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Ending tuberculosis in risk groups in Europe: challenges from travel and population movement

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As many countries in Europe make progress in tuberculosis (TB) control, TB incidence in Europe is diverse; in low-incidence countries (those with an incidence less than 20 per 100,000 [1]) the TB burden is increasingly borne by specific risk groups, such as migrants from high- to lower-incidence countries, persons with social risk factors such as homelessness and individuals who have been in contact with a TB patient. Strategies to control TB within these risk groups include screening for active disease and sometimes latent infection [2,3], followed by treatment where appropriate. The effectiveness of screening strategies to identify patients needing treatment varies. For example, the yield of active TB among migrants from high- to low-burden countries ranged from 7 to 10,186 per 100,000 people screened, depending on various factors including the TB prevalence in the country of origin [2]. In this World TB Day issue of Eurosurveillance, four papers describe the risks of TB infection and disease in two potentially high-risk groups: migrants [4,5] and airline passengers [6,7].

Migrants are considered to be at high risk of TB, for reasons such as the possibility of reactivation of latent infection acquired in their home country, frequent travel to high-incidence areas, and perhaps transmission within migrant communities in the receiving countries [8]. At European Union (EU) level, Hollo et al. report that TB rates are higher, and declining more slowly, in individuals not native to the reporting countries compared with the native population [4]. This highlights important health inequalities and major challenges to the control of TB, while it also illustrates difficulties in combining data from multiple countries. Besides differences in the definition of TB cases of 'foreign origin' between countries, several points complicate interpretation of these data. Migrants constitute a heterogeneous group of individuals from multiple countries and with varying risk factor profiles, thus simply being 'foreign born' is not necessarily a good proxy for having a high risk of TB infection or disease, and particular risk factor profiles may be more common in some countries than in others, e.g. due to differences in migration patterns. The implications of migration for TB incidence thus depend on detailed patterns of migration [9]. There is therefore a need to further investigate, at country level, risk factors for TB in migrants and to further elucidate detailed migration and travel patterns and develop tailored solutions specific to the epidemic affecting each group [10].

Addressing the needs of a specific group of migrants, namely asylum seekers, Bozorgmehr and colleagues systematically review the yield of upon-entry screening for active TB of asylum seekers entering Germany, a low-incidence country [5]. Like many European countries, Germany sees a higher rate of TB among foreign-born compared with native-born individuals. Pooling results from the six diverse studies included in the review, the authors report that 3.47 cases of active TB were identified per 1,000 asylum seekers screened. However, there was substantial heterogeneity between studies, and the authors highlight the need to understand reasons for this variation. Explanations might include differences in study populations e.g. countries of origin, age distribution, prevalence of co-morbidities, case definitions and diagnostic methods. Furthermore, cost-effectiveness of screening approaches including cost per quality-adjusted life year should inform the selection of screening methods and the prioritisation of populations.

Arguably more controversial than screening migrants is the issue of screening individuals exposed to patients with active TB on board aircraft. While the World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) recommend contact investigations among passengers seated within two rows of an infectious case on flights lasting 8 hours or longer [11,12], both organisations and

others [13] acknowledge that there is only limited evidence to quantify the risk of transmission on aircraft. Two papers in this issue discuss screening of airline contacts for latent TB infection (LTBI): one is an intensive contact investigation following a fatal case of extensively drug-resistant (XDR)-TB [7], while the other reports the overall yield based on multiple investigations conducted in Japan [6]. Both report very low yields. The XDR-TB study included tuberculin skin tests (TST) and interferon gamma release assays (IGRAs) within 8 weeks from exposure and at least 8 weeks after exposure. One case of possible transmission (TST conversion) from the XDR-TB patient occurred among 112 people screened for LTBI. An additional 14 people had LTBI, however, and recent transmission could be neither established nor ruled out, due to the absence of baseline test results. The Japanese study reported that, of 651 contacts meeting the WHO criteria for investigation, 25 (3.8%) had a positive IGRA result, but data on conversions were not available. Neither study identified any cases of active TB resulting from onboard transmission.

Difficulties inherent in TB epidemiology, particularly in distinguishing recent from earlier infection, complicate the interpretation of findings from contact investigations in general. Dealing with the diverse and likely geographically dispersed contacts in airline exposures presents additional challenges. Data on TST or IGRA conversions, indicating recent infection, would help to better quantify the risk of transmission following exposure on an airplane, but conducting repeat tests among passengers (who may subsequently leave the investigating country) would be logistically difficult. However, the low prevalence of positivity reported in these and other studies suggests that the risk of transmission may be low, suggesting that other TB control interventions might be prioritised over exposed air passenger screening. However, even in the absence of solid evidence of the benefit of screening air passenger contacts of active TB, and especially in situations which appear to pose a particularly high-risk, a precautionary approach may be adopted. This was part of the rationale for investigating the apparently dramatic XDR-TB incident despite a relatively short flight duration [7].

Although screening for active TB and LTBI is generally considered worthwhile, the four studies presented in this issue illustrate that substantial uncertainty remains regarding the best ways to implement screening. Critically, screening of any population is only beneficial if a positive result leads to effective action. Therefore robust systems must be in place to enable those with a positive result to access and complete treatment. Effectiveness and cost-effectiveness of strategies targeting different populations and using different diagnostic tests need to be assessed in the context of local TB epidemiology – and should account not only for the direct benefits of identifying and treating cases, but also for the reductions in incidence achieved by preventing onward transmission. As the movement of people, including those with TB, becomes increasingly common, approaches to TB control need to become correspondingly international. Cooperation within the EU and the wider international community is essential if we are to successfully control the disease.

Conflict of interest

CJ has undertaken paid consultancy work for Otsuka Pharmaceutical outside the scope of this publication. IA declares no conflict of interest.

Authors' contributions

Both authors jointly wrote the manuscript and have seen and approved the final version.

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Tuberculosis notification rate decreases faster in residents of native origin than in residents of foreign origin in the EU/EEA, 2010 to 2015

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To estimate trends in tuberculosis (TB) notification rates by geographical origin, we retrieved surveillance data from 2010 to 2015 for 29 European Union and European Economic Area countries. The TB notification rate decreased at an annual rate of 5.3%. The decrease in notification rate was higher in native residents (7.0%) than in those of foreign origin (3.7%). Targeted screening and facilitated access to care and treatment could help prevent and control TB in migrants.

The tuberculosis (TB) notification rate in the European Union (EU) and European Economic Area (EEA) has been decreasing consistently since 2002 at an annual rate of around 5% [1]. In 2015, the EU/EEA notification rate was 11.7 per 100,000 population, close to the 'End TB 2035' target of less than 10 cases per 100,000 set by the World Health Organization (WHO) [2]. This encouraging figure masks important disparities both across and within countries. In 2015, rates were already below 10 per 100,000 in 22 countries but still above 50 per 100,000 in Lithuania and Romania [1]. Studies have also identified vulnerable groups for TB in low-incidence countries, such as prison inmates, people living with HIV, or migrants [3]. Here, we report TB notification rate trends for both native and foreign residents of the EU/EEA and assess progress towards TB elimination by predicting TB notification rates to 2025.

Tuberculosis surveillance in the EU/EEA

The surveillance of TB in Europe is carried out by the European Tuberculosis Surveillance Network under the joint coordination of the European Centre for Disease Prevention and Control (ECDC) and the WHO. Each year, 30 EU/EEA countries upload all TB cases meeting the EU case definition [4] to a database hosted by ECDC (the European Surveillance System, TESSy). Information collected includes main epidemiological (time, place, sex, age, patient origin) and case management variables such as laboratory results or treatment outcome. A more detailed description of data collection methods is available elsewhere [1]. In most EU/EEA countries, a TB case of foreign origin is a case with a country of birth different from the reporting country. For Austria, Belgium, Greece, Hungary and Poland, a TB case of foreign origin is a case with citizenship different from the reporting country. For the purpose of this analysis, we included all TB cases reported for the period from 2010 to 2015. Data for Croatia were excluded because case-based data were only available from 2012 onwards.

Population data and analysis

We obtained population denominator data by origin from the Statistical Office of the European Union (Eurostat) [5]. We used population by country of birth for most countries and population by citizenship for Austria, Belgium, Greece, Hungary and Poland. Where population data were missing (Bulgaria in 2010 and Norway in 2015), we used the data of the year after for Bulgaria and the year before for Norway. We estimated annual rates of change by origin and their 95% confidence intervals (CI) using a log-linear regression of notification rates over the period 2010 to 2015. Assuming constant rates of decrease, we estimated notification rates by origin until 2025. We did not forecast until 2035 (target year of the End TB strategy) because only six years of denominator data were available.

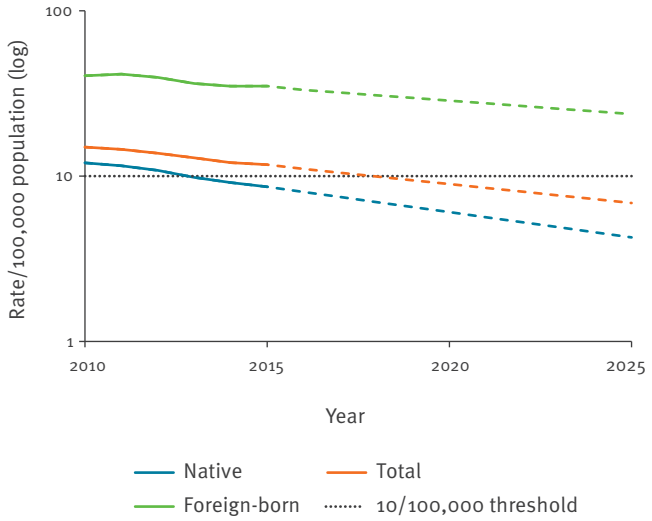
Trends

Over the period from 2010 to 2015, 29 countries reported 404,551 TB cases, of which 394,110 (97.4%) had information on origin. Of these 394,110 cases, 283,426 (71.9%) were born in or citizens of the reporting country and 110,684 (28.1%) were of foreign origin (Table).

The proportion of cases of foreign origin continuously increased from 25.9% in 2010 to 31.1% in 2015. Over the same period, the proportion of EU residents of foreign origin remained stable at 9.4% in 2010 and 10.0%

Figure

Notification rate of tuberculosis cases per 100,000 population, by year and origin, EU/EEA, 2010–2015, and prediction for 2016–2025



EU/EEA: European Union/European Economic Area.

Solid lines: rates calculated from reported cases; dotted lines: estimated prediction.

in 2015. Overall, the TB notification rate decreased at an annual rate of 5.3% (95% CI: 4.4–6.1) over the study period. This decrease was more pronounced in native residents (7.0%, 95% CI: 6.0–8.0) than in cases of foreign origin (3.7%, 95% CI: 1.7–5.8). The rate ratio of TB cases of foreign origin over native residents increased from 3.4 in 2010 to 4.1 in 2015. Assuming that similar decreases in notification rates would be observed in the following years, the overall TB notification rate would cross the 10 per 100,000 threshold by 2018 (Figure).

By 2025, the estimated notification rate in native residents would be at 4.3 per 100,000, approaching the pre-elimination target of less than 1 case per 100,000 [3]. However, the notification rate in cases of foreign origin would still be higher than 20 cases per 100,000.

Discussion

The TB notification rate is decreasing in the EU/EEA, but the pace differs depending on cases' geographical origin. Residents of foreign origin have a three- to four-fold higher notification rate compared with natives. This was observed in most countries except Bulgaria, Hungary, Latvia, Lithuania, Poland and Romania, where higher TB notification rates were reported in natives. Studies have suggested that TB rates in migrants are strongly associated with the incidence in their country of origin [6,7]. It is therefore not surprising to observe high rates of TB in residents of foreign origin in some EU/EEA countries because a considerable proportion of them originate from high-TB-incidence countries [8]. Since 2000, TB incidence has also been decreasing globally but at a slower rate than in EU/EEA countries [2]. Thus, TB cases of foreign origin are and will remain a challenge for TB elimination, especially in low-incidence countries where they account for a substantial proportion of TB cases [9].

The main reason explaining the higher TB burden in residents of foreign origin in high-income countries is thought to be reactivation of remotely acquired latent tuberculosis infection [10]. This does not exclude other possible explanations such as travel-associated infection when visiting friends or relatives in the country of origin [11] or infection in the receiving country where migrants may face poor living conditions. The latter two reasons could also partly explain why also second-generation migrants may be at higher risk for TB infection compared with native residents [12].

The main limitation of this analysis is that we classified all cases with a birthplace different from the reporting country as cases of foreign origin regardless of their time of arrival or the duration of their stay in the receiving countries. Also, we were not able to distinguish between migrants from low- and high-TB incidence countries. Characteristics of migrants and travellers are of increasing complexity which is challenging to capture through binary variables. Global travel and migration patterns have changed and intra-regional migration has increased [8]. Migrants may have stayed in other countries on their journey to the receiving country and been exposed to TB in other places than their country of origin. Estimates at EU/EEA level may mask important disparities across countries in which patterns of migration differ.

To address the challenge of TB among migrants in low-incidence countries, targeted prevention and control strategies should be implemented taking into account the origin of migrants but also their demographic characteristics. As most cases of foreign origin are likely to have been infected in their country of origin, preventive strategies in the host countries may have limited impact on the overall notification rate. A recent review suggested that targeted pre-arrival screening for active TB and post-arrival screening for latent TB infection in migrants would be the most efficient strategy [10]. Strategies reaching migrants arriving through irregular channels should also be explored.

Conclusion

The TB notification rate in individuals of foreign origin reported by EU/EEA countries is higher, and decreasing at a slower pace, than in native residents. This will be one of the main challenges for EU/EEA countries when trying to reach the TB elimination target in the coming years, especially in countries where individuals of foreign origin account for a large proportion of TB cases. Targeted screening and facilitated access to care and treatment could help tackle this issue.

Table

Number and rate of tuberculosis cases per 100,000 population and population by origin, EU/EEA, 2010–2015 (n = 404,551)[a]

Year	Native			Foreign origin			Unknown origin[b]	Total		
	Cases	Population (million)	Rate	Cases	Population (million)	Rate	Cases	Cases	Population (million)	Rate
2010	54,956	456.9	12.0	19,242	47.5	40.5	1,376	75,574	504.4	15.0
2011	52,753	457.3	11.5	19,504	47.1	41.4	1,045	73,302	504.4	14.5
2012	49,498	457.4	10.8	19,038	48.2	39.5	994	69,530	505.6	13.8
2013	44,877	456.7	9.8	17,742	48.9	36.3	2,549	65,168	505.5	12.9
2014	41,870	457.8	9.1	17,319	49.5	35.0	2,079	61,268	507.3	12.1
2015	39,472	458.0	8.6	17,839	50.9	35.1	2,398	59,709	508.9	11.7

EU/EEA: European Union/European Economic Area.

[a] Croatia excluded.

[b] Without denominator, rates were not calculated for cases of unknown origin.

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Conflict of interest

None declared.

Authors' contributions

Vahur Hollo coordinated the data analysis, wrote the manuscript and contributed to the study design. Julien Beauté drafted parts of the manuscript, contributed to the study design, revision of the manuscript and data analysis. Csaba Ködmön contributed to the data analysis and revision of the manuscript. Marieke Johanna van der Werf contributed to the design of the study, interpreted the results and revised the manuscript.

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Yield of active screening for tuberculosis among asylum seekers in Germany: a systematic review and meta-analysis

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All asylum seekers in Germany undergo upon-entry screening for tuberculosis TB, but comprehensive evidence on the yield is lacking. We compared the national estimates with the international literature in a systematic review and meta-analysis of studies reporting the yield of TB, defined as the fraction of active TB cases detected among asylum seekers screened in Germany upon entry. We searched 11 national and international databases for empirical studies and the internet for grey literature published in English or German without restrictions on publication time. Among 1,253 screened articles, we identified six articles reporting the yield of active TB based on German data, ranging from 0.72 (95% confidence interval (CI): 0.45–1.10) to 6.41 (95% CI: 4.19–9.37) per 1,000 asylum seekers. The pooled estimate across all studies was 3.47 (95% CI: 1.78–5.73; $I^2 = 94.9\%$; $p < 0.0001$) per 1,000 asylum seekers. This estimate was in line with international evidence ($I^2 = 0\%$; p for heterogeneity 0.55). The meta-analysis of available international estimates resulted in a pooled yield of 3.04 (95% CI: 2.24–3.96) per 1,000. This study provides an estimate across several German federal states for the yield of TB screening in asylum seekers. Further research is needed to develop more targeted screening programmes.

Introduction

Substantial progress has been made in the control of tuberculosis (TB) since the ratification of the Millennium Development Goals, but the disease still remains a major global health problem and a leading cause of death worldwide [1]. Because of increasingly complex forms of migration [2], including migration from high-incidence TB countries and perimigration factors favouring transmission or re-activation of TB, the disease remains a public health concern also for low-incidence countries with notification rates below 10 per 100,000 population [3]. The incidence (not the transmission [4-6]) of TB in many low-incidence countries is driven largely by international migration. The epidemiology in these countries is characterised by the progression of latent TB infection rather than recent transmission, and by a high concentration of cases in vulnerable and hard-to-reach risk groups such as migrants, in particular refugees from high-incidence TB countries [3]. Between 2015 and 2016, the European Union (EU) received more than 1.3 million first-time asylum applicants. Among the top 10 countries of origin of asylum seekers in this period, six countries (Afghanistan, Eritrea, Nigeria, Pakistan, Russia and Ukraine) with TB incidence rates above 50 per 100,000 accounted for more than 25% of the total number of asylum applicants [7].

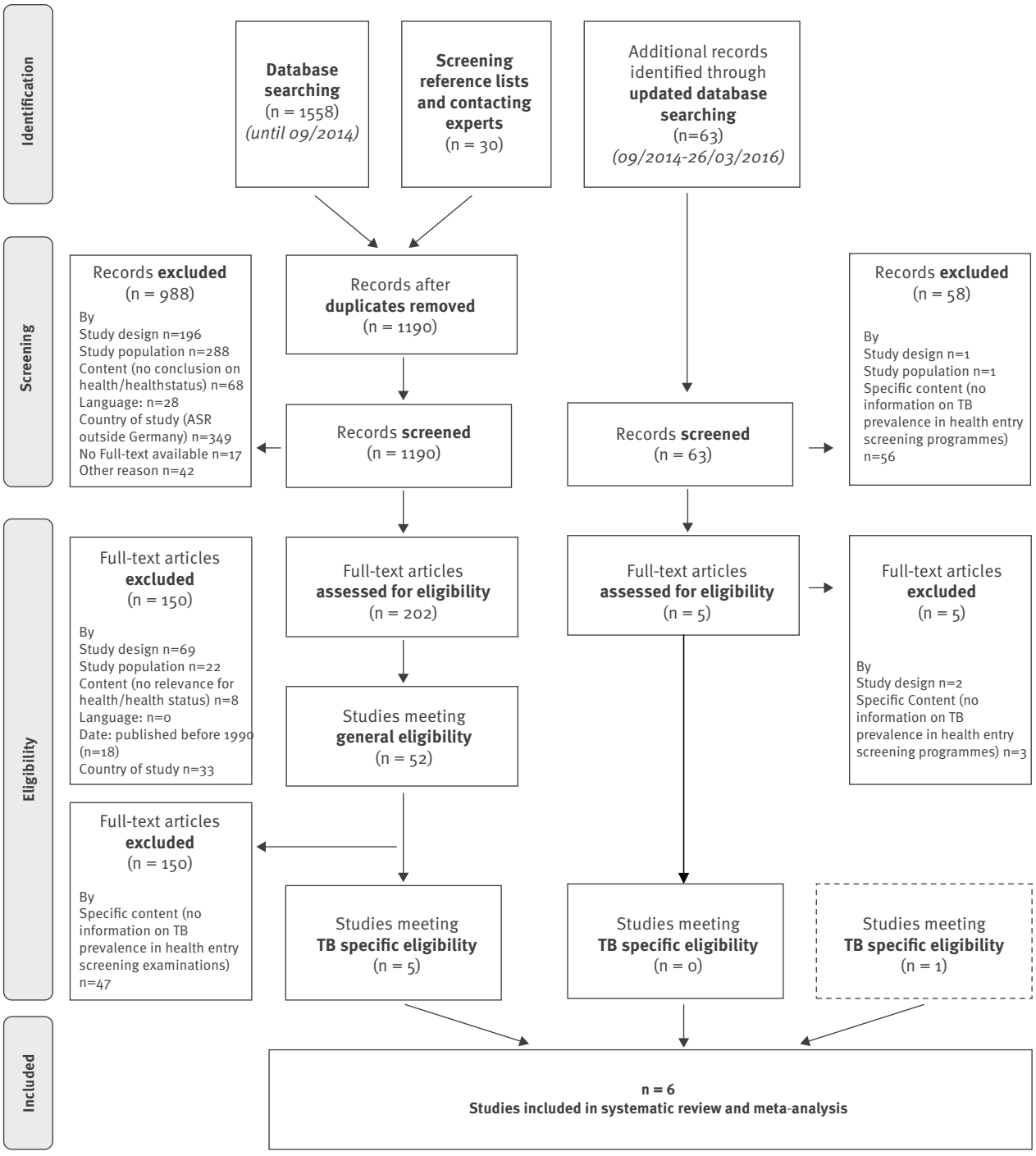
Immigration medical screening has played a major role in TB control programmes for more than a century [8]. In many low-incidence countries, it is a cornerstone of national TB control programmes [9] and comprises pre-entry, upon-entry and post-entry screening programmes [9,10]. The majority of EU countries [9,11] and member countries of the Organisation for Economic Co-operation and Development (OECD) [12] have mandatory upon-entry TB screening programmes for immigrants, including refugees and asylum seekers. Chest radiography (X-ray) alone or in combination with other screening approaches (such as clinical examination or tuberculin skin test) constituted the most frequently applied measure in 22 of 29 OECD countries to screen for active TB in the year 2010 [12].

Germany is a low-incidence TB country with an incidence rate of 5.6 cases per 100,000 population (4,488 cases were notified in 2014) [13]. Screening for TB in migrants is regulated by national law and restricted to specific

Figure 1

Flowchart of the review process, tuberculosis screening among asylum seekers in Germany

Yield of active screening for tuberculosis among asylum-seekers in Germany: a systematic review and meta-analysis



PRISMA 2009 Flow Diagram, Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009).
Preferred Reporting Items for Systematic Reviews and Meta-Analyses:The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

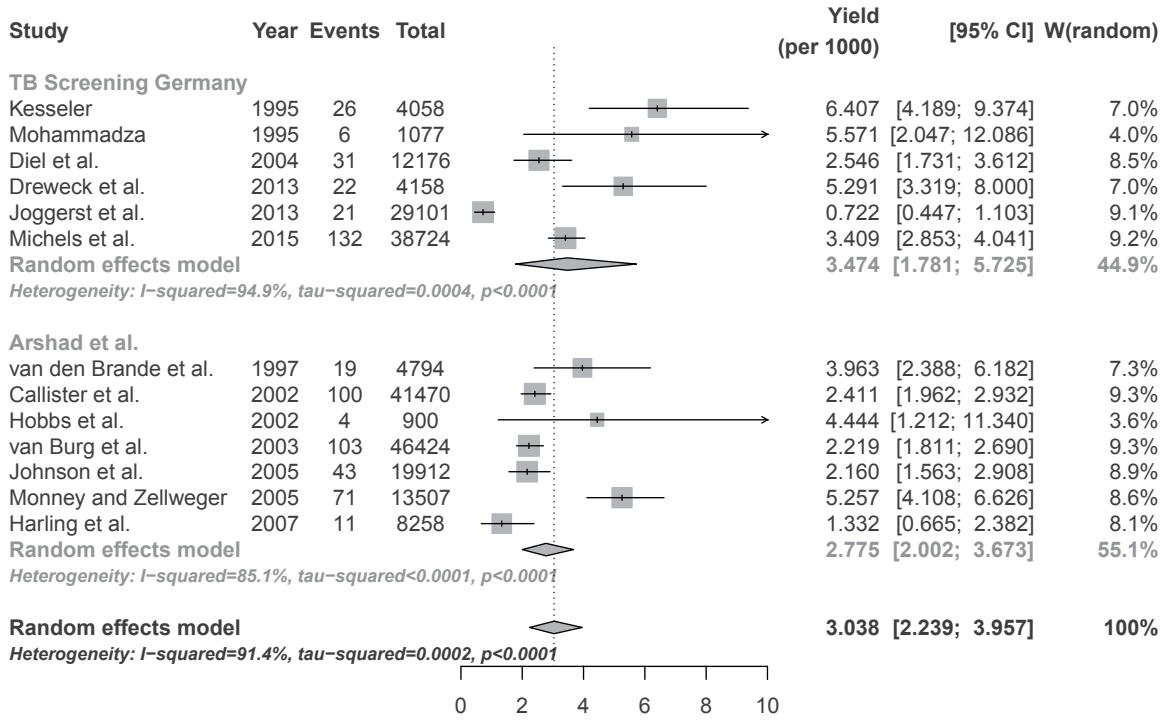
ASR: asylum seekers or refugees; TB: tuberculosis.

Dotted line: grey literature.

PRISMA 2009 flow diagram, adapted from: [45].

Figure 2

Forest plots of the yield of tuberculosis cases in screening studies in Germany (n = 6 studies) and in component studies included in an international review (n = 7 studies), as well as joint pooled estimate



CI: confidence interval; TB: tuberculosis; W (random): weight of study in random effects model.

Component studies from the international review are taken from Arshad et al. [22].

migrant groups. According to §62 of the Asylum Law (Asylgesetz, AsylG – formerly: Asylverfahrensgesetz) in combination with §36 of the Infection Protection Act (Infektionsschutzgesetz, IfSG), foreigners (except pregnant women) aged 16 years or older and living in shared accommodation facilities such as reception centres or shelters for asylum seekers must undergo a compulsory chest X-ray examination, primarily to identify active pulmonary tuberculosis. Further measures of upon-entry screening for TB, especially in children or pregnant women, are governed by different policies at the level of the 16 federal states [14].

In 2014, TB incidence in residents with foreign nationalities in Germany was 33.6 cases per 100,000 population, which is 13 times higher than the incidence in German citizens (2.5 cases per 100,000 population) [15]. Between 2001 and 2014, 2.9% of all notified TB cases were identified in the scope of the above legal frameworks among asylum seekers. While the share of TB cases in asylum seekers among all incident TB cases in Germany was 0.8% in 2008, this proportion rose to 10.6% in 2014 [15]. The number of refugees seeking asylum in Germany increased continuously in the same time period [16] and reached 1.1 million in 2015 [17].

Germany has a well-functioning national TB surveillance programme with mandatory reporting since 1934. TB notification data can be stratified by nationality and by 'reason of the diagnostic measure'. This allows distinguishing between cases identified by passive vs active case finding, e.g. in the scope of (active) upon-entry screening among asylum seekers.

While notification of identified cases is mandatory in the decentralised German health system, there is no legal obligation to document nor to report the number of asylum seekers screened upon entry within the framework of related legal frameworks (AsylG, IfSG). Therefore, incidence rates cannot be calculated routinely for this group, and no information on the yield of TB screening programmes is easily available on national level. This information, however, would be of high importance for evaluating effectiveness and cost-effectiveness and for attempts to prioritise specific high-risk groups. The aim of this study was to synthesise evidence on the yield of entry screening programmes for TB among asylum seekers in Germany, and to compare the estimate with international evidence.

Methods

Study design

We performed a systematic review and meta-analysis of the literature reporting the yield of entry screening programmes for TB among asylum seekers in Germany. Yield was defined as the fraction of active TB cases detected among 1,000 asylum seekers screened.

The literature was retrieved in the scope of a broader configurative systematic review [18] aimed at identifying and mapping all empirical studies on health and healthcare among asylum seekers and refugees in Germany [19]. The protocol of the configurative systematic review and evidence-mapping study was registered in an international prospective register of systematic reviews (PROSPERO 2014:CRD42014013043) and published in a peer-reviewed journal before starting the review [19]. The evidence map and synthesis generated by the configurative review laid the foundation for this aggregative review. This type of review seeks to add up and average (homogenous) empirical observations in order to make empirical statements within narrower predefined concepts to inform decisions. Aggregative reviews can follow configurative ones, which aim to provide concepts and patterns among heterogeneous and more complex fields [18].

Review question and outcome

The question for this systematic review and meta-analysis was formulated as follows: What is the yield of upon-entry screening for TB among asylum seekers in Germany? The primary outcome was the yield of TB among asylum seekers screened in the scope of active screening programmes (according to §62 AsylG in combination with §36 IfSG).

Search strategy

A three-tiered search strategy was applied:

1. We searched 11 bibliographical databases for indexed articles: PubMed/MEDLINE, ISI Web of Science, International Bibliography of Social Sciences (IBSS), Sociological Abstracts, Social Science Citation Index (SSCI), Worldwide Political Science Abstracts (WPolScA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Sowiport, Applied Social Sciences Index and Abstracts (ASSIA), Medpilot, German National Library (DNB). In addition, we searched the Internet via Google in order to identify grey literature. The searches were performed in August and September 2014 (Web of Science, Medpilot: 22 Aug 2014; SSCI, ASSIA: 24 Aug 20e Aug 2114; PubMed, IBSS, Sociological Abstracts, WPolScA: 9 Sep 2014; CINAHL, DNB: 30 Sep 2014; Google: 2 Sep 2014).

2. We reviewed the reference lists of included articles to retrieve further indexed articles.

3. We contacted 47 experts from 31 organisations inquiring for grey literature.

4. We updated the database search in PubMed/MEDLINE for the period from September 2014 to 26 March 2016 to ensure that articles published since the initial search were considered.

No time limitation was set for the searches. For the full text screening, we excluded studies published before 1990 due to their historical character, since major legal regulations governing screening for TB in asylum seekers (AsylVfG) were not introduced in national law before the 1990s.

Search terms

Search terms were tailored to the broader scope of the configurative systematic review and evidence-mapping study and did not include terms specific for tuberculosis screening [19]. The search terms *((refugee* OR asylum*) AND (health* OR access OR utilisation) AND german*)* were used for international databases; the terms *(Flüchtling OR asyl* AND gesundheit*)* for German databases. The search in databases included titles, abstracts and keywords, without any restriction regarding time period or language. For the Internet search, different search term combinations were used as documented in the review protocol [19].

Inclusion and exclusion criteria

General eligibility

Articles fulfilling all of the following criteria were eligible for inclusion in the broader evidence-mapping study: (i) empirical articles (i.e. quantitative or qualitative primary studies, as well as reviews of empirical studies), (ii) articles focusing on asylum seekers and refugees in Germany as a distinct study population, (iii) articles reporting on any parameter of health or healthcare provision as outcomes and (iv) articles published in German or English.

The specific type of outcome (e.g. a specific disease or condition) was not defined as a criterion for inclusion or exclusion into the configurative review and evidence-mapping study.

Exclusion criteria for the configurative review were unclear study populations (e.g. migrants of unknown status or lack of stratified results for asylum seekers/refugees as part of general migrant populations) and undocumented migrants, ethnic German resettlers (*Aussiedler*), persons internally displaced in the context of World War II or refugees from the German Democratic Republic as the study population. We also excluded non-empirical literature (commentaries, working papers, journalistic interviews, policy reports, books, conference transcripts or congress abstracts without available full texts).

Studies were excluded and assigned to a residual category not considered for the evidence mapping if they reported findings of international studies without

Table A

Characteristics and extracted details of included studies on tuberculosis screening in asylum seekers in Germany (n = 6)

Reference	Type of publication	Study objective(s)	Study design	Setting/ context of study	Year of data collection	Coverage (%)	Country/ countries of origin of the screened population	Men (%)	Age groups (in years): % or n	Sampling strategy	Stratification	Diagnostic methods	Case definitions of TB	Main limitations (as reported)	Additional (main) limitations identified by review-team	Funding sources/ conflicts of interest	Level of evidence
Diel et al. (2004) [23]	International journal, externally peer-reviewed	To study the characteristics of TB in foreign-born individuals living in Hamburg	Prospective, population-based molecular-epidemiological study	State of Hamburg	1997–2002	95.5	Afghanistan: 48.6%, Turkey: 7.5%, Iran: 6.5%, Burkina Faso: 4.9%, ex-Yugoslavia[a]: 4.3%, Sierra Leone: 4.1%, Russia: 2.7%, Guinea: 1.7%, Togo: 1.5%, Egypt: 1.3%, Other: 17.3%	48.1	No age groups given (NA)	All patients with culture-confirmed TB reported to the seven district public health departments in Hamburg; this includes 12,176 of 12,751 asylum seekers in Hamburg who were screened at entry	None	General health examination; chest X-ray; tuberculin skin testing; Bacterial strains and drug susceptibility testing; IS6110 DNA fingerprint analysis	Extrapulmonary TB (defined as disease with no evidence of lung involvement) and pulmonary TB (sputum-positive or culture-positive)	Limitation of the study period to 5.5 years resulted in an underestimation of the real trans- mission rate between foreign-born and German-born individuals	Study limited to Hamburg	Robert Koch Institute, Berlin, Germany, and the EU Concerted Action project "New Generation Genetic Markers and Techniques for the Epidemiology and Control of Tuberculosis"	1b
Dreweck et al. (2013) [24]	National journal, externally peer-reviewed	NA (implicitly: to provide a descriptive epidemiological report on TB epidemiology in Munich)	Cross-sectional descriptive study	City of Munich	2011, 2012	NA	NA	NA	NA	TB screening of all asylum seekers	None	X-ray	No case definitions provided	Not reported	(i) Denominator not reported precisely, detailed denominator provided after contacting authors; denominators for other years completely missing (ii) No information on countries of origin, age or sex	None reported	3b
Joggerst and Käßmann (2013) [25]	Supplement/ congress abstract in national journal (further information provided in the form of a detailed poster)	To analyse the results of the health entry examination at the reception centre Karlsruhe over a period of 10 years	Prospective population-based study, cross-sectional time-series	Main reception centre of the State of Baden-Wurttemberg	2002–11	NA	Irak: 16.1%, Turkey: 9.7%, Serbia: 6.7%, Pakistan: 5.4%, Iran: 5.1%, Cameroon: 4.7%, Afghanistan: 4.7%, Nigeria: 4.4%, Russia: 4.4%, China: 4.4%, Sri Lanka: 4%, India: 3.8%	72.3	0–10: 8.5%, 11–20: 17.8%, 21–30: 43.8%, 31–40: 20.3%, 41–50: 5.7%, 51–60: 1.9%, 61–70: 1.0%,	Screening of all asylum seekers allocated to the State of Baden-Wurttemberg	By country of origin, age, sex	X-ray for asylum seekers ≥ 16 years; tuberculin test < 16 years	No case definitions provided	Not reported	Abstract; assessment of observed vs expected cases only descriptive and based on a single year of WHO data (2011)	None reported	1b

CT: computed tomography; EU: European Union; IGRA: interferon gamma release assay; NA: not available. TB: tuberculosis; WHO: World Health Organization.

[a] Country name listed as per original publication.

[b] Kosovo under UN Security Council Resolution 1244 in 1996.

Table B

Characteristics and extracted details of included studies on tuberculosis screening in asylum seekers in Germany (n = 6)

Reference	Type of publication	Study objective(s)	Study design	Setting/ context of study	Year of data collection	Coverage (%)	Country/ countries of origin of the screened population	Men (%)	Age groups (in years): % or n	Sampling strategy	Stratification	Diagnostic methods	Case definitions of TB	Main limitations (as reported)	Additional (main) limitations identified by review-team	Funding sources/ conflicts of interest	Level of evidence
Kesseler et al. (1995) [26]	National journal, externally peer-reviewed	To evaluate the prevalence of active and latent TB in asylum seekers	Prospective observational study	Nine public health offices in North Rhine-Westphalia	1992–94	100	Europe: 70%, Yugoslavia[a]: 42%, Romania: 14%, Bulgaria: 3%, Turkey: 7%, Africa: 13%, Asia: 7%	72	Range: 1–89. 0–10: 86, 11–20: 716, 21–30: 1,953, 31–40: 875, 41–50: 261, 51–60: 113, >61: 53	All asylum seekers in study area (9 Health Offices in NRW) from June 1992 to January 1994	None	Chest X-ray, tuberculin test	Active pulmonary TB (culture-positive, smear-positive or smear-negative)	Not reported	No further characteristics provided/ assessed in stratified analysis which could affect TB prevalence identified by screening	None reported	1b
Michels and Bartz (2015) [28]	National journal, in-house peer-reviewed	To report the results of the TB screening among asylum seekers in the scope of the health entry examination at the reception centre Trier	Prospective population-based study	Main reception centre of the State of Rhineland-Palatinate	2001–14	100	Reported only for a subsample of the year 2014 (n=10,528): Syria: 2,835, six cases, 212/100,000; Kosovo[b]: 1,130, four cases, 354/100,000 Serbia: 1,057, six cases, 568/100,000; Eritrea: 898, nine cases, 1,002/100,000 Albania: 660, one case, 152/100,000; Somalia: 540, 11 cases, 2,037/100,000 No countries reported: 3,408, 10 cases	NA	NA	Screening of all asylum seekers allocated to the State of Rhineland-Palatinate	By country (only for a subsample of the year 2014)	Chest X-ray (adults) tuberculin test (children/ adolescents<16 years, pregnant women); in single cases additionally IGRA, sputum diagnostic, further serological tests (not further specified), chest CT scan	22 cases: culture/sputum-positive 21 cases: culture/sputum-negative four cases: unclear	Not reported	Age and sex of screened population and of cases not reported; unclear how many cases were identified by which diagnostic method; countries reported only for a subset of the 2014 population; comparison with WHO prevalence rates only descriptive and only for 2014	None reported	1b
Mohammadzadeh (1995) [27]	National journal, externally peer-reviewed	To evaluate the Initial Health Examination Programme in Bremen	Retrospective study of medical records	Initial Health Examination Programme in Bremen	June 1993-June 1994	59.9	ex-Yugoslavia[a], Romania, Commonwealth of Independent States, Algeria, Turkey, Sierra Leone, Liberia, Togo, Iran, Bulgaria (no further details reported)	80.4	NA	All asylum seekers who sought care in the programme	Adults vs children (categories not further specified)	Methods of diagnosis not specified, chart review of medical records/routine data collected in the programme	Reported cases include history of TB, suspected TB, extrapulmonary (nodal) TB, and pulmonary TB (all types: not further specified)	NA	No descriptive information on study population; missing information on data collection/ diagnostic methods	Programme conducted by Health Office Bremen	2c

CT: computed tomography; EU: European Union; IGRA: interferon gamma release assay; NA: not available. TB: tuberculosis; WHO: World Health Organization.

[a] Country name listed as per original publication.

[b] Kosovo under UN Security Council Resolution 1244 in 1996.

stratified data for Germany or turned out to be secondary literature not exclusively based on empirical material.

Tuberculosis-specific eligibility

Articles meeting the above general criteria were eligible for inclusion in this review if: (i) they reported the number of active TB cases detected in the scope of entry screening programmes and (ii) provided accurate information on denominators of the screened population of asylum seekers.

Articles retrieved by the updated database search were screened using the general criteria (i), (ii) and (iv) together with the TB-specific eligibility criteria in one step, i.e. without the intermediate step of applying the general eligibility criterion (iii).

Screening and study selection

All retrieved references (titles and abstracts) were screened independently by two reviewers of the initial review team [19,20]. The full texts of articles included after abstract/title screening were again screened independently by the same reviewers. Any discrepant judgements on eligibility were discussed in consensus meetings among at least three members of the initial review team [19,20] and articles were included or excluded after reaching mutual agreement. References retrieved in the updated search (titles, abstracts and full texts) were screened by the first author (KB).

Effectiveness of the search strategy and sensitivity analysis

The effectiveness of the search strategy of the configurative review was assessed by calculating its specificity and sensitivity. Specificity was assessed by the proportion of eligible articles among all search results. Sensitivity was calculated as the proportion of eligible articles identified by the search among all truly eligible articles (true positives and false negatives) using a test set of articles a priori defined and listed by the authors before starting the review [20]. In order to rule out the possibility of a selection bias for the aggregative review, we performed a sensitivity analysis: the updated search in Pubmed/MEDLINE (Sep 2014–26 Mar 2016) was repeated with extended search terms including terms for migrants derived from medical subject headings (MeSH). The final Boolean operator for the updated search with extended search terms was: *(refugee* OR asylum* OR foreign* OR immigrant* OR migrant* OR emigrant*) AND (health* OR access OR utilisation) AND german**. Applying the same inclusion/exclusion criteria, we assessed whether this extended search yielded any further eligible articles that were not previously identified.

Data extraction

We systematically extracted generic information on included articles (authors, year of publication, type of publication and funding sources) and the following content-specific information: research questions, study context/setting, study period, study populations and socio-demographic variables (age, sex and country of origin), sampling strategy, total number of asylum seekers, number of asylum seekers undergoing upon-entry screening, number of active TB cases identified, case definitions and diagnostic methods as reported, limitations as reported and statements on generalisability with respect to the outcome of the review.

Critical appraisal

Studies were categorised according to the Levels of Evidence (LoE) of the Oxford Centre for Evidence-Based Medicine based on the study type of the primary article [21]. Additional limitations beyond those reported in the primary articles were identified by the reviewers and documented in the extraction sheets. We assessed the external validity of studies on the basis of reported limitations, reported external validity and additional limitations identified by the reviewers. We also categorised the generalisability of findings with respect to the local, regional or supraregional level. In this context, 'local' referred to the generalisability of findings to the population of one single accommodation, 'regional' referred to the generalisability to the population of one city or region and 'supraregional' referred to the generalisability across federal states.

Statistical analysis and evidence synthesis

We calculated the coverage of screening programmes as the proportion of asylum seekers undergoing screening among total numbers of asylum seekers. The yield of TB screening programmes was calculated as the fraction of active TB cases detected among the number of asylum seekers undergoing screening (expressed as cases per 1,000 persons). Authors of primary studies were contacted for further information if the reported data was not sufficient to calculate the yield.

In a random-effects meta-analysis, the yield was synthesised across studies and pooled estimates along with corresponding 95% confidence intervals (CI) were calculated, weighting each study by its inverse variance, applying the DerSimonian-Laird estimator for between-study variance and the arcsine transformation to calculate the overall yield. As considerable clinical heterogeneity was expected, a random-effects rather than a fixed-effect model was applied. Sensitivity analyses were performed to assess the influence of potential over-reporting of active TB cases in primary studies with imprecise case definitions. In order to estimate the numbers of asylum seekers that would need to be screened to detect one case of TB, the pooled estimates of the yield and corresponding confidence limits were inverted. Results of a meta-analysis of the yield of TB screening among asylum seekers with no restriction of the host country (but not including studies from Germany) performed by Arshad et al. were used for comparison with international studies [22]. An updated pooled estimate combining the individual studies included in this review and in Arshad et al. [22] was calculated using the same approach as

described above. Minor differences compared with the results reported by Arshad et al. were due to a slightly different meta-analytical approach, e.g. in the computation of confidence intervals. The meta-analyses were performed in the R language and environment for statistical computing (Version 3.3, The R Foundation for Statistical Computing) using the R-package 'meta' (Version 4.5–0).

Results

After removal of 398 duplicates, the search in databases and reference lists and the queries among experts yielded 1,190 hits. Another 63 hits were obtained by updating the search in PubMed/MEDLINE, so that a total of 1,253 articles were screened (Figure 1).

Of these, we excluded 1,046 (83%) after screening of titles and abstracts. The full texts of the remaining 207 articles (of which 12 had some reference to TB) were checked against the general and specific inclusion criteria. This led to the exclusion of another 202 articles so that a total of five studies (0.4% of all hits) were included in the systematic review and meta-analysis via formal searches [23-27]. A relevant grey-literature article published in 2015 after the initial search had been conducted was included while writing up the report [28], so that in total six articles were included in the final analysis.

The included studies [23-28] reported the yield of screening for tuberculosis among asylum seekers upon-entry in three large federal states [25,26,28], two of the smallest federal states [23,27] and in the city of Munich [24]. No study reported findings across more than one federal state (Table).

Characteristics and quality of included studies

The included studies were very heterogeneous with respect to primary objectives, study design and type of publication. The primary objective of three studies was to assess TB prevalence in asylum seekers in the scope of screening programmes [25,26,28]. The remaining studies pursued other primary objectives and reported the yields of screening programmes as secondary findings [23,24,27].

Further heterogeneity was found in study designs: four articles were prospective observational studies (LoE 1b), one was a cross-sectional (LoE 3b) [24] one a retrospective medical records study (LoE 2c) [27].

All reports were published in peer-reviewed journals (including those with in-house peer review), but only one was published in English and in an international journal [23]. The reports included a published congress abstract which we included since additional information (in form of a poster) and access to the primary data were granted by the authors so that sufficient information was at hand to ensure eligibility [25].

The findings of five studies were regionally generalisable at the level of the respective federal states [23,25-28]. None of the studies made formal comparisons with the characteristics of asylum seeker populations at national level, so that an assessment of the representativeness of samples beyond regional boundaries was not possible. Only one study reported study limitations in detail [23]. Limitations of the primary reports identified by the review team are provided in the Table.

Case definitions ranged from none [24] or poorly reported ones [27] to clear definitions of identified TB cases [23,26,28]. The chest X-ray as a diagnostic method to screen for active TB cases was clearly reported by all but one study [27]. Studies reporting more than one diagnostic method did not report the number of cases identified by each method [28]. Three studies reported stratified results [25,27,28], but stratification was incomplete and rudimentary in all but one [25]. One study provided detailed stratification of results only for migrants, but not for the sub-group of asylum seekers [23].

Sample sizes and yield of screening programmes

The sample sizes of screened asylum seekers ranged from n = 1,077 (smallest study) to n = 38,724 (largest study), the mean and median numbers of screened asylum seekers were n = 14,882 and n = 8,167, respectively. The included studies comprised a total of 89,294 asylum seekers (Figure 2, upper part).

The number of reported TB cases identified by upon-entry screening ranged from six to 132 (mean: 24; median: 39.7). The yield of screening programmes in primary studies ranged from 0.72 (95% CI: 0.45–1.10) [25] to 6.41 (95% CI: 4.19–9.37) [26] cases per 1,000 asylum seekers. The pooled estimate for the yield of TB screening programmes across all studies was 3.47 (95% CI: 1.78–5.73) cases per 1,000 asylum seekers (Figure 2, upper part). This corresponded to 288 (95% CI: 175–561) asylum seekers that would need to be screened to detect one case of TB. The meta-analysis revealed substantial statistical heterogeneity among the studies ($I^2 = 94.9\%$; test for heterogeneity: $p < 0.0001$).

In a sensitivity analysis, we calculated a conservative estimate by excluding four TB cases (suspected cases and histories of TB) reported by Mohammadzadeh [27]. The conservative pooled estimate for the yield of upon-entry screening across all studies was 12.1% lower (3.05 (95% CI: 1.50–5.14) per 1,000 asylum seekers) than the yield of the non-conservative estimate (3.45 (95% CI: 1.78–5.73) per 1,000 asylum seekers), which would correspond to 327 (95% CI: 194–667) asylum seekers to be screened in order to detect of one case of TB.

The pooled point estimate of the yield of TB identified by screening programmes in the German studies

was slightly higher than the pooled point estimate of 2.70 (95% CI: 1.98–3.42) per 1,000 asylum seekers reported by Arshad et al. who performed a meta-analysis of seven international primary studies with a total of 351 TB cases identified by screening of 135,265 asylum seekers [22]. In a re-analysis of the data included in Arshad et al., using the same methods as applied above for the German data, we obtained a point estimate of 2.77 (95% CI: 2.05–3.75) per 1,000 asylum seekers, as shown in Figure 2 (lower part). The meta-analytic comparison of the pooled estimate of the yields reported by German studies and that of international studies [22] exhibited no statistical heterogeneity ($I2 = 0\%$; test for heterogeneity: $p = 0.55$; data not shown). The pooled overall yield was 3.04 (95% CI: 2.24–3.67), as shown in Figure 2, which corresponded to 329 (95% CI: 253–447) asylum seekers that would need to be screened to detect one case of TB.

Effectiveness of the search strategy and sensitivity analysis

The search strategy for the configurative review identified 52 relevant articles from a total of 1,190 hits. This corresponded to a specificity of 4.4%, which was to be expected when applying such a broad search strategy. The sensitivity of the search strategy was 98.1% when based on the articles of the test set [19] including grey literature and 100% when based on the articles from peer-reviewed journals.

The sensitivity analysis using extended search terms related to migration yielded 295 hits in the updated search (compared with 63 hits when using specific search terms for the migrant population in question, Figure 1). Of these, 288 were excluded for study design ($n = 117$), for study population, i.e. lack of focus on asylum seekers or refugees ($n = 56$), for specific content, i.e. no relation to TB or no information on TB yield in health entry screening programmes ($n = 93$) or for country of study ($n = 22$). The remaining seven articles [29-35] were assessed in full text for eligibility. These were excluded for study design ($n = 3$), for lack of reference to TB or TB yield in screening programmes ($n = 3$), or for country ($n = 1$), so that no additional studies were included in the systematic review after broadening the search terms to include a reference to overall migrant groups.

Discussion

The yield of upon-entry screening programmes for TB in asylum seekers as assessed by this systematic review and meta-analysis of studies in Germany was 3.47 (95% CI: 1.78–5.73) per 1,000 asylum seekers. This corresponds to a number needed to screen (NNS) of 288 (95% CI: 175–561) asylum seekers to identify one case of TB. The pooled estimate derived from the meta-analysis of German studies concurs with international findings on the yield of active TB screening programmes for asylum seekers upon entry [22]. The joint yield of German and international studies was 3.04 (95% CI: 2.24–3.67), corresponding to a slightly higher NNS of 329 (95% CI: 253–447) to identify one case of TB in asylum seekers. The review by Arshad et al. considered studies performing both radiological and microbiological tests to identify cases of active tuberculosis [22], so that the applied screening strategies are comparable. According to a systematic review performed in 2013 by the World Health Organization (WHO), the overall median NNS of immigration screening (considering mixed migrant groups in the scope of immigrant, border and refugee screening) was 156 (95% CI: 66–320) [36]. The weighted mean NNS based on 3,429,573 individuals screened in 38 studies was 108 (95% CI: 6–1,630) [36]. The overall NNS in our study was higher, corresponding to a lower yield of screening. This may be explained by differences in migrant groups, migration routes and countries of origin. Other reviews comparing different types of screening (pre-, upon- or post-entry screening) for TB in migrants in low-incidence TB countries report high variations in the yield of screening [37]. This may explain the different conclusions of health economic evaluations regarding the cost-effectiveness of screening for active TB [38]. Further health-economic analyses and rigorous studies on the effectiveness of TB screening are thus needed to assess the impact on both transmission of TB and individual health outcomes [38,39].

Similar to the primary studies identified by Arshad et al. only few primary studies in our review reported yields stratified by age [25,27], sex [25] or country of origin [25,28], which may partly be explained by low case numbers limiting the possibility of reporting across multiple strata. Important post-migration factors such as median length of stay in the host country and characteristics of the accommodation were not reported either by the primary studies in our review. It is known that the underlying incidence of TB in the countries of origin affects the yield of screening approaches in different settings [36,40]. Better reporting of country-stratified yields may therefore help to prioritise special risk groups among the heterogeneous population of asylum seekers. Two studies [25,28] additionally compared the TB yields by country of origin descriptively with the prevalence rates of asylum seekers' countries of origin reported by the WHO. Michels and Bartz [28] reported much higher yields among a subsample of asylum seekers originating mostly from high-prevalence countries in the year 2014 than could be expected based on WHO prevalence rates for the respective countries of origin (Albania, Eritrea, Serbia, Somalia and Syria). Joggerst and Käßmann [25] also found more cases than expected for some countries (Turkey and countries within the area of the former Republic of Yugoslavia), but reported fewer cases than expected for others (Afghanistan, Iraq, Liberia and Pakistan). They hypothesised that two different phenomena co-occur among asylum seekers: a 'healthcare-seeking migration' from countries that are geographically closer (implying that persons with TB have a higher probability of migrating) and a 'healthy migrant effect' for geographically more

distant countries (implying that persons with TB have a lower probability of migrating).
Further factors beyond selection effects, such as transmission and re-activations during the flight, as well as post-migration factors such as accommodation, may also explain the increased yields.

Strengths and limitations

The major strength of this systematic review is the comprehensive search for and meta-analysis of studies on the yield of TB screening programmes in asylum seekers in Germany. This is the only migrant group which systematically undergoes active screening for TB. We generated the first estimate of yields of active screening for TB beyond boundaries of single federal states. All studies but one were published in German, which may be the reason why they were not included in the review by Arshad et al. [22]. We are aware of only one international systematic review [9] that included two studies from Germany [23,26]. Our study provides evidence accessible to an international community on the effectiveness of screening programmes in one of the largest recipient countries for asylum seekers in Europe.

Our analysis is, however, limited by the heterogeneity in study characteristics and also in study results (estimates of the yield of TB) across primary studies. This includes poorly reported case definitions and heterogeneous diagnostic methods (except for the chest X-ray). Because of the limited socio-demographic information provided in primary reports and the lack of stratified findings and numbers of events it was not possible to track the reason for this heterogeneity. A likely explanation is that we pooled estimates from different waves of asylum seekers which differed with respect to the major countries of origin, the reasons for migration and the conditions during migration and reception.

Our search strategy was broad and unspecific, but highly sensitive. We therefore rule out the possibility of a selection bias as explanation for the small number of identified studies. We identified all relevant articles on the group of asylum seekers and on migrant groups labelled as 'refugees' in Germany and included those with a reference to active screening for TB in the aggregative review. We excluded studies on other specified migrant populations (e.g. undocumented migrants), but studies reporting populations of 'general migrants' or 'immigrants' in the abstract or title without any further specifications were not excluded at the stage of screening the abstracts and titles and included in the full-text screening. They were only excluded if it became clear at the stage of full-text screening that the study population, i.e. asylum seekers, was not addressed or not specifically distinguished in the results section.

Although the initial search terms did not include terms related to migration in general, our search strategy identified relevant studies that used the term 'immigrant' in the title (e.g. [23]), but reported the study population of concern for our review (asylum seekers) in the abstract or as part of the keywords. Our search terms were maximally broad with respect to the outcomes (health and healthcare), and broadening the population to include general 'migrants' in the searches would have decreased specificity even further to unacceptably low levels, increasing the work load. The numbers of hits yielded by the updated search with extended terms was about five times (4.7) higher than the number of hits yielded by the search with more specific search terms. However, no additional studies were identified despite the broader search. Firstly, there is no TB screening for regular immigrants or general migrants in Germany. Active screening for TB is performed exclusively among asylum seekers, so broadening the population to general migrants would not yield more relevant articles in the German context.

Recommendations for further research

More research is necessary to assess the yield of screening programmes for TB depending on country of origin. This is not a purely academic issue, but has highly important practical implications. Screening for TB among asylum seekers upon entry in times of high immigration constitutes a substantial challenge for public health authorities [14]. The limited evidence provided by country-stratified analysis shows the importance of a targeted approach such as prioritising high-risk groups when time and personnel resources are limited, especially during periods of large-scale immigration of asylum seekers.

However, targeted screening among immigrants was performed in only six of 25 OECD countries in 2010 using thresholds based on the TB incidence in their country of origin. Incidence thresholds at which screening was initiated ranged from more than 15 to more than 100 cases per 100,000 population [12].

Another question of public health relevance is to establish the effectiveness of screening programmes beyond yields. Timeliness of case detection and treatment outcomes are highly important, but evidence on these aspects in asylum seekers is rare. National [20] and international systematic reviews [41] identified only one study analysing TB treatment outcomes in asylum seekers in Germany [42]. This study shows that treatment failure is disproportionately higher among asylum seekers than among the native population [42].

Furthermore, data on cases with drug resistance or multidrug resistance would be necessary to fully understand the risk posed by specific subgroups. As cases of resistant or multidrug-resistant TB are far more dangerous, screening in subgroups with a known high risk of resistance needs to be more extensive, even if absolute case numbers are low.

There is no or no comprehensive screening for children among refugees [43]. National TB screening protocols

(AsylG, IfSG) do not address the issue of TB screening for children younger than 15 years. In 2013, TB incidence in Germany in children was 1,6 per 100,000; 35% of cases were foreign-born children [44]. The individual risk of children to develop serious and generalised infections is high, and there is no evidence for an age limit at which there is no risk for transmissions [44]. The tuberculin skin test (TST) is recommended for screening of asylum-seeking children under the age of 5 years, and TST or interferon-gamma release assay are recommended for screening of children aged 5–14 years [44]. However, TB screening policies at federal state level handle this issue very heterogeneously. Because reporting is not stratified by age and the links between diagnostic methods and identified cases are not clear, we could not estimate the TB yield in asylum-seeking children based on the included studies.

Further studies with more detailed information on case finding rates by specific characteristics of the heterogeneous population of asylum seekers are necessary to move from retrospective evaluations of the effectiveness of screening programmes to a prospective prediction of TB risk (by age, sex, country of origin and other characteristics) among newly arriving asylum seekers. Given the unexpectedly high yields in some subgroups, it would also be important to establish factors during migration and initial accommodation which may lead to higher transmission rates or re-activation of latent TB infections, and to prioritise targeted screening in situations of high workload or limited resources.

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Conflict of interest

None declared.

Authors' contributions

Conceived the study: KB. Data collection: KB. Data extraction: KB, DS. Quality appraisal: KB, OR, CS. Data analysis: CS, KB, DS. First and last version of manuscript: KB. All authors contributed to the study design, participated in drafting the article and revising it critically for important intellectual content, and gave final approval of the version to be submitted.

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Research article

Contact investigation after a fatal case of extensively drug-resistant tuberculosis (XDR-TB) in an aircraft, Germany, July 2013

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In July 2013, a passenger died of infectious extensively drug-resistant tuberculosis (XDR-TB) on board of an aircraft after a 3-hour flight from Turkey to Germany. Initial information indicated the patient had moved about the aircraft coughing blood. We thus aimed to contact and inform all persons exposed within the aircraft and to test them for newly acquired TB infection. Two-stage testing within 8 weeks from exposure and at least 8 weeks after exposure was suggested, using either interferon gamma release assays (IGRAs) or tuberculin skin test (TST). The TST cut-off was defined at a diameter ›10 mm; for differentiation between conversion and boosting, conversion was defined as increase of skin induration ›5 mm. Overall, 155 passengers and seven crew members were included in the investigation: the questionnaire response rate was 83%; 112 (69%) persons were tested at least once for TB infection. In one passenger, who sat next to the area where the patient died, a test conversion was registered. As of March 2017, no secondary active TB cases have been reported. We describe an unusual situation in which we applied contact tracing beyond existing European guidelines; we found one latent tuberculosis infection in a passenger, which we consider probably newly acquired.

Introduction

In July 2013, the responsible German health authorities were informed about a young adult passenger who died from acute massive haemoptysis on board of an aircraft travelling from Turkey to Germany. They were travelling alone and had taken a previous flight from a country in the eastern part of the World Health Organization (WHO) European Region to Turkey; no passenger from the second flight with the incident had shared the first flight.

The aircraft from Turkey to Germany was almost fully booked with 156 of 181 seats occupied. Several passengers stated initially that the passenger who later died on the plane had moved about the aircraft during the 3-hour flight coughing blood; furthermore, the patient had mentioned having tuberculosis (TB) to one of the passengers, so this information became quickly known to the persons giving first aid. First aid was given in the back part of the aircraft (in the cabin toilet area). Four days after the event, autopsy results confirmed that the deceased passenger had infectious cavitary pulmonary TB. Besides the lungs, no other organs were affected. By molecular diagnostic, specific genome sequences belonging to the *Mycobacterium tuberculosis* complex were detected from swabs taken during autopsy from the trachea, the bronchi and both lungs.

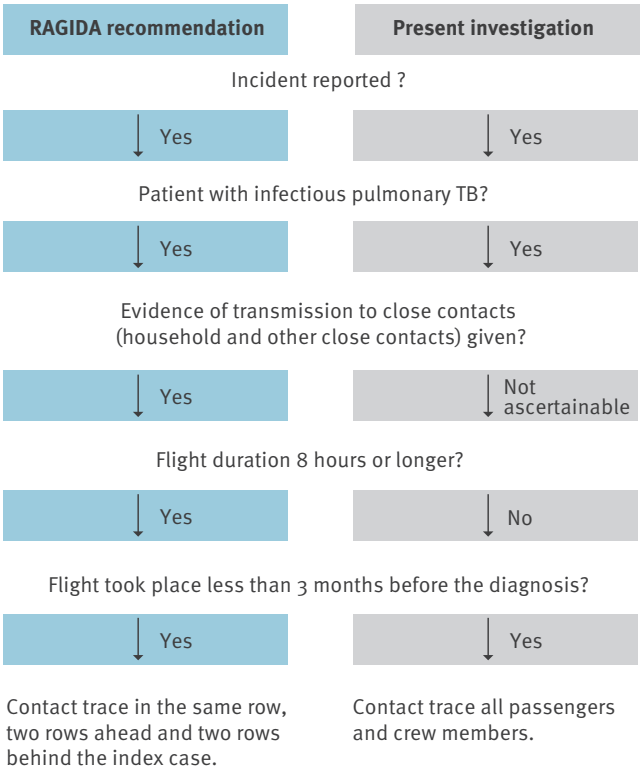
Germany is a low TB incidence country with a TB notification rate of 5.2 cases per 100,000 population in 2012, the year preceding the event, corresponding to an absolute case number of 4,220 [1].

The overall rate of multidrug-resistant (MDR)-TB between 2002 and 2013 in Germany was 0.7% among patients born in Germany. However, the patient came from one of the 27 countries with a high MDR-TB burden. For these countries, WHO estimated in 2008 at least 4,000 MDR-TB cases occurring annually and/or at least 10% of newly registered TB cases with MDR [2]. Hence, the origin of the patient raised a suspicion of MDR-TB.

The involved German health authorities immediately initiated a risk assessment that was based on the Risk assessment guidelines for infectious diseases transmitted on aircraft (RAGIDA) for TB criteria [3] and

Figure 1

Criteria for initiating contact tracing after tuberculosis exposure on aircraft [3] vs TB contact tracing after XDR-TB-exposure in an aircraft, Germany, 2013



RAGIDA: Risk Assessment Guidance for Infectious Diseases transmitted on Aircraft; TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

guided by the analysis of this dramatic and unusual fatal event. Overall, the risk of attracting a TB infection after flight exposure is assessed to be very low [4,5]. A summary of evidence on TB transmission on aircraft in 2016 included 21 studies and data collected from 279 flights [5]. Among 2,791 contacts tested, the authors estimated that 0.1–1.3% of aircraft contacts in flights lasting more than 8 hours might have contracted the infection from a sputum-smear-positive index patient.

Contact tracing is generally not recommended on flights of less than 8 hours duration and there is little evidence of TB transmission during air travel [4,5]. However, considering the severity of symptoms, including massive haemoptysis, the reported mobility of this potentially highly infectious passenger within the aircraft and the known drug resistance rates in the patient's home country, the decision was made to start comprehensive contact tracing investigations of all passengers and crew members.

The contact investigation procedures were initiated within 3 days after the fatal event while waiting for antimicrobial drug susceptibility testing (DST) results of autopsy samples by the German National Reference Center for Mycobacteria in Borstel. Two weeks after the flight, DST results confirmed resistance to rifampicin. Another two weeks later, the National Reference Centre for Mycobacteria reported to the local health authority that the patient suffered from extensively drug-resistant XDR-TB, resistant to isoniazid, rifampicin, protionamide, pyrazinamide, ethambutol, streptomycin, ofloxacin, moxifloxacin, amikacin, capreomycin and rifabutin. The isolated *M. tuberculosis* strain was sensitive to linezolid only. Preventive treatment was not an option in potentially identified secondary latent TB infection (LTBI) cases due to the resistance pattern of the index patient.

A general information about the event was shared within the European Union through the European Commissions's Early Warning and Response System (EWRS) and with the WHO through the International Health Regulations (IHR) National Focal Point. To our knowledge, no contact tracing investigation was initiated for the flight from the respective country in the eastern part of the WHO European Region to Turkey.

Here we describe the contact investigation conducted by the concerned German health authorities for the flight from Turkey to Germany. The objectives of our investigation were to describe the exposure situation, to identify potentially exposed persons, to be able to inform the identified contact persons about the incident and to initiate laboratory investigations of potential TB infections in order to better assess the exposure situation, to inform about the risk of becoming infected and to prevent further infections. The study should add evidence of the risk of TB transmission on aircraft.

Methods

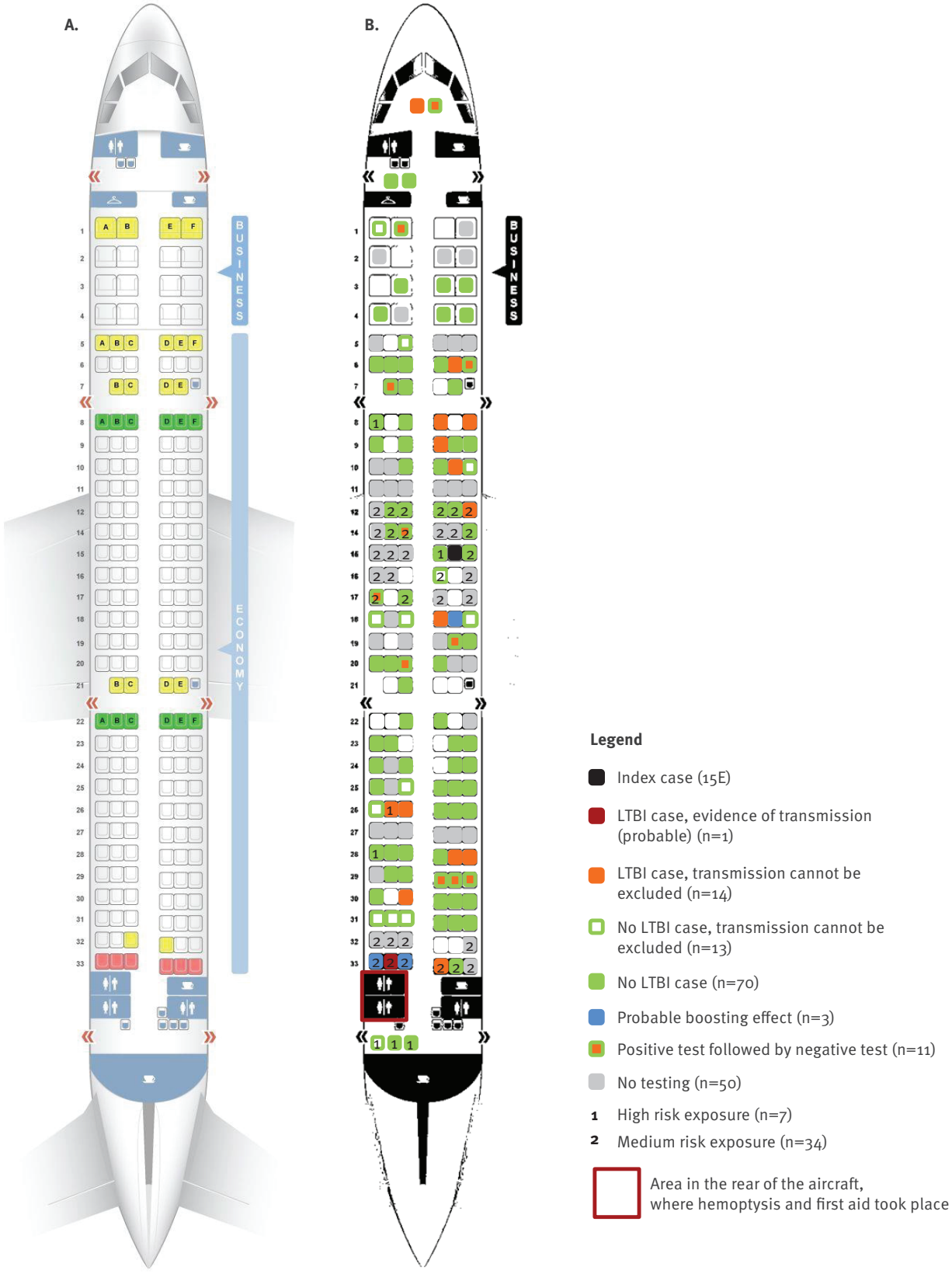
Criteria for contact tracing after TB exposure on aircraft as recommended by RAGIDA [3] vs criteria used in the present investigation are shown in Figure 1.

We used standardised definitions for case assessment. The exposure was defined as sharing the same flight as the index patient from Turkey to Germany in July 2013; case assessment, categories of exposures and case definitions are shown in Table 1.

The comprehensive contact investigation strategy included (i) contacting the National Focal Point for the IHR in the country of origin of the index patient in order to obtain information on the course of the disease, the therapy given and potential evidence for transmissions to household contacts or other close contacts as recommended by the RAGIDA guidelines; (ii) requesting a list of all passengers and crew members with their contact details from the involved airline by the responsible health authority; (iii) contacting by telephone one of the passengers who gave first aid and by email the involved crew members through their countries health authorities to establish more specific information on the exposure during the flight; (iv) distribution of a structured questionnaire to the responsible health

Figure 2

Affected aircraft (A) without labelling; (B) with labelling of passengers and crew, by high and medium exposure risk groups for tuberculosis progression and by LTBI case definition categories, tuberculosis contact tracing after XDR-TB-exposure on aircraft, Germany, 2013



LTBI: latent tuberculosis infection; TST: tuberculin skin test; XDR-TB: extensively drug-resistant-TB.

TST positivity: induration › 10 mm.

Table 1

Standardised definitions for case assessment, categories of exposures and for cases, tuberculosis (TB) contact tracing after XDR-TB-exposure in an aircraft, Germany, 2013

Criteria for case assesment	
Increased risk of acquiring LTBI or increased risk of progression to active TB	Specific case assessment for children younger than 5 years of age (because of an increased susceptibility to infection and the risk of rapid progression), pregnant women, persons with comorbidities such as diabetes mellitus, cancer or immunodeficiencies and for immunocompromised persons (because of an increased risk for progression from TB infection to active TB).
Increased risk for pre-existing LTBI	Contact persons who fulfilled one of the following criteria: birth or prolonged stay, including residency, in a high incidence country for TB (› 40 TB disease cases per 100,000 inhabitants) [22]; previous contact to a patient with infectious TB, regular contact with TB risk populations or a positive TST- and / or IGRA-result in the past.
BCG vaccination	Documentation or recall of at least one administered BCG vaccination.
Categories of exposure	
High risk exposure	Persons who gave first aid to the index patient, who were in the close proximity of the index case while coughing, who talked to the index patient or who had contact with potentially infectious material or performed an aerosolising measure (e. g. intubation).
Medium risk exposure (extended RAGIDA group [3])	Contact persons who sat within two rows in front or behind the index patient or those who sat within the last two rows of the aircraft where the bleeding occurred, if not in the high risk exposure group.
Low risk exposure	Not in the high or medium risk exposure group.
Case definitions	
LTBI case, pre-existing before the flight exposure	A contact person with at least one positive TST or IGRA tested within 3 weeks after the exposure.
LTBI case, evidence of transmission (probable)	A contact person tested negative by TST or IGRA within 8 weeks after the exposure AND tested at least once positive by TST or IGRA between 8th week and 9 months after the exposure.
LTBI case, evidence of transmission (possible)	A person tested negative by TST or IGRA within 3 weeks after the exposure AND tested at least once positive by TST or IGRA between the 3rd and 8th weeks after the exposure.
LTBI case, transmission cannot be excluded	A contact person in whom TST or IGRA were not performed within 3 weeks after the exposure AND EITHER tested at least once positive by TST or IGRA between the 3rd and 8th week after the exposure OR in whom TST or IGRA were not performed between the 3rd and 8th week after the exposure AND tested at least once positive by TST or IGRA between the 8th week and 9th month after the exposure.
No LTBI case, transmission cannot be excluded	A contact person tested at least once with TST or IGRA within 8 weeks after the exposure, all test results negative AND no further TST or IGRA was performed between the 8th week and 9th month after exposure.
No LTBI case, no evidence of transmission	A contact person tested at least once with TST or IGRA, all test results negative and tested at least once negative with tests performed between the 8th week and 9th month after the exposure.
Person probably showing the boosting effect	A contact person tested positive by TST following a first negative TST with an induration increase of ≤ 5 mm.
Person with a negative test following a positive test	A contact person with a negative test following a positive test (TST or IGRA).

BCG: Bacillus Calmette–Guérin; IGRA: interferon gamma release assays; LTBI: latent TB infection; RAGIDA: Risk Assessment Guidance for Infectious Diseases transmitted on Aircraft; TST: tuberculin skin test; TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

authorities both in Germany and abroad containing questions on the history of TB, Bacillus Calmette-Guérin (BCG) vaccination status, existing underlying diseases, category of exposure during the flight, results of tests for LTBI; (v) requesting testing of all contact persons for LTBI coordinated by the responsible health authorities.

To distinguish previous TB infections from those newly acquired, the responsible health authorities were asked to test the contact persons twice: once as early as possible after the exposure and once at least 8 weeks after the exposure. In Germany, interferon gamma release assays (IGRA) were used in adults and tuberculin skin test (TST) in children according to the national recommendations [6]. In children, additional IGRA testing was requested to improve the sensitivity of LTBI diagnosis. Health authorities outside of Germany were asked to follow their respective national guidelines. A positive TST was regarded as an induration size of›10 mm diameter; TST test conversion›5 mm induration increase was considered as newly acquired infection to be distinguished from the boosting effect [7,8]. All contact persons with at least one positive TST or IGRA were supposed to have active TB excluded according to national guidelines.

The collected data were analysed descriptively using STATA (StataCorp. 2015. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP): age, sex, criteria for case assessment, exposure categories, case definitions, test systems, test results and other key factors were considered.

Ethics and data protection

A formal ethical review process and approval was not required for this outbreak investigation in accordance with article 25, section 1 of the IfSG (The German Protection against Infection

Table 2

Number of tested contact persons (passengers and crew members) by categories of exposure and LTBI case definitions, tuberculosis contact tracing after XDR-TB exposure on aircraft, Germany, 2013 (n = 112)

	Risk exposure group (number of persons)			
Case definition	High	Medium	Low	Total
LTBI case, evidence for transmission (probable)	0	1	0	**1**
LTBI case, transmission cannot be excluded	1	2	11	**14**
No LTBI case, transmission cannot be excluded	1	1	11	**13**
No LTBI	5	9	56	**70**
Probably boosting effect	0	2	1	**3**
Negative test following positive test	0	2	9	**11**
Total	**7**	**17**	**88**	**112**

LTBI: latent tuberculosis infection; XDR-TB: extensively drug-resistant tuberculosis

Act–Infektionsschutzgesetz) [9]. All questionnaires and samples were fully anonymised before analysis.

Results

Information from the country of origin of the index patient about the course of the disease, the therapy administered and potential transmission in this country was not available despite several requests.

One month after the flight, contradictory to the information gained from passengers at the very beginning of the investigation, the interview conducted with the passenger giving first aid to the deceased patient and the information provided by the crew members suggested that the index patient stayed seated until ca 30 min before landing in Germany and did not move about the whole aircraft. The haemoptysis event was limited in time and place: it explicitly occurred in the last half hour of the flight in the back part of the aircraft where first aid also was given.

A passenger list with contact information of the passengers was available 22 days after the incident took place (a first passenger list without contact information was available the day of the event); it contained contact details of the majority of passengers (95%; 147/155). All seven crew members were reached through the health authorities of the airline's home country. The 155 passengers and seven crew members were of 17 different nationalities but predominantly German (n = 67; 41%) and Turkish (n = 51; 31%). The median age of the contact persons was 34 years (range: 1 to 71 years); five were younger than 5 years of age, nine were between 5 and 14 years, 112 (69%) were between 15 and 49 years and 36 were 50 years old or older. Of all, 96 (59%) were male.

The questionnaire response rate was 83% (135/162); stratified in exposure groups, the response rates were 100% (7/7) in the high risk exposure group, 62% (21/34) in the medium risk exposure group (extended RAGIDA group) and 88% (107/121) in the low exposure group. Overall, 80 questionnaires were provided by health authorities in Germany and 55 by health authorities in other countries. Several countries considered the duration of the flight too short to warrant TB contact tracing.

Table 2 summarises the main results regarding categories of exposure and case definitions.

Criteria for case assessment

Overall, 9 (8%) of the 112 contact persons tested had an increased risk for acquiring LTBI or increased risk for progression to active TB: four contact persons were children younger than 5 years of age; five persons reported comorbidities (diabetes mellitus (n = 4); cancer (n = 1)). No one reported being pregnant or immunocompromised.

An increased risk for pre-existing LTBI was documented in two (2%) of the 112 contact persons tested: one person originated from a high incidence country for TB, another person reported a previous contact to an infectious TB patient. None of the contact persons stated a positive TST or IGRA or a TB treatment in the past.

A total of 39 (35%) of the 112 persons tested declared that they had received BCG vaccination, 28 persons also stated the date of vaccination. The BCG vaccinated contact persons were mainly Turkish (n = 28), but also German (n = 9) and Japanese (n = 2). While 14 (13%) persons declared that they had never received a BCG vaccination, the BCG status of 59 (53%) persons remained unknown.

Categories of exposures

Seven (6%) of the 112 contact persons tested had a high risk exposure: 5 had given first aid to the index patient (3 crew members and 2 passengers); one passenger sat in the close proximity of the index patient when coughing and another passenger talked to the index patient. The latter passenger was seated right next to the index patient and therefore was only assessed in the high risk exposure group.

Seventeen (15%) of the 112 contact persons tested were grouped in the medium risk exposure group as they sat within two rows in front or behind the index patient or within two rows from the rear toilet.

Another 88 (79%) of the 112 contact persons tested were classified into the low risk exposure group.

Case definitions

LTBI testing was performed in 112 (69%) contact persons; stratified in exposure groups, the testing rates were 100% (7/7) in the high risk exposure group, 50% (17/34) in the medium risk exposure group (extended RAGIDA group) and 73% (88/121) in the low risk exposure group. However, the assessment of a test conversion was only possible in 61 (54%) of the 112 persons tested. Seventy (63%) of them were male. Twenty-nine (26%) of the 112 contact persons tested positive for LTBI at least once; of those, 12 were male. By use of logistic regression we could not find any tendency between age groups and test positivity (data not shown).

Evidence of probable transmission of LTBI was established in one passenger. This person was a young Turkish adult, who had received BCG vaccination and sat in the last row close to the cabin toilet, where the index patient collapsed (medium risk exposure). Six weeks after the exposure, their TST induration was 2 mm and 6 months after the exposure, the TST induration was 14 mm; no abnormality was detected in an X-ray which was performed at the same time as the first TST (Figure 2). This passenger did not recall any contact with another TB case in the past or between the two tests.

In 14 LTBI cases, recent transmission could not be excluded; of those, 12 were of Turkish and two of German nationality; of the 10 who had received BCG vaccination, all had Turkish nationality. Most (n = 11) were grouped in the low exposure group, two persons were classified into the medium exposure group (one German passenger with diabetes mellitus and one Turkish passenger who was had received BCG vaccination and sat in the last row), and one person was categorised in the high exposure group (Turkish passenger who gave first aid and had unknown BCG vaccination status) (Figure 2). However, this person might have been exposed to TB during their professional life as emergency physician.

Three persons, of Turkish nationality, showed a probable boosting effect (increase of induration < 6 mm). Two of them sat in the last row (medium exposure group), one of them had received BCG vaccination. Induration was in both persons 10 mm in the first TST and 15 mm in the second TST. The third person was from the low exposure group and their induration increased by 4 mm (Figure 2).

Overall, 11 cases had a negative test result following a positive test result; they were of German (n = 6), Turkish (n = 4) and United States (US) (n = 1) nationality. Three persons had received BCG vaccination.

Three children younger than 5 years of age with no history of BCG vaccination belong to this category: they all were TST-negative in July/August and in October 2013, but IGRA-positive in October 2013 (0.62; 0.92; and 1.00 IU/mL; the cut off is 0.35 IU/mL); these positive results could not be confirmed in January/February 2014 (all IGRA negative: 0.12; and each 0.00 IU/mL). Chest X-rays were normal. All three children belonged to the low risk exposure category and were born in Germany (Figure 2).

No active TB was diagnosed in any of the contacts with at least one positive TST or IGRA.

A total of 83 (74%) contact persons tested LTBI-negative at least once: 13 of those were not tested again at least 8 weeks after the flight exposure, therefore a possible test conversion could not be excluded; for 70 (63%) there was no evidence of infection (Figure 2).

Discussion and conclusion

We describe a rare fatal event on board of an aircraft that involved a person with XDR-TB travelling from a country in the eastern part of the WHO European Region via Turkey to Germany. The subsequent contact tracing revealed one LTBI in an exposed passenger, which we consider a probable newly acquired infection.

For a comprehensive assessment of the patient's infectiousness, relevant information from the country of origin could not be obtained. Strengthening information exchange within the IHR (2005) [10] is crucial not only for prevention of cross-border transmission of disease but also for rational planning of contact tracing and control activities.

This incident raises an important issue about the strategy of contact tracing investigations in situations that go beyond common scenarios. Contact tracing is recommended only when the flight duration equals or exceeds 8 hours [3,11]. The flight from Turkey to Germany lasted only 3 hours, and no information was available whether any transmission to close contacts had already occurred before travelling. Nevertheless, German health authorities jointly with health authorities from abroad, started and proceeded with the investigation on the grounds that the index patient presumably had highly infectious pulmonary cavitary XDR-TB, and therefore posed a public health threat. The contact investigation activities also went beyond the recommended tracing of passengers sitting in seats of the same row, two rows ahead and behind the index patient, as the index patient was initially reported by several passengers as having moved around in the aircraft and coughing blood, which may have resulted in potential spread of aerosols during the flight. However, the reports regarding the index patient's behaviour were contradictory: in contrast to some passengers'

observations, one passenger giving first aid and the airline crew stated at a later point in time, that the haemoptysis event occurred in the last half hour of the flight, in the back part of the aircraft where the cabin toilets are.

The airline supported the investigation in general very well. To further ease the assessment of the exposure situation, a short written summary of the event would have been helpful at the beginning of the investigation, as suggested by the International Air Transport Association [12].

While no appropriate preventive treatment for latent infection by XDR-TB strains is available, professional risk communication and provision of information to exposed passengers and crew members can help avoid diagnostic delays and ensure rapid drug susceptibily testing and effective treatment, should they develop TB following the event. This is particularly important in contacts with an increased risk for progression, such as young children or persons with co-morbidities and immunosuppression, who require careful follow-up [13].

There are examples of similar decisions made in France [14] in case of an exposure to an XDR-TB case who travelled to Paris on a 5-hour flight. Canadian guidelines recommend performing contact tracing regardless of the flight duration if former transmission to close contacts cannot be determined and laryngeal TB, MDR-TB or XDR-TB is present [15].

The contact investigation is an example of good international cooperation: the response rate (83%) from the standardised contact tracing questionnaire was rather high, most probably due to the unusual event and the enduring efforts made by the investigation team; most of the health authorities abroad supported the investigation by using the provided questionnaire and sharing results. However, some countries chose not to perform contact tracing; one reason given was the duration of exposure which was less than 8 hours.

Health authorities were asked to follow their national guidelines. Therefore, testing approaches and test intervals differed substantially, which impacts comparability and interpretation of test results. Results of second tests were accepted if performed within 9 months after exposure. This increases the chance of being re-exposed, especially for persons originating from countries or settings with a higher TB prevalence.

One of the biggest challenges was the absence of a fast reliable testing method for detection of a recent TB infection. The confirmation of a newly acquired infection with acceptable certainty requires two tests within a defined and narrow time period; however, for various reasons this strategy is often difficult to put into practice. TB exposure during flights frequently becomes evident very late, and early testing may therefore not be feasible.

Even though 69% of the contact persons could be tested for LTBI at least once, assessment for test conversion was only feasible in 54% of them. One reason was that some contacts were only tested once, another reason was that some contacts were tested twice but not early enough for the first time (according to the WHO guidelines, within 3 weeks after exposure [11]) to find out their basic status of infection. This underlines the importance of a standardised testing procedure. The relatively high LTBI prevalence (26%) among contact persons highlights the significance of performing a first test for TB infection within 3 weeks after exposure, to identify pre-existing LTBI. A similar positivity rate was found in a US study about TB contact tracing on aircrafts, where within a 1.5 year period, 182/758 individuals (24%) were found to be positive [16].

The sensitivity of an IGRA (85–90%) and a TST is comparable, but the specificity is higher in IGRA (98%) [17,18], as BCG vaccinations and most non-tuberculous mycobacteria infections do not induce a false-positive result [19]. In this investigation, 35% of contact persons stated to be vaccinated against TB. The boosting effect could not be excluded in vaccinated contact persons; most contact persons with Turkish nationality should have received BCG vaccination. In Turkey, BCG vaccination after birth is obligatory and until the late 1990s it was recommended to be repeated at 7, 14 and 20 years of age [19-21]. Therefore, we are well aware that TST results in Turkish contact persons, who stated not to have received BCG vaccination, should be interpreted with caution. In vaccinated contact persons IGRA tests should be used to rule out boosting due to BCG [7,8,19]. Excluding contacts with known BCG vaccination by default seems questionable, as these contacts remain at risk for infection and progression to active disease.

We regarded one contact person with a TST conversion as a probable LTBI secondary case even though they stated having received BCG vaccination. Transmission cannot be excluded in the LTBI-positive contact person who gave first aid to the index patient; however, they might have been exposed to TB during their professional life as emergency physician.

Notably, there were 11 persons whose LTBI test result eventually reverted from positive to negative, however, it is impossible to differentiate between false-positive or false-negative test results. Among the 11, three were children younger than 5 years of age; their treating paediatricians reasoned that the positive IGRA-results from October 2013 were false-positive and LTBI was not probable in these children. The use of both testing procedures (TST and IGRA) was regarded as worthwhile by these paediatricians. Strikingly, four persons with positive TST or IGRA sat in the last row of the aircraft: the probable secondary LTBI case, two persons with possible boosting effect who both sat next to the

probable LTBI case, and one person with LTBI that was possibly acquired before the flight exposure.
Keeping in mind that passengers who are apparently ill might be asked to change seats, we deem it important to include in the current RAGIDA TB guidelines that the responsible health authority should check whether index patients switched seats or suffered a disease-specific event within the aircraft which necessitates an expansion of the number of contacts to be traced.

Contact tracing after an exposure on aircraft is a resource-intensive measure and its initiation should be well-balanced with the expected outcome. However, in situations that are considered to be extremely serious due to potential risk of transmission of M/XDR-TB, an individual risk assessment is needed.

The yield of the investigation strongly depends on the performance of the diagnostic test and an applicable test strategy. Further efforts are needed to develop eligible tests which allow the detection of a newly acquired TB infection and which indicate the risk of progression of TB infection to active TB.

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Conflict of interest

None declared.

Authors' contributions

MadH, BH, LF, GG-P, MS, CS, AG and WH developed the strategy for the contact tracing, MadH, GG-P and MS conducted the contact tracing, SR-G investigated patient's samples, MadH, BH and LF drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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Risk of tuberculosis among air passengers estimated by interferon gamma release assay: survey of contact investigations, Japan, 2012 to 2015

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Although the World Health Organization recommends contact investigations around air travel-associated sputum smear-positive tuberculosis (TB) patients, evidence suggests that the information thus obtained may have overestimated the risk of TB infection because it involved some contacts born in countries with high TB burden who were likely to have been infected with TB in the past, or because tuberculin skin tests were used, which are less specific than the interferon gamma release assay (IGRA) particularly in areas where Bacillus Calmette-Guérin (BCG) vaccination coverage is high. We conducted a questionnaire survey on air travel-associated TB contact investigations in local health offices of Japan from 2012 to 2015, focusing on IGRA positivity. Among 651 air travel-associated TB contacts, average positivity was 3.8% (95% confidence interval (CI): 2.5–5.6) with a statistically significant increasing trend with older age ($p < 0.0094$). Positivity among 0–34 year-old contacts was 1.0% (95% CI: 0.12–3.5%), suggesting their risk of TB infection is as small as among Japanese young adults with low risk of TB infection (positivity: 0.85–0.90%). Limiting the contact investigation to fewer passengers (within two seats surrounding the index case, rather than two rows) seems reasonable in the case of aircraft with many seats per row.

Introduction

International air travel has become widely accessible and the International Civil Aviation Organization has forecast that scheduled passenger traffic around the world will more than double, from 2.7 billion in 2011 to 6 billion annually by 2030 [1]. This will increase the frequency of transmission of communicable diseases [2] such as influenza [3], measles [4], SARS [5] and particularly tuberculosis (TB) during air travel [6].

The World Health Organization (WHO) issued a guideline on TB and air travel in 1998, and the third edition was published in 2008 [7], recommending that member states should conduct contact investigations for close contacts of not only smear-positive but also culture-positive TB patients, if the index case was diagnosed with multidrug-resistant TB. However, the guideline itself acknowledges that the available evidence for the risk of TB transmission during air travel and outcome data from passenger contact investigations are limited and it calls for a coordinated international approach to research, data collection, analysis and dissemination to strengthen the evidence base for operational decision-making and policy development. Moreover, a systematic review on contact investigations associated with air travel in 2010 argued that the evidence for TB transmission in commercial aircraft is limited and that there is reason doubt the value of actively screening air passengers for infection with *Mycobacterium tuberculosis* [8]. A more recent systematic review on the subject did not find any further evidence of TB transmission and concluded that the risk of TB transmission aboard aircraft seems to be very low [9].

The challenges in estimating risk of contracting TB infection associated with air travel include the difficulty of obtaining the appropriate evidence: (i) Contact investigation for air passengers is often complicated by the unavailability or reluctance of the airline companies to share the flight manifest and by the unavailability of contacts. (ii) Contacts may have been infected with TB in the past, e.g. those born in countries with a high burden of TB. (iii) The specificity of tuberculin skin testing (TST) used in most contact investigations is low, leading to high positivity among the contacts, e.g. 24% in data from the United States Centers for Disease Control and Prevention (US CDC) [10].

In Japan, the TB notification rate has declined in the past six decades from 698.4 per 100,000 population in 1951 to 17.7 per 100,000 population in 2013 [11], which is equivalent to the rate in Poland (17.6/100,000) and Estonia (18.4/100,000) in 2014 [12]. However, 8,000

Table 1

Results of questionnaire survey on tuberculosis contact investigations among air passengers, Japan, 2012–2015 (n = 651 IGRA-tested)

Reporting health offices	Initiator health offices[a]	Implementer health offices[b]
Number of health offices reported	17	70
Number of index TB cases	19	23
Number of flights involved in contact investigations	35	27
Median duration of flights in hours (range)	11 (6–12)	10 (7–12)
Number of eligible contacts[c]	942 (100%)	unknown
Number of eligible contacts reached[d]	580 (61.6%)	unknown
Number of eligible contacts screened for TB	574 (60.9%)	unknown
Number of eligible contacts tested with IGRA	523 (55.5%)	128

IGRA: interferon gamma release assay; TB: tuberculosis.

[a] Initiator health office: the health office that initiated the contact investigation.

[b] Implementer health office: the health office that implemented health screening for the contacts at the request of the initiator health office.

[c] Those contacts who had contact with the index cases outside the aircrafts were excluded.

[d] Number of eligible contacts reached is a sum of the number of eligible contacts screened and the number of eligible contacts who declined being tested.

smear-positive TB cases are still reported every year [13] and more than 65% of those involve persons aged 65 years or older, reflecting the ageing population. Therefore, incidents in which infectious, particularly elderly, TB cases travel by air unaware of their infectiousness, are not uncommon. On the other hand, almost all children and young adults are estimated to be uninfected [14-16], therefore the positivity among children and young adults could be used as a surrogate marker for the risk of contracting TB in contact investigations. The local governments of Japan usually comply with the WHO guidelines and conduct contact investigations for contacts of smear-positive index TB patients associated with air travel. However, in Japan, no literature has been published on the contact investigations associated with air travel and the outcomes of contact investigations have not been reported.

Interferon gamma release assays (IGRA) can diagnose latent TB infection more sensitively and specifically than TST because TST also reacts to Bacillus Calmette-Guérin (BCG) vaccination and the interpretation of TST results is likely to be ambiguous where BCG vaccination coverage is high [15-18]. Two IGRA are currently available in Japan, the T-Spot TB (T-SPOT; Oxford Immunotec, Abingdon, United Kingdom) and the QuantiFERON-TB Gold In-Tube assay (QFT-GIT, Qiagen, the Netherlands), and they are widely used in contact investigations, including those associated with air travel [19].

We conducted a questionnaire survey on air travel-associated TB contact investigations in the local health offices of Japan from 2012 to 2015, focusing on IGRA positivity among the contacts. The purpose of the study was to estimate the risk of TB transmission associated with air travel, particularly using the IGRA positivity among children and young adult contacts as the outcome indicator.

Methods

Case definition for contact investigation associated with air travel

An incident of infectious TB involving air travel was defined as an event in which the WHO guidelines for initiating contact investigations were met [7] and in which the local health offices decided to undertake an investigation. Events with an index case with smear-negative TB or unknown smear status, or with a flight duration shorter than 6 hours were excluded. Since in most of the contact investigations, only the flight time was available but not the ground delays after boarding or after landing, we decided that a flight duration of 6 hours or more would meet the definition of the total flight duration of 8 hours or longer stipulated in the WHO guideline.

Contact investigations of tuberculosis contacts in Japan

The practice of contact investigations of TB contacts in Japan is similar to that recommended elsewhere [20]. Briefly, once a TB case is reported to a local health office by a physician, a public health nurse of the health office where the patient lives visits the patient to conduct an interview about contacts. When the case is smear-positive, the health office initiates a contact investigation (initiator health office). When a contact is a resident of another health office's jurisdiction, the initiator health office requests the health office at the residency (implementer health office) to conduct health screening for the contact on its behalf. When a ministry of health of a foreign country requests the national TB programme (NTP) of Japan to conduct a contact investigation associated with air travel for a Japanese resident, the NTP asks the health office of the contact's residence to conduct health screening.

Table 2

Positivity of interferon gamma release assay among tuberculosis contacts during air travel, by age groups, Japan, 2012–2015 (n = 651)

Age group (years)	Contacts investigated	IGRA-positive contacts	IGRA positivity (%)a	95% LCL	95% HCL
0–14	20	0	0.0	0.0	16.8
15–24	46	1	2.2	0.0	11.5
25–34	139	1	0.7	0.0	3.9
35–44	140	3	2.1	0.4	6.1
45–54	115	6	5.2	1.9	11.0
55–64	86	6	7.0	2.6	14.6
65–74	70	7	10.0	4.1	19.5
75–84	13	0	0.0	0.0	24.7
Unknown	22	1	4.5	0.1	24.7
Total	**651**	**25**	**3.8**	**2.5**	**5.6**

HCL: higher confidence limit; IGRA: interferon gamma release assay; LCL: lower confidence limit.

[a] A Cochran-Armitage test revealed there was a statistically significant increasing trend between age group and positivity of IGRA test results ($p<0.0094$).

The health screening usually involves IGRA tests and, if indicated, a chest X-ray.

In contact investigations associated with air travel, the initiator health office usually obtains information from the airline company on seating positions of the index case as well as the contacts who were seated in the two rows in front of and behind the index case and on the contact details of the contacts. It then sends letters to the health offices where the contacts live to request health screening. When a contact is a resident of a foreign country, the initiator health office normally asks the NTP of Japan to coordinate the investigation with the ministry of health of that country.

Data collection

In November 2015, we sent a questionnaire to all 486 local health offices in Japan and asked whether they had conducted contact investigations associated with air travel from 2012 through October 2015. Those who conducted contact investigations as either an initiator or an implementer health office, or both, were further asked about the index cases and the outcomes of the contact investigations via a structured questionnaire. The data collection was conducted from late November 2015 through March 2016.

Data collected included characteristics of the index case (age group, sex, smear test result, presence of cough at diagnosis and a brief description of chest X-ray shadow), the boarded flights (flight numbers, destinations and duration), outcomes of the contact investigation, particularly the number of the eligible contacts defined as those who were on two rows in front of and behind the index case, the number of contacts screened for TB, including the number of the contacts with IGRA, and how many were positive in the IGRA. Those contacts who also had contact with the index case outside the airplane, such as family members or travel companions, were excluded.

Data entry

The data on the events were entered into Microsoft Excel. The events reported both from the initiator and the implementer health offices were sorted by the date of the flight, the flight number or the airline company, and the destination. When we found duplicated events, only the data reported from the initiator health offices were used. The events with unknown flight dates, unknown flight numbers or airline companies or unknown destinations were excluded.

Data analysis

The investigated contacts were pooled and classified by age groups, and the positivity was calculated as a whole, by age under 35 years and by age groups.

Statistical tests

A binomial estimation of the 95% confidence intervals (CI) was performed using R software (Version 3.01, The R Foundation for Statistical Computing, Vienna, Austria) to compare the IGRA positivity between the age groups.

Results

Of the 486 local health offices of Japan, 451 (93%) responded. Table 1 shows the overview of the questionnaire survey. A total of 17 health offices reported that they took the lead in one or more of the contact investigations on 19 index TB patients who boarded airplanes between February 2012 and September 2015. The median duration between the dates of the air travel and the TB diagnosis of the patients was 1 month, ranging from 1 to 4 months. The total number of eligible contacts the initiator health offices reported, excluding those who had contact with the index cases outside of the airplanes, was 942, of whom 574 (61%) were screened for TB and 523 (56%) had IGRA test results available. Six eligible contacts declined TB screening. Thus, the response rate (the sum of those who were screened and who declined, divided by the number of eligible contacts) was 62%. An additional 70 health offices reported that they implemented the contact investigations for one or more of the contacts of 23 index TB patients (requested by foreign countries and the health offices that did not respond in our study) and provided IGRA test results on 128 contacts.

Of the total 651 contacts, 25 (3.8%; 95% CI: 2.5–5.6) were positive for IGRA (Table 2). Among 205 contacts aged 0–34 years, two (1.0%; 95% CI: 0.12–3.5) were positive for IGRA. All of the 651 contacts were resident in Japan, however, details on their nationality were not known. The Cochran–Armitage test revealed that there was a statistically significant increasing trend towards a correlation between age group and positivity of IGRA test results ($p<0.0094$).

For eight contacts with negative IGRA test results reported by the implementer health offices, the information on flight date, flight route or flight number was not available, and we were unable to cross-check this with the information from the initiator health offices. Thus, we excluded the eight contacts from the database.

No contact developed TB disease after contact with a TB case on an airplane.

Discussion

We conducted a questionnaire survey on air travel-associated TB contact investigations conducted in Japan. We found that 3.8% of the contacts had positive IGRA test results, with the positivity among the child and young adult contacts being 1.0%, which is almost equivalent to the IGRA positivity in Japanese medical students with no previous risk of TB infection (0.85%) [15] and in healthy university students (0.90%) [16]. This suggests that the risk of contracting TB infection associated with air travel is minuscule.

This level of risk is consistent with published data (0–4%) from 1993 to 2008 [10,21-23] but much lower than the risk reported in the early 1990s (30%) [24,25].

There was a statistically significant increasing trend of IGRA positivity with older age. This might reflect accumulated TB infection in the past [26,27], particularly in the 1950s and 1960s when the TB notification rates in Japan were higher than 150 per 100,000 population [28], rather than recent TB infection associated with air travel. Even in the late 1970s, the TB notification rates were higher than 60 per 100,000 population [28]. We therefore believe that it is reasonable to exclude those aged older than 35 years when analysing the risk of TB associated with air travel in our study.

The reason why the risk of TB infection associated with air travel is minuscule is that most commercial aircrafts used for long-distance flights have installed good ventilation systems with air exchange rates of more than 10 times per hour [29] and HEPA filters [30], which are equivalent to the requirements for isolation areas of healthcare facilities in the US [31], reducing the risk of TB infection during air travel. We have collected the IGRA test results of more than 600 passenger contacts, enabling us to stratify them into age groups and analyse the data of the age group of 0–34 years-olds, who are least likely to have been infected with TB before the relevant air travel.

In addition, since the positivity of IGRA was used as the main outcome indicator for the contact investigation, the data we report here were more sensitive and specific than those obtained using TST, particularly for areas where BCG vaccination coverage is very high. As we obtained information on contact investigations of TB associated with air travel from almost all the health offices of Japan and included in this study, we believe that these data are representative of the risk of contracting TB infection during air travel to and from Japan.

However, our study has some limitations: Since most health offices did not conduct the IGRA tests for the contacts immediately after the contact with TB cases, we were not able to calculate conversion rates. Considering the delay between contact with a TB case, diagnosis of the TB case and initiation and implementation of the contact investigation by different health offices, we believe it would be next to impossible to conduct the first IGRA tests within two or three weeks of contact with a TB case, and thus this limitation is practically unavoidable.

Although we assumed that contacts younger than 35 years were almost naïve to TB infection before the relevant air travel, this may not have been the case. Combined with the unavailability of the IGRA conversion rates mentioned above, we may have overestimated the TB risk associated with air travel. However, considering the low IGRA positivity (1.0%) among children and young adult contacts, we believe the main conclusion would not change.

Because the study was a questionnaire survey administered to the health offices of Japan, it has additional limitations. Some health offices may not have reported having conducted air travel-associated contact investigations and thus may not be listed in our database. However, because we employed an inventory method to collect information on the contact investigations from both the initiator and the implementer health offices, including the central NTP unit, we believe that we have done our best to obtain an almost complete picture on air travel-associated contact investigations conducted in Japan.

The information some implementer health offices provided was incomplete and therefore excluded from the database, leading to a possible bias. However, considering that only eight contacts were excluded and that all of them were negative in IGRA, the potential bias is small and the IGRA positivity may be overestimated, but not underestimated. Finally, it should also be noted that the authors do not know the quality of IGRA tests conducted for the contacts at each health office.

From our findings, we believe that the WHO could narrow the criteria for initiating air travel-associated contact investigations to, for example, only smear-positive TB, as is recommended by the European Centre for Disease Prevention and Control (ECDC) in the risk assessment guidelines for infectious diseases transmitted on aircraft (RAGIDA) related to TB [32]. As the ECDC guideline further recommends, the infectiousness of the index case, such as transmission to household members or other close contacts, should be considered before initiating air travel-associated contact investigations [9]. As modelling studies suggest, the risk of contracting TB infection on an aircraft varies

from low to moderate and is highest in the rows closest to the index case [33]. Limiting the contact investigation to fewer passengers (within two seats surrounding the index case, rather than two rows) in the case of wide aircraft with many seats per row seems reasonable [9]. Countries with a high burden of TB should prioritise other, more important, activities [8].

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Conflict of interest

None declared.

Authors' contributions

MO wrote the protocol of the study, managed all the process of the implementation of the study, including the submission of the proposal to the ethics committee, writing the questionnaire, communications with the local health offices, entering the data into computer, analyses, and writing the manuscript. SK raised the research question, came up with the idea of conducting the questionnaire survey, and provided key inputs in the every step of the study procedure.

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