Review

Systematic review on tuberculosis transmission on aircraft and update of the European Centre for Disease Prevention and Control risk assessment guidelines for tuberculosis transmitted on aircraft (RAGIDA-TB)

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As a setting for potential tuberculosis (TB) transmission and contact tracing, aircraft pose specific challenges. Evidence-based guidelines are needed to support the related-risk assessment and contact-tracing efforts. In this study evidence of TB transmission on aircraft was identified to update the Risk Assessment Guidelines for TB Transmitted on Aircraft (RAGIDA-TB) of the European Centre for Disease Prevention and Control (ECDC). Electronic searches were undertaken from Medline (Pubmed), Embase and Cochrane Library until 19 July 2013. Eligible records were identified by a two-stage screening process and data on flight and index case characteristics as well as contact tracing strategies extracted. The systematic literature review retrieved 21 records. Ten of these records were available only after the previous version of the RAGIDA guidelines (2009) and World Health Organization guidelines on TB and air travel (2008) were published. Seven of the 21 records presented some evidence of possible in-flight transmission, but only one record provided substantial evidence of TB transmission on an aircraft. The data indicate that overall risk of TB transmission on aircraft is very low. The updated ECDC guidelines for TB transmission on aircraft have global implications due to inevitable need for international collaboration in contract tracing and risk assessment.

Background

Air travel has greatly increased in recent decades [1]. To guide countries and harmonise actions in case of potential tuberculosis (TB) transmission on an aircraft, the World Health Organization (WHO) published a first edition of guidelines on TB prevention and control in regards to air travel in 1998, which recommended informing passengers of the exposure with appropriate advice on follow-up. In 2006 and 2008 [2], updates that recommended more extensive screening of in-flight contacts of infectious TB patients followed the first edition. These changes were influenced by specific incidents. For example, in 2007, notable media attention was attracted by a case of a multidrug-resistant (MDR-) TB patient who flew on two long-haul flights [3-7]. In 2009 the European Centre for Disease Prevention and Control (ECDC) published their Risk Assessment Guidelines for Infectious Diseases Transmitted on Aircraft (RAGIDA) [8], where TB was included among 11 other communicable diseases. Compared with the WHO guidelines, RAGIDA-TB limited the extent of investigations. A subsequent systematic review found limited evidence of TB transmission and further challenged the premise for more intense contact investigation [9]. In 2013, ECDC conducted a stakeholder survey to assess the current overall RAGIDA guidelines in order to guide their further development. Based on the replies, a process to update several chapters of the guidelines, including the RAGIDA-TB chapter, was initiated [10]. This paper presents the results of the systematic literature review conducted to update the evidence base on the risk of TB transmission during air travel. It summarises the ECDC recommendations and discusses the major differences compared with other widely used TB and air travel guidelines.

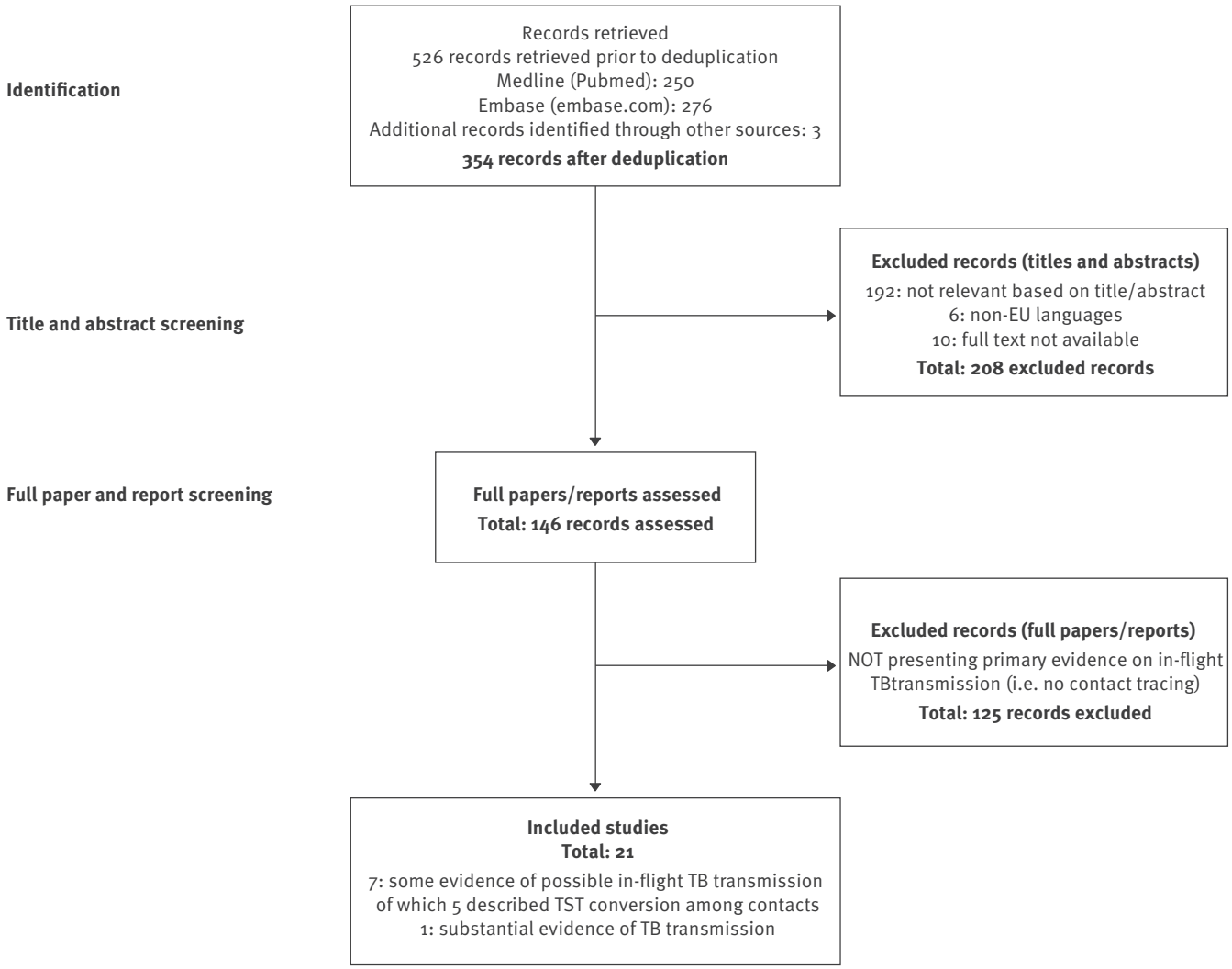
Methods

Literature search

Electronic searches identified primary evidence on TB transmission on aircraft from Medline (Pubmed) and Embase up to 19 July 2013. A general search of Cochrane Library identified relevant systematic reviews. No

Figure

Risk Assessment Guidelines for Infectious Diseases Transmitted on Aircraft (RAGIDA) tuberculosis literature search: study selection



language or date restrictions were applied. The search strategies are presented in the Box.

The titles and abstracts of all identified hits were filtered by two reviewers. Only human exposures in aircraft settings were retained. For records lacking abstracts, the full text of records with relevant titles was considered. Consensus between the two reviewers was reached on the records to be retained in the analysis. Subsequently, full texts of those abstracts chosen were evaluated in depth by one reviewer for primary evidence on TB transmission on aircraft. Additional records missed by the searches were detected in the lists of references of relevant records. The data extracted were: flight characteristics, such as origin, destination and type of aircraft, year of flight, total in-flight time including ground delay, total number of passengers; characteristics of the index cases such as age, sex, symptoms before and during the flight and at diagnosis, infectiousness, resistance profile of the isolate, and seating characteristics; country initiating passenger contact tracing, time period and strategy of contact tracing, total number of contacts and successfully traced contacts as well as contacts with positive test results and test converters. Records in non-European Union (EU) languages were excluded.

A possible event of in-flight transmission of TB was defined as: tuberculin skin test (TST) conversion (negative baseline result and a subsequent positive result eight weeks or more after exposure) or positive test for TB infection (TST or interferon-gamma release assay (IGRA)) with no other known previous TB exposure or risk factors for a positive test (such as Bacillus Calmette–Guérin (BCG) vaccination), diagnosed during a contact investigation eight weeks or more after TB exposure on an aircraft. The risk of transmission was estimated by calculating the proportions of converters and test-positive contacts (including the converters) without other risk factors among all tested passenger contacts. We calculated the proportion as indicator of transmission risk separately for incidents where the

Box

European Centre for Disease Prevention and Control (ECDC) risk assessment guidelines for tuberculosis transmitted on aircraft: literature search strategies, July 2013

Embase (embase.com)

#1 'aerospace medicine'/exp OR 'aircraft'/exp OR 'flight'/exp OR 'airplane crew'/exp OR 'airplane pilot'/exp OR 'aviation'/exp OR 'aero transport':ab,ti OR aircraft*:ab,ti OR aeroplane*:ab,ti OR airline*:ab,ti OR airplane*:ab,ti OR flight*:ab,ti OR aircrew:ab,ti OR airflight*:ab,ti OR aviation:ab,ti OR airport*:ti,ab OR aeroport*:ti,ab OR 'air port':ti,ab OR steward:ti,ab OR stewardess:ti,ab OR inflight:ti,ab OR 'in-flight':ti,ab OR 'cabin crew':ti,ab OR cabin:ti,ab OR cabins:ti,ab OR 'air-travel':ab,ti OR ((travel* OR transport* OR journey* OR trip OR trips) NEAR/4 air):ab,ti OR 'air-transport':ti,ab OR ((plane OR planes) AND (air OR travel* OR transport* OR journey* OR trip OR trips)):ti,ab OR ((passenger* OR crew OR traveller* OR personnel OR staff) NEAR/4 (flying OR air OR fly)):ab,ti

#2 'tuberculosis'/exp OR 'mycobacterium tuberculosis'/exp OR tb:ab,ti OR tuberculosis:ab,ti OR tuberculoses:ab,ti OR mtb:ab,ti OR tuberculous:ab,ti

#3 ('time-of- flight' AND spectrometry):ti,ab

#4 #1 AND #2

#5 #4 NOT #3

Limits: no limits

Results: 250

Medline (Pubmed)

#1 "Aerospace Medicine"[Mesh] OR "Aircraft"[Mesh] OR "Aviation"[Mesh] OR "Airports"[Mesh] OR aircraft*[tiab] OR aeroplane*[tiab] OR airline*[tiab] OR flight*[tiab] OR aircrew[tiab] OR airflight*[tiab] OR airplane*[tiab] OR aviation[tiab] OR airport*[tiab] OR aeroport*[tiab] OR "aero transport"[tiab] OR "air port"[tiab] OR steward[tiab] OR stewardess[tiab] OR inflight[tiab] OR "in-flight"[tiab] OR "cabin crew"[tiab] OR cabin[tiab] OR cabins[tiab] OR ((travel*[tiab] OR "Travel"[Mesh] OR transport*[tiab] OR journey*[tiab] OR trip[tiab] OR trips[tiab]) AND air[tiab]) OR ((plane[tiab] OR planes[tiab]) AND (air[tiab] OR travel*[tiab] OR "Travel"[Mesh] OR transport*[tiab] OR journey*[tiab] OR trip[tiab] OR trips[tiab])) OR ((passenger*[tiab] OR crew[tiab] OR traveller*[tiab] OR personnel[tiab] OR staff[tiab]) AND (flying[tiab] OR fly[tiab] OR air[tiab]))

#2 "Tuberculosis"[Mesh] OR "Mycobacterium tuberculosis"[Mesh] OR tb[tiab] OR tuberculosis[tiab] OR tuberculosis[tiab] OR mtb[tiab] OR tuberculous[tiab]

#3 ("time of flight"[tiab] AND spectrometry[tiab])

#4 #1 AND #2

#5 #4 NOT #3

Limits: no limits

Results: 276

Results without duplicates: 351

Date of searches 19 July 2013

contact-tracing strategy included all passengers and for cases where only five rows surrounding the index case were traced.

RAGIDA-TB update 2014

The relevant publications served as an evidence base for the RAGIDA-TB update by an expert group during a meeting in Stockholm in October 2013, coordinated by the ECDC. The data extracted during the systematic literature review were peer-reviewed by the expert group. The guidance document was finalised by the experts in the first quarter of 2014.

All decisions of the expert group were evaluated using GRADE criteria [11], considering: (i) quality of evidence; (ii) the balance between desirable and undesirable effects (whether the benefits are directed to the right group, i.e. the passengers suspected of having contracted TB infection); (iii) uncertainty or variability in values and preferences, i.e. whether the individuals (contacts) are willing to be screened for TB, and (iv) whether the intervention represents a wise use of resources.

Results

Literature search

The literature search retrieved 354 unique hits (Figure).

During the abstract screening stage 208 records were excluded (six based on title and keywords only). Ten records were discarded because their full texts were no longer available (nine were published in the 1950s or before, and one was published in 1995 but was not available from the publisher). At the full text screening stage, 125 records were discarded where the setting was not aircraft and/or population not human, i.e. not presenting data on contact tracing after in-flight exposure. Finally, 21 records (of which three were unindexed records that were detected by browsing in the lists of references of the records identified in the literature search) were retained [3,4,12-30]. Within these 21 records, 27 flights were described where contact tracing was initiated following a potential TB transmission from a passenger, and three records presented aggregated data from the United States, Canada and the United Kingdom (UK) on 252 flights [28-30]. Furthermore, three incidents where the index case was a crew member were described [15,23,24]. Ten of the 21 records [3,4,12,17-19,24,28-30] had not been included in the 2009 version of RAGIDA-TB [8]. A summary of the extracted data is presented in Table 1.

In 14 of the 21 studies, no evidence of in-flight TB transmission was identified. Seven of the 21 studies [15,16,21,24-26,29] presented some evidence of possible in-flight transmission. All flights had lasted more than eight hours. Five of these articles [15,16,21,26,29] described TST conversion among contacts.

Table 1 a

Summary of evidence on tuberculosis (TB) transmission on aircraft, systematic review 2013 (n=21 studies)

Study	Number of flights	Flight duration (h)	Contact tracing strategy	Infectiousness during the flight	Resistance profile of isolate	Total number of aircraft contacts	Number of aircraft contacts tested/ results available (% of all contacts)	Positive contacts/ converters	Converters	Positive contacts including converters/ converters possibly infected during the flight, with no other risk factors for TB infection positivity	Other information on positive contacts possibly infected during the flight
Kim 2012 [17]	1	>8	5 rows	Smear-positive, cavitary disease	Not known	15	2 (13)	0	0	No	No
Thibeault 2012 [24]	Crew member flying for 1 month	NA	Crew	Smear-positive, cavitary disease	Not known	56	32 (57)	6	Not known	6/0	6 TST-positive crew members of whom 4 tested with IGRA ⇢ 1 positive Country of origin not known Age: two contacts<45 y, 4 contacts 45 y or older
Lynggaard 2011 [19]	1	12	5 rows	Smear-positive	DS-TB	28	22 (79)	1	0	No	No
Scholten 2010 [30]	109[a]	Aggregated data	5 rows	Culture-positive	Aggregated data	Not known	Not known	Not known	Not known	No	No
Marienau 2010 [29]	131	≥8	5 rows	Pulmonary/ laryngeal TB without adequate treatment	Aggregated data	4,638	758 (16)	182	8	12/1	Passengers seated in the same row or within 2 rows Not originating from a high TB prevalence country, ages not known
Kornylo-Duong 2009 (1) [18]	2	14/15	5 rows	Smear-positive, cavitary disease	MDR-TB	79	45 (57)	16	3	No	No
Kornylo-Duong 2009 (2) [18]	2	7.5	5 rows	Smear-positive, cavitary disease	DS-TB	78	26 (33)	0	0	No	No
Chemardin 2007 [14]	1	5	5 rows	Smear-positive, severe cough	XDR-TB	11	3 (27)	0	0	No	No
Abubakar 2008 [28]	11	≥8	5 rows	Aggregated data	Aggregated data	Not known	2 (not known)	0	0	No	No
Buff 2008/ECDC 2007 [3,4]	2	>8	5 rows	Smear-negative	MDR-TB	72	54 (75)	21	0	No	No

DS: drug-susceptible; IGRA: interferon-gamma release assay; MDR: multidrug-resistant; NA: not applicable; TB: tuberculosis; TST: tuberculin skin testing; US: United States; y: years; XDR: extensively drug-resistant.

[a] 110 in the article, but one of the incidents has been published separately [3,4].

Table 1 b

Summary of evidence on tuberculosis (TB) transmission on aircraft, systematic review 2013 (n=21 studies)

Study	Number of flights	Flight duration (h)	Contact tracing strategy	Infectiousness during the flight	Resistance profile of isolate	Total number of aircraft contacts	Number of aircraft contacts tested/ results available (% of all contacts)	Positive contacts/ converters	Converters	Positive contacts including converters/ converters possibly infected during the flight, with no other risk factors for TB infection positivity	Other information on positive contacts possibly infected during the flight
Whitlock 2001 [27]	2	8	Same cabin section/all passengers and crew	Smear-positive, cavitary disease	DS-TB	238	142 (60)	24	4	No	No
Wang 2000 [26]	1	14	All passengers and crew (Taiwan residents)	Smear-positive, cavitary disease	Not known	308	212 (69)	193	9	3/3	Passengers seated at a distance of at least 12 rows from the index case Resided in Taiwan, ages 55–57 years
Parmet 1999 [23]	Crew member, contact exposure time 8–60 hours	NA	Crew	Not known	Not known	48	38 (79)	0	0	No	No
Vassiloyanakopoulos 1999 [25]	1	>8	All passengers and crew	Smear-positive	Monoresistant TB	148	7 (5)	1	0	1/0	Passenger with positive baseline test<12 weeks after exposure, exact time of testing or seating in relation to index case not known
Beller 1996 [12]	1	2.5	All passengers and crew	Smear-positive	DS-TB	12	9 (75)	0	0	No	No
Kenyon 1996 [16]	4	8/2/2/9	All passengers and crew with known US or Canadian residence	Smear-positive, cavitary disease	MDR-TB	1,042	760 (73)	29	6	6/4	2 converters and 2 positive contacts seated within two rows Countries of origin not known Ages 36–55 years

DS: drug-susceptible; IGRA: interferon-gamma release assay; MDR: multidrug-resistant; NA: not applicable; TB: tuberculosis; TST: tuberculin skin testing; US: United States; y: years; XDR: extensively drug-resistant.

Table 1 c

Summary of evidence on tuberculosis (TB) transmission on aircraft, systematic review 2013 (n=21 studies)

Study	Number of flights	Flight duration (h)	Contact tracing strategy	Infectiousness during the flight	Resistance profile of isolate	Total number of aircraft contacts	Number of aircraft contacts tested/ results available (% of all contacts)	Positive contacts/ converters	Converters	Positive contacts including converters/ converters possibly infected during the flight, with no other risk factors for TB infection positivity	Other information on positive contacts possibly infected during the flight
Miller 1996 [21]	2	8.5/1.5	All passengers and crew	Smear-positive	DS-TB	219	120 (55)	34	5	No	All positive passenger contacts had other risk factors, but TST positivity was associated with sitting within 1 row.
Moore 1996 [22]	2	1	All passengers and crew with known US residence	Smear-positive, cavitary and laryngeal disease	DS-TB	227	100 (44)	5	Not known	No	No
CDC 1995 [13]	5	0.5/3/9/3/0.5	All passengers with US residence	Smear-positive, cavitary disease	Not known	753	109 (14)	24	Not known	No	No
Driver 1994 [15]	Crew member flying during 6 months	NA	Crew members and frequent flyers who flew with the index case	Smear-positive, cavitary disease	DS-TB	345	271 (79)	27	2	6/2	2 crew members converted, 4 frequent flyers positive. Crew members both from US, ages not known Passengers from Northern America, ages not known
McFarland 1993 [20]	1	8	All US citizens (passengers and crew)	Smear-positive, cavitary disease	MDR-TB	343	79 (23)	8	Not known	No	NA
Total	**279**	**NA**	**NA**	**NA**	**NA**	**8660**	**2791**	**571**	**37**	**34/10**	**NA**

DS: drug-susceptible; IGRA: interferon-gamma release assay; MDR: multidrug-resistant; NA: not applicable; TB: tuberculosis; TST: tuberculin skin testing; US: United States; y: years; XDR: extensively drug-resistant.

In two of the studies [15,24] the index case and the contacts positive for TB infection were crew members, and it was not possible to exclude transmission on the ground (before and after the flight when the aircraft ventilation system is not in full-function mode as well as outside the aircraft). However, in one of these papers [15] TB transmission from the index case to passengers was implied. In five other studies [16,21,25,26,29] with possible TB transmission, the index case was a smear-positive passenger (i.e. sputum sample positive for acid-fast bacilli in microscopic examination). In the study by Wang et al. [26], three converters with no prior TB exposure or BCG vaccination were found among 212 passenger contacts. However, all of them had been seated at least 15 rows away from the index case and an in-flight transmission does not seem probable. Vassiloyanakopoulos et al. [25] found one passenger contact with a positive TST, but the infection could have been acquired before the flight. The study from Marienau et al. [29] presented aggregated data from 131 flights where contact tracing was initiated following a suspected TB transmission. Test results were available for 758 contacts, including one TST converter and 11 other positive contacts with no risk factors for prior TB infection.

Only one study provided substantial evidence of TB transmission [16]: Six test-positive passengers with no other risk factors for test positivity, including four TST converters, were seated in the same aircraft section as the index case [16]. Four of these six test-positive passengers (including two TST converters) had been seated within two rows of the index patient, and two others reported having frequently visited friends during the flight who were seated very near the index patient. In addition, the index case had transmitted the disease to several household contacts before air travel. In the study by Miller and colleagues [21], all 34 test-positive contacts, including five converters, could be somewhat likely explained by BCG vaccination or prior exposure to TB in TB-endemic countries, but TST positivity was associated with sitting within one row's distance from the index case. No case of active TB following transmission on an aircraft has so far been reported.

One of the records identified included a smear-negative index case [3,4]. No evidence on transmission of the disease to other passengers or close contacts could be found. In six studies describing results of 10 contact investigations the index case was infected with an MDR or extensively drug-resistant (XDR) strain [3,4,14,16,18,20], however, only one flight provided evidence that transmission had possibly occurred [16]. An IGRA test was used in only three of the records. Thibeault et al. [24] found one IGRA-positive crew member among four that were tested, and Lynggaard et al. [19] reported one positive passenger among 16 who were tested with IGRA, and who was likely not to have contracted the infection during the flight. In one of the records [18] IGRAs were used but not reported separately from TSTs. Only one incident was found where the contact tracing had been started more than three months after the flight [18]. The type of aircraft was reported in seven of the 21 records [16,19,21-23,26,27] comprising 12 flights. On six of the aircraft a high-efficiency particulate air (HEPA) filter was used (data not shown).

Estimation of the risk of transmission

Pooling the data from the records identified in the literature review where the contact tracing strategy included all passengers and crew [12,16,20-22,25,26], among a total of 1,287 aircraft contacts for whom a test result was available, 10 (0.8%) passengers were possibly infected during the flight (positives with no other risk factors for test positivity), seven (0.5%) of whom had a TST conversion. For incidents where only five rows surrounding the index case were traced [3,18,19,29], among a total of 905 aircraft contacts with test results, 12 (1.3%) passengers were possibly infected during the flight (positives with no other risk factors for test positivity), one (0.1%) of whom had a TST conversion. It should be noted that there were notable differences in proportions of contacts tested and diagnostic schemes, so these figures are only an estimate. Main reasons for unavailability of TB testing results were insufficient contact information, lost to follow up, residence in a foreign country and previous TB infection positivity. In addition, the infectiousness of the index patients varied across the records (see Table 1).

Discussion

Literature review

Based on currently available evidence, the risk of TB transmission during air travel is very low. In our study a rough estimate of 0.1–1.3% of aircraft contacts in long-haul flights (›eight hours) might have contracted the infection from a sputum-smear-positive index case. The risk of infection seems to be the highest among passengers seated within two rows of the index case.

In the studies performed before 2007, all passengers and crew were considered as contacts whereas in more recent studies only five rows in the proximity of the index case have been screened. The latter strategy has given a somewhat better yield of test-positive contacts (0.8% and 1.3%, respectively). Our estimates are likely biased due to the heterogeneity of the data. National authorities may have more success in tracing and testing contacts who are national residents. This will not necessarily alter the yield of the tested passengers but may alter the effectiveness of reaching all contacts. It is likely that the prevalence of test positivity before the flight is underestimated, and the transmission risk hence overestimated. In addition, in half of the studies it was not specifically mentioned whether household/close contacts were travelling with the index case and excluded from the results of the passenger investigation. If infected close contacts were included in the

Table 2

Comparison of criteria for risk assessment in European Centre for Disease Prevention and Control, World Health Organization, and Centers for Disease Control and Prevention guidelines on tuberculosis transmission on aircraft

	ECDC/RAGIDA 2014 [35]	ECDC/RAGIDA 2009 [8]	WHO 2008 [2]	CDC 2012 [17]
Infectiousness	Same as in 2009	Infectious pulmonary TB (smear-positive in spontaneous or induced sputum or bronchoalveolar lavage).	**Infectious TB**: all cases of respiratory (pulmonary or laryngeal) TB which are sputum smear-positive and culture-positive (if culture is available). **Potentially infectious TB:** all cases of respiratory (pulmonary or laryngeal) TB that are sputum smear negative and culture positive (susceptible, MDR-TB or XDR-TB). Additional information should be requested to conduct a risk assessment and determine whether a contact investigation should be considered.	Diagnosis of the index case was confirmed by sputum culture or nucleic acid amplification AND is: (i) sputum smear-positive for acid-fast bacilli AND cavitation is present on a chest radiograph; OR (ii) confirmed to have a multidrug-resistant isolate (regardless of the smear or chest radiograph. results).
M/XDR-TB	Same as 2009 Additionally, the infected contacts should be given advice on what actions to take if symptoms develop, such as informing the treating physician of the possibility of infection with a MDR strain.	No special considerations, the risk of infection of passengers with M/XDR-TB should be assessed using national guidelines.	Consequences of transmission of an M/XDR strain should be included in the risk assessment.	Stricter for MDR-TB (see previous row)
Pre-travel	Same as WHO 2008 Risk of infection of passengers with M/XDR-TB should be assessed using national guidelines.	Patients with confirmed infectious pulmonary TB should avoid air travel. If unavoidable, a specific travel protocol should be agreed upon. Risk of infection of passengers with M/XDR-TB should be assessed using national guidelines.	People with infectious or potentially infectious TB should not travel by commercial air transportation on a flight of any duration.	Not specifically mentioned
Evidence of transmission	Same as 2009 Additionally, if previous contact investigation results cannot be obtained despite considerable efforts, the tracing should be initiated only in exceptional circumstances.	Evidence of transmission to other contacts (refers to cases with evidence of transmission in household or other close contacts).	Documented transmission to close contacts is one of the criteria to consider in the risk assessment to decide whether a contact tracing is initiated if index case is classified as 'potentially infectious'.	Considered only in exceptional cases
Flight duration	Same as 2009	≥8 h (including ground delays)	Total flight duration ≥8 h (including ground delays after boarding, flight time and ground delays after landing)	≥8 hours gate-to-gate (including boarding and deplaning time or delays on the tarmac)
Time passed since flight	Same as 2009 Additionally, relevant national authorities may consider longer time lags in specific cases.	Time to diagnosis less than three months	3 months before notification	Index case was diagnosed within 3 months of the flight AND the flight occurred within 3 months of notification
Contacts to suggest screening to	Same as 2009. Addition: for wide aircrafts, only contacts seated within two seats may be included	Contacts seated in the same row, two rows ahead and two rows behind the index case	Contacts seated in the same row, two rows ahead and two rows behind the index case	Contacts seated in the same row, two rows ahead and two rows behind the index case
Special considerations for susceptible groups	Same as 2009	If tracing initiated, special efforts should be made to trace particularly susceptible contacts, such as children/infants.	Timely medical examination, radiograph & follow-up regardless of the TST	Not specifically mentioned

CDC: Centers for Disease Control and Prevention; ECDC: European Centre for Disease Prevention and Control; RAGIDA: Risk Assessment Guidelines for TB Transmitted on Aircraft; MDR-TB: multidrug-resistant tuberculosis; WHO: World Health Organization; XDR-TB: extensively-drug resistant tuberculosis.

flight-related contact tracing, a yield towards a higher risk value could have been obtained.

Additionally, the quality of all the evidence that we found varied from low to very low, due to the fact that it is generated only via observational studies with several types of challenges, such as lack of timely acquisition of passenger contact details and patient follow-up. Indeed, several studies highlighted the difficulty of obtaining complete passenger contact information [14,20,25]. Abubakar et al. found no association between notification delay from the date of flight to the notification to a public health authority within the range of 21 to 61 days and the availability of information from airlines (England and Wales 2007–2008) [28]. In Canada, availability of adequate passenger contact information from the airlines improved between 2006 and 2008 [30]. The approaches taken in the studies varied from descriptions of isolated incidents to routine data collection over several years. It can also be speculated that publication bias favours the studies where possible flight-related infections have been found and that published data represent a very small proportion of real exposure of travellers on aircraft since many countries may not carry out flight-related TB screening, or do not publish the results.

Marienau et al. estimated the in-flight TB transmission risk for contacts within two rows to vary between 1.1% and 24% using a large US dataset including 131 contact investigations with 758 passenger contacts tested [31]. However, a large proportion of the passengers considered to have contracted TB infection on an aircraft had other risk factors for TB infection or held a passport from a high-incidence country [29], so these risk rates might be overestimated. In a systematic review performed by Fox et al., the prevalence of latent TB infection among close contacts of TB patients (including other than smear-positive cases) in all types of settings was shown to be 28% in high-income environments and 45% in low- and middle-income environments, and 19% among casual contacts of TB cases in high-income settings [32]. This implies that the transmission risk of TB infection in aircraft is substantially lower than that in other settings. Although smear-negative patients have been shown to contribute to TB transmission rates in other settings [33], our literature search did not identify any in-flight transmission from smear-negative patients.

In two contact investigations the risk of acquiring TB infection during the flight was associated with sitting within two rows of the index case [16,21]. No new evidence concerning the number of rows/seats that should be screened was found to have been published after the launch of the first RAGIDA-TB guidelines in 2009. Most modern aircraft that re-circulate cabin air are equipped with HEPA filters although for small jets typically used on short-haul flights it is less common [34]. All the types of aircraft used on flights exceeding eight hours that were mentioned in the records included in the literature review were relatively recent models where HEPA filters were likely to have been employed. The cabin air flows downwards from the overhead outlets, limiting the potential exposure from a TB patient to the close environment [2].

It can also be noted that under a prospective literature search monitoring undertaken after the revision of the RAGIDA-TB and until 31 December 2015, using the same criteria, 23 new records were identified. None of these contained additional primary evidence on TB transmission on aircraft, and so no new records would have been included in an analysis extending to 31 December 2015.

RAGIDA-TB update 2014 and comparison to World Health Organization and United States Centers for Disease Control and Prevention guidelines

An overview of modifications to the second edition of RAGIDA-TB is presented in Table 2. The RAGIDA-TB document with the complete risk assessment algorithm is available [35].

In regards to GRADE criteria, all decisions were based on evidence supplemented by expert opinion. The RAGIDA-TB 2013 expert group agreed that all modifications serve the best interest of the exposed passengers, balancing the chances of doing good with the chances of unnecessary testing while using resources wisely [11]. The expressed will of the exposed passengers, however, could not be assessed and is likely to vary substantially.

The evidence indicates that airline passengers exposed to a TB patient should not be considered as close contacts but rather as belonging to the second circle of contacts that is examined only if transmission to close contacts has occurred, following the principle of concentric circles of exposure [36]: A virtual ‘first circle’ of the most intensively exposed contacts is defined (usually reserved for prolonged contacts such as persons living and sleeping in the same room or under the same roof); one or more ‘outer’ circles with less exposed contacts are defined, with contacts to be investigated only if infected persons are found in the next inner circle. In view of the specificities of ventilation of modern passenger aircraft (air flow from roof to bottom in each segment, HEPA filters), which constantly removes air-borne particles and the limited amount of time spent even on long-haul flights, aeroplane passengers should not be considered to be in the innermost circle.

In support of this, the only study that provided considerable evidence on TB transmission occurring during air travel [16] reported that the index case had also transmitted the disease to closer contacts. However, in practice it can be difficult to obtain reliable information on the index case’s contact tracing results, and in many countries contact tracing is not carried out even for close contacts. Results of contact investigation may

only become available months after diagnosis and the discovery that the patient has been on a flight. In case this information cannot be obtained despite considerable efforts or will become available only later, contact tracing should be initiated only in exceptional circumstances.

In the scope of suspected in-flight transmission of TB, only cases with positive smear microscopy should be considered infectious. As there is no evidence of higher infectiousness of MDR-TB strains [37,38], the risk assessment for infection should be the same as for susceptible strains. However, as the potential consequences of an M/XDR-TB infection are more severe, the risk of transmission should be assessed using national guidelines. Individuals found to be potentially infected after exposure to an M/XDR-TB strain should be advised to inform the treating physician about the resistance status in case symptoms develop.

RAGIDA-TB recommends that contact investigations among passengers are initiated only if the index case is diagnosed within three months after the flight, due to the difficulties of assessing infectiousness at the time of the flight, interpreting test results to determine recent vs remote infection, and obtaining passenger travel and seating information [2,35]. The consideration of time passed between the flight and notification of the incident is left to the discretion of the relevant authorities; however, it should be kept in mind that the longer the notification delay, the poorer the results of the contact tracing will be. In addition, there is a possibility that the infection may have already progressed to active disease. The first edition of the 1998 WHO guidelines set the three-month limit on the grounds that information becomes more difficult to obtain after this time.

The recommended strategy for contact tracing in RAGIDA-TB follows the WHO guidelines [2], encompassing the passengers seated in the same row as the index case, and those two rows in front and two rows behind. Modelling studies have shown that the risk of contracting TB infection on an aircraft varies from low to moderate, and is the highest in the rows closest to the index case [39,40]. Based on the RAGIDA-TB 2013 expert group's opinion, the updated RAGIDA guidelines suggest, as a possibility to consider, limiting the contact investigation to fewer passengers (within two seats surrounding the index case instead of two rows) in the case of wide aircraft with many seats per row. If particularly susceptible individuals, such as infants and children, are identified among the contacts, special efforts should be given to trace them. Other particularly susceptible individuals among the passenger contacts, such as HIV-positive and diabetic persons, are usually impossible to identify. If this information is available, these contacts should be prioritised as is done with infants and children.

Table 2 compares the risk assessment guidelines for TB transmission on aircraft between RAGIDA-TB, WHO and CDC. The three sets of guidelines share many similarities in terms of criteria for initiating contact tracing, such as minimum flight duration and contact screening strategy. In addition, all three guideline documents stipulate that patients with untreated smear- or culture-positive pulmonary TB should not travel by air.

In contrast to the other two sets of guidelines, RAGIDA-TB recommends contact tracing only if there is already evidence of transmission from the smear-positive index case to close contacts outside of the aircraft setting, as discussed above. While WHO recommends assessing the risk of transmission to passengers from infectious (sputum and culture positive) as well as potentially infectious (culture-positive but smear-negative) patients, RAGIDA-TB only considers index cases that are positive by microscopy in spontaneously produced or induced sputum or bronchoalveolar lavage. Further, the CDC guidelines recommend that for index cases with MDR-TB, contact tracing should be performed even for smear-negative patients.

The CDC guidelines were revised in 2011 [17]. According to the updated criteria, contact investigations should be initiated if the index case is smear and cavitation positive, whereas in the previous 2008 CDC guidelines only smear-positivity was required. In addition, the maximum time elapsed between flight and notification has been shortened from six months to three months. The revision therefore results in a smaller number of contact investigations. The comparative public health risk of the effects of the revision has been analysed against benefits of cost savings, concluding that the more exclusive protocol imposes minimal risks to public health while requiring only half of the costs and is more beneficial from both epidemiological and economic perspectives [31,41].

According to the UK National Institute for Health and Care Excellence (NICE) guidelines contact tracing of passengers should not be undertaken routinely [42]: instead, the passengers seated close to the index case should be provided with information on the risk of TB and what actions to take if symptoms develop. To our knowledge, the guidelines issued by Public Health Agency of Canada are the most stringent; according to these, contact investigation is initiated even in the case of smear-negative index patients when there are no data available to indicate that transmission did not occur in non-flight contacts [43]. In addition, the contact investigation should be started regardless of the time passed between the flight and the notification of the incident, and for cases of MDR, XDR and laryngeal TB regardless of duration of the flight if there is insufficient data to exclude transmission to non-flight contacts.

Conclusions

This systematic literature review compiled the most up-to-date evidence base on transmission of TB during air

travel. We identified observational studies providing only low-quality evidence, but it can still be concluded that the risk of TB transmission on aircraft seems to be very low. Despite the lack of good quality data, the RAGIDA-TB 2013 expert group concluded that this is not a research gap that should be prioritised and TB research resources are better directed elsewhere.

The RAGIDA-TB update resulted in clear and evidence-focused guidelines which will help to use resources in an effective way [35]. These guidelines provide a clear framework for risk assessment but leave room for flexibility in unusual cases. There is notable variation and opportunities remain for improvement via harmonisation between different national and supranational TB guidelines for risk assessment of transmission on aircraft.

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Conflict of interest

None declared.

Authors' contributions

Study concept and design: I. Abubakar, L. Payne Hallström, S.M. Kotila. Analysis and/or interpretation of the data: all authors. S.M. Kotila had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.M. Kotila and L. Payne Hallström reviewed the records found in the literature search to select the relevant records. All authors had access to the extracted data. Drafting of the manuscript: S.M. Kotila. Revision of the manuscript for important intellectual content: I. Abubakar, L. Payne Hallström, P. Helbling, N. Jansen.

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