Active and latent tuberculosis in refugees and asylum seekers: a systematic review and meta-analysis

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Abstract

Background: In 2018, there were 70.8 million refugees, asylum seekers and persons displaced by wars and conflicts worldwide. Many of these individuals face a high risk for tuberculosis in their country of origin, which may be accentuated by adverse conditions endured during their journey. We summarised the prevalence of active and latent tuberculosis infection in refugees and asylum seekers through a systematic literature review and meta-analyses by country of origin and host continent.

Methods: Articles published in Medline, EMBASE, Web of Science and LILACS from January 2000 to August 2017 were searched for, without language restriction. Two independent authors performed the study selection, data extraction and quality assessment. Random effect models were used to estimate average measures of active and latent tuberculosis prevalence. Sub-group meta-analyses were performed according to country of origin and host continent.

Results: Sixty-seven out of 767 identified articles were included, of which 16 entered the meta-analyses. Average prevalence of active and latent tuberculosis was 1331 per 100 thousand inhabitants [95% confidence interval (CI) = 542-2384] and 37% (95% CI = 23-52%), respectively, both with high level of heterogeneity (variation in estimative attributable to heterogeneity [I^2] = 98.2% and 99.8%). Prevalence varied more according to countries of origin than host continent. Ninety-one per cent of studies reported routine screening of recently arrived immigrants in the host country; two-thirds confirmed tuberculosis bacteriologically. Many studies failed to provide relevant information.

Conclusion: Tuberculosis is a major health problem among refugees and asylum seekers and should be given special attention in any host continent. To protect this vulnerable population, ensuring access to healthcare for early detection for prevention and treatment of the disease is essential.

Background

In 2018, there were 70.8 million refugees, asylum seekers and displaced persons worldwide, the largest number ever recorded(1). A refugee is someone who “owing to well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality and is unable or, owing to such fear, is unwilling to avail himself of the protection of that country”(2). Asylum seekers are persons who claim to be admitted to a country as refugees and are awaiting the authorities’ decision(3).

Refugees and asylum seekers may have a significant burden of infectious diseases, such as tuberculosis, malaria, viral hepatitis and parasitic infections, as a result of the prevalence of such diseases in their country of origin and of exposure to adverse conditions during migration and after arrival at the host country(4–7). They usually come from countries where different communicable diseases are endemic and often received minimal medical care prior to departure(8,9). In addition, confinement for years in conditions of overcrowding and insalubrity in shelters, rural camps or urban slums make them highly vulnerable to communicable diseases(10–12).

Tuberculosis is a major cause of human mortality globally(13). *Mycobacterium tuberculosis* infects 23% of the global population,(14) and in the absence of treatment for latent *M. tuberculosis* infection (LTBI), 5 to 10% of these individuals can develop active tuberculosis, most within two years of infection(15). Risk of progression from LTBI to active disease among migrants is higher throughout their journey and may last longer after arrival in host countries(16,17). Effective treatment of LTBI can reduce up to 90% the risk of progression to active tuberculosis, and is considered now a major action to eliminate the disease by 2050, as proposed by the End Tuberculosis Strategy(18).

Refugees, asylum seekers and internally displaced migrants live in heterogeneous socio-economic conditions and have various origins, reasons for fleeing and legal status. Yet, overall, compared with other categories of immigrants, they may be at higher risk for tuberculosis either having arrived with active tuberculosis in the destination country, or from developing active tuberculosis from previous LTBI or from acquiring the disease upon arrival(19,20). The debatable “healthy migrant effect” may not apply to this highly vulnerable population(21).

A previously published systematic review(20) has analysed the prevalence of tuberculosis among all immigrants and summarised data from 1980 to 2004, before the more recent migratory crisis. Additionally, a narrative review on infectious diseases in refugees was published, with data on active and latent tuberculosis from 29 articles from 2010 to 2016(22). Other reviews have also been published on refugees in specific scenarios, such as the effectiveness and coverage of tuberculosis screening in Europe(23,24), tuberculosis in refugee camps(17), yield of screening for active tuberculosis in Germany(25), and prevalence of tuberculosis in the United Kingdom(26). To our knowledge, no systematic review on active and latent tuberculosis prevalence in refugees is available. The current study aimed to summarise the prevalence of LTBI and active tuberculosis in refugees and asylum seekers, despite their high heterogeneity as a population.

Methods

Search strategy

We searched the bibliographic databases MEDLINE, EMBASE, LILACS and Web of Science, using the terms “tuberculosis”, “prevalence”, “refugee”, “asylum seekers”, “forced migration”, as MeSH terms and text word. Strategy searches are available in the supplement material (Table S1 and S2).

The search was conducted in August 2017, without language or other restrictions. Studies published between January 2000 and August 2017 were eligible in order to contemplate the recent immigration crisis. The cut-off for the initial date was based on the trend of numbers of manuscripts published (Figure S1). We also searched the lists of references of the included studies, reviews and government reports.

Study selection

The study selection, data extraction and quality assessment of studies were carried out by two independent reviewers (RP and FMS). Disagreements were solved by consensus or by two other reviewers (AT and MB). In addition, a 10% sample of the excluded studies was examined by reviewers AT and MB.

Reference data were stored in the EndNote Web reference manager [Thomson Reuters (SCIENTIFIC), NYC, USA], and duplicate references were discarded. The selection was performed in two steps: screening of titles and abstracts, and full text evaluation. Although the search did not restrict language, only studies written in English, French, Spanish or Portuguese were included in the following steps. All studies on active tuberculosis or LTBI in the targeted population were included if the estimation of prevalence was reported or data were available for its calculation. Studies including mixed populations, i.e., not exclusively refugees and asylum seekers were also included if prevalence could be extracted by stratum.

There were no restrictions on the tuberculosis clinical characteristics (pulmonary or extrapulmonary, drug susceptible or resistant) or study population (as to sex, age or country of origin and host continent). Cross-sectional, cohort studies and clinical trials were eligible. We restricted the selection to studies with at least 30 individuals.

For the diagnosis of active tuberculosis, smear microscopy, culture or molecular tests (Xpert® MTB/RIF and others), as well as clinical and radiological criteria, were accepted. For the diagnosis of LTBI, tuberculin skin testing (TST) or interferon-gamma release assays (IGRA) were accepted, and the presence of LTBI was considered if any of the two tests was positive(27). We followed TST cut-off points for LTBI definition used by the study authors.

Data collection process

Data extraction was conducted using an electronic form built on the EpiData 3.1 software (Epidata Association, Odense, Denmark). Whenever available, information on the number of individuals, events of interest and prevalence rates was collected by country of origin and host continent, to perform subgroup analyses. Studies with inpatients were classified as “hospitalised populations”. If the study was carried out in a hospital with outpatients, participants were not classified as hospitalised.

Methodological quality of studies

Quality assessment of studies was carried out by two independent reviewers (RP and FMS) based on the document “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE)(28). Differences were resolved by consensus. High quality was defined as at least 80% of STROBE criteria fulfilled, average quality as 50-79% of criteria were fulfilled and low quality as less than 50% of criteria fulfilled. Additionally, non-bacteriologically confirmed diagnosis of tuberculosis was considered to increase the risk of information bias, and non-routine screening was considered to increase the risk of selection bias. All studies that reported the necessary information (i.e., country of origin or host continent) were included in the meta-analyses, regardless of their quality.

Data analyses

Study characteristics, population profile, setting and methodological aspects were described using frequency tables. Refugees and asylum seekers constitute a highly heterogeneous group of people, depending not only on individual cultural and socio-economic characteristics, but also on the reasons for fleeing their country and their legal status in the host country. We hypothesised that origin and destination could influence the prevalence of active tuberculosis and LTBI and thus opted to perform a meta-analysis by country of origin and a subgroup analysis by continent of destination. For these analyses, we used the studies that contained this information. Average prevalence rates and their 95% confidence intervals (CI) were estimated using a random effect model. Freeman-Tukey transformation was used to stabilise variance measures. Heterogeneity analysis was performed using variation in estimative attributable to heterogeneity (I^2) statistics and Q chi-square test. All statistical analysis and Forest plots were performed using the STATA 13 software (module metaprop) (StataCorp LP, College Station, USA)(29).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (30) was used for reporting. A filled PRISMA form for this manuscript is available in the supplementary material (Chart S1). The full review protocol is available in PROSPERO, registration number CDR42016052361.

Results

We identified 767 references, of which 282 were duplicated and thus excluded. After reading the titles and abstracts of the 485 studies, 170 were selected for full text reading. For abstract selection, initial agreement between the two main reviewers was 88%. In the 10% sample selected for check by the two additional reviewers, initial agreement was 93%. For full texts, initial agreement between the two main reviewers was 85%. In the 10% sample checked by the two additional reviewers, initial agreement was 80%. Final consensus was obtained in 100% of them.

Sixty-seven studies were included in the present review. Reasons for exclusion of the other 103 studies are displayed in Figure 1. Information on countries of origin and host continent was available in 16 studies, which were included in the meta-analyses.

Sixty-six studies were published in English and one in French(31). Fifteen studies reported active tuberculosis prevalence, 21 reported LTBI prevalence and 31 reported both. The total screened population was 599,072.

Active Tuberculosis Prevalence

Study Characteristics and Population

Among the 46 studies that reported active tuberculosis prevalence, 56.5% were cross-sectional; none were clinical trials (Table 1). Two thirds of these studies were published after 2009, and among them, half completed data collection before 2011. Sixty-three per cent of studies included over 500 people.

The total of individuals screened for active tuberculosis was 537,218, with a single study evaluating 232,738 individuals. Eighty-one per cent of studies were conducted in refugees (n=437,264), 18% in asylum seekers (n=95,283), and 0.9% in both (n=4671).

The mean age, reported by 33% of studies(4,10,32–44), ranged from 18 to 40.7 years. Prevalence by sex was reported by only 17% of the studies.

The average time since arrival of refugees and asylum seekers to the host country to the time of evaluation for tuberculosis was 3.9 months (ranging from 0.7 to 12.8 months) in the 9% of studies(45–48) conveying this information.

Sixty-seven (31/46) per cent of studies concomitantly evaluated the presence of LTBI in their populations. Among these, 57% used the LTBI diagnostic as a prerequisite to investigate the presence of active tuberculosis. In other words, they performed a diagnostic test for LTBI with TST or IGRA to rule out active tuberculosis; if they were positive, a chest X-ray was also performed and if it was indicative of active tuberculosis, bacteriological tests were conducted. Otherwise, TST or IGRA-positive individuals were considered to have LTBI.

Main findings

Active tuberculosis prevalence rates varied from 0 to 11,364 per 100 thousand inhabitants, with 89% of studies reporting values less than 5000 per 100 thousand. Considering studies that reported the prevalence by country of origin, the average prevalence of active tuberculosis was 1331/100 thousand inhabitants (95% CI, 542-2384), with high heterogeneity ($I^2=98\%$, Figure 2). The prevalence was higher among refugees from Syria (11,364/100 thousand inhabitants, 95% CI, 3794-24,558), observed in a single study with 44 hospitalised participants. Studies with individuals from Ethiopia, Ghana and Tunisia had results with large confidence intervals, in samples smaller than 100 persons (10,48).

With regards to the host continent, refugees who immigrated to Europe, Asia and America presented a similar average prevalence of 1458, 860 and 1080 per 100 thousand inhabitants, respectively (Figure 3). Europe was the continent that received refugees from the most diverse nationalities, better allowing an assessment of heterogeneity. In the other continents, this individual evaluation was not possible due to the small numbers. Refugees from Eritrea, Ethiopia and Somalia immigrated to Europe(10,48) in the three studies that contained this information, and had a slightly larger tuberculosis prevalence. More information about the meta-analyses data on active tuberculosis can be found on the supplement material (Table S3).

LTBI Prevalence

Study Characteristics and Population

Fifty-four per cent of the 52 studies that reported LTBI prevalence were cohort studies; there were no clinical trials (Table 2). Sixty per cent of studies were published after 2009, and among them half

completed data collection before 2011; one study did not provide this information. Thirty-one studies included over 500 participants.

A total of 271,544 individuals were screened for LTBI: 233,688 individuals were refugees (reported by 67% of studies) and 27,960 individuals were asylum seekers (reported by 21% of studies). The remaining were studies including both types of situations.

The mean age, reported by 33% of studies(4,10,31–38,49–55), ranged from 3.5 to 39 years, with the lowest prevalence in a study that included only children (mean age 3.5 years). Only 21% of studies reported the prevalence by gender.

The average time since arrival of refugees and asylum seekers to the host country at the time of evaluation for LTBI was 3.8 months (range: 0.7-12.8 months) among the 13% of studies that reported this information(45–48,56–58).

Eighty-nine per cent of studies performed TST and 77% of those reported the TST cut-off point used to define LTBI: 10 mm was used in 78% of studies. Some studies considered different cut-off points to different populations (children, human immunodeficiency virus (HIV)-infected or BCG-vaccinated individuals).

Main findings

Prevalence of LTBI ranged from 0.4% to 81.5%, with 61% of the studies reporting a prevalence rate higher than 30%.

In the meta-analysis by country of origin, prevalence rates were highly heterogeneous ($I^2 = 99.8\%$), with an average measure of 37% (95% CI, 23-52) (Figure 4). Refugees from Cuba and Iraq presented the lowest rates, 0.4 and 5% respectively, and from North Korea, the highest rate, 81%, systematically screened when arriving in South Korea(6). Targeted populations and sample sizes varied largely, with the Cuban study(55) evaluating 241 children under 7 years of age (and finding one LTBI case) and large systematic screening for active tuberculosis of Iraq refugees(58,59) applying for visa or recently arrived in the United States of America (USA). Small sample sizes eventually resulted in very wide confidence intervals(10).

In the subgroup analysis by host continent, refugees who immigrated to Europe presented the highest prevalence (41%, 95% CI, 20-65), followed by those who went to the Americas (28%, 95% CI, 18-40) (Figure 5). However, one study in the USA excluded individuals with immunosuppressive conditions and thus had a high risk of false negative results(56). Somali refugees who went to America had a higher prevalence rate (54%) than those who went to Europe (38%), while Iraq refugees who went to the Americas had a higher prevalence rate (14%) than those who went to Asia (2%). Overall, there were very few studies with information on country of origin and host continent. More information about the meta-analyses data on LTBI can be found on the supplement material (Table S4).

Quality of studies and risk of bias

None of the 65 studies fulfilled all quality criteria. Among the 33 cross-sectional and the 32 cohort studies, only 13 and 11 respectively were considered high quality (Figure S2 and S3); 14 and 18 studies were of medium quality; and 6 cohort and 3 cross-sectional studies were considered low quality. Two studies(58,61) were organization reports; it was not possible to perform the quality assessment.

In 85% of studies (n=569,880), routine screening of all the individuals who arrived in the host country was the reason for the enrollment and 9% of studies tested individuals who sought health service with symptoms (n=11,234). Only one study was conducted in refugee camps(60) (n=15,455). Among the 37 studies that informed the diagnostic method for active tuberculosis, 73% confirmed tuberculosis bacteriologically.

Six per cent of studies involved hospitalised populations (n=4). In these studies, overestimation of the prevalence is likely. Three studies (43,44,70) reported only active tuberculosis prevalence, and one described both active and latent tuberculosis (77). None of them entered the meta-analyses.

Finally, only fifteen articles used the 1951 United Nations Convention or a very similar definition of refugee and asylum seeker.

Discussion

This systematic review and meta-analysis on tuberculosis prevalence in refugees identified 67 studies with a total of 599,072 evaluated individuals, of whom nearly half were evaluated for LTBI. The main finding was the high prevalence of active tuberculosis in these populations. Although some studies involving hospitalised populations may have overestimated the prevalence of the disease, most of the studies were conducted as routine screening in symptom-free individuals. The lower positive predictive value in symptom-free individuals may also result in overestimation of the prevalence, but despite these possible risks of bias, the prevalence is high.

Prevalence rates found in the current study, albeit very heterogeneous, were comparable to other very-high risk groups, such as prisoners and homeless(62,63). Although the highest prevalence rates were found in Syrians and among those who migrated to the Americas, these figures are based, respectively, on one and two studies solely. Furthermore, the results among Syrians refugees are from a highly selected setting and are based on a small sample: 5 among 44 hospitalised patients. Yet, this finding is worth highlighting: between 1990 and 2011 the tuberculosis prevalence in Syria had decreased from 85 to 23/100,000(64). Armed conflicts and wars destroy the basic medical infrastructure, undermine health agendas and cause significant shortages of health professionals and medicines, leading the prevalence of tuberculosis to a possible underestimation(8,64). Symptoms of the active phase of tuberculosis, such as coughing and fatigue, may go unnoticed to already infected individuals and health care workers in crisis settings, because they are insidious(17). Dangerous situations encountered during migration, including overcrowding, incarceration, malnutrition, challenges to access health care, low adherence to treatment, associated risk of HIV infection and exposure to other migrants from higher incidence

countries also contribute to the risk of contamination by *M. tuberculosis* and progression to disease(8,64–66).

In regard to latent tuberculosis infection (LTBI), reported prevalence rates were also high, similar to those observed in populations characterised by high vulnerability to infection, such as prisoners(67), when compared to the overall population, in whom LTBI is expected to be 23%(14). The exception was a study in children, an expected finding, as LTBI prevalence increases with age. LTBI prevalence was the highest among Somali refugees, in particular those who migrated to the Americas, in spite of possible underestimation due to exclusion of those with the highest probability of a false negative test result (immunosuppressed persons) in one of the two studies. The difference may reflect true heterogeneity in the populations migrating to these continents but could also reflect different methods of screening (TST cut-off, TST versus IGRA versus TST and IGRA) or targeted populations for screening in both continents. Alternatively, it could reflect differences in methodology regarding targeted population or testing criteria, but we did not find such differences. We cannot discard differences due to the choice of the continent of destiny or the journey itself, but this hypothesis remains speculative. Again, albeit based on few studies and the possible biases, the finding is noteworthy. Somalia is one of the poorest countries in the world and has also been facing a civil war in the Horn of Africa.

Despite the few studies per country of origin and per host continent, which limits the analysis according to these variables, and in spite of the heterogeneous populations involved, the high overall rates of active and latent tuberculosis found in the present review emphasise the responsibility of host countries to meet refugees' specific health needs and of the global health community to fight tuberculosis in low-income countries from where most refugees flee, in order to attain WHO's End Tuberculosis Strategy to eliminate the disease by 2050(18). In the host countries, there are still many challenges that need to be overcome for better care of refugees, such as lack of training of professionals, fear of breaches of confidentiality, fear of stigma and social rejection due to illness, fear of consequences in the immigration process due to the diagnosis of disease, insufficient information on the screening and treatment process, difficulty in communicating due to language differences, among others(23).

To the best of our knowledge, this is the first summarised analysis of tuberculosis among this specific subpopulation of migrants, and the first to include average measures according to their origin and destination. Among this review strengths is the reporting quality of most studies. In regard to bias, active tuberculosis was bacteriologically confirmed, and almost all derived from routine screening. These characteristics reduce the likelihood of overestimation.

Nonetheless, reported prevalence rates may be overestimated among symptomatic individuals in health facilities such as hospitals. Also, studies in populations applying for visa in countries with health restrictions may have underestimated prevalence of LTBI, since those known to be positive may give up application.

Moreover, this is a very heterogeneous group of individuals, and attempts to summarise any measure are challenging. The definition of "refugee" or "asylum seekers" was not clear in all studies. Age groups were

highly heterogeneous as well, and prevalence of LTBI increases with age, thus influencing findings; in addition, language difficulties, fear of immigration authorities, lack of awareness of symptoms and fear of stigma may reduce the efficacy of tuberculosis detection mechanisms(8).

Origin and destination may reflect socio-economic status, reasons for fleeing, and tuberculosis setting, which explains our choice for meta-analyses. However, many studies could not be included in the meta-analyses due to lack of information about the country of origin. Thus, because only a few studies were eligible, all had to be included regardless of their quality. Some findings included in the meta-analyses refer to one or two studies only. Meta-regression could not be performed due to information gaps regarding study populations (e.g., gender, age, follow-up).

Additionally, most studies were performed in developed countries, and thus do not represent the majority of current refugees, who are hosted in low- and medium-income countries(68). Generalizability and assertive conclusions are thus restricted. Lastly, although our bibliographic searches were finalised in August 2017, recent waves of forced migration are not entirely covered, because several studies refer to data collected up to 2011. More efforts and funds should be dedicated to international cooperation studies on tuberculosis – and other health issues - among forced migrants(69).

Conclusion

Despite the highly heterogeneous prevalence across countries, active and latent tuberculosis seem to be frequent health issues among refugees and asylum seekers. Rapid screening is necessary in order to allow early detection and prompt treatment - or prevention - of the disease. This policy should aim at their protection against the disease, rather than their exclusion and discrimination. Efforts to guarantee their right to adequate health care cannot be overemphasised.

List Of Abbreviations

Confidence intervals (CI)

Human immunodeficiency virus (HIV)

Interferon-gamma release assays (IGRA)

Latent tuberculosis infection (LTBI)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

Tuberculin skin testing (TST)

Variation in estimative attributable to heterogeneity (I^2)

Declarations

Ethics approval and consent to participate

The study consists of a published literature review analysis; thus, no ethical approval was necessary.

Consent to publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The corresponding author is a member of the editorial board of this journal. The other authors declare that they have no competing interests.

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Authors' contributions

RP and FMS searched, selected and extracted the data. RP also contacted the author of relevant studies. MLB and AT were the third and fourth reviewers for study selection and data extraction. RP, FMS, AT and EF established the inclusion criteria, analysed and interpreted the data. RP, FMS and AT wrote the first manuscript draft. RC and JUB performed overall and subgroup meta-analyses and graphs. AT and EF supervised the study and with JUB and RC, critically reviewed the report. All authors read, made contributions and approved the final manuscript.

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Tables

Please see the supplementary files section to access the tables.

Supplemental File Legends

Figure S1 – Number of publications on Medline from 1945 to 2015 using descriptor “Tuberculosis AND Refugee”

Figure S2 – Evaluation of the quality of reporting of cohort studies according to STROBE criteria

Figure S3 - Evaluation of the quality of reporting of cross-sectional studies according to STROBE criteria

Table S1 – Key words used according to the bibliographic databases

Table S2 – Structured search strategy according to PICOS axiom and bibliographic databases

Table S3 – Studies included in the metanalyses for prevalence active tuberculosis (n=10)

Table S4 – Studies included in the metanalyses for prevalence of latent tuberculosis infection (n=13)

Chart S1 – Prisma Checklist

Figures

Figure 1

Flowchart showing inclusions and exclusions from the systematic review

Figure 2. Prevalence of active tuberculosis in refugees and asylum seekers by country of origin

Figure 2

Prevalence of active tuberculosis in refugees and asylum seekers by country of origin

Figure 3. Prevalence of active tuberculosis in refugees and asylum seekers by host continent and country of origin

Figure 3

Prevalence of active tuberculosis in refugees and asylum seekers by host continent and country of origin

Figure 4. Prevalence of latent tuberculosis infection in refugees and asylum seekers by country of origin

Abbreviations: LTBI Latent tuberculosis infection; ES Effect size; CI Confidence interval; I² Variation in estimative attributable to heterogeneity *Percent

Figure 4

Prevalence of latent tuberculosis infection in refugees and asylum seekers by country of origin

Figure 5. Prevalence of latent tuberculosis infection in refugees and asylum seekers by host continent and country of origin

Abbreviations: LTBI Latent tuberculosis infection; ES Effect size; CI Confidence interval; I² Variation in estimate attributable to heterogeneity. *Percent

Figure 5

Prevalence of latent tuberculosis infection in refugees and asylum seekers by host continent and country of origin

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