A scoping review on the risk of tuberculosis in specific population groups: can we expand the World Health Organization recommendations?

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Shareable abstract (@ERSpublications)
Recommendations to test for and treat tuberculosis infection are currently limited to 11 high-risk groups. Our review suggests that new evidence is available on other potential at-risk populations that might deserve updated recommendations from the WHO. https://bit.ly/3VCE5Qi

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Abstract

Since 2015, the World Health Organization (WHO) has recommended prioritising testing and treatment of tuberculosis (TB) infection (TBI) in 11 high-risk groups. With new options emerging for TB preventive treatment, we conducted a scoping review, in consultation with the WHO's Global Tuberculosis Programme, to explore the evidence for other population groups at potentially high risk of progression to active TB. We searched six databases for preprints and articles published between 2000 and August 2022. 18 out of 33 668 screened records were included (six meta-analyses and 12 original research studies). Most were observational studies reporting the incidence of active TB in a risk group *versus* control. Glomerular diseases had the strongest association with active TB (standardised incidence ratio 23.36, 95% CI 16.76–31.68) based on an unpublished study. Other conditions associated with increased risk of active TB included hepatitis C, malignancies, diabetes mellitus, rheumatoid arthritis and vitamin D deficiency. Corticosteroid use was also associated with increased risk in several studies, although heterogeneous definitions of exposure and indications for use challenge interpretation. Despite methodological limitations of the identified studies, expanding the recommendations for TBI screening and treatment to new risk groups such as those reported here should be considered. Further group-specific systematic reviews may provide additional data for decision-making.

Introduction

A quarter of the world's population is estimated to be infected with *Mycobacterium tuberculosis* [1], but only 5–10% of people with tuberculosis (TB) infection (TBI) will develop active TB disease in their lifetime [2]. The risk of progression to TB is not the same in all individuals; those with certain risk factors are at significantly higher risk of progression than the general population with TBI. In the absence of an effective vaccine against TB, prevention of progression from TBI to active TB through preventive treatment is one of the most important tools for controlling TB and represents a key component of the World Health Organization (WHO)'s 2015 End TB Strategy [3, 4]. However, population-wide TBI testing and treatment are not feasible due to costs and the risk of adverse events associated with TB drugs [5]. Therefore, when the WHO released its first guidelines for the management of TBI [6] as part of its post-2015 End TB Strategy [7], it recommended prioritising testing and treatment of TBI only in the population groups at high risk of progression to active TB.

The guidelines identified 11 population groups in which systematic TBI screening is recommended: people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or haematological transplantation, patients with silicosis, prisoners, healthcare workers, immigrants from high TB burden countries, homeless persons and illicit drug users [6]. In subsequent revisions of the guideline, in 2018 [8] and 2020 [5], updated searches for new evidence on target populations were not carried out.

7 years after the work that produced the list of 11 population groups, the WHO is looking for an assessment of new evidence that may have become available on populations at risk, particularly as newer options for TB preventive treatment, including shorter and safer regimens, potentially allow the treatment of more people due to diminished concerns about adverse events and issues with adherence [9–11]. The aim of this scoping review is to explore the available evidence for other groups that may be at high risk of progression to active TB.

Methods

Research question

We conducted a scoping review of the literature based on the following objectives.

1) To identify at-risk groups, other than those already included in the WHO guidelines for the management of TBI, who would benefit from systematic testing and treatment of TBI.
2) To collate the evidence concerning the risk of progression from TBI to active TB disease and/or the risk of developing active TB regardless of TBI status for each newly identified risk group relative to the general population.
3) To collate the evidence concerning the risk of developing active TB, dying from TB, experiencing drug-related adverse events or experiencing adverse pregnancy outcomes (*e.g.* pre-term birth, low birthweight, congenital anomalies, intrauterine growth retardation, *etc.*) in individuals in each newly identified risk group receiving tuberculosis preventive treatment (TPT) after a positive TBI test relative to those receiving TPT without a positive TBI test.

Our review was based on a pre-specified protocol (not publicly registered), and we report it according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews [5].

Search strategy

In consultation with a librarian (G. Gore), a search strategy was developed to identify relevant literature in MEDLINE (Ovid), Embase (Ovid), Web of Science Core Collection (all indexes), CENTRAL (Cochrane Library), Global Health (Ovid) and Europe PMC for preprints using search terms related to the concepts of latent TB and risk of progression to active TB disease. We did not decide *a priori* which risk groups to focus on, so the search terms were intentionally broad. Additionally, ongoing studies were identified through ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. The search was limited to articles, preprints or conference abstracts published between 1 January 2000 and 26 August 2022. No language filters were applied to the search. Studies included in systematic reviews without meta-analyses that were selected through title/abstract screening had their full texts manually screened for eligibility along with additional sources identified in consultation with the WHO. Full search strategies are provided in supplementary material 1.

Study selection

Three reviewers (J. Bigio, A. Viscardi and G. Sulis) conducted title/abstract screening, with each title/abstract independently screened by a combination of two of the three reviewers. Two reviewers (J. Bigio and A. Viscardi) independently conducted full-text screening of records selected by title/abstract. Although we pre-defined a set of inclusion and exclusion criteria to guide the assessment of each article, those criteria were refined throughout the process in line with standard practice for scoping reviews. Conflicts at each stage were resolved through discussion between the three reviewers.

We included observational and experimental studies, such as randomised and nonrandomised studies, cohort studies and case–control studies, which reported on any of the outcomes of interest (detailed later) in one or more populations of interest that were not among the 11 groups already included in previous WHO recommendations [5]. Relevant meta-analyses were also included, whereas systematic and narrative reviews without meta-analyses were excluded after screening their reference lists for potentially relevant studies. Studies were included regardless of the methods used to ascertain TBI status and detect active TB disease.

We excluded cross-sectional studies, case reports or case series, economic analyses, modelling studies, qualitative studies, editorials or commentaries with no primary data. In addition, we excluded studies that focused exclusively on the prevalence of TBI in different groups with no data on progression to active TB, those that reported only on one or more of the 11 groups already included in previous WHO guidelines and those which contributed to meta-analyses already included in this review. For conference or poster abstracts, attempts were made to contact authors for further information. If authors could not be contacted or if further details could not be retrieved, these studies were excluded.

Outcome measures

Studies were considered eligible for inclusion if they reported on at least one of the following outcome measures.

1) Risk ratio or odds ratio, or other related measure of association, comparing the risk or odds of progression from TBI to active TB of individuals from a given risk group compared with the general population of people with TBI.
2) Risk ratio or odds ratio or other related measure, comparing the risk or odds of incident TB of individuals from a given risk group compared with the general population, regardless of TBI status.
3) Within a given risk group, risk ratio or odds ratio or other related measure, comparing the risk or odds of incident TB among those with TBI *versus* those without TBI.
4) Within a given risk group, risk ratio or odds ratio or other related measure, comparing the risk or odds of incident TB among those receiving TPT following a positive TBI test *versus* those receiving TPT without a positive TBI test.

Additionally, we explored the evidence concerning additional outcomes of interest such as TB-related mortality, drug-related toxicity and pregnancy outcomes (*e.g.* low birthweight, congenital anomalies, intrauterine growth retardation, *etc*).

Data extraction

Data were extracted using a standardised form in Microsoft Word (Microsoft Corporation, Redmond, WA, USA). One reviewer (J. Bigio) performed the extraction, which was checked by a second reviewer (A. Viscardi). Discrepancies were resolved through discussion between the extractors and a third reviewer (G. Sulis). Data extracted from original studies included country, study period, study design, characteristics of risk groups and comparator groups, main quantitative findings, data sources and other relevant notes on the study methods and findings. Data from meta-analyses were extracted separately from original studies. Extracted data for meta-analyses included search period, inclusion and exclusion criteria, pooled estimates and number of studies contributing to pooled estimates.

Data synthesis

Extracted data were summarised in descriptive tables. Due to between-study heterogeneity of population groups, settings, outcome measures and methods of outcome ascertainment, no quantitative data synthesis was undertaken.

Results

After deduplication of search results, 33 668 unique citations were identified. Of these, 33 540 records were excluded after title/abstract screening, leaving 128 records (including 38 conference abstracts) for further assessment. In addition, 51 further records were identified through reference checks of systematic and narrative reviews. 175 out of 179 assessed full texts were published in English, with the remaining four in languages for which we had the capacity for translation (French, German and Spanish). 18 studies (six meta-analyses and 12 original research articles, of which one [12] was a conference abstract whose authors kindly shared additional currently unpublished data for the purpose of this work) met the eligibility criteria for inclusion in this review. All included studies were published in English. The remaining 161 records were deemed ineligible and were excluded (figure 1). The primary reason for exclusion was the lack of data on at least one of our outcomes of interest (n=87). Other common reasons for exclusion were studies which contributed to meta-analyses included in this review (n=22), studies which focused exclusively on the acquisition of TBI in different groups with no data on progression to active TB (n=17) or studies which reported only on one or more of the 11 groups already included in previous WHO guidelines (n=11). Full details on reasons for exclusion and publication language are given in supplementary material 2.

Main characteristics of included studies

Of the 12 included original studies, three were on patients with rheumatoid arthritis [13–15], three were on patients with other rheumatic diseases receiving a variety of treatments [16–18], one was on patients

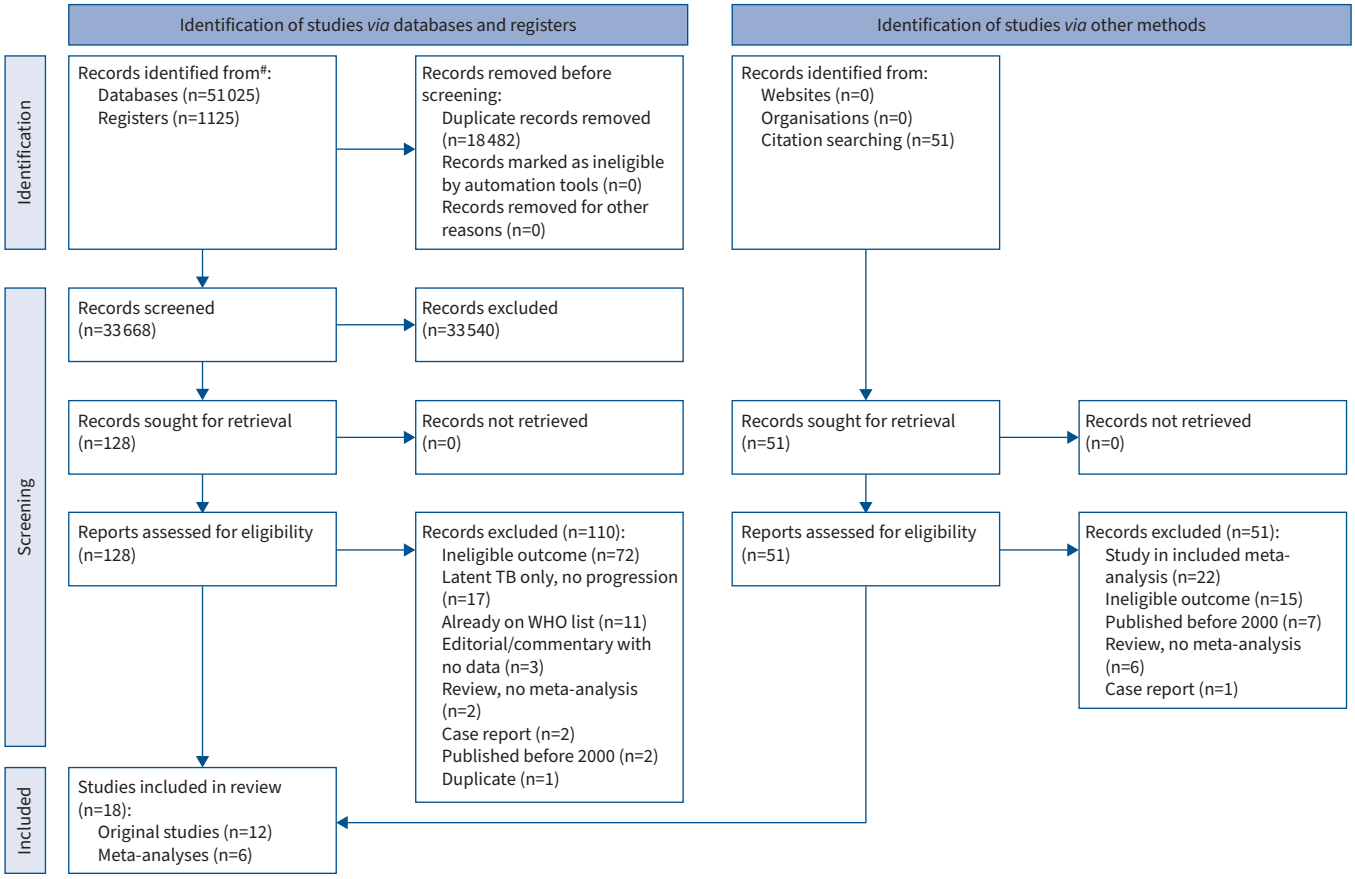

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study screening and selection. TB: tuberculosis; WHO: World Health Organization.

receiving corticosteroids for any indication [19] and one each were on patients with the following conditions: diabetes mellitus [20], glomerular diseases [12], hepatitis C virus (HCV) infection [21], malignancies [22] and vitamin D deficiency [23]. 11 of the 12 studies were peer-reviewed, while one, on glomerular disease [12] comprised unpublished data shared with us by the authors after our search identified their preliminary findings in a conference abstract.

11 (92%) of the 12 studies used data from high-income countries [12–20, 22, 23], while the other used data from Georgia [21], a lower-middle-income country. There was high heterogeneity of populations, exposure definitions, analytical methods and estimated outcome measures across studies. 10 (83%) of the 12 studies were analyses of data from large administrative health insurance, medical claims or disease surveillance databases [12–21], while two (17%) used data from individual hospitals [22, 23]. Eight (67%) were retrospective cohort studies [12, 13, 15, 17, 20–23], two (17%) were nested case–control studies [18, 19] and two (17%) utilised both designs [14, 16]. The main features and findings from the 12 original studies are summarised in table 1.

Only one study reported on the risk of progression from TBI to active TB in a risk group compared with a control group of people with TBI [23]. All others compared the incidence of active TB in each risk group with a control group. No evidence was found comparing the risk of incident TB in a given risk group among those with TBI *versus* those without TBI, or among those receiving TPT following a positive TBI test *versus* those receiving TPT without a positive TBI test. No evidence was found concerning additional outcomes of interest mentioned in objective 3 of the methods section.

We identified six meta-analyses: three on the risk of active TB among patients with diabetes mellitus [24–26], two on the risk among patients with obstructive lung diseases taking inhaled corticosteroids [27, 28] and one on the risk among patients with malignancies [29]. The main features and findings from these meta-analyses are displayed in table 2.

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TABLE 1 Main features and findings of studies reporting on tuberculosis (TB) incidence and/or risk of TB progression among individuals with select risk factors: corticosteroid use (n=1), diabetes mellitus (n=1), glomerular disease (n=1), hepatitis C (n=1), malignancies (n=1), rheumatoid arthritis (n=3), other rheumatic diseases and their treatments (n=3) and vitamin D deficiency (n=1)

First author, year [reference]	Country and study period	Study design	Population characteristics		Main quantitative findings (95% CI)	Data sources and other notes
			Risk group/cases	Comparator group/controls		
Corticosteroid use						
Lai, 2015 [19]	Taiwan January 1999 to December 2011	CC (nested within a cohort of 1 000 000 randomly selected subjects from the NHIRD)	6229 people aged >15 years with active TB; mean age 59.1 years; 30.4% female	622 900 people aged >15 years without active TB; mean age 59.1 years; 30.4% female 100 controls selected for each case using risk-set sampling	Adjusted IRR of active TB according to: Corticosteroid use within previous 30 days of TB diagnosis date 2.76 (2.44–3.11) Corticosteroid use within previous 31–90 days 1.99 (1.73–2.31) Corticosteroid use within previous 91–365 days 1.17 (1.06–1.29)	NHIRD Using a time-matched CC sampling scheme, conditional odds ratios were used to estimate rate ratios Corticosteroid use could be oral or *i.v.* for any indication
Diabetes mellitus						
Lin, 2018 [20]	Taiwan January 1998 to December 2010	RC (subcohorts from a cohort of 1 000 000 randomly selected subjects from the NHIRD)	49 028 adults aged 20–100 years with newly diagnosed T2DM; mean age 50.7 years; 48.9% female	49 028 adults without T2DM, frequency matched for age, sex, region and year of T2DM diagnosis; mean age 50.6 years; 48.9% female	Adjusted HR of active TB 2.01 (1.80–2.25)	All claims data from the NHIRD
Glomerular disease						
Gunning, 2021 (not peer-reviewed) [12]	Canada 2000 to 2012	RC (province of British Columbia)	3079 adults aged ⩾18 years diagnosed on native kidney biopsy with glomerular diseases; mean age at biopsy 50.9 years; 48.6% female	Age-standardised population of the province, sample size not reported; sex data not reported	SIR of active TB 23.36 (16.76–31.68) Unadjusted HR of active TB with use of immunosuppressive agents 2.13 (1.13–4.03) (immunosuppressive agents categorised as corticosteroids, calcineurin inhibitors, antimetabolites, cyclophosphamide and rituximab)	Provincial pathology database; provincial clinical information system for patients with kidney disease; BC Vital Statistics; Population Data BC

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TABLE 1 Continued

First author, year [reference]	Country and study period	Study design	Population characteristics		Main quantitative findings (95% CI)	Data sources and other notes
			Risk group/cases	Comparator group/controls		
Hepatitis C						
Baliashvili, 2022 [21]	Georgia January 2015 to September 2020	RC (among all adult residents of Georgia tested for anti-HCV antibodies)	1) 70 341 HCV-positive adults who had not finished the HCV treatment course (untreated HCV) 2) 53 456 HCV-positive adults who had finished the HCV treatment course (treated HCV) Age and sex data not reported	1 708 017 HCV-negative adults (uninfected HCV); age and sex data not reported	Adjusted HR of active TB in: Untreated HCV *versus* uninfected HCV 2.9 (2.4–3.4) Treated HCV *versus* uninfected HCV 1.6 (1.4–2.0)	National HCV screening registry; hepatitis C elimination programme clinical database "Elimination C" (ElimC); national TB surveillance database managed by the National Center for TB and Lung Disease
Malignancies						
Cheon, 2020 [22]	Republic of Korea January 2000 to December 2014	RC (one hospital in Ulsan province)	34 783 adults aged ⩾20 years newly diagnosed with malignancies, based on ICD-10 codes C000-C999; median age 58 years (IQR 48–68 years); 49.8% female	1) 69 566 age- and sex-matched adults with no history of cancer who visited the hospital for health screening during the risk group enrolment period and were followed for >3 years afterwards 2) 1 151 402 people, the total population of Ulsan province, averaged over period 2000–2017; age and sex data not reported	1) IRR of active TB in cancer patients *versus* comparator group 1: 10.68 (8.83–12.99) for all TB 5.82 (4.41–7.67) for clinically diagnosed TB 14.30 (11.91–17.18) for bacteriologically confirmed TB 2) IRR of active TB in cancer patients *versus* comparator group 2: 9.71 (8.99–10.48) for all TB	Ulsan University Hospital Information of Clinical Ecosystem; Korean Statistical Information Service
Rheumatoid arthritis						
Brassard, 2006 [13]	USA September 1998 to December 2003	CC (nested within a cohort constructed from PharMetrics database of medical claims data from >85 managed care organisations)	386 adults aged ⩾18 years with RA and TB; mean age 54 years; 77.2% female	38 600 adults aged ⩾18 years with RA but not with TB; mean age 56 years; 73.7% female	Adjusted IRR of active TB according to medication use in the previous year: Traditional DMARDs 1.2 (1.0–1.5) NSAIDs 0.9 (0.8–1.1) COX-2 inhibitors 0.9 (0.7–1.2) Corticosteroids 1.7 (1.3–2.2)	PharMetrics Patient-Centric Database

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TABLE 1 Continued

First author, year [reference]	Country and study period	Study design	Population characteristics		Main quantitative findings (95% CI)	Data sources and other notes
			Risk group/cases	Comparator group/controls		
Brassard, 2009 [14]	Canada January 1980 to December 2003	RC (from physician billing codes in the province of Quebec)	24 282 people with one or more occurrences of the physician billing code for RA during an inpatient or outpatient visit; mean age 61.7 years; 70.1% female	General population of Quebec; sample size unclear; age and sex data not reported	SIR of active TB in patients with RA *versus* the general population 10.9 (7.9–15.0)	Provincial physician billing codes No details given on route of corticosteroid administration
		CC (nested within aforementioned RC)	50 people with RA and TB; mean age 65.6 years; 50% female	1500 people with RA but not with TB; mean age 67.6 years; 70.0% female	Adjusted IRR of active TB according to medication use in the previous year: Any DMARD 3.0 (1.6–5.8) Corticosteroids 2.4 (1.1–5.4) COX-2 inhibitors 1.4 (0.5–4.4) NSAIDs 1.2 (0.6–2.3)	
Carmona, 2003 [15]	Spain 1990–2000	RC (random selection of patients from 34 clinical centres throughout the country)	788 people aged ⩾16 years with RA; mean age at baseline visit 61 years; mean age at RA onset 48 years; 72.1% female	Age- and sex-standardised general population of Spain; sample size not reported; age and sex data not reported	IRR of active TB (any TB location) 4.13 (2.59–6.83) IRR of active pulmonary TB 3.68 (2.36–5.92)	National Network of Epidemiological Surveillance; clinical registries of the participating clinics
Other rheumatic diseases and their treatments						
Chen, 2013 [16]	Taiwan 1996–2008	RC (from NHIRD)	81 266 people with psoriasis or psoriatic arthritis; median age 43.0 years (IQR 28.7–57.8 years)	General population of Taiwan; sample size not reported; age and sex not reported	Crude IRR of active TB 1.22 (1.18–1.33)	NHIRD Antipsoriatic drugs defined as methotrexate, acitretin, cyclosporine, azathioprine and mycophenolate mofetil Corticosteroids were systemic, with no details given on route of administration
		CC (nested within the aforementioned RC)	497 people with psoriasis and TB; mean age 59.7 years; 17.5% female	1988 people with psoriasis without TB; mean age 59.7 years; 17.5% female	Adjusted odds ratios of active TB according to: Antipsoriatic drugs 0.83 (0.52–1.31) Corticosteroids 3.98 (3.12–5.06) NSAIDs 2.20 (1.76–2.76) COX-2 inhibitors 1.20 (0.71–2.01)	
Cho, 2020 [17]	Republic of Korea January 2012 to December 2018	RC (from National Health Insurance Service database)	2803 people aged ⩾10 years who were administered ustekinumab for psoriasis, psoriatic arthritis and Crohn's disease; median age not reported; 32% female	"General Korean population"; sample size not reported; age and sex not reported	IRR of active TB 0.76 (0.59–2.02)	National Health Insurance service database; annual report on notified TB by Korea Centers for Disease Control and Prevention

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TABLE 1 Continued

First author, year [reference]	Country and study period	Study design	Population characteristics		Main quantitative findings (95% CI)	Data sources and other notes
			Risk group/cases	Comparator group/controls		
Wu, 2017 [18]	Taiwan January 1999 to December 2011	CC (nested within a cohort of 1 000 000 randomly selected subjects from the NHIRD)	1) 123 419 person-years from adults aged ⩾18 years taking traditional NSAIDs (mostly but not exclusively with arthritis or other rheumatic conditions); mean age 63.1 years; 31.4% female 2) 16 392 person-years from people aged ⩾18 years taking COX-2 inhibitors (mostly but not exclusively with arthritis or other rheumatic conditions); mean age 75.5 years; 36.4% female	Adults aged ⩾18 years not using traditional NSAIDs or COX-2 inhibitors (from general population, not matched on comorbidities); 340 396 person-years; mean age 55.9 years; 28.0% female 100 controls selected for each case using risk-set sampling	Adjusted IRR of active TB according to: Use of traditional NSAIDs within the previous 31–90 days 1.19 (1.05–1.35) Use of COX-2 inhibitors within the previous 31–90 days 1.07 (0.78–1.48)	NHIRD NSAID and COX-2 inhibitor use defined as having a prescription record ⩾7 days Using fractional polynomial disease risk scores, odds ratios were used to estimate rate ratios
Vitamin D deficiency						
Patterson, 2020 [23]	UK April 2010 to January 2019	RC (individuals diagnosed with LTBI in one London hospital)	1) 320 adults aged ⩾18 years with moderately deficient vitamin D levels (25[OH]D 25.0–50.0 nmol·L^{-1}) 2) 114 adults aged ⩾18 years with profoundly deficient vitamin D levels (25[OH]D <25.0 nmol·L^{-1}) Age and sex data not reported	554 adults aged ⩾18 years with sufficient vitamin D levels (25[OH]D >50.0 nmol·L^{-1}); age and sex data not reported	Adjusted HR of active TB in: Moderately deficient *versus* sufficient vitamin D levels 2.14 (0.84–5.48) Profoundly deficient *versus* sufficient vitamin D levels 5.68 (2.18–14.82)	London North West University Healthcare electronic medical records; London TB Register, Extended Tuberculosis Surveillance Vitamin D levels within 14 days before and up to 365 days after the time of LTBI diagnosis were linked to individuals in the LTBI cohort

CC: case–control study; NHIRD: National Health Insurance Research Database; IRR: incidence rate ratio; RC: retrospective cohort study; T2DM: type 2 diabetes mellitus; HR: hazard ratio; SIR: standardised incidence ratio; HCV: hepatitis C virus; ICD-10: International Classification of Diseases, tenth revision; IQR: interquartile range; RA: rheumatoid arthritis; DMARDs: disease-modifying antirheumatic drugs; NSAIDs: nonsteroidal anti-inflammatory drugs; COX: cyclooxygenase; LTBI: latent TB infection.

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TABLE 2 Main features and findings of meta-analyses reporting on tuberculosis (TB) incidence among individuals with selected risk factors: use of inhaled corticosteroids (ICS) in obstructive lung diseases (n=2), diabetes (n=3) and malignancies (n=1)

First author, year [reference]	Inclusion criteria for studies	Exclusion criteria for review	Number of studies and study types, where relevant	Pooled estimates of active TB (95% CI) *versus* reference groups
Inhaled corticosteroid use in obstructive lung diseases				
Castellana, 2019 [27]	Design: nonrandomised studies Exposure: patients with obstructive lung diseases, including asthma, using ICS Comparators: patients with obstructive lung diseases not using ICS Search period: up to September 2018	Randomised trials Studies without data on ICS use	RC with medical record review (2 studies)	Pooled OR of active TB in people with obstructive lung diseases using ICS *versus* those not using ICS: 4.48 (1.85–10.86) (Current users of ICS defined as those using inhalers in the 3 months leading up to TB diagnosis date, or those with a prescription for ICS in the 30 days leading up to the date), I^2=0%
			RC with nested CC (7 studies)	Pooled OR of active TB in people with obstructive lung diseases using ICS *versus* those not using ICS: 1.31 (0.94–1.82), I^2=97%
			RC with nested CC (3 studies)	Pooled OR of active TB in people with obstructive lung diseases using ICS *versus* those not using ICS, with simultaneous oral corticosteroid use: 1.22 (0.92–1.62), I^2=38%
			RC with nested CC (4 studies)	Pooled OR of active TB in people with obstructive lung diseases using ICS *versus* those not using ICS, without simultaneous oral corticosteroid use: 1.63 (1.05–2.52), I^2=94%
Dong, 2014 [28]	Design: RCTs lasting ⩾6 months Exposure: patients with COPD of any severity using ICS Comparators: RCT control groups Search period: up to July 2013	Trials that included patients with asthma Trials that did not involve pre-defined intervention or control treatments	5 studies	Pooled OR of active TB in people with COPD using ICS *versus* those not using ICS: 2.29 (1.04–5.03), I^2=0.4%
Diabetes mellitus				
Jeon, 2008 [25]	Design: cohort, CC or CS studies Exposure: adults with diabetes mellitus Comparators: general population Search period: up to March 2007	Studies that did not adjust for age Studies that employed different methods for assessing TB among individuals with and without diabetes mellitus or for assessing diabetes mellitus among TB patients and controls Studies that investigated the reverse association of the impact of TB disease or TB treatment on diabetes mellitus	RC (3 studies) CC (8 studies)	Pooled risk ratio of active TB: 3.11 (2.27–4.26), I^2=39% Authors did not calculate a pooled estimate as they felt the between-study heterogeneity (I^2=68%) was too high. Risk ratios of active TB varied from 1.61 (0.58–2.32) to 7.83 (2.37–25.9)

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TABLE 2 Continued

First author, year [reference]	Inclusion criteria for studies	Exclusion criteria for review	Number of studies and study types, where relevant	Pooled estimates of active TB (95% CI) *versus* reference groups
Al-Rifai, 2017 [24]	Design: studies that provided or allowed computation of an estimate of the association between active TB and diabetes mellitus Exposure: adults with diabetes mellitus Comparators: "control arm or comparator group", not specified Search period: up to December 2015	Studies where TB patients with diabetes mellitus were not separated from those with other comorbidities Studies that did not report adjusted estimates of the TB–diabetes mellitus association	44 studies	Pooled OR/IRR/risk ratio/HR of active TB: 2.00 (1.78–2.24), I^2=90.5%
Foe-Essomba, 2021 [26]	Design: cohort, CC or CS studies Exposure: patients with diabetes mellitus Comparators: "controls", not specified Search period: up to October 2020	Studies with other designs	Overall (49 studies) RC (10 studies) CC (23 studies) CS (16 studies)	Pooled OR of active TB 2.33 (2.00–2.71), I^2=94.2% Pooled OR of active TB 1.92 (1.53–2.40), I^2=94.3% Pooled OR of active TB 2.38 (1.96–2.89), I^2=93% Pooled OR of active TB 2.51 (1.82–3.47), I^2=95.2%
Malignancies				
Dobler, 2017 [29]	Design: varied designs Exposure: patients with cancer Comparators: control group specified for the study or general population with or without adjustment for potential confounders Search period: up to December 2016	CS studies Studies that used cumulative incidence without adjustment for time at risk Studies in which TB diagnosis preceded cancer diagnosis or the temporal relationship was not specified Studies only reporting TB risk in subgroups of cancer patients considered to have an increased pre-test probability of TB infection (*e.g.* because of abnormal chest radiographs)	11 studies 2 studies 4 studies 3 studies 8 studies 3 studies 3 studies 3 studies	Pooled IRR of active TB in adults with cancer 2.61 (2.12–3.22), I^2=91% Pooled IRR of active TB in adults with haematological malignancies 3.53 (1.63–7.64), I^2=96% Pooled IRR of active TB in adults with lung cancer 6.14 (1.97–19.20), I^2=76% Pooled IRR of active TB in adults with gastric cancer 2.63 (1.96–3.52), I^2=93% Pooled IRR of active TB in adults with breast cancer 2.17 (1.98–2.38), I^2=0% Pooled IRR of active TB in adults with liver cancer 2.02 (0.83–4.91), I^2=83% Pooled IRR of active TB in adults with colon cancer 2.00 (1.16–3.43), I^2=75% Pooled IRR in children with cancer 16.82 (8.81–32.12), I^2=79%

RC: retrospective cohort study; CC: case–control study; RCT: randomised control trial; IRR: incidence rate ratio; HR: hazard ratio; CS: cross-sectional study.

Findings by risk group

Corticosteroid use for a range of indications

A nested case–control study from Taiwan [19] compared age- and sex-matched people with and without TB and presented adjusted incidence rate ratios (IRRs) for active TB according to the use of oral or intravenous corticosteroids at different time points. The highest IRR was for corticosteroid use within the previous 30 days of TB diagnosis date (2.76, 95% CI 2.44–3.11), with lower values for use within the previous 31–90 days (1.99, 95% CI 1.73–2.31) and the previous 91–365 days (1.17, 95% CI 1.06–1.29). However, the reasons for taking corticosteroids were extremely heterogeneous and corticosteroid exposure was assumed when there was a reimbursement code for corticosteroids with a prescription length of ⩾7 days. Details on dosage were not reported.

Inhaled corticosteroid use in obstructive lung diseases

One meta-analysis of studies published up to 2018 [27] compared the odds of active TB among individuals with obstructive lung diseases (including asthma) who were using inhaled corticosteroids (ICS) with those who were not using ICS. The pooled odds ratio obtained from two retrospective cohort studies from Canada based on medical record review (4.48, 95% CI 1.85–10.86) differed substantially from the pooled odds ratios obtained from seven nested case–control studies all carried out in Taiwan or the Republic of Korea (1.31, 95% CI 0.94–1.82). The definition of current users of ICS was unclear: "Patients with a prescription within 30 days of or using inhalers until 3 months prior to the index date were classified as current" [27]. Details on dosage were not reported and analyses were not controlled for severity of disease or smoking status.

A separate meta-analysis of studies published up to 2013 [28] included five randomised controlled trials (RCTs) lasting ⩾6 months and found a pooled odds ratio for active TB of 2.29 (95% CI 1.04–5.03) in people with COPD using ICS compared with those not using ICS. Four out of the five trials were multicentre trials on multiple continents, and the fifth was a multicentre trial from China. Details on dosage were not reported and analyses were not controlled for severity of disease or smoking status.

Diabetes mellitus

A meta-analysis published in 2021 with a search up to 2020 [26] found 49 studies reporting on the risk of TB in adults with diabetes mellitus *versus* a range of comparator groups. The overall pooled odds ratio estimate of active TB from the 49 studies was 2.33 (95% CI 2.00–2.71), with high between-study heterogeneity (I^2=94.2%) (table 1). Similar estimates were obtained across subgroup meta-analyses by study design. The 49 studies were set in 18 different countries with 16 conducted in the People's Republic of China and 11 in the USA.

A meta-analysis published in 2017 with a search up to 2015 [24] included many of the same studies captured in the aforementioned 2021 meta-analysis [26] and presented an overall pooled summary estimate of 2.00 (95% CI 1.78–2.24) combining any measure of association (odds ratio/risk ratio/IRR/hazard ratio (HR)) from 44 studies, with high between-study heterogeneity (I^2=90.5%). Similar estimates were obtained across subgroup analyses by design and measure of association.

An earlier meta-analysis of studies published up to 2007 [25] reported a pooled risk ratio estimate for active TB of 3.11 (95% CI 2.27–4.36) from three cohort studies (I^2=39%). Additionally, the authors presented individual risk ratio estimates from eight case–control studies (risk of active TB in adults with diabetes mellitus *versus* those without diabetes mellitus) which varied from 1.61 (95% CI 0.58–2.32) to 7.83 (95% CI 2.37–25.9), but did not calculate a pooled estimate as they felt the between-study heterogeneity (I^2=68%) was too high (table 2).

In addition, we identified an original study conducted in Taiwan and published in 2018 [20], which reported an adjusted HR of 2.01 (95% CI 1.80–2.25) for active TB in adults with type 2 diabetes mellitus compared with adults without diabetes, which is consistent with findings from the 2017 meta-analysis described earlier [24] (table 1).

Glomerular disease

According to unpublished data from a Canadian cohort study, shared with us by the authors after our search identified their preliminary findings in a conference abstract [12], the risk of active TB seems to be considerably higher in patients with glomerular diseases *versus* the general population. The authors estimated a standardised incidence ratio (SIR) of 23.36 (95% CI 16.76–31.68) comparing adults with biopsy-diagnosed glomerular diseases with the age-standardised population of the province of British Columbia. However, the estimate was not adjusted for potential confounders beyond age. The unadjusted

hazard of active TB in patients with glomerular diseases was higher in those who had used immunosuppressive agents in the past 6 months than in those who had not taken immunosuppressants (HR 2.13, 95% CI 1.13–4.03).

Hepatitis C

A retrospective cohort study conducted in the Republic of Georgia, which was originally identified as a conference abstract and has been published recently [21], compared the risk of active TB in adults with HCV infection with the risk in uninfected adults. They estimated an adjusted HR of 2.9 (95% CI 2.4–3.4) comparing adults with untreated HCV infection with uninfected adults and an adjusted HR of 1.6 (95% CI 1.4–2.0) comparing HCV-infected adults who had completed antiviral treatment with uninfected adults. The model was adjusted for age, sex, imprisonment status and municipality of residence as a proxy for socioeconomic status, but not for injection drug or alcohol use.

Malignancies

We identified a meta-analysis published in 2017 [29] that included 13 studies reporting on the risk of active TB in patients with cancer. The authors estimated pooled IRRs of 2.61 (95% CI 2.12–3.22) in adults (11 studies) and 16.82 (95% CI 8.81–32.12) in children (two studies) with cancer. Most of the pooled studies were from Taiwan or the Republic of Korea. For adults, subgroup meta-analyses by cancer location were also performed, indicating an increased risk of developing active TB across locations: gastric cancer (eight studies; 2.63, 95% CI 1.96–3.52), haematological malignancies (four studies; 3.53, 95% CI 1.63–7.64), lung cancer (three studies; 6.14, 95% CI 1.97–19.20), breast cancer (three studies; 2.17, 95% CI 1.98–2.38) and colon cancer (three studies; 2.00, 95% CI 1.16–3.43). Only for liver cancer (three studies; 2.02, 95% CI 0.83–4.91) was there no evidence of increased risk compared with the reference groups. TB diagnosis was microbiological or based on symptoms and chest radiographic findings. Reference groups could have been the general population with or without adjustment for potential confounding factors.

A later retrospective cohort study from a single hospital in the Republic of Korea [22] presented an IRR of 10.68 (95% CI 8.83–12.99) for active TB in adults with newly diagnosed malignancies compared with age- and sex-matched adults with no history of cancer who attended the same hospital. In addition, it presented an IRR of 9.71 (95% CI 8.99–10.48) for active TB in adults with newly diagnosed malignancies compared with the total population of the province. No adjustments were made for potential confounding factors.

Rheumatoid arthritis

A retrospective cohort study from Canada presented a SIR of 10.9 (95% CI 7.9–15.0) for active TB in patients with rheumatoid arthritis compared with the general population of the province of Quebec [14], but did not adjust for any potential confounders beyond age and sex. A retrospective cohort study in Spain found an IRR of 4.13 (95% CI 2.59–6.83) for active TB in patients with rheumatoid arthritis compared with the general population of the country, but also only included age and sex as potential confounders. The Spanish study did not report details about the treatment of patients with rheumatoid arthritis.

The Canadian study [14] and a study from the USA [13] had nested case–control components comparing people with rheumatoid arthritis with and without TB and presented adjusted IRRs for active TB according to the use of various drug classes in the previous year. Both studies showed increased IRRs in rheumatoid arthritis patients taking corticosteroids (1.7, 95% CI 1.3–2.2 [13] and 2.4, 95% CI 1.1–5.4 [14]), but not in those taking nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase (COX)-2 inhibitors.

Other rheumatic diseases and their treatments

A retrospective cohort study from the Republic of Korea [17] compared people aged ⩾10 years who were administered ustekinumab (a biologic inhibiting interleukins 12 and 23) for psoriasis, psoriatic arthritis or Crohn's disease with the general Korean population and presented an unadjusted IRR of 0.76 (95% CI 0.59–2.02) for active TB [17].

A retrospective cohort study from Taiwan [16] compared people with psoriasis or psoriatic arthritis with the general Taiwanese population and found an unadjusted IRR of 1.22 (95% CI 1.18–1.33) for active TB. The same study had a nested case–control component comparing people with psoriasis with and without TB and presented adjusted odds ratios (aORs) for active TB according to the use of various drug classes in the previous year. The authors estimated higher odds of developing TB disease in people taking corticosteroids (aOR 3.98, 95% CI 3.12–5.06) and NSAIDs (aOR 2.20, 95% CI 1.76–2.76), but not

COX-2 inhibitors or a group of antipsoriatic drugs (methotrexate, acitretin, cyclosporine, azathioprine and mycophenolate mofetil) compared to people who were not taking these medications.

A separate nested case–control study from the same cohort in Taiwan over a similar time period [18] compared adults with a prescription record for traditional NSAIDs or COX-2 inhibitors for ⩾7 days (who mostly, but not exclusively had arthritis or other rheumatic conditions) with adults from the general population not matched on comorbidities who were not taking NSAIDs or COX-2 inhibitors. It showed an increased adjusted IRR for active TB in those using traditional NSAIDs within the previous 31–90 days (1.19, 95% CI 1.05–1.35), but not in those using COX-2 inhibitors in the same period.

Vitamin D deficiency

A retrospective cohort study from the UK [23] examining the effect of vitamin D deficiency was the only study identified that reported on the risk of progression from TBI to active TB, rather than on the risk of active TB without information on prior TBI status. The authors estimated an adjusted HR for active TB of 5.68 (95% CI 2.18–14.82) when comparing a group of TBI-diagnosed adults with profoundly deficient vitamin D levels with a group with sufficient vitamin D levels and of 2.14 (95% CI 0.84–5.48) when comparing a group with moderately deficient levels with a group with sufficient levels. Definitions of vitamin D deficiency were based on thresholds recommended by the National Institute for Health and Care Excellence in the UK [30]. Vitamin D levels were adjusted for seasonality to enable the prediction of individual mean annual levels and linked to individuals in the TBI cohort.

Discussion

In this scoping review, we identified 12 original studies and six meta-analyses examining the risk of active TB in specific population groups other than those already included in previous WHO guidance [5]. Except for one meta-analysis of RCTs examining inhaled corticosteroid use in patients with COPD [28], the remaining studies were observational, with limited evidence for most potential risk groups. Only one study, on patients with vitamin D deficiency [23], reported on the risk of progression from TBI to active TB, which is the most direct measure of whether TB preventive treatment may be required for patients with TBI in a particular risk group. All other studies and meta-analyses reported on the incidence of active TB in a risk group without including data on TBI infection, a less direct measure of whether TB preventive treatment is warranted.

The strongest association we identified was between glomerular diseases and active TB [12]. However, despite the high SIR, it is hard to draw conclusions from a single observational study in one province of Canada which has yet to undergo peer review, so further research into this risk group should be performed.

Studies from Canada [14] and Spain [15] examining data from cohorts at the end of the 20th century found strong associations between rheumatoid arthritis and active TB (SIR 10.9, 95% CI 7.9–15.0 and IRR 4.13, 95% CI 2.59–6.83, respectively). We did not identify any data on the risk of TB among patients with rheumatoid arthritis published after 2009.

Several studies and meta-analyses with varied designs in a range of patient groups found that exposure to corticosteroids was associated with higher risk of TB disease compared with no exposure. However, even when the studies were based on prescription data, the definition of corticosteroid exposure, including its route, dosage, duration and frequency, was vague and heterogeneous. Additionally, confounding by individual patient-level factors and by indication for corticosteroid use make the results of these studies difficult to interpret.

Although older biologics such as anti-TNF inhibitors are known to be associated with an increased risk of active TB [6], treatment of immunological diseases is an area of intensive expansion, with several new molecules reaching the market that may not be associated with TB. Analysis of national health insurance data from the Republic of Korea showed no evidence of an increased risk of active TB in patients taking ustekinumab, a biologic treatment inhibiting interleukins 12 and 23 [17].

Analysis of a large dataset from the Republic of Georgia showed a higher risk of active TB in adults with HCV infection [21]. Interestingly, the magnitude of increased risk diminished in those patients who had completed a treatment course compared with those who had not. These findings suggest that scaling up HCV treatment would be highly beneficial, not only to reduce the morbidity and mortality from HCV infection, but also to reduce the risk of TB disease in populations that are heavily affected by both conditions. Whether TB preventive therapy could be considered in individuals with HCV infection who

are yet to receive antiviral treatment is a matter of debate, weighing potential benefits with the potential risks of hepatotoxicity.

A study from the UK found a strong association between profound vitamin D deficiency and progression from TBI to active TB [23]. This observation is extremely interesting, as it suggests a role of vitamin D deficiency in TBI progression. In countries in which vitamin D deficiency is a condition of public health concern, vitamin D supplementation may be a better solution than the use of TB preventive treatment.

Two meta-analyses from 2017 showed relatively modest increased risks of active TB in adults with diabetes mellitus [24] and malignancies [29]. There is no clear cut-off for a risk ratio beyond which TB preventive treatment should be recommended. As well as the magnitude of effect, such decisions need to consider the size of the population group in question and the risk of adverse events associated with preventive treatment. With continual improvements in treatment [9–11], the list of risk groups warranting preventive treatment should therefore be expected to expand over time.

Despite the limitations of the studies we identified, it is time to consider expanding the recommendations for systematic screening and treatment of TBI to new risk groups such as those reported in this review. Future studies which use reliable data sources, have large sample sizes and measure more informative outcomes such as the number needed to screen or number needed to treat with TBI will assist in the production of better-informed global guidelines.

Additionally, there are potential risk groups not mentioned in this review that also need consideration. For example, we found no data on the risk of progression to active TB in people who have had coronavirus disease 2019 (COVID-19). Given the major clinical and public health implications in both low and high TB burden countries, studies of this association should be undertaken. However, given the extremely large number of people who have had COVID-19, it may prove more practical to target specific high-risk subgroups for TB preventive treatment, such as those who have been hospitalised with COVID-19, if emerging data support such a distinction.

The main strength of our scoping review is that our intentionally broad search terms identified relevant studies on risk groups we did not anticipate *a priori*. However, this strength is also one of its main limitations: as we did not include terms related to specific risk groups of interest, we may have missed potentially relevant sources, although we did our best to compensate by screening reference lists of narrative and systematic reviews identified by our search. Despite our broad search terms, our outcomes of interest were relatively specific for a scoping review and it is possible that some relevant papers were missed because they did not correspond with our specific outcome measures. In addition, although we did not restrict our search to published articles and did not apply language filters, the potential for publication bias remains an inherent limitation of this work, as is the case with any knowledge synthesis study. Finally, this review does not allow us to draw conclusions on aspects such as the influence of level of *M. tuberculosis* exposure and does not provide numbers needed to screen or numbers needed to treat with TPT, which would be more informative for clinical and public health decision-making.

In summary, our review contributes to the understanding of whether enough new evidence has emerged since 2014 to require the attention of the WHO and the update of their recommendations for population groups prioritised for systematic screening and treatment of TBI.

Points for clinical practice and questions for future research

- Systematic screening and treatment for TB infection is currently recommended for 11 high-risk populations.
- Other risk groups also require attention due to their increased risk of developing active TB.
- More studies are needed to better understand the risk profile of individuals with select conditions, such as glomerular diseases, hepatitis C or vitamin D deficiency, for which limited evidence currently exist.
- Future research should also evaluate whether having had COVID-19 affects an individual's risk of progression from tuberculosis infection to active disease.
- Targeted systematic reviews and meta-analyses may be helpful to examine group-specific evidence in greater detail in order to inform decision-making.

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