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

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Abstract

Background: In 2017, there were 68.5 million refugees, asylum seekers and persons displaced by wars and conflicts worldwide. Tuberculosis prevalence in the country of origin and adverse conditions endured during their journey may increase their risk for tuberculosis.

Objective: We summarized the prevalence of active and latent tuberculosis infection among refugees and asylum seekers through a literature systematic review and meta-analysis by country of origin. **Methods:** Articles published in Medline, EMBASE, Web of Science and LILACS from 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 pooled measures of active and latent tuberculosis prevalence. Sub-group analysis was performed according to country of origin and host continent.

Results: Sixty-seven out of 767 identified papers were included, of which 16 entered the meta-analysis. Pooled prevalence of active and latent tuberculosis was 1% [95% confidence interval (CI)=1-2%] and 37% (95% CI=23-52%), respectively, both with high level of 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. **Key words:** Forced migration. Mycobacterium Tuberculosis. Latent tuberculosis infection. Prevalence. Global health.

Background

By 2017, there were 68.5 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):3. Asylum seekers are persons who claim to be admitted to a country as refugees and are awaiting the authorities decision on their request for refuge(3).

Although they are a very heterogeneous group, refugees 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 condition in their country of origin and of exposure to adverse conditions during migration and after arrival at the host country(4–7). They usually originate from countries where different communicable diseases are endemic and often receive 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 also make them highly vulnerable to communicable diseases(10–12).

Tuberculosis is a major cause of human mortality globally(13). *Mycobacterium tuberculosis* (MTB) infects 23% of the global population(14) and in the absence of treatment, 5 to 10% of these individuals can develop active tuberculosis within two years after infection(15). Risk for progression from latent infection (LTBI) to active tuberculosis among migrants is higher and may last longer upon 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 are a very heterogeneous group of individuals, with different socio-economic conditions, 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—and heterogeneous - population(21).

A previously published systematic review(20) has targeted prevalence of tuberculosis among all immigrants and summarized data from 1980 to 2004, i.e., 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 among refugees in specific scenarios, such as effectiveness and coverage of tuberculosis screening in Europe(23,24), tuberculosis in refugee camps(17), yield of active tuberculosis in Germany(25), and prevalence of tuberculosis in United Kingdom(26). Thus, no systematic review on active and latent tuberculosis prevalence in refugees is available. The current study aimed to summarize the prevalence of LTBI and active tuberculosis among this specific group of immigrants—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 decided based on the trend of numbers of manuscripts published (Figure S1). We also searched the lists of references of the included studies, reviews and governmental 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 duplicated 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 published 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 forms (pulmonary or extrapulmonary, drug susceptible or resistant) or population (as to sex, age or country of origin and host continent). Cross-sectional, cohort studies or 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 to perform subgroup analyses. Individuals were also classified according to host continent.

Methodological quality of studies

Quality assessment of study was based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)(28). Additionally, non-bacteriologically confirmed diagnosis of tuberculosis was considered to increase risk for information bias, and non-routine screening was considered to increase risk for selection bias.

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 current legal status in the host country. We hypothesized that one of the sources of heterogeneity—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 included a subgroup of studies that contained this information discriminated among the population of interest. Pooled prevalence rates and their 95% confidence intervals (CI) were estimated using a random effect model. Freeman-Tukey transformation was used to stabilize variance measures. Heterogeneity analysis was performed using I² 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) was used for reporting(30). 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. 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), of which 15 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; we did not identify any clinical trial (Table 1). Two thirds of these studies were published after 2009, among them half completed data collection before 2011. Sixty-three percent of studies included over 500 people.

The total screened population for active tuberculosis was 537,218, with one single study having a sample of 232,738 individuals. Eight one percent of studies were conducted among refugees (n = 437,264), 18% among asylum seekers (n = 95,283), and 0.9% among 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) among the 9% of studies(45–48) conveying this information.

Sixty-seven (31/46) percent 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 method for LTBI with TST or an IGRA to rule out active tuberculosis; if they were positive, a chest X-ray was performed; and if it was indicative of active tuberculosis, bacteriological tests were conducted. Otherwise, individuals were considered to have LTBI.

Main findings

Active tuberculosis prevalence rates varied from 0 to 35%, with 89% of studies reporting values under 5%. Considering studies that reported the prevalence by country of origin, the pooled measure was 1% (95% CI, 1–2), with high heterogeneity ($I^2 = 98\%$) (Figure 2). The prevalence was higher among refugees from Syria (11%, 95% CI, 4–25), found in one single study with 44 hospitalized participants. Ethiopia, Ghana and Tunisia also had large confidence intervals, with populations smaller than 100 persons(10,48).

With reference to the host continent, refugees who emigrated to Europe, Asia and America presented a pooled prevalence of 1% (Figure 3). Europe was the continent that received refugees from most diverse nationalities, thus allowing an assessment of heterogeneity. In the other continents, this individual evaluation was not possible because of small numbers. Refugees from Eritrea, Ethiopia and Somalia immigrated to Europe(10,48) in the studies that presented this information, and with a slightly larger prevalence.

LTBI Prevalence

Study Characteristics and Population

Fifty four percent of the 52 studies that reported LTBI prevalence were cohort studies; no clinical trial was included (Table 2). Sixty percent of studies were published after 2009, among them half completed data collection before 2011; one study did not show 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%). 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. 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 percent of studies performed TST and 77% of these 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) but did not report prevalence according to these cut-off points.

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 a pooled measure of 37% (95% CI, 23–52) (Figure 4). Refugees from Cuba and Iraq presented the lowest rates, 0 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 finding one LTBI case and large systematic screening for active tuberculosis of the Iraq refugees(58,59) applying for visa or recently arrived in the USA. Very small sample sizes resulted in some cases 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 U.S. A. 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 the ones who went to Europe (38%), whilst Iraq refugees who went to the Americas had a higher prevalence rate (14%) than the ones who went to Asia (2%). Overall, there were very few studies with information by each country of origin and host continent.

Risk of bias

In 85% of studies ($n = 569,880$), routine screening of all the individuals who arrived in the host country was the reason for the enrolment 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.

None of the 65 studies fulfilled all quality criteria. Among the 33 cross-sectional and the 32 cohort studies, only 13 and 11 respectively fulfilled 80% or more of the quality criteria (Figure S2 and S3). Two studies(58,61) were organization reports; it was not possible to perform the quality assessment.

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 less than half were evaluated for LTBI. The main finding was the high prevalence of active tuberculosis in these populations, despite most of the studies being conducted as routine screening in symptom-free individuals. Prevalence rates found in the current study, albeit very heterogeneous, were overall 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 low participating population: 5 among 44 hospitalized 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 and 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 MTB and progression to disease(8,64–66).

With regards to latent tuberculosis infection (LTBI), reported prevalence rates were also high, similar to those observed in populations characterized by high vulnerability to infection, such as prisoners(67), when compared to the overall population, in whom LTBI is expected to be 23%(14). LTBI prevalence was the highest among Somali refugees, in particular those who migrated to the Americas, in spite of possible underestimation from exclusion of those with the highest probability of a false negative test result in one of the two studies. Again, albeit based on few studies and possible selection bias, 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 number of studies from each country of origin and to host continent limiting our analysis by these variables, and in spite of the very heterogeneous populations involved, the high overall rates of active and latent tuberculosis found in the present review emphasize 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 because of 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).

The present study has several strengths. Most studies were of reasonable quality, confirmed bacteriologically active tuberculosis and almost all derived from routine screening, reducing the likelihood of overestimation. Nonetheless, most 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). Moreover, this is a very heterogeneous group of individuals, and attempts to summarize any measure are challenging. Origin and destination may reflect socio-economic status, reasons for fleeing, and tuberculosis setting, which explains our choice for meta-analyses. To the best of our knowledge, this is the first summarized analysis of tuberculosis among this specific subpopulation of migrants, and the first to include pooled measures according to their origin and destination.

On the other hand, 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. 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).

Other limitations should be mentioned. Many studies could not be included in the meta-analyses due to lack of information about the country of origin. Generalizability and assertive conclusions are restricted because most studies were conducted in high-income countries; also, 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). Lastly, although our bibliographic searches were finalized 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 a frequent health issue among refugees and asylum seekers. Continuous and 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 overemphasized.

Abbreviations

Mycobacterium tuberculosis (MTB)

Latent tuberculosis infection (LTBI)

Tuberculin skin testing (TST)

Interferon-gamma release assays (IGRA)

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

Confidence intervals (CI)

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

Human immunodeficiency virus (HIV)

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, analyzed 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

Due to technical limitations, the tables have been placed in the Supplementary Files section.

Figures

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Supplementary Files

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