Effectiveness and outcomes of air travel-related TB incident follow-up: a systematic review

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The evidence behind criteria for initiating airplane tuberculosis contact tracing is weak. It has been widely demonstrated that active screening is labour-intensive and unlikely to be effective. Formal, comprehensive contact tracing may be of limited utility. https://bit.ly/2U1ebHI

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ABSTRACT The World Health Organization (WHO) recommends following up passengers after possible exposure to a case of infectious tuberculosis (TB) during air travel. This is time-consuming and difficult, and increasingly so with higher numbers each year of flights and passengers to and from countries with high TB endemicity. This paper systematically reviews the literature on contact tracing investigations after a plane exposure to active pulmonary TB. Evidence for in-flight transmission was assessed by reviewing the positive results of contacts without prior risk factors for latent TB.

A search of Medline, EMBASE, BIOSIS, Cochrane Library and Database of Systematic Reviews was carried out, with no restrictions on study design, index case characteristics, duration of flight or publication date.

In total, 22 papers were included, with 469 index cases and 15 889 contacts. Only 26.4% of all contacts identified completed screening after exposure. The yield of either a single positive tuberculin skin test (TST) or a TST conversion attributable to in-flight transmission was between 0.19% (95% CI 0.13%–0.27%) and 0.74% (95% CI 0.61%–0.88%) of all contacts identified (0.00%, 95% CI 0.00%–0.00% and 0.13%, 95% CI 0.00%–0.61% in random effects meta-analysis). The main limitation of this study was heterogeneity of reporting.

The evidence behind the criteria for initiating investigations is weak and it has been widely demonstrated that active screening of contacts is labour-intensive and unlikely to be effective. Based on our findings, formal comprehensive contact tracing may be of limited utility following a plane exposure.

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Introduction

Air travel has become a common and increasingly popular form of transport, with ~4.1 billion passengers worldwide in 2017. The number of people taking long-haul flights to and from countries with high endemicity of tuberculosis (TB) is also expanding [1]. This increases the likelihood of passengers on aircraft coming into contact with patients with infectious pulmonary TB. The World Health Organization (WHO) recommends passenger follow-up after possible TB contact as an important control measure [2]. WHO guidelines state that the four criteria which should initiate a contact tracing investigation are a flight of ⩾8 h, an index case who is culture positive, that no more than 3 months has elapsed between the incident and notification, and that only contacts sat within two rows of the index case be notified.

Contact tracing passengers on flights after possible exposure to a case of infectious TB can be a difficult and time-consuming process [3]. Contact tracing is well established in low-prevalence countries as an effective control strategy after household and occupational exposure [4]. This paper systematically reviews the literature on contact tracing passengers after exposure to TB on flights, including new studies that have been published since the European Centre for Disease Prevention and Control (ECDC) "Risk Assessment Guidelines for Infectious Diseases transmitted on Aircraft" (RAGIDA) report to inform future policies with respect to contact tracing after air travel [5]. The results are discussed in light of the WHO guidelines and the evidence upon which they are based [2].

The recommendation that only exposures on flights lasting ⩾8 h should be followed up has been consistent in all the WHO guidance since the first one was published in 1998, and is based on two studies [6–8]. Driver *et al.* [6] carried out a cohort study investigating the transmission risk from a flight attendant to fellow crew members over a 6-month period. The results revealed that increased flying time was a strong predictor of a positive tuberculin skin test (TST) in the contacts, and that all but two of the contacts included had at least a 14-h exposure to the index case. Kenyon *et al.* [7] reported a study of an index case with advanced pulmonary TB who travelled on several flights of different durations over the course of a month, taking the last flight 2 weeks before dying of the disease. Four contacts on the last flight that she took, of 8 h duration, had a TST conversion after the flight. The 8-h rule has been repeated in later versions of the WHO guidance, but these two studies are unlikely to be typical of in-flight exposures, because one involved crew members and the other involved an index case with extremely advanced disease.

The principle objective of this review was to assess the yield of a positive TB screening test found among passengers who had been exposed to active TB on an aircraft, and whom had not previously had risk factors for latent TB. This included both TSTs and interferon-γ release assays (IGRAs). Secondary objectives were to assess the overall yield of positive TB screening results in the same population, and to calculate the proportion of those passengers who completed screening. A sub-analysis was performed to determine whether there was any difference in transmission between flights lasting more or less than 8 h.

Methods

A systematic search of Medline, EMBASE, BIOSIS, Cochrane Library and Database of Systematic Reviews was carried out on March 7, 2019, to identify journal articles relating to TB contact tracing investigations following in-flight exposure. Key conference abstracts from the last 5 years (American Thoracic Society, British Thoracic Society, The Union World Conference on Lung Health, European Respiratory Society Congress) were searched separately, along with grey literature and published guidelines. There were no restrictions on study design, index case characteristics, duration of flight or publication date. Reference lists of included studies and relevant systematic reviews were hand-searched, and included studies were cross-checked to identify any further references not captured by the search. Two authors independently screened titles, abstracts and full texts.

Eligible studies for the systematic review reported on the results of contact tracing investigations following exposure to a case of active pulmonary TB on an aircraft. This included case reports and collective retrospective reviews. In cases where incidents had been reported twice by both the Centers for Disease Control and Prevention (CDC) and the individual authors, the latter have been presented. Studies were excluded if they did not involve TB exposure on a flight.

Data were extracted by two authors. These included index case and flight details, screening methods, contact success rates and subsequent results. These data were aggregated to form a total value across those studies that reported on each variable. Proportions of the total number of contacts identified who were notified, completed screening, had results available, had positive results and were without risk factors for latent TB infection (LTBI) were calculated to provide a "screening" cascade. Risk factors were taken into account to assess the evidence specifically for in-flight transmission. Where no value was available for the proportion notified or who completed screening, we estimated a best and worst case scenario and assigned a value of 0% or 100% to provide the lowest and highest possible estimates for those steps. The highest

estimates were used to graph the results. We employed a random effects meta-analysis with Freeman–Tukey double arcsine transformation in Stata using the "metaprop" command to account for between-study heterogeneity [9]. This provided an adjusted pooled proportion along with 95% confidence intervals for each stage in the cascade. To give a broader view of potential transmission, the total number of positive test results to which known LTBI risk factors could have contributed were divided into quartiles from no impact on positive results to accounting for 100% of the positive results.

Screening results were extracted for cases for which a single screening test was reported as well as for which baseline and repeat testing had been carried out to assess for TST conversion. Conversion of an initial baseline negative TST immediately following a plane exposure to a positive TST result after the lag phase of the development of cell-mediated immunity provides more reliable information on whether the plane exposure resulted in transmission than a single-point positive test result. The WHO quotes demonstration of TST conversion in recent contacts of active pulmonary TB as best practice [10]. However, given that many studies used a single screening method to report on risk following aircraft exposure, all positive results here have been aggregated to give the highest possible estimate of overall risk. This represents the upper limit of possible transmission on which decisions about the rationale for screening could be based. Data were extracted on the number and proportion of contacts with positive screening results and their risk factors for latent TB, as specified by the authors, to give added information for that estimate. In individuals for whom the risk factors for latent TB were not known, a range was calculated based on the assumption that all and none of those individuals had risk factors.

Flights were stratified into those of <8 h duration and those of >8 h duration. Studies reporting multiple flights of different durations have been included where the screening results were reported separately. Studies including flights of different durations where the screening results could not be disaggregated were excluded from this analysis. The positive screening results were analysed as a proportion of screening results available, rather than all contacts identified or notified, given that the latter were rarely available by individual flight. A range was calculated based on the assumption that all and none of the contacts with positive results had risk factors for latent TB.

Studies were stratified into two groups depending on whether a single or repeat test was used, and the proportions of contacts completing screening calculated using the "metareg" command in Stata following arcsine transformation.

Two different authors assessed all included studies for quality using the Risk of Bias Assessment Tool for Nonrandomised Studies [11]. The results are reported as per the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols 2015 statement [12].

Results

Papers

We retrieved 657 citations in total. Of the 488 potentially relevant unique citations, we excluded 410 after review of the title and abstract (figure 1). Of the remaining 78 papers selected for full text review, 56 were excluded because they did not contain data on contact tracing investigations, and 22 papers were included (table 1 and supplementary table S1) [3, 6, 7, 13–31]. One paper contained six separate reports of contact investigations by the CDC, four of which were subsequently published as separate studies and are included separately [6, 7, 16, 17, 23]. The publication years ranged between 1993 and 2017.

Of the included papers, 11 studies were case reports of a single passenger index case and three reported results from a crew member flying on multiple flights, of which one was conducted as a retrospective cohort study and the remainder were case reports. Eight studies reported retrospectively on a series of cases notified over a period of time. The studies contained information on 469 separate index cases travelling on 659 flights, of which 170 lasted >8 h. Scholten *et al.* [29] reported on the availability of passenger contact information but not screening results, and was excluded from the remainder of the analyses. Several studies that looked collectively at multiple flights did not report on the number or duration of the individual flights (supplementary table S1). The majority of index cases were smear positive (404 of 469, 86.1%), but there were 54 smear-negative index cases (11.5%) and eight culture or nucleic acid amplification test-negative index cases (1.7%) included, with the remainder unreported (table 1). Drug sensitivity results were reported in 391 cases, of which 23 (5.8%) were multidrug resistant (MDR) and two (0.5%) were extensively drug resistant (XDR) (table 1).

Quality assessment of the included studies was limited by the lack of clear methodological details employed in some of the contact tracing investigations, which in some cases were only a paragraph long. Two studies included comparison groups to try to ascertain an expected baseline rate of positive screening results [6, 18]. In the remainder of the studies, the nature of the investigation meant this was not possible; this was considered to lead to a potentially high risk of bias in the interpretation of the end results.

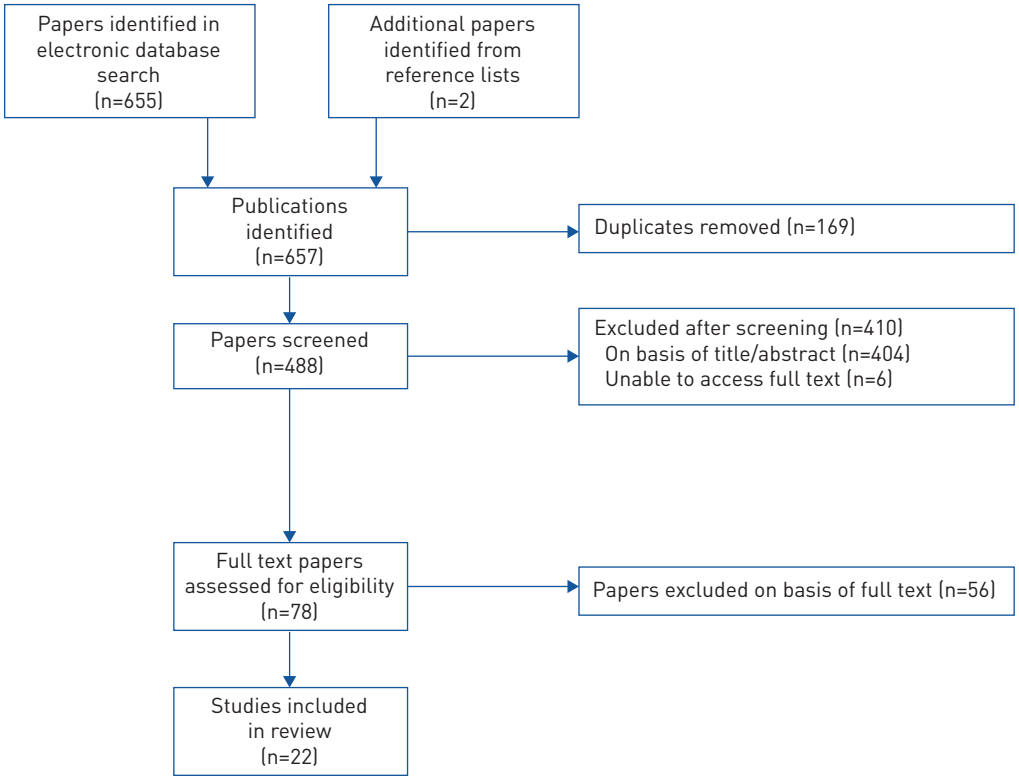

FIGURE 1 Flow chart of included studies.

Blinding to knowledge of exposure was universally absent, leading to possible bias in the interpretation of screening tests. Five studies were considered at high risk of bias for not detailing that previous TB infection or positive TST results were taken into consideration when interpreting results [3, 13, 14, 27, 30] (figure 2 and supplementary table S2).

A number of different screening methods for LTBI were used (table 1). In total, 19 studies used TST screening; of these, seven used a single test and nine carried out baseline and repeat testing to look for conversion (in three studies, the specific method was not reported) [3, 6, 7, 15–26, 28, 30, 31]. Positive TST results were defined as ⩾5 mm in seven studies and ⩾10 mm in three studies (with nine studies not specifying). IGRAs were used in seven studies [15, 18, 21, 24, 25, 27, 31]. One study following exposure to a case with XDR-TB specifically assessed for active TB disease using chest radiography over a 12-month period owing to limited options for treatment of latent TB [13].

There were 15 889 contacts identified in total. Overall, between 76.7% (95% CI 60.3%–89.9% in random effects modelling) and 87.6% (95% CI 80.1%–93.6%) of contacts identified were notified, and between 39.8% (95% CI 27.1%–53.3%) and 47.2% (95% CI 34.2%–60.4%) of contacts identified completed screening (figure 3 and table 2; includes all unadjusted pooled proportions). Ota and Kato [27] did not report on the number of contacts notified, and two studies did not report on the number of contacts completing screening [3, 14,]. Six studies removed results from their analysis after screening was completed because the contacts reported a history of known TB infection, and, additionally in the case of Driver *et al.* [6], because the contact was foreign-born, a social contact of the index case, or HIV positive, which meant the proportion of contacts identified with available screening results dropped slightly to 38.6% (95% CI 25.8%–52.3%) [6, 15, 17, 22, 25, 28].

Main findings

Overall, 5.1% of contacts identified (weighted proportion 647 of 15 889, 95% CI 2.6%–8.1% in random effects modelling; unadjusted pooled proportions in table 2) tested positive on a screening test (including both single-point testing and TST conversions) if risk factors for LTBI were not taken into account. Risk factors across the studies included a combination of country of birth, residence in an endemic country, known previous exposure to someone with active TB and previous Bacillus Calmette-Guérin (BCG) vaccination. These were all considered to have had a potential impact on the validity of TST results as a measure of evidence of in-flight transmission. Data on these risk factors for latent TB were known for a

TABLE 1 Summary of included studies

	Total
Studies included	22 (100)
Case reports	21 (95)
Retrospective cohort study	1 (5)
Index case details	469 (100)
Passenger	466 (99)
Crew member	3 (1)
Smear positive	404 (86)
Smear negative	54 (12)
Smear unknown/unreported	11 (2)
Culture positive	456 (97)
Culture negative	8 (2)
Culture unknown/unreported	5 (1)
Fully sensitive	313 (67)
Mono resistant	53 (11)
Multidrug resistant	23 (5)
Extensively drug resistant	2 (0)
Drug sensitivity unknown/unreported	78 (17)
Flight details	659 (100)
Flight duration >8 h	170 (26)
Flight duration <8 h	10 (2)
Flight duration unknown/unreported	479 (72)
Screening method	19 studies (100)
TST	
Single TST	7 (37)
Two-step TST	9 (47)
TST unspecified	3 (16)
Interferon-γ release assay	7 studies
All in combination with TST	
Chest radiography	1 study
Screening method unknown/unreported	2 studies

Data are presented as n (%), unless otherwise indicated. TST: tuberculin skin test.

total of 14389 contacts, of which 553 had positive screening tests, and 30 were found to have had no previous risk factors (0.21% of total contacts for whom risk factor information was available). Assuming that the remaining contacts either all had risk factors for latent TB or had no known risk factors for latent TB, the range of contacts with positive results attributable to in-flight transmission across all of the studies was between 0.000% (95% CI 0.000%–0.003%) and 0.13% (95% CI 0.00%–0.61%) (table 2; includes all unadjusted pooled proportions). The exact contribution of LTBI risk factors to positive screening results in the contacts was not known. A range was calculated for in-flight transmission if LTBI risk factors contributed to the positive result in 0%, 25%, 50%, 75% and 100% of contacts where present (table 3). This shows an overall maximum possible transmission risk of 0.2%–4.1% (unadjusted).

Very high I^2 values indicated that a large percentage of the overall variance of the pooled estimate was attributable to heterogeneity, *i.e.* there was extensive heterogeneity between studies.

Nine studies carried out two-step testing to try to determine a more accurate measure of transmission due to a specific plane exposure. In six cases, a baseline TST was performed with a repeat after 12 weeks if the initial test was negative [7, 17, 19, 20, 22, 30]. In the remaining three studies the cut-off was 8 weeks [15, 21, 25]. The time between infection with *Mycobacterium tuberculosis* and a positive TST is usually between 2 and 10 weeks [32]. In these nine studies, there were 36 conversions among 6806 contacts, giving a possible in-flight transmission risk of 0.63% (95% CI 0.05%–1.63%; unadjusted pooled proportion 0.53%, 95% CI 0.37%–0.73%). Driver *et al.* [6] reported on two contacts with a positive TST result known to have had a previous negative result. These were not included in this calculation of risk because the repeat testing was not systematic across the study. In total, eight contacts with TST conversions had no risk factors for latent TB (0.00%, 95% CI 0.00%–0.09%; unadjusted pooled proportion 0.12%, 95% CI 0.05%–0.23%). If these risk factors are taken into consideration as potentially affecting the validity of a positive result in TST conversions, the range of transmission risk in these studies assessing TST conversions was between 0.0% and 0.63%. The range of unadjusted pooled proportions was 0.12%–0.53%, and was lower than that of the unadjusted pooled proportions for all positive results (0.19%–0.74%).

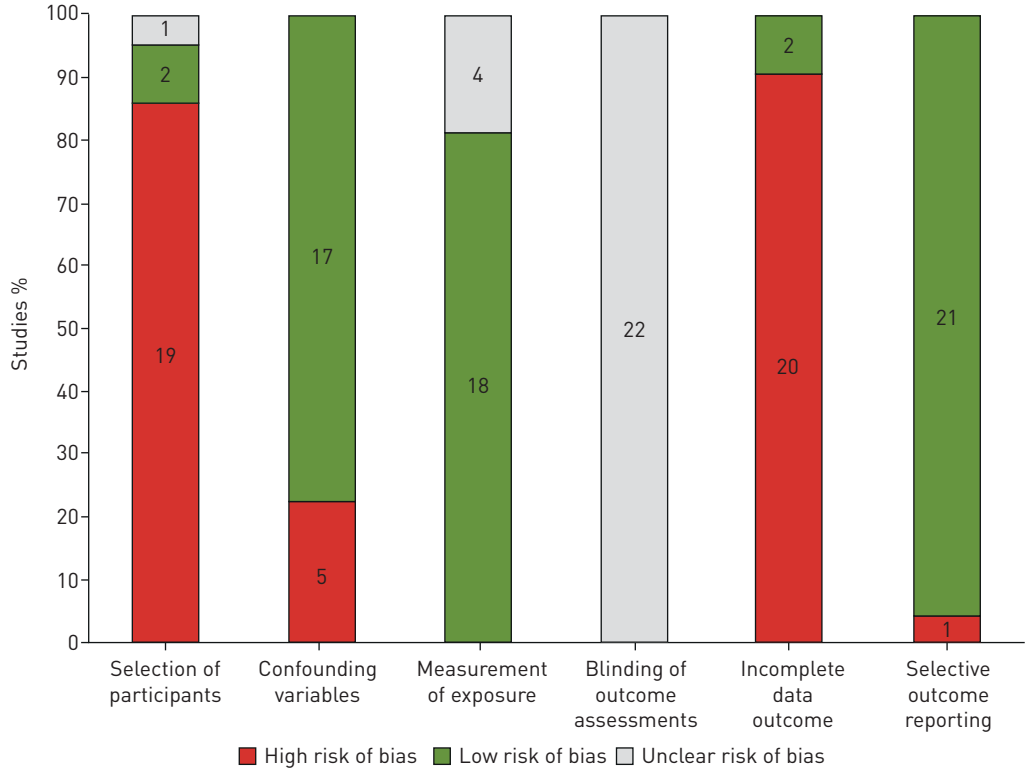

FIGURE 2 Quality assessment of included studies. Numbers in bars represent the actual number of studies.

The range of contacts with positive TST results (between either all or none having risk factors for latent TB) was 0.04% (95% CI 0.00%–0.68%; 0.79%, 95% CI 0.36%–1.50% unadjusted pooled proportion) to 0.16% (95% CI 0.00%–1.03%; 1.05%, 95% CI 0.05%–1.83% unadjusted pooled proportion) for flights lasting ⩾8 h. For flights of <8 h, the range was between 0.00% (95% CI 0.00%–0.37%; 0.44%, 95% CI 0.05%–1.58% unadjusted pooled proportion) and 0.00% (95% CI 0.00%–0.66%; 0.88%, 95% CI 0.24%–2.24% unadjusted pooled proportion) (table 4 and figure 4).

Repeat testing (TST/IGRA or chest radiography or combination) compared to single-point screening affected follow-up, with lower completion with multiple visits (48% *versus* 34%; p=0.514 in meta-regression analysis).

Discussion

This systematic review provides an up-to-date and comprehensive evaluation of the available studies examining evidence of TB transmission as a result of exposure on a flight. The first key finding is that only

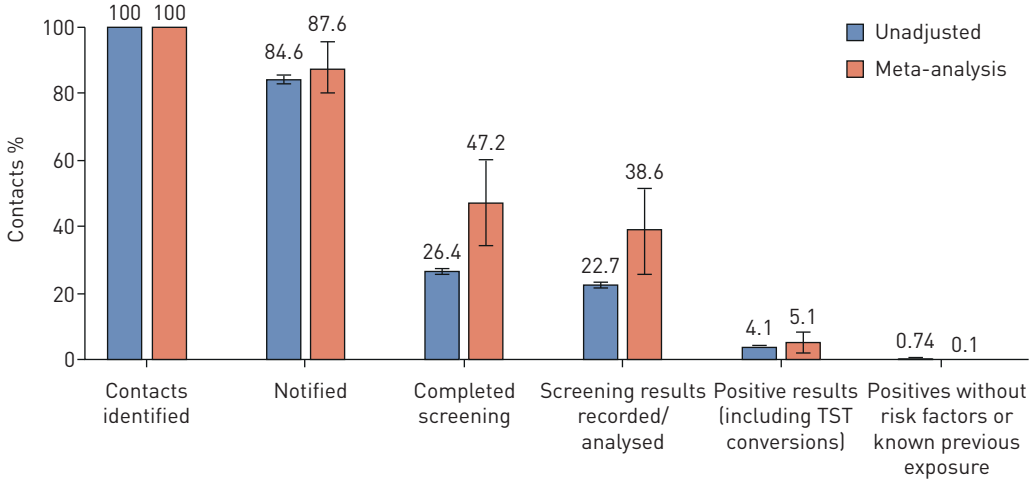

FIGURE 3 Screening cascade. Data are presented as mean (95% CI). TST: tuberculin skin test.

TABLE 2 Number and percentage of contacts at each stage of screening cascade

Study[#]	Total contacts identified n	Notified		Completed screening		Screening results available		Positive results		Positive without known risk factors	Positive with unknown risk factors	Inferred results if all unknown are with risk factors		Inferred results if all unknown are without risk factors	
		n	%	n	%	n	%	n	%	n	n	n	%	n	%
McFarland *et al.* [16]	343		[¶]	79	23	79	23	8	2.3	0	0	0	0	0	0
Driver *et al.* [6]	274	274	100	266	97.1	212	77.4	23	8.4	2	21	2	0	23	8.4
CDC 1995 [23]	92	75	81.5	22	23.9	22	23.9	10	10.9	0	0	0	0	0	0
CDC 1995 [23]	345	345	100	87	25.2	87	25.2	14	4.1	0	0	0	0	0	0
Kenyon *et al.* [7]	1042	925	88.8	802	77	802	77	29	2.8	7	0	7	0.7	7	0.7
Miller *et al.* [17]	219	169	77.2	120	54.8	120	54.8	34	15.5	2	0	2	0.9	2	0.9
Moore *et al.* [26]	203	161	79.3	120	59.1	100	49.3	5	2.5	0	0	0	0	0	0
Beller [22]	12	12	100	11	91.7	11	91.7	0	0	0	0	0	0	0	0
Parmet [28]	48	48	100	47	97.9	47	97.9	0	0	0	0	0	0	0	0
Vassiloyanakopoulos *et al.* [30]	144	20	13.9	1	0.7	1	0.7	1	0.7	0	1	0	0	1	0.7
Wang [19]	308	277	89.9	212	68.8	212	68.8	173	56.2	3	0	3	1	3	1
Whitlock *et al.* [20]	238	206	86.6	142	59.7	142	59.7	24	10.1	0	0	0	0	0	0
Chemardin *et al.* [13]	11	7	63.6	1	9.1	1	9.1	0	0	0	0	0	0	0	0
Abubakar [3]	247	50	20.2	[¶]	[¶]	4	1.6	0	0	0	0	0	0	0	0
Kornylo-Duong *et al.* [15]	131	79	60.3	67	51.1	59	45	16	12.2	0	0	0	0	0	0
Marienau *et al.* [25]	4550	3375	74.2	861	17.4	687	15.1	182	4	12	40	12	0.03	52	1.1
Kim *et al.* [14]	15	15	100	[¶]	[¶]	2	13.3	0	0	0	0	0	0	0	0
Thibeault *et al.* [18]	56	56	100	30	53.6	30	53.6	6	10.7	0	0	0	0	0	0
Flanagan *et al.* [24]	232	198	85.3	24	10.3	24	10.3	4	1.7	0	0	0	0	0	0
Ahmadi *et al.* [31]	6275	5713	91	653	10.4	386	6.2	78	1.2	3	0	3	0.05	3	0
An der Heiden *et al.* [21]	162	154	95.1	61	37.7	61	37.7	15	9.3	1	0	1	0.6	1	0.6
Ota and Kato [27]	942		[¶]	523	55.5	523	55.5	25	2.7	n/a	25	0	0	25	2.7
Total (highest estimate); unadjusted proportion (95% CI)	15889	13444	84.6 (84.0–85.2)	4194	26.4 (25.7–27.1)	3612	19.9 (19.3–20.5)	647	4.1 (3.8–4.4)	30	87	30	0.19 (0.13–0.27)	117	0.74 (0.61–0.88)
Total (highest estimate); weighted proportion (95% CI)	15889	13444	87.6 (80.1–93.6)	4194	47.2 (34.2–60.4)	3612	38.6 (25.8–52.3)	647	5.1 (2.6–8.1)	30	87	30	0.000 (0.000–0.003)	234	0.13 (0.00–0.61)
I^2 (%)			99.2		99.5		99.6		97.5				43.2		88.7
Total (lowest estimate); unadjusted proportion (95% CI)	15889	12761	80.3 (79.7–80.9)	4135	26.0 (25.3–24.7)	3612	22.7 (22.1–23.4)								
Total (lowest estimate); weighted proportion (95% CI)	15889	12761	76.7 (60.3–89.8)	4135	39.8 (27.1–53.3)	3612	39.8 (27.1–53.3)								
I^2 (%)			99.7		99.6		99.6								

Data are presented as n (% of contacts identified), unless otherwise indicated. [#]: Scholten *et al.* [29] not included in the analysis because they did not report on contact screening; [¶]: for missing results, the highest and lowest estimate of totals were calculated on the basis that the value is either 100% of the previous column or following column.

TABLE 3 Number and percentage of contacts with positive results if risk factors for latent tuberculosis are considered to contribute in differing proportions

	Total contacts identified	Positive results if known prior LTBI risk factors attributable in differing proportions									
		0%		25%		50%		75%		100%	
		n	%	n	%	n	%	n	%	n	%
McFarland *et al.* [16]	343	8	2.3	6	1.7	4	1.2	2	0.6	0	0.0
Driver *et al.* [6]	274	23	8.4	18	6.6	13	4.7	7	2.6	2	0.7
CDC 1995 [23]	92	10	10.9	8	8.7	5	5.4	3	3.3	0	0.0
CDC 1995 [23]	345	14	4.1	11	3.2	7	2.0	4	1.2	0	0.0
Kenyon [7]	1042	29	2.8	24	2.3	18	1.7	13	1.2	7	0.7
Miller *et al.* [17]	219	34	15.5	26	11.9	18	8.2	10	4.6	2	0.9
Moore *et al.* [26]	203	5	2.5	4	2.0	3	1.5	1	0.5	0	0.0
Beller [22]	12	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Parmet [28]	48	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Vassiloyanakopoulos *et al.* [30]	144	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Wang [19]	308	173	56.2	131	42.5	88	28.6	46	14.9	3	1.0
Whitlock *et al.* [20]	238	24	10.1	18	7.6	12	5.0	6	2.5	0	0.0
Chemardin *et al.* [13]	11	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Abubakar *et al.* [3]	247	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Kornylo-Duong *et al.* [15]	131	16	12.2	12	9.2	8	6.1	4	3.1	0	0.0
Marienau *et al.* [25]	4550	182	4	140	3.1	97	2.1	55	1.2	12	0.3
Kim *et al.* [14]	15	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Thibeault *et al.* [18]	56	6	10.7	5	8.9	3	5.4	2	3.6	0	0.0
Flanagan *et al.* [24]	232	4	1.7	3	1.3	2	0.9	1	0.4	0	0.0
Ahmadi *et al.* [31]	6275	78	1.2	59	0.9	41	0.7	22	0.4	3	0.0
An der Heiden *et al.* [21]	162	15	9.3	11	6.8	7	4.3	4	2.5	1	0.6
Ota and Kato [27]	942	25	2.7	19	2.0	13	1.4	6	0.6	0	0.0
Total; unadjusted proportion (95% CI)	15889	647	4.1 (3.8–4.4)	495	3.1 (2.8–3.4)	339	2.1 (1.9–2.4)	186	1.2 (1.0–1.3)	30	0.2 (0.1–0.3)
Total; weighted proportion (95% CI)	15889	647	5.1 (2.6–8.1)	495	3.7 (1.9–6.0)	339	2.4 (1.1–4.0)	186	1.1 (0.4–2.0)	30	0.000 (0.000–0.003)
I^2 (%)			97.5		96.5		94.5		89.3		43.2

Data are presented as n (% of contacts identified), unless otherwise indicated. LTBI: latent tuberculosis infection.

26.4% of contacts identified across all studies completed screening following exposure, demonstrating the considerable difficulty in carrying out these investigations. Second, the yield of positive test results attributable to in-flight transmission was very low, at between 0.00% (95% CI 0.00%–0.00%) and 0.13% (95% CI 0.00%–0.61%) of all contacts identified, when contacts with risk factors for latent TB were considered not to have had a positive result from a flight exposure. The risk of transmission was 0.00% (95% CI 0.00%–0.09%) to 0.63% (95% CI 0.05%–1.63%) if only TST conversions were considered to represent infection. The overall positivity rate was much higher at 5.1% if risk factors for latent TB were not taken into consideration, but the rate of TST conversion (even without taking into account risk factors at 0.63%) was consistent with the much lower estimates for in-flight transmission risk when positive results from contacts with known risk factors were excluded.

In this review, we have not found any cases of active TB acquired from in-flight transmission, despite the majority of contacts identified in this study not completing the screening process and therefore not receiving post-exposure prophylaxis. There is also strong evidence that a screening method that involves repeat testing reduces the number of people completing screening.

There was not a distinct differentiation found in positive screening results between flights of more or less than 8 h duration (flights ⩾8 h: 0.00%, 95% CI 0.00%–0.00% to 0.00%, 95% CI 0.00%–0.00%; flights <8 h: 0.00%, 95% CI 0.00%–0.37% to 0.00%, 95% CI 0.00%–0.66%) (table 4 and figure 4). The WHO recommendation that only exposures on flights lasting ⩾8 h duration should be followed up was based on the findings of the studies by Driver *et al.* [6] and Kenyon *et al.* [7] in the initial 1998 WHO guidelines [8] and has been repeated in subsequent versions (supplementary table S1). However, a recent consensus document from the WHO on reducing TB transmission concluded that the available evidence does not enable the establishment of a cut-off time of 8 h [33].

TABLE 4 Screening results stratified by flight time

Flight	Screening results available	Positive results		Positive without known risk factors	Positive with unknown risk factors	Inferred results if all unknown are with risk factors		Inferred results if all unknown are without risk factors	
	n	n	%	n	n	n	% (of screening results available)	n	% (of screening results available)
>8 h									
McFarland *et al.* [16]	79	8	10.1	0	0	0	0	0	0
Kenyon [7]: flight 1	298	7	2.3	0	0	0	0	0	0
Kenyon [7]: flight 4	249	15	6.0	6	0	6	2.4	6	2.4
Miller *et al.* [17]: flight 2#	101	29	28.7	0	2	0	0	2	2.0
Vassiloyanakopoulos *et al.* [30]	1	1	100.0	0	1	0	0	1	100.0
Wang [19]	212	173	81.6	3	0	3	1.4	3	1.4
Whitlock *et al.* [20]: both flights	142	24	16.9	0	0	0	0	0	0.0
Kornylo-Duong *et al.* [15]: flight 1	15	11	73.3	0	0	0	0	0	0.0
Kornylo-Duong *et al.* [15]: flight 2	18	5	27.8	0	0	0	0	0	0.0
Flanagan *et al.* [24]: all flights	24	4	16.7	0	0	0	0	0	0.0
Total	**1139**	**277**	**24.3**	**9**	**3**	**9**	**0.8**	**12**	**1.1**
Unadjusted proportion (95% CI)			24.3 (21.9–26.9)				0.79 (0.36–1.50)		1.05 (0.05–1.83)
Weighted proportion (95% CI)			25.7 (6.9–50.8)				0.04 (0.00–0.68)		0.16 (0.00–1.03)
I^2 (%)			98.6				39.7		44.2
<8 h									
Kenyon [7]: flight 2	104	4	3.8	0	0	0	0	0	0
Kenyon [7]: flight 3	109	3	2.8	1	0	1	0.9	1	0.9
CDC 1995 [23]	22	10	45.5	0	0	0	0.0	0	0
Miller *et al.* [17]: flight 3#	20	6	30.0	0	2	0	0.0	2	10
Moore *et al.* [26]: both flights	100	5	5.0	0	0	0	0.0	0	0
Beller [22]	11	0	0.0	0	0	0	0.0	0	0
Kornylo-Duong *et al.* [15]: flight 3	9	0	0.0	0	0	0	0.0	0	0
Kornylo-Duong [15]: flight 4	17	0	0.0	0	0	0	0.0	0	0
An der Heiden *et al.* [21]	61	15	24.6	1	0	1	1.6	1	1.6
Total	**453**	**43**	**9.5**	**2**	**2**	**2**	**0.4**	**4**	**0.9**
Unadjusted proportion (95% CI)			9.5 (7.0–12.6)				0.44 (0.05–1.58)		0.88 (0.24–2.24)
Weighted proportion (95% CI)			8.6 (2.1–18.0)				0.00 (0.00–0.37)		0.00 (0.00–0.66)
I^2 (%)			52.2				0.0		3.9

#: one passenger with a positive tuberculin skin test was on both flights; risk factors for contacts not disaggregated by flight but only two passengers overall had no known risk factors for latent tuberculosis.

In this review, 11.5% of the index cases were smear negative with 1.7% being culture negative. The WHO guidelines recommend considering contact tracing in smear-negative, culture-positive passengers, especially in the context of MDR- or XDR-TB [2]. Published molecular epidemiology studies suggest that smear-negative index cases can contribute to between 10% and 20% of transmission events [34, 35]. The new ECDC European guidelines recommend that airline contacts should only be traced if there has been documented transmission to close household contacts of the index case [5]. Broeder *et al.* [36] retrospectively assessed the effect of changing the Dutch contact tracing policy in line with the ECDC

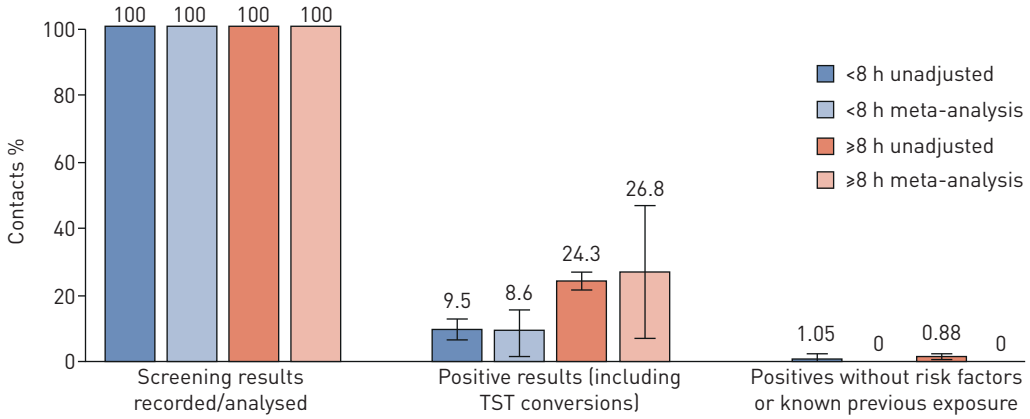

FIGURE 4 Screening results stratified by flight time. Data are presented as mean (95% CI). TST: tuberculin skin test.

guidance and found that there were considerably fewer notifications being followed by contact investigations, but no increase in yield of positive results. Unfortunately, it was not possible in this review to perform a sub-analysis based on smear or culture positivity owing to the lack of data that could be disaggregated.

Strengths and limitations of this review

The main strength of this review is the large number of contacts included, considerably more than in both the previous reviews by Abubakar *et al.* [37] (4328 contacts) and the ECDC RAGIDA report [5] (8660 contacts). Flights of all durations regardless of the WHO criteria were included (which was not the case in the ECDC review) to allow a comprehensive overview and robustly appraise guidelines. The total percentage of people with any positive screening test was lower than in other reviews, owing to the inclusion of additional low-yield studies published since. Abubakar *et al.* [37] and the RAGIDA study [5] found that 7.9% (340 of 4328) and 6.6% (571 of 8660), respectively, of contacts identified had a positive screening result. The current review carried out 10 years after the initial Abubakar *et al.* [37] review found only 4.1% of contacts identified (unadjusted) had a positive screening result. The total percentage of contacts identified with TST conversions was 0.86% (30 of 3472) in the review by Abubakar *et al.* [37], but was only 0.63% in this review.

The random effects meta-analysis proportions were lower than the observed proportions without adjustment owing to weighting of studies (supplementary annex). A sensitivity analysis was performed with fixed effect analysis, and similar results were observed given the significant heterogeneity. For example, the study by Marienau *et al.* [25] contributed nearly half of the final outcomes (52 of 117), but in a fixed effect analysis received 29% of the weight. The Driver *et al.* [6] study contributed 23 of 117 outcomes, but received 2% weight in the fixed analysis; therefore, the contributions of these studies to the overall proportion are down-weighted in the meta-analysis. The meta-analysis estimate is likely more valid, although any average of the studies is difficult to interpret because of the marked heterogeneity; the proportion will likely vary depending on setting, contact tracing approach and other unknown variables.

It is clear that, over time, with more contacts and an expanding evidence base, there has been a drop in the overall yield of positive results from screening tests. The Abubakar *et al.* [37] review concluded that evidence for transmission in this setting was limited and that there was also insufficient evidence to recommend screening of air passenger contacts. That seems to be even more the case from this review with a still lower risk of TST conversion. The rates of TST conversion as a percentage of the screening results available is higher, but in this review with a much larger number of total contacts, this is likely to be an artefact of the availability of results being lower at 40% compared to 63.8% in the review by Abubakar *et al.* [37].

This systematic review is a comprehensive assessment of the literature on transmission risk of TB following in-flight exposure; however, the studies included were mostly low to medium quality case reports with potential for a high risk of bias (figure 2 and supplementary table S2). There was wide variation in how the screening was performed, in particular with respect to single and combination LTBI tests and their interpretation, and also TST interpretation. The extent of this heterogeneity makes it more difficult to interpret the results of pooled analyses. Only one study used a control group, so it was not possible to more broadly compare proportions of TST positivity against controls to try to resolve some of the

difficulties around interpretation of positive results. One of the major limitations is that we have made an assumption that risk factors for latent TB account for all of the positive TST results found. To address this, we have provided a range of transmission risks assuming that risk factors for latent TB both are and are not relevant for TST conversions.

Another limitation when trying to determine a transmission risk is the very high proportion of contacts who do not undergo screening (60% in this review). This is clearly an important consideration when assessing the utility and effectiveness of contact tracing. It was not possible to perform a sub-analysis based on smear or culture positivity of the index case, or drug-resistance profiles, owing to the lack of data that could be disaggregated or standardised. Stratification by aircraft seating was not possible, because the number of contacts within and outside of the two rows around the index case were not described in the studies.

Conclusion

The yield of positive results from contact tracing following in-flight exposure is very small, not least due to the large proportion of contacts who do not complete screening. There have been no published standalone reports of cases of active TB where the only identifiable risk factor has been in-flight exposure, despite the high proportion of contacts not receiving screening or prophylaxis. The evidence behind the criteria for initiating investigations implemented in many national protocols is weak and it has been widely demonstrated that active screening of contacts is labour-intensive and unlikely to be effective. The implications of this review suggest that the risk of transmission is very low, and the utility of formal comprehensive contact tracing following a plane exposure is therefore likely to be low.

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