Mesh]
#16 Oman[tiab]
#17 Qatar[Mesh]
#18 Qatar[tiab]
#19 Jordan[Mesh]
#20 Jordan[tiab]
#21 Israel[Mesh]
#22 Israel[tiab]
#23 Lebanon[Mesh]
#24 Lebanon[tiab]
#25 Syria[Mesh]
#26 Syria[tiab]
#27 Egypt[Mesh]
#28 Egypt[tiab]
#29 Libya[Mesh]
#30 Libya[tiab]
#31 Tunisia[Mesh]
#32 Tunisia[tiab]
#32 Algeria[Mesh]
#33 Algeria[tiab]
#34 Mauritius[Mesh]
#35 Mauritius[tiab]
#36 Canada[Mesh]
#37 Canada[tiab]
#38 "United States"[Mesh]
#39 USA[tiab]

#40 "United States of America"[tiab]
#41 America[tiab]
#42 Mexico[Mesh]
#43 Mexico[tiab]
#44 Bahamas[Mesh]
#45 Bahamas[tiab]
#46 Cuba[Mesh]
#47 Cuba[tiab]
#48 Jamaica[Mesh]
#49 Jamaica[tiab]
#50 "Saint Lucia"[Mesh]
#51 "Saint Lucia"[tiab]
#52 "Saint Vincent and the Grenadines"[Mesh]
#53 "Saint Vincent and the Grenadines"[tiab]
#54 Barbados[Mesh]
#55 Barbados[tiab]
#56 Grenada[Mesh]
#57 Grenada[tiab]
#58 Guatemala[Mesh]
#59 Guatemala[tiab]
#60 "El Salvador"[Mesh]
#61 "El Salvador"[tiab]
#62 "Costa Rica"[Mesh]
#63 "Costa Rica"[tiab]
#64 Suriname[Mesh]
#65 Suriname[tiab]
#66 Trinidad and Tobago[Mesh]
#67 "Trinidad and Tobago"[tiab]
#68 Argentina[Mesh]
#69 Argentina[tiab]
#70 Uruguay[Mesh]
#71 Uruguay[tiab]
#72 Iceland[Mesh]
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#77 "United Kingdom"[tiab]
#78 UK[tiab]
#79 "Great Britain"[tiab]
#80 England[tiab]
#81 Portugal[Mesh]

#82 Portugal[tiab]
#83 Spain[Mesh]
#84 Spain[tiab]
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#86 France[tiab]
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#88 Italy[tiab]
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#90 Malta[tiab]
#91 Cyprus[Mesh]
#92 Cyprus[tiab]
#93 Switzerland[Mesh]
#94 Switzerland[tiab]
#95 Belgium[Mesh]
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#97 Netherlands[Mesh]
#98 Netherlands[tiab]
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#100 Luxembourg[tiab]
#101 Germany[Mesh]
#102 Germany[tiab]
#103 Denmark[Mesh]
#104 Denmark[tiab]
#105 Sweden[Mesh]
#106 Sweden[tiab]
#107 Norway[Mesh]
#108 Norway[tiab]
#109 Finland[Mesh]
#110 Finland[tiab]
#111 Slovakia[Mesh]
#112 Slovakia[tiab]
#113 "Czech Republic"[Mesh]
#114 Czechia[tiab]
#115 "Czech Republic"[tiab]
#116 Slovenia[Mesh]
#117 Slovenia[tiab]
#118 Croatia[Mesh]
#119 Croatia[tiab]
#120 "Bosnia and Herzegovina"[Mesh]
#121 "Bosnia and Herzegovina"[tiab]
#122 Bosnia[tiab]
#123 Montenegro[Mesh]

#124 Montenegro[tiab]

#125 Albania[Mesh]

#126 Albania[tiab]

#127 Greece[Mesh]

#128 Greece[tiab]

#129 "Republic of North Macedonia"[Mesh]

#130 "North Macedonia"[tiab]

#131 Macedonia[tiab]

#132 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131

#133 "Delayed Diagnosis"[Mesh]

#134 "Diagnos*"[tiab]

#135 "Diagnosis dela*"[tiab]

#136 "Diagnostic dela*"[tiab]

#137 "Total dela*"[tiab]

#138 "Patient dela*"[tiab]

#139 "Healthcare dela*"[tiab]

#140 "Health care dela*"[tiab]

#141 "Global dela*"[tiab]

#142 #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 #84 #143 #4 AND #132 AND #142

Table S3. List of excluded studies and the reason for exclusion

First Author and Year	Title	Reason for exclusion
Jurčev-Savičević 2012	[Delays in diagnosing and treating tuberculosis in Croatia][3]	Does not follow inclusion criteria for language
Pourostadi 2018	Frequency of Smear-Negative Tuberculosis in Northwest Iran	Unspecified time frame
Murphy 2017	Spot sputum samples are at least as good as early morning samples for identifying Mycobacterium tuberculosis	Does not follow inclusion time frame
Bishara 2013	[Tuberculosis in pregnancy and puerperium]	Does not follow inclusion criteria for type of study
Bowerman 2015	The promise of rapid detection of active pulmonary tuberculosis in rural Alaska	Does not follow inclusion criteria for type of study
Leutscher 2012	Demographic and clinical characteristics in relation to patient and health system delays in a tuberculosis low-incidence country	Does not follow inclusion time frame
Jurcev-Savicevic 2012	Health-care seeking behaviour for tuberculosis symptoms in Croatia	Does not follow inclusion time frame
Kato 2012	[Factors associated with delay in seeking medical treatment in pulmonary tuberculosis patients in Japan]	Does not follow inclusion criteria for language
Matsumoto 2012	[The association between smoking and sputum smear-positive pulmonary tuberculosis in Osaka City]	Does not follow inclusion criteria for language
Saldana 2013	Factors affecting delay in initiation of treatment of tuberculosis in the Thames Valley, UK	Does not follow inclusion time frame
Lalor 2017	Recent household transmission of tuberculosis in England, 2010-2012: retrospective national cohort study combining epidemiological and molecular strain typing data	No distinction between TB types
Muzzi 2014	Post-exposure rate of tuberculosis infection among health care workers measured with tuberculin skin test conversion after unprotected exposure	Does not follow inclusion time frame

[3] All articles' name in this table which are between brackets have their titles translated to English, having their original title in another language.

	to patients with pulmonary tuberculosis: 6-year experience in an Italian teaching hospital	
Peri 2018	Determinants of patient and health care services delays for tuberculosis diagnosis in Italy: a cross-sectional observational study	No distinction between TB types
Tuberculosis Surveillance Center 2012	[Tuberculosis annual report 2010--(5) Case finding]	Does not follow inclusion criteria for language
Hayer 2013	Culture confirmation of tuberculosis cases in Birmingham, UK	No reference to delay association
Cayci 2017	An evaluation of false-positive rifampicin resistance on the Xpert MTB/RIF	No reference to delay association
Ersson 2019	Perceptions of Tuberculosis Among Individuals Born in a High-Endemic Setting, Now Living in a Low-Endemic Setting	Does not follow inclusion criteria for type of study
van Hest 2009	[Tuberculosis control in homeless persons in European Union: more than words alone]	Does not follow inclusion criteria for language
Montuori 2019	Lung ultrasonography in pulmonary tuberculosis: A pilot study on diagnostic accuracy in a high-risk population	No mention to Pulmonary TB
Hsairi 2016	Tuberculosis cost in tunisia	Does not follow inclusion criteria for type of study
Bothamley 2016	Pregnancy in patients with tuberculosis: a TBNET cross-sectional survey	Does not follow inclusion time frame
Mears 2016	The prospective evaluation of the TB strain typing service in England: a mixed methods study	No reference to delay association
Jacquemyn, 2012	Disseminated tuberculosis in pregnancy unknown to doctors in Western Europe case presentation: 'part of the routine study in infertility'	No mention to Pulmonary TB
Gatey 2012	Impact of early chest radiography and empirical antibiotherapy on delay in the diagnosis of pulmonary tuberculosis	Does not follow inclusion time frame
Faccini 2013	Tuberculosis outbreak in a primary school, Milan, Italy	No reference to delay association

Jurcev-Savicevic 2013	Health system delay in pulmonary tuberculosis treatment in a country with an intermediate burden of tuberculosis: a cross-sectional study	Does not follow inclusion time frame
Tamura 2016	Tuberculosis and Lung Cancer	Does not follow inclusion time frame
Matsumoto 2015	[Anti-tuberculosis therapy and paradoxical response when tuberculosis develops under the influence of biologics for rheumatoid arthritis]	Does not follow inclusion criteria for language
Abbara 2019	Time to diagnosis of tuberculosis is greater in older patients: a retrospective cohort review	Does not follow inclusion time frame
Dale 2017	Gender differences in tuberculosis diagnosis, treatment and outcomes in Victoria, Australia, 2002-2015	Does not follow inclusion time frame
Hoheisel 2009	[Pulmonary and pleural tuberculosis in the elderly]	Does not follow inclusion criteria for language
Mor 2013	Tuberculosis diagnostic delay and therapy outcomes of non-national migrants in Tel Aviv, 1998-2008	Does not follow inclusion time frame
Tuberculosis Surveillance Center 2016	[Tuberculosis Annual Report 2014--(2) Tuberculosis in Pediatric and Elderly Patients]	Does not follow inclusion criteria for language
Eisenberg 2014	Same but different: tuberculosis treatment and care among migrants from different countries of origin in Israel	Does not follow inclusion time frame
Sánchez-Rojas 2017	Factors Associated with a Long Mean Hospital Stay in Patients Hospitalized with Tuberculosis	Does not follow inclusion time frame
Nazar 2020	Bayesian Spatial Survival Analysis of Duration to Cure among New Smear-Positive Pulmonary Tuberculosis (PTB) Patients in Iran, during 2011-2018	No reference to delay association
Potter 2020	The NHS visitor and migrant cost recovery programme - a threat to health?	No reference to delay association
Cruz-Ferro 2014	Epidemiology of tuberculosis in Galicia, Spain, 16 years after the launch of the Galician tuberculosis programme	Does not follow inclusion time frame

Gressens 2021	Pulmonary tuberculosis: Evaluation of current diagnostic strategy	No reference to delay association
Doosti 2023	The Pattern of Tuberculosis in Iran: A National Cross-Sectional Study	No distinction between TB types
Heffernan 2021	Individual and public health consequences associated with a missed diagnosis of pulmonary tuberculosis in the emergency department: A retrospective cohort study	No reference to delay association

Table S4. List of selected articles

First Author and Year	Title	Authors	Year of Publication	Study Design	Study period beginning	Study period end	Country	Country TB incidence
Zão 2019	Why does it take so long? The reasons behind tuberculosis treatment delay in Portugal	Zão, I., Ribeiro, A.I., Apolinário, D., Duarte, R.	2019	Observational descriptive Study: cross-sectional study	2010	2014	Portugal	16.71 in 2009 and 13.04 in 2019.
Ibrahim 2016	Diagnostic Delay among Adults with Pulmonary Tuberculosis in a High Gross Domestic Product Per Capita Country: Reasons and Magnitude of the Problem	Ibrahim, W., Alousi, F., Al-Khal, A., Bener, A., AlSalam, A., Aamer, A., Khaled, A., Raza, T.	2016	Observational descriptive Study: cross-sectional study	2007	2015	Qatar	18.4 in 2009 and 12.46 in 2019
Tattevin 2012	Factors associated with patient and health care system delay in the diagnosis of	Tattevin, P., Che, D., Fraisse, P., Gatey, C., Guichard, C., Antoine, D.,	2012	Observational descriptive Study: cross-sectional study	2010	2010	France	7.88 in 2009 and 6.62 in 2019

	tuberculosis in France	Paty, M.C., Bouvert, E.						
Quattrocchi 2018	Determinants of patient and health system delay among Italian and foreign- born patients with pulmonary tuberculosis: a multicentre cross-sectional study	Quattrocchi, A., Barchitta, M., Nobile, C.G.A., Prato, R., Sotgiu, G., Casuccio, A., Vitale, F. Agodi, A.	2018	Observational descriptive Study: cross-sectional study	2014	2016	Italy	9.71 in 2009, and 7.29 in 2019
Loutet 2018	Delay from symptom onset to treatment start among tuberculosis patients in England, 2012–2015	Loutet, M.G., Sinclair, C., Whitehead, N., Cosgrove, C., Lalor, M.K., Thomas H.L.	2018	Analytic Observational Studies: cohort study	2012	2015	United Kingdom	15.39 in 2009 and 9.24 in 2019
Kalan 2018	The identification of risk factors associated with patient and healthcare system delays in the treatment of	Kalan, M.E., Sis, H.Y., Kelkar V., Harrison, S.H., Goins, G.D.,	2018	Observational descriptive Study: cross-sectional study	2012	2014	Iran	14.31 in 2009 and 12.4 in 2019

	tuberculosis in Tabriz, Iran	Jafarabadi, M.A., Han, J.						
Kelly 2017	Delayed tuberculosis diagnosis and costs of contact investigations for hospital exposure: New York City 2010 – 2014	Kelly, A.M., D'Agostino, J.F., Andrada, L.V., Liu, J. Larson, E.	2017	Observational descriptive Study: cross-sectional study	2010	2014	USA	3.44 in 2009 and 2.47 in 2019
Auer 2018	Health-seeking behaviour and treatment delay in patients with pulmonary tuberculosis in Switzerland: some slip through the net	Auer C., Kiefer S., Zuske M., Schindler C., Wyss K., Blum J., Bosch-Capblanch X., Widmer U., Sauthier S., Janssens J., Bossard K., Chatonnet C., Mazza-Stalder J., Zacek B.,	2018	Observational descriptive Study: cross-sectional study	2014	2016	Switzerland	6.57 in 2009 and 5.68 in 2019

		Zellweger J., Altpeter E., Mäusezahl M.						
Amar 2015	Pulmonary tuberculosis: Diagnostic delay in Tunisia	Amar, J.B., Hassairi, M., Salah. N.B., Charfi, R., Tritar,F., Fourati, R., Gamara, D., Aouina, H., Bouacha, H.	2015	Observational descriptive Study: cross-sectional study	2014	2014	Tunisia	19.1 in 2009 and 14.78 in 2019
Evenden 2019	Presentation and healthcare delays among people with tuberculosis in London, and the impact on treatment outcome	Evenden, P., Roche, A., Karo, B., Balasegaram, S., Anderson, C.S.	2019	Analytic Observational Studies: cohort study (retrospective)	2012	2018	United Kingdom	15.39 in 2009 and 9.24 in 2019
Williams 2018	Delays in presentation and diagnosis of pulmonary tuberculosis: a retrospective study of a tertiary	Williams, E., Cheng, A., Lane, G.P.; Guy, S.D.	2018	Analytic Observational Studies: cohort study (retrospective)	2011	2014	Australia	5.83 in 2009 and 5.59 in 2019

	health service in Western Melbourne, 2011-2014							
Cherif 2014	Diagnosis delay of pleural and pulmonary tuberculosis	Cherif, J., Mjid M., Ladhar A., Toujani S., Mokadem S., Louzir B., Mehiri N., Béji M.	2014	Observational descriptive Study: cross-sectional study	2009	2010	Tunisia	19.1 in 2009 and 14.78 in 2019
Yazdani-Charati 2017	Treatment Delay and Total Delay among Pulmonary Tuberculosis Patients in the North of Iran: Application Survival Data Analysis	Yazdani-Charati, J., Rezai, M.S., Fendereski, A., Mohammadi, S.,Alipour, N.	2017	Observational descriptive Study: cross-sectional study	2009	2015	Iran	14.31 in 2009 and 12.4 in 2019
Nunes 2016	Modelling the time to detection of urban tuberculosis in two big cities in Portugal: a spatial survival analysis	Nunes, C., Taylor B.M.	2016	Analytic Observational Studies: cohort study (retrospective)	2010	2013	Portugal	16.71 in 2009 and 13.04 in 2019

O'Connell 2022	Delayed Tuberculosis Treatment and Cost of Care in a Low-Incidence Country	O'Connell, J., Reidy, N., McNally, Cora., Barra, E., Stanistreet, D., McConkey, S.	2022	Mixed-method. Epidemiological setting - Observational descriptive Study: cross-sectional study	2018	2019	Ireland	7.9 in 2009 and 5.64 in 2019
Vigneswaran 2023	Factors leading to diagnostic delay in tuberculosis in the tropical north of Australia	Vigneswaran, N., Parnis, R., Lowbridge, C.,Townsend, D., Ralph, A.P.	2023	Analytic Observational Studies: cohort study (retrospective)	2010	2020	Australia	5.83 in 2009 and 5.59 in 2019
Grant 2022	Symptoms to script: delays in tuberculosis treatment in the west of Ireland	Grant, C., McHugh, J., Ryan, C., Scarry, M., O'Regan, A., Tuite, H., Fleming, C.	2022	Observational descriptive Study: cross-sectional study	2014	2019	Ireland	7.9 in 2009 and 5.64 in 2019
Roberts 2020	Factors associated with delay in treatment initiation for pulmonary tuberculosis	Roberts, D.J., Mannes, T., Verlander, N.Q. , Anderson, C.	2020	Analytic Observational Studies: cohort study (retrospective)	2011	2015	United Kingdom	15.39 in 2009 and 9.24 in 2019

Table S5. Article's additional characteristics and outcomes

First Author and Year	Total delay	Patient delay	Healthcare delay	Risk Group (Yes/No)	Type of risk group	Age	Sex	Sample Size
Zão 2019	Not possible to calculate due to lack of data regarding healthcare delay	Median (men): 34 days; Median (women): 32.5 days	Based on a different definition of healthcare delay, not presented here for that reason.	Yes	Immigrants, individuals experiencing socioeconomic deprivation, incarcerated, homeless	Only presented as age groups, without data to calculate the mean age	Female: n = 2380; Male: n = 4458	6838
Ibrahim 2016	Mean: 53 days; Median: 30 days	Mean: 45.7 days; Median: 30 days	Mean: 46.3 days; Median: 30 days.	Yes	Expatriates from high incidence TB countries, unemployed	Mean Age: 33.8 years old	Female: n = 23; Male: n = 77;	100
Tattevin 2012	Mean: 97 days; Median: 68 days	Mean: 47 days; Median: 14 days	Mean: 48 days; Median: 25 days	Yes	Immigrants, alcohol dependence, smokers, injected drug users, individuals with chronic diseases	Mean Age: 45.5 years old	Female: n = 89; Male: n = 136;	225
Quattrocchi 2018	Not possible to calculate based on the provided data	Median: 30 days	Median: 7 days	Yes	Immigrants, individuals with low education level, homeless, prison inmates, individuals	Mean age: 40.7 years old; Median age: 38.0 years old	Female: n= 92; Male n=161	253

					living in nursing homes, unemployed, smokers, alcohol dependence, people with chronic diseases			
Loutet 2018	Not possible to calculate based on the provided data and healthcare delay definition	Median: 1.2 months	Based on a different definition of healthcare delay, not presented here for that reason	Yes	Immigrants, elderly, people with social risk factors, drug misuse, alcohol misuse, homeless, prison inmates	Only presented as age groups for pulmonary tuberculosis, without data to calculate the mean age	Female: n =3216; Male: n=5245	8461
Kalan 2018	Not possible to calculate based on the provided data and healthcare delay definition	Median: 13	Based on a different definition of healthcare delay, not presented here for that reason	No	Not reported	Mean age: 55.6 years old; Median: 59.0 years old	Female: n=85; Male: n=88	173
Kelly 2017	Not reported	Not reported	Not reported	No	Not reported	Not reported	Not reported	NA
Auer 2018	Not possible to calculate based on	Median: 5.2 weeks;	Based on a different definition of	Yes	Immigrants, HIV coinfected, elderly, people with low	Median age: 35 years old	Female: n=55; Male: n= 107	162

	the provided data and healthcare delay definition	Mean: 2 weeks	healthcare delay, not presented here for that reason		education levels, unemployed.			
Amar 2015	Not possible to calculate based on the provided data and healthcare delay definition	Mean: 29.54 days	Based on a different definition of healthcare delay, not presented here for that reason	No	Elderly, low education levels, unemployed	Mean Age: 42.2 years old	Female: n=110; Male: n=242	352
Evenden 2019	Not possible to calculate based on the provided data and healthcare delay definition	Median presentation delay: 35 days	Based on a different definition of healthcare delay, not presented here for that reason	Yes	Immigrants, elderly, people with history of drug use, history of homelessness, history of imprisonment, alcohol misuse, unemployed	Median Age: 38 years old	Female: n=1621; Male: n=2918	4539
Williams 2018	Median: 89 days	Median: 28 days	Median: 18 days	Yes	Elderly, immigrants from high TB risk counties, unemployed, people with comorbidities, and injected drug users	Median age: 35 years old	Female: n=44; Male: n=89	133

Cherif 2014	Not possible to calculate based on the provided data and healthcare delay definition	Mean: 43.6 days	Based on a different definition of healthcare delay, not presented here for that reason	Yes	Smokers, alcohol misuse, cardiovascular disease patients, other comorbidities	Mean age: 39 years old	Female: n=22; Male: n=78	100
Yazdani-Charati 2017	Not possible to calculate based on the provided data and healthcare delay definition	Not reported	Based on a different definition of healthcare delay, not presented here for that reason	Yes	HIV positive, unknown contact with TB patients, immigrants, prison inmates	Mean age: 47.40 years old	Female: n=574; Male: n=1120	1694
Nunes 2016	Lisbon: Median: 62 days, Mean: 81.01 days; Oporto: Median: 60 days, Mean: 79.5 days.	Not reported	Not reported	Yes	Migrants, HIV infected individuals, alcoholic individuals, prison inmates, intravenous drug users, homeless patients	Mean age (Lisbon): 44.16 years old; Median age (Lisbon): 42 years old; Mean age (Oporto): 47.01 years old; Median age	Female (Lisbon): n=1028; Male (Lisbon): n=1678; Female (Oporto): n=676; Male (Oporto) n=1207	4589

						(Oporto): 46 years old		
O'Connell 2022	Not possible to calculate based on the provided data and healthcare delay definition	Median: 60 days	Based on a different definition of healthcare delay, not presented here for that reason	Yes	HIV infected individuals, immunosuppression, homelessness, drug users, diabetics, alcohol dependence	Median age: 41.4 years old	Female: n=7; Male n=12	19
Vigneswaran 2023	Median: 90 days	Median: 53 days	Median: 21 days	Yes	Elderly, immigrants, smokers, patients with comorbidities, report of overcrowding, incarceration, homelessness, or detention	Median age: 45 years old	Female: n = 24; Male: n = 60	84
Grant 2022	Not possible to calculate based on the provided data and healthcare delay definition	Mean: 109 days	Based on a different definition of healthcare delay, not presented here for that reason.	Yes	Immigrants, HIV positive, known treated latent tuberculosis; known untreated latent tuberculosis; drug/alcohol dependence, chronic kidney disease,	Mean age: 40 years old	Not reported for patients having pulmonary tuberculosis	85

					diabetes mellitus, biologic therapy			
Roberts 2020	Not possible to calculate based on the provided data and Healthcare delay definition	Median: 30 days	Based on a different definition of healthcare delay, not presented here for that reason	Yes	People living in high TB incidence areas, elderly, people having social risk factors	Only presented as age groups, without data to calculate the mean age	Female n=327; Male n=485	812

Table S6. List of barriers and previous knowledge or TB suspicion

First Author and Year	Presence/absence of healthcare access barriers	Previous knowledge/suspicion of tuberculosis
Zão 2019	Mostly in immigrants it is mentioned the presence of both cultural and economic barriers.	Not reported.
Ibrahim 2016	Not reported.	Not reported regarding patients' knowledge. Nevertheless, it is mentioned that when immigrants arrive to the country TB symptoms are explained to them. Adding to this, there is a mention on failure in healthcare services to suspect of PTB.
Tattevin 2012	Possibly for immigrants there might be a competitive effect of two different phenomenon: in one hand there seems to be a lower threshold to identify TB, with lower healthcare delays in this group, however, there is the possibility for delay increase due to migrant status, or lack of medical insurance.	Not reported regarding patients. However, it is mentioned that multiple consultations were found in this study, which means that the suspicion of TB is being suboptimal.
Quattrocchi 2018	Among cultural aspects, TB-related stigma drives individuals to hide their condition from others and refusing seeking healthcare. Focusing on foreign-born patients, language barriers, poor knowledge of symptoms, fear of immigration authorities and long wait for appointment have been associated with delay in seeking care.	It is mentioned that foreign-born patients reported being less aware of TB characteristics as an infectious disease, its treatment, way of transmission and potentiality for multiple drug resistance. Besides, mostly on foreign-born patients it was found a lack of knowledge of the disease.
Loutet 2018	Not reported.	Not reported regarding patients' knowledge. However, it was found that migrants in the United Kingdom (UK) for more than 10 years had no diagnostic delay differences when compared with UK-born cases. It is postulated that the professionals' threshold for detection might be

		reduced in relation to the time a person has been living in a low TB incidence country.
Kalan 2018	Not reported. It was also stressed that financial unaffordability in being tested was not associated with diagnostic delay, being postulated that it would be because treatment procedures in Iran are free.	Not reported for patients. However, a possible lack of suspicion of TB by clinicians was identified, including a high proportion of misdiagnosis when first attending healthcare facilities.
Kelly 2017	Not reported.	Not reported for patients' knowledge, however, misdiagnosis was mentioned.
Auer 2018	Not reported, despite being stressed that foreign-born patients had longer patient delay but shorter healthcare delay.	Patients were inquired about knowledge of TB. It was found that most people (3/4 of patients) knew about the disease, its ability to kill and that it could be treated. The most common outcomes after the first healthcare visit would suggest low clinician suspicion towards TB in their patients (prescription of medicines other than TB medication, referral to second visit or hospital). The foreign-born subgroup seems to be less affected to this fact due to lower healthcare delay among these patients.
Amar 2015	Financial barriers might be present, however no significant difference was observed between private and public facility attendance. Adding to this, since patient delay would be more frequently observed in patients whose first medical appointment was to a specialist instead of a family physician, long waiting times to get an appointment might be present. Regarding psychological/social barriers, being ashamed of TB infection and thoughts on TB negatively impacting one's professional life and marital relationships were identified.	Not reported.
Evenden 2019	Not reported.	Not reported.

Williams 2018	It is speculated that barriers to recent migrants may exist due to poor access to healthcare, poor health literacy, fear of costs associated to health care, fear of impact of TB diagnosis on visa and residency status and stigma/misunderstanding about TB diagnosis and treatment. Lower levels of health literacy and English language skill in recent residents (<6 years) may explain longer delay among migrants, when compared with their Australian-born or longer-term resident counterparts.	Less awareness of recent migrants (<6 years) from low incidence TB countries on Tuberculosis infection when compared with Australian-borne and longer-term residents.
Cherif 2014	Females tend to have more access barriers to healthcare, especially in rural areas, requiring her husband or a close relative to take them to a hospital/health clinic. Financial constraints are also affecting unemployed patients, reason by which patients wait for the end of the month to perform diagnostic exams (out of pocket expenses).	Because of its insidious clinic, many patients take the symptoms for a cold, or a mild gravity respiratory disease.
Yazdani-Charati 2017	Treatment delay for women seem to be longer than for their male counterparts because of needs for transportation. It also seems to exist more efficient healthcare access for people in rural areas because of this regions' higher number of TB patients found in those places.	Not reported regarding patients' knowledge, however, misdiagnosis was reported, possibly due to physicians' difficulty in recognizing TB among other diseases' symptoms.
Nunes 2016	Not mentioned. It was also stressed that by the fact that both cities are in the same country there are commonalities regarding culture, healthcare systems, laws, and other contextual factors, which could affect delay.	Not reported.
O'Connell 2022	Costs and long wait times constitute barriers for a country with no universal healthcare, especially in vulnerable groups.	Not reported.

Vigneswaran 2023	Discrimination, economic and social disadvantages, and ongoing impacts of colonization were identified as possibly contributing to a reduced healthcare access among Indigenous Australians.	Not reported regarding patients, however, lower levels of suspicion of TB infection by clinicians regarding autochthonous patients were reported.
Grant 2022	Not reported.	Not reported.
Roberts 2020	Language barriers were identified as having an association with longer healthcare delay.	Not reported.

Table S7. Outcome results

Outcome Variable	Independent Variable	First Author and Year	Effect measure	Value	95% CI	P-value	Population	Observations
Total delay	Being an older patient	Yazdani-Charati 2017	HR	0.997	0.994-0.999	0.008	Patients from Mazandaran center, Iran	Multivariate analysis results: Cox multi-variable analysis adjusting for age, gender, nationality, place of residence, prison status, date of diagnosis, date of first symptom, date of treatment, contact history with TB patient, type of Pulmonary TB, HIV test status and treatment delay.
Total delay	Smear-negative result at first admission	Yazdani-Charati 2017	HR	1.116	0.992-1.255	0.068	Patients from Mazandaran center, Iran	Multivariate analysis results: Cox multi-variable analysis adjusting for age, gender, nationality, place of residence, prison status, date of diagnosis, date of first symptom, date of treatment, contact history with TB patient, type of Pulmonary TB, HIV test status and treatment delay.
Total delay	First healthcare contact in hospital setting	Tattevin 2012	OR	0.320	Not reported	0.004	French population (all ages)	Univariate analysis results
Total delay	Several healthcare contacts	Tattevin 2012	OR	2.290	1.410-3.730	0.001	French population (all ages)	Multivariate analysis results: multivariate logistic regression adjusted for: Medical insurance, previous treatment for tuberculosis, number of healthcare contacts, fever at symptom onset, being followed by a general practitioner, first healthcare contact in hospital, antibiotic treatment, medical insurance, asthenia at first healthcare contact
Total delay	Medical Insurance	Tattevin 2012	OR	0.240	0.080-0.750	0.014	French population (all ages)	Multivariate analysis results: multivariate logistic regression adjusted for: Medical insurance, previous treatment for tuberculosis,

								number of healthcare contacts, fever at symptom onset, being followed by a general practitioner, first healthcare contact in hospital, antibiotic treatment, medical insurance, asthenia at first healthcare contact
Total delay	Previously having TB	Tattevin 2012	OR	0.280	0.080-1.000	0.049	French population (all ages)	Multivariate analysis results: multivariate logistic regression adjusted for: Medical insurance, previous treatment for tuberculosis, number of healthcare contacts, fever at symptom onset, being followed by a general practitioner, first healthcare contact in hospital, antibiotic treatment, medical insurance, asthenia at first healthcare contact
Total delay	Being a Foreigner	Yazdani-Charati 2017	HR	0.812	0.593-1.113	0.196	Patients from Mazandaran center, Iran	Multivariate analysis results: Cox multi-variable analysis adjusting for age, gender, nationality, place of residence, prison status, date of diagnosis, date of first symptom, date of treatment, contact history with TB patient, type of Pulmonary TB, HIV test status and treatment delay.
Total delay	Performing a smear-test	Cherif 2014	Not reported	Not reported	Not reported	0.050	Patients from Centre Hospitalalier Universitaire La Rabta, Tunis, Tunisia	Multivariate analysis results: Model adjusted for: history of TB contact, alcohol, cough, asthenia, fever, sweating, number of consultations, place of first consultation, absence of X-ray at first consultation, antibiotic therapy, type of TB, confirmation test. In this case, positive association was found, with statistically significance, but no measure of effect was reported.

Total delay	Unknown HIV status	Yazdani-Charati 2017	HR	1.286	1.131-1.463	<0.001	Patients from Mazandaran center, Iran	Multivariate analysis results: Cox multi-variable analysis adjusting for age, gender, nationality, place of residence, prison status, date of diagnosis, date of first symptom, date of treatment, contact history with TB patient, type of Pulmonary TB, HIV test status and treatment delay.
Total delay	Unknown contact history	Yazdani-Charati 2017	HR	0.668	0.599-0.746	<0.001	Patients from Mazandaran center, Iran	Multivariate analysis results: Cox multi-variable analysis adjusting for age, gender, nationality, place of residence, prison status, date of diagnosis, date of first symptom, date of treatment, contact history with TB patient, type of Pulmonary TB, HIV test status and treatment delay.
Total delay	Being a male patient	Yazdani-Charati 2017	HR	0.975	0.877-1.084	0.635	Patients from Mazandaran center, Iran	Multivariate analysis results: Cox multi-variable analysis adjusting for age, gender, nationality, place of residence, prison status, date of diagnosis, date of first symptom, date of treatment, contact history with TB patient, type of Pulmonary TB, HIV test status and treatment delay.
Total delay	Being a Foreigner	Nunes 2016	RR	0.870 (Lisbon), 1.010 (Oporto)	0.800-0.960 (Lisbon), 0.780-1.290, (Oporto)	Significant in Lisbon, but p-value not reported	Lisbon and Oporto (Portugal)	Multivariate analysis results: Spatial survival analysis model (fixed effects), adjusted for: sex, alcohol, intravenous drug user, prison inmate, homelessness, HIV status, migration status. In the model, lower RR implies longer delay, while higher RR implies shorter delay
Total delay	Absence of Alcohol misuse	Nunes 2016	RR	1.030 (Lisbon), 1.020 (Oporto)	0.910-1.180 (Lisbon), 0.880-	Not reported	Lisbon and Oporto (Portugal)	Multivariate analysis results: Spatial survival analysis model (fixed effects), adjusted for: sex, alcohol, intravenous drug user,

					1.180 (Oporto)			prison inmate, homelessness, HIV status, migration status. In the model, lower RR implies longer delay, while higher RR implies shorter delay
Total delay	Absence of HIV infection	Nunes 2016	RR	0.850 (Lisbon), 0.810 (Oporto)	0.760-0.950 (Lisbon), 0.690-0.990 (Oporto)	Significant, but p-value not reported	Lisbon and Oporto (Portugal)	Multivariate analysis results: Spatial survival analysis model (fixed effects), adjusted for: sex, alcohol, intravenous drug user, prison inmate, homelessness, HIV status, migration status. In the model, lower RR implies longer delay, while higher RR implies shorter delay
Total delay	Being a male patient	Nunes 2016	RR	1.190 (Lisbon), 1.180 (Oporto)	1.090-1.290 (Lisbon), 1.070-1.300 (Oporto)	Significant, but p-value not reported	Lisbon and Oporto (Portugal)	Multivariate analysis results: Spatial survival analysis model (fixed effects), adjusted for: sex, alcohol, intravenous drug user, prison inmate, homelessness, HIV status, migration status. In the model, lower RR implies longer delay, while higher RR implies shorter delay
Patient delay	Being a Foreigner	Zão 2019	TR	1.777	1.091-1.270	Not described	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction
Patient delay	Being a Foreigner	Quattrocchi 2018	OR	1.670	0.960-2.890	0.069	Native and non-native patients from 4 Italian regions (all ages)	Multivariate analysis results: Logistic regression analysis adjusted to: Stigma, pay for transportation to reach the heath center, close distance to the first visit place, chest pain. Patient delay

								expressed as delay being longer than 30 days.
Patient delay	Being a Foreigner	Williams 2018	OR	0.30	0.120-0.740	0.010	Symptomatic patients at least 18 years old in western Melbourne, Australia.	Multivariate analysis results: Model adjusted for: Time since migration (time considered after migration of at least 6 years), TB risk in country of migration, weight loss, diabetes mellitus and current smoking.
Patient delay	Alcohol misuse	Zão 2019	TR	1.169	1.072-1.276	Not reported	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction
Patient delay	Drug addition	Zão 2019	TR	1.153	1.027 to 1.295	Not reported	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction
Patient delay	Being a younger patient	Roberts 2020	TR (time ratio)	0.230	0.090-0.590	0.002	Residents on the southeast of England	Multivariate analysis results: Logistic regression model: ethnicity, mental health barriers, rurality, physical health, language barriers, sex, prior TB diagnosis, age group years, social risk factors, time resident in UK, quintile of index of multiple deprivation. In this study, being a younger patient considered as in the 0-14 age group.

Patient delay	Presence of Non-pulmonary comorbidities	Zão 2019	TR	0.935	0.878-0.996	Not described	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction
Patient delay	Resident in moderately urban areas	Zão 2019	TR	0.865	0.791-0.946	Not described	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction
Patient delay	Resident in predominantly rural areas	Zão 2019	TR	0.955	0.850-1.073	Not described	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction
Patient delay	Long distance from a healthcare service	Zão 2019	TR	0.961	0.942-0.979	Not described	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction

Patient delay	Long distance from a healthcare service	Quattrocchi 2018	OR	2.300	1.150-4.620	0.018	Native and non-native patients from 4 Italian regions (all ages)	Multivariate analysis results: Logistic regression analysis adjusted to: Stigma, pay for transportation to reach the heath center, close distance to the first visit place, chest pain. Patient delay expressed as delay being longer than 30 days.
Patient delay	Medical Insurance	Tattevin 2012	OR	0.360	Not described	0.011	French population (all ages)	Univariate analysis results
Patient delay	Being followed by a GP	Tattevin 2012	OR	0.220	0.080-0.610	0.004	French population (all ages)	Multivariate analysis results: multivariate logistic regression adjusted for: Medical insurance, previous treatment for tuberculosis, number of healthcare contacts, fever at symptom onset, being followed by a general practitioner, first healthcare contact in hospital, antibiotic treatment, medical insurance, asthenia at first healthcare contact
Patient delay	Presence of Fever at symptom onset	Tattevin 2012	OR	0.420	0.190-0.920	0.030	French population (all ages)	Multivariate analysis results: multivariate logistic regression adjusted for: Medical insurance, previous treatment for tuberculosis, number of healthcare contacts, fever at symptom onset, being followed by a general practitioner, first healthcare contact in hospital, antibiotic treatment, medical insurance, asthenia at first healthcare contact
Patient delay	Stigma towards TB infection	Quattrocchi 2018	OR	2.640	1.510-4.610	0.001	Native and non-native patients from 4 Italian regions (all ages)	Multivariate analysis results: Logistic regression analysis adjusted to: Stigma, pay for transportation to reach the heath center, close distance to the first visit place, chest pain. Patient delay

								expressed as delay being longer than 30 days.
Patient delay	Low economic capacity	Kalan 2018	Crude OR	0.540	0.290-1.010	Not described	Iranian population (all ages)	Univariate analysis results: Article's outcome variable expressed as Patient delay longer than 13 days.
Patient delay	Presence of chest pain	Quattrocchi 2018	OR	1.970	1.080-3.610	0.026	Native and non-native patients from 4 Italian regions (all ages)	Multivariate analysis results: Logistic regression analysis adjusted to: Stigma, pay for transportation to reach the heath center, close distance to the first visit place, chest pain. Patient delay expressed as delay being longer than 30 days.
Patient delay	Presence of weight loss	Quattrocchi 2018	OR	4.410	2.480-7.830	<0.001	Native and non-native patients from 4 Italian regions (all ages)	Multivariate analysis results: Logistic regression analysis adjusted to: Stigma, pay for transportation to reach the heath center, close distance to the first visit place, chest pain. Patient delay expressed as delay being longer than 30 days.
Patient delay	Presence of weight loss	Williams 2018	OR	2.230	1.000-4.960	0.050	Symptomatic patients at least 18 years old in western Melbourne, Australia	Multivariate analysis results: Model adjusted for: Time since migration (time considered after migration of at least 6 years), TB risk in country of migration, weight loss, diabetes mellitus and current smoking.
Patient delay	Need to pay for transportation	Quattrocchi 2018	OR	3.180	1.770-5.730	<0.001	Native and non-native patients from 4 Italian regions (all ages)	Multivariate analysis results: Logistic regression analysis adjusted to: Stigma, pay for transportation to reach the heath center, close distance to the first visit place, chest pain. Patient delay expressed as delay being longer than 30 days.
Patient delay	Presence of chronic disease	Quattrocchi 2018	OR	2.170	1.210-3.900	0.009	Native and non-native patients from 4 Italian	Multivariate analysis results: Logistic regression analysis adjusted to: Stigma, pay for

							regions (all ages)	transportation to reach the heath center, close distance to the first visit place, chest pain. Patient delay expressed as delay being longer than 30 days.
Patient delay	Presence of chronic disease	Williams 2018	OR	3.020	1.040-8.780	0.040	Symptomatic patients at least 18 years old in western Melbourne, Australia	Multivariate analysis results: Model adjusted for: Time since migration (time considered after migration of at least 6 years), TB risk in country of migration, weight loss, diabetes mellitus (chronic disease) and current smoking.
Patient delay	Being employed	Kalan 2018	Crude OR	5.860	1.590-21.640	Not reported	Iranian population (all ages)	Univariate analysis results: Article's outcome variable expressed as Patient delay longer than 13 days.
Patient delay	Attendance to public hospital or clinic	Kalan 2018	Crude OR	2.640	1.010-6.850	Not reported	Iranian population (all ages)	Univariate analysis results: Article's outcome variable expressed as Patient delay longer than 13 days.
Patient delay	Being a male patient	Kalan 2018	Crude OR	2.280	1.290-4.390	Not reported	Iranian population (all ages)	Univariate analysis results: Article's outcome variable expressed as Patient delay longer than 13 days.
Patient delay	Having language barriers	Roberts 2020	TR	1.400	1.010 to 1.940	0.042	Residents on the southeast of England	Multivariate analysis results: Logistic regression model: ethnicity, mental health barriers, rurality, physical health, language barriers, sex, prior TB diagnosis, age group years, social risk factors, time resident in UK, quintile of index of multiple deprivation
Patient delay	Having mental health barriers	Roberts 2020	TR	2.060	1.220-3.500	0.007	Residents on the southeast of England	Multivariate analysis results: Logistic regression model: ethnicity, mental health barriers, rurality, physical health, language barriers, sex, prior TB diagnosis, age group years, social risk factors, time resident in UK, quintile of index of multiple deprivation

Patient delay	Being a smoker	Williams 2018	OR	2.270	0.990-5.180	0.050	Symptomatic patients at least 18 years old in western Melbourne, Australia	Multivariate analysis results: Model adjusted for: Time since migration (time considered after migration of at least 6 years), TB risk in country of migration, weight loss, diabetes mellitus and current smoking.
Patient delay	Having fatigue	Williams 2018	OR	0.410	0.160-0.990	0.050	Symptomatic patients at least 18 years old in western Melbourne, Australia	Univariate analysis results
Healthcare delay	Being an older patient	Williams 2018	OR	4.290	1.550-11.890	0.010	Symptomatic patients at least 18 years old in western Melbourne, Australia	Multivariate analysis results: Model adjusted for: age, cough, emergency department review, and hospital admission. In this study, being an older patient considered as being older than 65.
Healthcare delay	Presence of coinfection	Zão 2019	TR	0.900	0.790-1.025	Not described	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, Urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction
Healthcare delay	Low economic capacity	Zão 2019	TR	0.974	0.958-0.991	Not described	Mostly Portuguese population	Multivariate analysis results: Multivariate Linear regression adjusted to: Place of birth, Urbanity level, distance to healthcare (km), homelessness, TB involvement, lung cancer, sarcoidosis, chronic obstructive pulmonary disease, HIV infection, other pulmonary comorbidities, alcohol addiction, drugs addiction

Healthcare delay	Presence of cough	Williams 2018	OR	0.090	0.010-0.790	0.030	Symptomatic patients at least 18 years old in western Melbourne, Australia	Multivariate analysis results: Model adjusted for: age, cough, emergency department review, and hospital admission.
Healthcare delay	Having fatigue	Williams 2018	OR	0.430	0.180-1.010	0.050	Symptomatic patients at least 18 years old in western Melbourne, Australia	Univariate analysis
Healthcare delay	Outpatient review	Williams 2018	OR	7.670	3.510-16.770	<0.001	Symptomatic patients at least 18 years old in western Melbourne, Australia	Univariate analysis
Healthcare delay	Emergency department review	Williams 2018	OR	0.430	0.170-1.070	0.070	Symptomatic patients at least 18 years old in western Melbourne, Australia	Multivariate analysis results: Model adjusted for: age, cough, emergency department review, and hospital admission.
Healthcare delay	Hospital admission	Williams 2018	OR	0.280	0.090-0.920	0.040	Symptomatic patients at least 18 years old in western Melbourne, Australia	Multivariate analysis results: Model adjusted for: age, cough, emergency department review, and hospital admission.
Healthcare delay	Chest X-ray showing cavity	Williams 2018	OR	0.250	0.090-0.670	<0.010	Symptomatic patients at least 18 years old in western Melbourne, Australia	Univariate analysis
Healthcare delay	Sputum NAT positive	Williams 2018	OR	0.140	0.030-0.620	0.010	Symptomatic patients at least 18 years old in western	Univariate analysis

							Melbourne, Australia	
Healthcare delay	Misdiagnosis with cold or viral infection	Kalan 2018	Crude OR	2.610	1.400-4.910	Not described	Iranian population (all ages)	Univariate analysis results: Article's outcome variable expressed as healthcare delay longer than 52 days.
Healthcare delay	Misdiagnosis asthma	Kalan 2018	Crude OR	0.580	0.180-1.840	Not described	Iranian population (all ages)	Univariate analysis results: Article's outcome variable expressed as healthcare delay longer than 52 days.
Healthcare delay	Misdiagnosis with chronic obstructive pulmonary disease	Kalan 2018	Crude OR	0.960	0.260-3.450	Not described	Iranian population (all ages)	Univariate analysis results: Article's outcome variable expressed as healthcare delay longer than 52 days.

Table S8. JBI critical appraisal checklists questions

JBI Tool	Question number	Question
JBI critical appraisal checklist for analytical cross-sectional studies	1	Were the criteria for inclusion in the sample clearly defined?
	2	Were the study subjects and the setting described in detail?
	3	Was the exposure measured in a valid and reliable way?
	4	Were objective, standard criteria used for measurement of the condition?
	5	Were confounding factors identified?
	6	Were strategies to deal with confounding factors stated?
	7	Were the outcomes measured in a valid and reliable way?
	8	Was appropriate statistical analysis used?
JBI critical appraisal checklist for cohort studies	1	Were the two groups similar and recruited from the same population?
	2	Were the exposures measured similarly to assign people to both exposed and unexposed groups?
	3	Was the exposure measured in a valid and reliable way?
	4	Were confounding factors identified?
	5	Were strategies to deal with confounding factors stated?
	6	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
	7	Were the outcomes measured in a valid and reliable way?
	8	Was the follow up time reported and sufficient to be long enough for outcomes to occur?
	9	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
	10	Were strategies to address incomplete follow up utilized?
	11	Was appropriate statistical analysis used?

Table S9. JBI critical appraisal checklist for analytical cross-sectional studies

First Author and Year	Question number								Decision
	1	2	3	4	5	6	7	8	
Zão 2019	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
Ibrahim 2016	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Exclude
Tattevin 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Quattrocchi 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Kalan 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Kelly 2017	Yes	Yes	Yes	Yes	No	No	Yes	No	Exclude
Auer 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Amar 2015	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Exclude
Cherif 2014	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
Yazdani-Charati 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
O'Connell 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Grant 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include

Table S10. JBI critical appraisal checklist for cohort studies

First Author and Year	Question Number											Decision
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Loutet 2018	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Not applicable	Yes	Include
Evenden 2019	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Not applicable	Yes	Exclude
Williams 2018	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Not applicable	Yes	Include
Nunes 2016	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Vigneswaran 2023	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Not applicable	Yes	Include
Roberts 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include

Table S11. GRADE summary table

Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty
Total delay	Low	Moderate	Low	Moderate	Moderate	Very Low
Patient delay	Low	High	Low	Moderate	Moderate	Very Low
Healthcare delay	Low	Moderate	Low	Moderate	Moderate	Very Low