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Early View

Review

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Air-travel related TB incident follow up – effectiveness and outcomes: a systematic review

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ABSTRACT

Background

The World Health Organization (WHO) recommends following up passengers following possible exposure to a case of infectious tuberculosis (TB) during air travel. This is known to be time consuming and difficult, and increasingly so with higher numbers of flights and passengers to and from countries with high TB endemicity each year.

Objectives

This paper systematically reviews the literature on contact tracing investigations following 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.

Data sources & Eligibility

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.

Results

Twenty-two papers were included, with a total of 469 index cases and 15,889 contacts. Only 26.4% of all contacts identified completed screening following exposure. The yield of either a single positive tuberculin skin test (TST) or a TST conversion attributable to in-flight transmission is 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).

Limitations

The main limitation is heterogeneity of reporting.

Conclusions and implications of key findings

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.

INTRODUCTION

Air travel has become a common and increasingly popular form of transport, with approximately 4.1 billion passengers worldwide in 2017. The number of people taking long haul flights to and from countries with high endemicity of TB is also expanding[1]. This increases the likelihood of passengers on aircrafts coming into contact with patients with infectious pulmonary tuberculosis (TB). Passenger follow up after possible TB contact has been recommended by the World Health Organization (WHO) as an important control measure[2]. The WHO guidelines state that the four criteria which should be met in order to initiate a contact tracing investigation are a flight of eight hours duration or longer, an index case who is culture positive, that no more than three 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 following exposure to TB on flights including new studies which 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 over eight hours duration 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 carried out a cohort study investigating the transmission risk from a flight attendant to fellow crew members over a six-month period[6]. The results revealed that increased flying time was a strong predictor of a positive TST in the contacts, and that all but two of the contacts included had at least 14 hours exposure to the index case. Kenyon et al reported a study of an index case with advanced pulmonary tuberculosis who travelled on several flights of different durations over the course of a month, taking the last flight two weeks before dying of the disease[7]. Four contacts on the last flight that she took, of eight hours duration, had a TST conversion after the flight. The eight-hour rule has been repeated in later versions of the WHO guidance, but these two studies are unlikely to be typical of in-flight exposures, as 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 tuberculin skin tests (TST) and Interferon Gamma Release Assays (IGRA). 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 eight hours.

METHODS

A systematic search of Medline, EMBASE, BIOSIS, Cochrane Library and Database of Systematic Reviews was carried out on 07 March 2019 to identify journal articles relating to TB contact tracing investigations following in-flight exposure. Key conference abstracts from the last five 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 have 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 separate authors. These included index case and flight details, screening methods and contact success rates, with the 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 without risk factors for latent TB infection (LTBI) were calculated to provide a 'screening' cascade. Risk factors were taken into account in order to assess the evidence specifically for in-flight transmission. Where no value was available for the proportion notified or completed screening, we estimated a best and worst case scenario and by assigning a value of 0% or 100% in order 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. In order to give a broader view of potential transmission, the total number of positive test results for 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 where a single screening test was reported as well as where baseline and repeat testing had been carried out to assess for tuberculin skin test (TST) conversion. Conversion of an initial baseline negative TST immediately following a plane exposure to a positive TST result after the lag phase of development of cell mediated immunity has passed provides more reliable information on whether the plane exposure has 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 where 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 under eight hours duration, or eight hours and above. In studies reporting multiple flights of different durations, these have been included where the screening results have been reported separately. Studies including flights of different durations where the screening results cannot be disaggregated have been 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 was 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.

All included studies were assessed for quality by using the Risk of Bias Assessment Tool for Nonrandomised Studies (RoBANS) by two different authors[11]. The results were reported as per the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 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, Supplementary Table 1)[3, 6, 7, 13-31]. One paper contains 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.

Eleven studies were case reports of a single passenger index case and three reported on 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 more than eight hours. Scholten et al reported on the availability of passenger contact information, but not screening results, and was excluded from the remainder of the analyses[29]. Several studies that looked collectively at multiple flights did not report on the number or duration of the individual flights (Supplementary Table 1). The majority of index cases were smear positive (404/469, 86.1%), but there were also 54 smear negative index cases included (11.5%) and eight culture or nucleic acid amplification test (NAAT) negative index cases (1.7%) with the remainder unreported (Table 1). Drug sensitivity results were reported in 391 cases, of which 23 were multi-drug resistant (5.8%) and two were extensively drug-resistant (0.5%) (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 in total length. Two studies included comparison groups in order 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, but nevertheless this was considered to have a potentially high risk of bias in the interpretation of the end results. 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, Supplementary Table 2).

A number of different screening methods for latent TB infection were used (Table 1). Nineteen studies in total 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 ≥5mm in seven studies and ≥10mm in a further three studies (with nine studies not specifying). Interferon Gamma Release Assays (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 x-rays (CXR) over a 12 month period, due 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; Table 2A; includes all unadjusted pooled proportions). Ota et al did not report on the number of contacts notified, and two studies did not report on the number of contacts completing screening [3, 14, 27]. Six studies removed results from analysis after screening was completed because the contacts reported a history of known TB infection and additionally in the case of Driver et al, 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% (weighted proportion 647/15889, 95%CI 2.6-8.1% in random effects modelling; unadjusted pooled proportions in Table 2A) of contacts identified tested positive on a screening test (including both single point of testing and TST conversions) if risk factors for latent TB infection are 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 BCG vaccination. These were all considered to have had 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 on a total of 14,389 contacts, of which 553 had positive screening tests, and 30 were found to have had no previous risk factors (0.21% total contacts where 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 2A; includes all unadjusted pooled proportions). Differing proportions to which known LTBI risk factors could have contributed to the positive results in order to give a range with quartiles have also been calculated (Table 2B). This shows an overall maximum possible transmission risk of 0.2-4.1% (unadjusted).

There is extensive heterogeneity between studies, with very high I-squared values indicating the high percentage of the overall variance of the pooled estimate attributable to heterogeneity.

Nine studies carried out two-step testing to try and 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], whereas in the remaining three studies the cut-off was eight weeks[15, 21, 25]. The time between infection with *M. tuberculosis* and a positive TST is usually between 2-10 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 reported on two contacts with a positive TST result known to have had a previous negative result[6]. 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 is between 0.0% to 0.63%. The range of unadjusted pooled proportions is 0.12% to 0.53%, and is lower than that of the unadjusted pooled proportions for all positive results (0.19% to 0.74%).

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 eight hours or longer. For flights lasting less than eight hours, 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 3, Figure 4).

Repeat testing (TST/IGRA or CXR or combination) compared to single point screening impacted on follow-up, with a lower completion with multiple visits (48% versus 34%; p=0.514 in metaregression 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 26.4% of contacts identified across all studies completed screening following exposure, demonstrating the considerable difficulty in carrying out these investigations. Secondly, the yield of positive test results attributable to in-flight transmission is 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 is 0.00%, (95%CI 0.00-0.09) to 0.63% (95%CI 0.05-1.63%) if only TST conversions are considered to represent infection. The overall positivity rate is much higher at 5.1% if risk factors for latent TB are not taken into consideration, but the rate of TST conversion (even without taking into account risk factors at 0.63%) is consistent with the much lower estimates for in-flight transmission risk when positive results from contacts with known risk factors are 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 which 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 eight hours (0.00%, 95%CI 0.00-0.00% to 0.00%, 95%CI 0.00-0.00% for flights over eight hours, and 0.00%, 95%CI 0.00-0.37% to 0.00%, 95%CI 0.00-0.66% for flights under eight hours) (Table 3, Figure 4). The WHO recommendation that only exposures on flights lasting over eight hours duration should be followed up was based on the findings of the studies by Driver et al and Kenyon et al in the initial 1998 WHO guidelines and has been repeated in subsequent versions (Supplementary Table 1)[6-8]. However, a recent consensus document from the WHO on reducing tuberculosis transmission has concluded that the available evidence does not enable the establishment of a cut-off time of eight hours[33].

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]. There have been molecular epidemiology studies published that suggest 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 retrospectively assessed the effect of changing the Dutch contact tracing policy in line with the ECDC guidance and found that there were considerably fewer notifications being followed by contact investigations, but that there was no increase in yield of positive results[36]. Unfortunately, it was not possible in this review to perform a sub-analysis based on smear or culture positivity due to the lack of data which 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 both the previous reviews by Abubakar et al and the ECDC 'Risk assessment guidelines for infectious diseases transmitted on aircraft' (RAGIDA) report (4328 and 8660 respectively)[5, 37]. Flights of all durations regardless of the WHO criteria were included (which was not the case in the ECDC review), in order to be able to have a comprehensive overview and be able to appraise guidelines robustly. The total percentage of people with any positive screening test was lower than in other reviews, due to the inclusion of additional low yield studies published since. Abubakar et al and the RAGIDA study found 7.9% (340/4328) and 6.6% (571/8660) respectively of contacts identified with a positive screening result. This review carried out ten years after the initial Abubakar 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% (30/3472) in the review by Abubakar et al, but dropped to 0.63% in this review.

The random effects meta-analysis (MA) proportions are lower than the observed proportions without adjustment due to weighting of studies (see Annex). Sensitivity analysis was performed with fixed effect analysis, and similar results were observed given the significant heterogeneity. For example, Marienau et al (2010) contributes nearly half of the final outcomes (52/117), but in a fixed effect analysis receives 29% of the weight. The Driver et al (1994) study has 23/117 outcomes, but receives 2% weight in the fixed analysis; therefore the contributions of these studies to the overall proportion are down-weighted in the meta-analysis. The MA estimate is likely more valid, although any average of the studies is difficult to interpret due to the marked heterogeneity; the proportion will likely vary depending on setting, contact tracing approach, and other unknown variables leading to the heterogeneity.

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 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[37]. 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 fact that the availability of results is 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, Supplementary Table 2). There was a 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, in order to try and 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. We have provided a range of transmission risks assuming that risk factors for latent TB both are and are not relevant for TST conversions in order to address this.

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). However, 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, due to the lack of data which can be disaggregated or standardised. Stratification by aircraft seating was not possible, as the number of contacts within and outside of the two rows around the index case were not described in the studies.

CONCLUSION

In 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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Table 1: Summary of included studies

Studies included	**Total (percentage)**	**22 (100)**
	Case Reports	21 (95)
	Retrospective cohort study	1 (5)
Index case details	**Total (percentage)**	**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	**Total**	**659 (100)**
	Flight duration > 8 hours	170 ()
	Flight duration < 8 hours	10 ()
	Flight duration unknown/unreported	479 ()
Screening method	**Tuberculin skin testing (TST)**	**19 studies (100)**
	Single TST	7 (37)
	Two-step TST	9 (47)
	Tuberculin skin test – unspecified	3 (16)
	Interferon Gamma Release Assay All in combination with TST	**7 studies**
	Chest X-Ray	**1 study**
	Screening method unknown/unreported	**2 studies**

Table 2A: Number and percentage of contacts at each stage of screening cascade

	Total contacts identified	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	% (of contacts identified)	n	n	n	% (of contacts identified)	n	% (of contacts identified)
McFarland	343		*	79	23	*79*	*23*	8	2.3	0	0	0	0	0	0
Driver	274	274	100	266	97.1	212	77.4	23	8.4	2	21	2	0	23	8.4
CDC 1995a	92	75	81.5	22	23.9	*22*	*23.9*	10	10.9	0	0	0	0	0	0
CDC 1995b	345	345	100	87	25.2	*87*	*25.2*	14	4.1	0	0	0	0	0	0
Kenyon	1042	925	88.8	802	77	*802*	*77*	29	2.8	7	0	7	0.7	7	0.7
Miller	219	169	77.2	120	54.8	*120*	*54.8*	34	15.5	2	0	2	0.9	2	0.9
Moore	203	161	79.3	120	59.1	100	49.3	5	2.5	0	0	0	0	0	0
Beller	12	12	100	11	91.7	*11*	*91.7*	0	0	0	0	0	0	0	0
Parmet	48	48	100	47	97.9	*47*	*97.9*	0	0	0	0	0	0	0	0
Vassiloyanokopoulos	144	20	13.9	1	0.7	*1*	*0.7*	1	0.7	0	1	0	0	1	0.7
Wang	308	277	89.9	212	68.8	*212*	*68.8*	173	56.2	3	0	3	1	3	1
Whitlock	238	206	86.6	142	59.7	*142*	*59.7*	24	10.1	0	0	0	0	0	0
Chemardin	11	7	63.6	1	9.1	*1*	*9.1*	0	0	0	0	0	0	0	0
Abubakar	247	50	20.2	*	*	4	1.6	0	0	0	0	0	0	0	0
Kornylo-Duong	131	79	60.3	67	51.1	59	45	16	12.2	0	0	0	0	0	0
Marienau	4550	3375	74.2	861	17.4	687	15.1	182	4	12	40	12	0.03	52	1.1
Kim	15	15	100	*	*	2	13.3	0	0	0	0	0	0	0	0
Thibeault	56	56	100	30	53.6	*30*	*53.6*	6	10.7	0	0	0	0	0	0
Flanagan	232	198	85.3	24	10.3	*24*	*10.3*	4	1.7	0	0	0	0	0	0
Ahmadi	6275	5713	91	653	10.4	386	6.2	78	1.2	3	0	3	0.05	3	0
An der Heiden	162	154	95.1	61	37.7	*61*	*37.7*	15	9.3	1	0	1	0.6	1	0.6
Ota	942		*	523	55.5	*523*	*55.5*	25	2.7	n/a	25	0	0	25	2.7
Totals (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)
Totals (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
Totals (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)								
Totals (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								

*Missing results. Highest and lowest estimate of totals calculated on basis that value is either 100% of previous column or following column

[α] Scholten et al (2010) not included in analysis as does not report on contact screening

Table 2B: Number and percentage of contacts with positive results if risk factors for latent TB are considered to contribute in differing proportions

	Total contacts identified	Positive results (0% attributable to known prior LTBI risk factors)		Positive results (25% attributable to known prior LTBI risk factors)		Positive results (50% attributable to known prior LTBI risk factors)		Positive results (75% attributable to known prior LTBI risk factors)		Positive results (100% attributable to known prior LTBI risk factors)	
		n	% (of contacts identified)	n	% (of contacts identified)	n	% (of contacts identified)	n	% (of contacts identified)	n	% (of contacts identified)
McFarland	343	8	2.3	6	1.7	4	1.2	2	0.6	0	0.0
Driver	274	23	8.4	18	6.6	13	4.7	7	2.6	2	0.7
CDC 1995a	92	10	10.9	8	8.7	5	5.4	3	3.3	0	0.0
CDC 1995b	345	14	4.1	11	3.2	7	2.0	4	1.2	0	0.0
Kenyon	1042	29	2.8	24	2.3	18	1.7	13	1.2	7	0.7
Miller	219	34	15.5	26	11.9	18	8.2	10	4.6	2	0.9
Moore	203	5	2.5	4	2.0	3	1.5	1	0.5	0	0.0
Beller	12	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Parmet	48	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Vassiloyanokopoulos	144	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Wang	308	173	56.2	131	42.5	88	28.6	46	14.9	3	1.0
Whitlock	238	24	10.1	18	7.6	12	5.0	6	2.5	0	0.0
Chemardin	11	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Abubakar	247	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Kornylo-Duong	131	16	12.2	12	9.2	8	6.1	4	3.1	0	0.0
Marienau	4550	182	4	140	3.1	97	2.1	55	1.2	12	0.3
Kim	15	0	0	0	0.0	0	0.0	0	0.0	0	0.0
Thibeault	56	6	10.7	5	8.9	3	5.4	2	3.6	0	0.0
Flanagan	232	4	1.7	3	1.3	2	0.9	1	0.4	0	0.0
Ahmadi	6275	78	1.2	59	0.9	41	0.7	22	0.4	3	0.0
An der Heiden	162	15	9.3	11	6.8	7	4.3	4	2.5	1	0.6
Ota	942	25	2.7	19	2.0	13	1.4	6	0.6	0	0.0
Totals; 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)
Totals; 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

Table 3: Screening results stratified by flight time

>8 hours	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	
Flight	n	n	%	n	n	n	% (of screening results available)	n	% (of screening results available)
McFarland	79	8	10.1	0	0	0	0	0	0
Kenyon - Flight 1	298	7	2.3	0	0	0	0	0	0
Kenyon - Flight 4	249	15	6.0	6	0	6	2.4	6	2.4
Miller - Flight 2*	101	29	28.7	0	2	0	0	2	2.0
Vassiloyanokopoulos	1	1	100.0	0	1	0	0	1	100.0
Wang	212	173	81.6	3	0	3	1.4	3	1.4
Whitlock - both flights	142	24	16.9	0	0	0	0	0	0.0
Kornylo-Duong - Flight 1	15	11	73.3	0	0	0	0	0	0.0
Kornylo-Duong - Flight 2	18	5	27.8	0	0	0	0	0	0.0
Flanagan - All flights	24	4	16.7	0	0	0	0	0	0.0
Totals	**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 hours	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	
Flight	n	n	%	n	n	n	% (of screening results available)	n	% (of screening results available)
Kenyon - Flight 2	104	4	3.8	0	0	0	0	0	0
Kenyon - Flight 3	109	3	2.8	1	0	1	0.9	1	0.9
CDC 1995a	22	10	45.5	0	0	0	0.0	0	0
Miller - Flight 3*	20	6	30.0	0	2	0	0.0	2	10
Moore - both flights	100	5	5.0	0	0	0	0.0	0	0
Beller	11	0	0.0	0	0	0	0.0	0	0
Kornylo-Duong - Flight 3	9	0	0.0	0	0	0	0.0	0	0
Kornylo-Duong - Flight 4	17	0	0.0	0	0	0	0.0	0	0
An der Heiden	61	15	24.6	1	0	1	1.6	1	1.6
Totals	**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 positive TST was on both flights; risk factors for contacts not disaggregated by flight but only 2 passengers overall had no known risk factors for latent TB

Supplementary Table 1: Included studies on contact tracing after in-flight exposure to pulmonary tuberculosis

Study	Index case details	Flight details	Screening method	Contact tracing yield	Results (% screened) *Single positive TST result and TST conversions reported separately*
McFarland et al USA 1993 Contact tracing investigation	Smear positive cavitary TB Culture confirmed; MDR-TB Passenger	9h London – Minneapolis*	Single TST or Heaf test All crew and passengers (343 total) Positive TST ≥5mm Positive Heaf reaction = 2 or more	91/97 US contacts notified (93.8%) 59/97 US contacts completed screening (60.8%) 20/246 non-US contacts completed screening (8.1%) Total completed screening 79/343 (23%)	Positive TST/Heaf test: 8 contacts (10%) total of which 1 US contact (1.7%) All considered to have risk factors Conclusion: No evidence of transmission
Driver et al USA 1994 Retrospective cohort study following exposure on multiple flights from May – October 1992	Smear positive cavitary TB Culture confirmed; fully sensitive Flight attendant Flying for six months while symptomatic	167 flights in total	Single TST test all crew members working with index case (274 total) Comparison control group of crew members who had not flown also tested Positive TST ≥ 5mm Analysis also performed for TST ≥ 10mm	274/274 contacts notified (100%) 266/274 contacts completed screening (97.1%) and 270 controls 54 contacts and 23 controls later removed from analysis (foreign-born, social contacts of index case, previous known TB infection or HIV positive)	Positive TST rate in contacts from May – July: 10/169; 5.9%; and controls: 13/247; 5.3% Positive TST rates in contacts from August – October (13/43 , 30.2%) compared to contacts from May – July (RR 5.11, 95% CI 2.41 – 10.85, p<0.01) or controls (RR 5.74, 95% CI 2.86 – 11.54, p<0.01) TST positive rates increased with increasing hours of exposure (only 2 contacts had <14.5 hours exposure) Two crew members with known previous negative TST results had conversions – neither with known risk factors Conclusion: Likely transmission to other crew members
Center for Disease Control & Prevention USA 1995 Review of six cases investigated by CDC between 1992 and 1995 (see also Driver et al,	Pulmonary TB No culture result Passenger	1.5h Mexico – San Francisco	Single TST testing all passengers (92 total)	75/92 contacts notified (81.5%) 22/92 completed screening (23.9%)	Positive TST: 10 contacts (45%) All considered to have risk factors Conclusion: No evidence transmission
	Pulmonary TB No culture result Passenger	4 flights: 3h/9h/3h/1.5h Taiwan – Tokyo – Seattle –	Single TST testing all passengers on each flight (661 total)	87/345 US citizens completed screening (25.2%) *Only US passengers contacted*	Positive TST: 14 contacts (16%) All considered to have risk factors All seated >5 rows away from index case Conclusion: Transmission cannot be excluded

McFarland et al, Miller et al and Kenyon et al)	Underlying immune disorder	Minneapolis – Wisconsin			
Kenyon et al USA 1996 Contact tracing investigation	Smear positive cavitary pulmonary TB Culture confirmed; MDR-TB Passenger Died 13 days after last flight from severe haemoptysis	4 flights: 8.5h/2h/2h/8.5h Honolulu – Chicago – Baltimore – Chicago - Honolulu	Baseline TST testing with repeat >12 weeks after exposure if initial negative Positive TST ≥ 10mm Conversion: ≥10mm increase All passengers and crew on each flight (1042 total)	925/1042 contacts notified (88.8%) 802/1042 completed screening (77%) Contacts analysed: 760	Positive TST: 23 contacts (3.0%) 20 with risk factors (2.6%) 3 no risk factors (0.4%): 1 on penultimate flight, 2 on last flight (both sat within two rows) TST conversion: 6 contacts (0.8%) 2 with risk factors (0.3%) 4 no risk factors (0.5%): Two sat within two rows, two sat between 12 – 13 rows away All on last flight Conclusion: Evidence of transmission
Miller et al USA 1996 Contact tracing investigation	Smear positive cavitary pulmonary TB Culture confirmed; fully sensitive Passenger	3 flights: Moscow – Frankfurt – New York – Cleveland	Baseline TST testing with repeat >12 weeks after exposure if initial negative Positive TST ≥5mm Conversion: ≥5mm increase All passengers and crew on last two flights (219 total)	153/203 passenger contacts and 16/16 crew members notified (77.2% total) 142/219 responded to questionnaire (64.8%) 22 known previous TB infection and excluded from further analysis 120/219 completed screening (54.8%)	Positive TST: 29 contacts (24%) 27 with risk factors (22.4%) 2 no risk factors (1.6%): sat >3 rows away from index case TST conversion: 5 contacts (4%) All with risk factors; all sat between 9 and 18 rows away from index case Conclusion: TB transmission unlikely, but could not be excluded
Moore et al USA 1996 Contact tracing investigation	Smear positive cavitary pulmonary TB Culture confirmed; fully sensitive Passenger	2 flights Both 1h15m USA domestic	Single TST testing Positive TST ≥5mm All crew and passengers resident in US (203 total)	146/188 passengers notified and 15/15 crew (79.3% total) 120/203 completed screening (59.1%) Contacts analysed: 100	Positive TST: 5 contacts (5%) All with risk factors All sat >5 rows away from index case Conclusion: Low likelihood transmission, but cannot be excluded
Beller USA 1996 Contact tracing investigation	Smear positive pulmonary TB Culture confirmed; RHE sensitive	2h30m Alaska – Anchorage	Baseline TST testing with repeat >12 weeks after exposure if initial negative All passengers and crew (12 total)	12/12 contacts notified (100%) 11/12 completed screening (91.7%) 1/12 contact not tested because known previous positive TST (8.3%)	No new positive TST results. Conclusion: No evidence of transmission

Parmet et al USA 1999 Contact tracing investigation following multiple exposures	Active tuberculosis No culture result Pilot	Multiple flights – no details specified	Single TST testing of all co-pilots flying with index case in previous six months (48 total)	48/48 co-pilots notified (100%) 1 refused testing Contacts analysed: 47 9 contacts known to have previous positive TST	No new positive TST results. Conclusion: Transmission in aircraft cabin is extremely rare
Vassiloyanokopoulos et al Greece 1999 Contact tracing investigation	Smear positive pulmonary TB Culture confirmed; INH-resistant Passenger	>8h Bangkok – Athens	Baseline TST testing with repeat >12 weeks after exposure if initial negative All passengers and crew (144 passengers total; crew unknown)	20/144 passenger contacts notified (13.9%) 3/144 passenger contacts screened (2.1%); only 1 completed screening	Positive TST: 1 contact (100%) No further details provided Conclusion: Contact tracing unlikely to be cost-effective
Wang et al Taiwan 2000 Contact tracing investigation	Smear positive cavitary pulmonary TB No culture result Passenger	14h USA - Taiwan	Baseline TST testing <4 weeks after exposure; then 1 week later and >12 weeks after exposure if negative Positive TST ≥ 10mm Booster phenomenon: ≥10mm on second test and ≥6mm increase Conversion: ≥10mm increase between first and last testing All passengers and crew (308 total)	277/308 contacts notified (89.9%) 225/308 contacts screened in first round (73.1%) 212/308 completed screening (68.8%)	Positive TST: 173 contacts (82%) Booster phenomenon: 11 contacts (5%) TST conversion: 9 contacts (4%) 6 with risk factors (3%) 3 no known risk factors (1%): sat between 15 and 23 rows away from index case Conclusion: Transmission could not be excluded
Whitlock et al New Zealand 2001 Contact tracing investigation	Smear positive cavitary pulmonary TB Culture confirmed; fully sensitive Passenger	Two flights: 8h/8h20m Auckland – Honolulu – Auckland	Baseline TST testing with repeat >12 weeks after exposure if initial negative All passengers in same section on first flight; all passengers on second flight (238 total)	206/238 contacts notified (86.6%) 142/238 contacts screened (59.7%)	Positive TST: 20 contacts (14%) All with risk factors TST conversion: 4 contacts (3%) All with risk factors Conclusion: Inconclusive evidence of transmission
Chemardin et al France	Smear positive cavitary pulmonary	5h	CXR at 0, 6 and 12 months for passengers seated	7/11 contacts notified (81.8%)	Active TB identified on CXR: 0 contacts (0%)

2007 Contact tracing investigation	TB Culture confirmed; XDR-TB Passenger Case died 10 days after travel from severe haemoptysis	Beirut - Paris	within two rows (11 total)	3/11 completed initial screening CXR (27.3%) 1/11 completed six-month CXR (9.1%)	Conclusion: No evidence at time of publication of transmission and progression to active TB
Abubakar et al UK 2008 Retrospective collective review of cases notified from 2007 – 2008	24 index cases: 19 smear positive 1 smear negative 4 unknown All culture confirmed: 3 fully sensitive 1 RIF-resistant 2 MDR-TB 18 unknown	39 flights total: Median flight duration 8.9h (IQR 8 – 11.7h) Origin/destination high burden country: 36	TST testing (criteria not specified)	Passenger manifest made available by airline for 5/24 index cases (20.8%) – 247 contacts total 50/247 contacts notified (20.2%) 4/247 screening results available (1.6%)	Positive TST: 0 contacts (0%) Conclusion: No evidence of transmission
Scholten et al Canada 2010 Retrospective review of cases notified to Public Health Agency of Canada between 2006 – 2008	101 index cases: 83 smear positive 18 smear negative 50 cavitary disease All culture confirmed: 9 cases ≥1 drug resistance Of those, 4 MDR-TB	244 flights total 108 not followed up as <8 hours; 26 referred to another country Median duration 10h (range 3 – 19h)	Not specified	Passenger manifest made available by airline for 94/110 flights (85.5%) Contact information available for 79/110 flights (71.8%) – 2472 contacts total Reported median percentage passengers with enough contact information = 96%	No results returned to PHAC on screening results Conclusion: Reports of air travel by individuals with active TB increasing; contact investigations need to be evaluated further
Kornylo-Duong et al USA 2010 Selective retrospective review of three cases reported to CDC between 2007 and 2008 (107 flights notified in total during same	3 index cases: All smear positive cavitary TB All culture confirmed: 1 fully sensitive 2 MDR-TB	Four flights: 14h Nepal – USA 15h Nepal – USA Two US domestic flights 7h40m each	Baseline TST or IGRA testing with repeat >8 weeks after exposure if initial negative Positive TST ≥5mm All passengers sat within two rows and not previously known to index	79/131 contacts notified (60.3%) 67/131 contacts completed screening (51.1%) 8 contacts known to have previous TB infection and discounted from analysis Contacts analysed = 59	Positive TST: 13 contacts (22%) All with risk factors TST conversion: 3 contacts (5%) All with risk factors Conclusion: Unable to exclude transmission

period)			case (131 total)		
Marienau et al USA 2010 Collective retrospective review cases reported to CDC between 2007 and 2008	131 index cases: 114 smear positive 16 smear negative 1 unknown 49 cavitary disease 123 culture/NAAT confirmed: 105 fully sensitive 7 mono-resistant 7 MDR-TB	159 flights total: 156 international with origin/destination USA	Baseline TST or IGRA testing with repeat >8 weeks after exposure if initial negative Positive TST ≥5mm All passengers sat within two rows and not previously known to index case (4550 total)	3375/4550 contacts notified (74.2%) 861/4550 screened of whom 790 completed screening (17.4%) 103 contacts known to have previous TB infection and excluded from analysis Contacts analysed: 687	Positive TST/IGRA: 174 contacts (25%) 127 with risk factors (18%) 11 no known risk factors (2%) 36 unknown risk factors (5%) TST/IGRA conversion: 8 contacts (1%) 3 with risk factors (0.4%) 1 no known risk factors (0.1%) 4 unknown risk factors (0.5%) Conclusion: Unable to determine transmission risk
Kim et al USA 2012 Contact tracing investigation	Smear positive cavitary TB No culture result Passenger	3 flights: >8h/<8h/<8h Japan – California – Illinois – Ohio	Testing method not specified Passengers on initial flight (>8h) sat within 2 rows only (15 in total)	15/15 contacts notified (100%) via nine US state health departments and two foreign ministries of health notified CDC notified of outcomes in 2/15 contacts (13.3%)	Both contacts identified as not to have been infected with TB (100%) – method unknown Conclusion: No evidence of transmission
Thibeault et al Canada 2012 Contact tracing investigation	Smear positive cavitary TB Culture confirmed; no sensitivities reported Crew member working for one month while symptomatic	No flight details reported	TST >8 weeks after exposure Positive TST ≥5mm If positive, referred for CXR and IGRA All crew members who had worked with index case for >8h total: 56	56/56 contacts notified (100%) 32/56 contacts screened (57.1%); of which 30/56 completed screening (53.6%)	Positive TST: 6 contacts (11%) All with risk factors IGRA performed on 4/6: 1 positive (3%) Conclusion: No evidence of transmission of TB infection to cabin crew, but cannot definitely exclude it
Flanagan et al Ireland 2016 Retrospective review of cases notified to Irish Health Protection Surveillance Centre between 2011 and 2014	6 index cases: All smear positive pulmonary TB All culture confirmed: 4 fully sensitive 2 INH resistant	9 flights total: Median flight duration 8h40m (range 8h-11h40)	Combination of TST, IGRA and CXR TST classified as positive or negative (criteria not specified) Total passenger contacts identified: 232	198/232 contacts notified (85.3%) 16/21 Irish citizens screening results returned 8/177 non-Irish citizens screening results returned (24/232 total; 10.3%) NB: Seven additional flights excluded from study as airline manifest unavailable	4/24 contacts diagnosed latent TB (17%) All with risk factors Conclusion: No evidence of transmission

Ahmadi et al Canada 2016 Retrospective review of cases notified to Public Health Agency of Canada between 2008 and 2012	146 index cases: 124 smear positive 19 smear negative 3 unknown Cavitary disease: 59 All culture confirmed: 103 fully sensitive 37 mono-resistance 6 MDR-TB	146 flights	Combination of TST or IGRA Total passenger contacts identified: 6275	5713/6275 contacts notified (91%) 653/6275 contacts screened (10.4%) Results made available to PHAC for 386 contacts (6.2%)	78 contacts diagnosed with latent TB (20%) 75 with risk factors (19%) 3 no known risk factors (1%) Conclusion: Inconclusive evidence of TB transmission
An der Heiden et al Germany 2017 Contact tracing investigation	Smear positive cavitary pulmonary Culture confirmed: XDR-TB Case died on board from acute massive haemoptysis	3h Turkey - Germany	Baseline TST or IGRA testing with repeat >8 weeks after exposure if initial negative Positive TST ≥ 10mm Conversion ≥5mm increase All crew and passengers (162 total)	147/155 passenger contacts notified (94.8%); 7/7 crew notified (100%) 112/162 contacts screened (69.1%); 61/162 completed screening (37.7%)	Positive TST: 14 contacts (13%) TST conversion: 1 contact (0.9%) Increased from 2mm at 6/52 to 14mm at 6/12 Known risk factors; sat within 2 rows Conclusion: Probable newly acquired infection in one case
Ota et al Japan 2017 Retrospective review of cases notified between 2012 and 2015; conducted via questionnaire survey of local health offices conducting contact tracing	42 index cases: All smear positive pulmonary TB All culture confirmed; no sensitivities reported	Total number flights unknown All duration >6h	IGRA and chest x-ray if indicated	Initiator health offices reported 942 total contacts for 19 index cases; IGRA results available for 523 (55.5%) Implementer health offices (those providing screening on behalf of foreign agencies) provided 128 IGRA results for 23 index cases (denominator unknown) Total IGRA results: 651	Positive IGRA: 25 contacts (4%) All Japanese residents Stratified by age: 2/205 positive in contacts age 0 – 34 (1.0%) which is comparable to known rate in healthy university students with no known previous risk Conclusion: Risk of contracting TB infection associated with air travel is “miniscule”

MDR-TB Multidrug-resistant TB; **XDR-TB** Extensively drug-resistant TB; **INH** Isoniazid; **RIF** Rifampicin; *Estimated duration

Supplementary Table 2: Quality assessment of studies using Risk of Bias for Nonrandomised Studies (RoBANS) tool

	Selection of	**Confounding**	**Measurement of**	**Blinding of**	**Incomplete data**	**Selective outcome**

	Participants	variables	Exposure	outcome assessments	outcome	reporting
McFarland	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Results stratified by country of birth/ BCG vaccination*	*All passengers on flight*	*Blinding not carried out*	*40% missing results could affect study outcome*	*No protocol or study description, but all outcomes I would expect were reported – i.e. TST results*
Driver	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*Comparison group of unexposed crew members included*	*Analyses excluded contacts or comparisons born outside USA, with previous positive TST or TB*	*All crew members who flew with index case and all frequent flyers*	*Blinding not carried out*	*23% missing results could affect study outcome*	*No protocol, but TST outcomes reported*
CDC 1995a	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Analyses excluded contacts born outside USA*	*All passengers on flight*	*Blinding not carried out*	*76% missing results*	*No protocol, but TST outcomes reported*
CDC 1995b	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group; contacts excluded if not US residents*	*Analyses excluded contacts born outside USA or with previous TST*	*All passengers on flight if from US*	*Blinding not carried out*	*75% missing results*	*No protocol, but TST outcomes reported*
Kenyon	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group; contacts excluded if not US or Canada residents*	*Analyses excluded contacts with previous positive TST or TB*	*All passengers on flight if from US or Canada*	*Blinding not carried out*	*23% missing results*	*No protocol, but TST outcomes reported*
Miller	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group; contacts excluded if not US residents*	*Analyses excluded contacts with previous positive TST or TB*	*All passengers on flight if from US*	*Blinding not carried out*	*45% missing results*	*No protocol, but TST outcomes reported*
Moore	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group;*	*Results stratified by*	*All passengers on*	*Blinding not carried*	*51% missing results*	*No protocol, but*

	contacts excluded if not US residents	*country of birth/ BCG vaccination*	*flight if from US*	*out*		*TST outcomes reported*
Beller	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias
Comment	*No control group*	*Previous positive TST excluded from testing*	*All passengers on flight*	*Blinding not carried out*	*8% missing results*	*No protocol, but TST outcomes reported*
Parmet	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias
Comment	*No control group*	*Previous positive TST results taken into account*	*All pilots flying with the index case*	*Blinding not carried out*	*2% missing results*	*No protocol, but TST outcomes reported*
Vassiloyanokopoulos	High risk of bias	High risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Previous positive TST or TB not considered*	*All passengers on flight*	*Blinding not carried out*	*98% missing results*	*No protocol, but TST outcomes reported*
Wang	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Previous positive TB accounted for*	*All passengers and crew on flight*	*Blinding not carried out*	*37% missing results*	*No protocol, but TST outcomes reported*
Whitlock	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Results stratified by country of birth/ BCG vaccination*	*All passengers and crew on flight*	*Blinding not carried out*	*40% missing results*	*No protocol, but TST outcomes reported*
Chemardin	High risk of bias	High risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Previous TB not considered*	*'Close contacts' as defined by WHO*	*Blinding not carried out*	*90% missing results*	*No protocol, but CXR findings reported*
Abubakar	High risk of bias	High risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Previous positive TST or TB not considered*	*No details given on how contacts chosen*	*Blinding not carried out*	*98% missing results*	*No protocol, but TST outcomes reported*
Kornylo-Duong	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Born or living in highly endemic country taken into account*	*Contacts sat within two rows of index case, as specified by WHO*	*Blinding not carried out*	*41% missing results*	*No protocol, but TST outcomes reported*
Marienau	High risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Results stratified by*	*Contacts sat within*	*Blinding not carried*	*85% missing results*	*No protocol, but*

		living in endemic country/previous TB	*two rows of index case, as specified by WHO*	*out*		*TST outcomes reported*
Kim	High risk of bias	High risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	High risk of bias
Comment	*No control group*	*Previous positive TST or TB not considered*	*Contacts sat within two rows of index case, as specified by WHO*	*Blinding not carried out*	*87% missing results*	*No protocol; TST outcomes not reported*
Thibeault	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*Comparison group of crew members with indirect contact included*	*Results stratified by likely BCG vaccination status*	*Direct contact – working as paired cabin crewmember; indirect contact – working on same aircraft*	*Blinding not carried out*	*46% missing results*	*No protocol, but TST outcomes reported*
Flanagan	High risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Born or living in highly endemic country taken into account*	*Contacts followed up differed with each flight, with no further details*	*Blinding not carried out*	*76% missing results*	*No protocol, but TST outcomes reported*
Ahmadi	High risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group*	*Results stratified by previous TB status*	*Not clearly defined how contacts were determined on each flight*	*Blinding not carried out*	*94% missing results*	*No protocol, but TST outcomes reported*
An der Heiden	Unclear risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group assigned, but stratified participants into low, medium or high exposure*	*Previous positive TST or TB considered*	*All passengers on flight*	*Blinding not carried out*	*39% missing results*	*No protocol, but TST outcomes reported*
Ota	High risk of bias	High risk of bias	Unclear risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias
Comment	*No control group; comparison made with university*	*Previous positive IGRA or TB not considered*	*Not clearly defined how contacts were determined on*	*Blinding not carried out*	*44% missing results*	*No protocol, but IGRA outcomes reported*

	student population		*each flight*			

Figure Legends

Figure 1: Flow chart of included studies

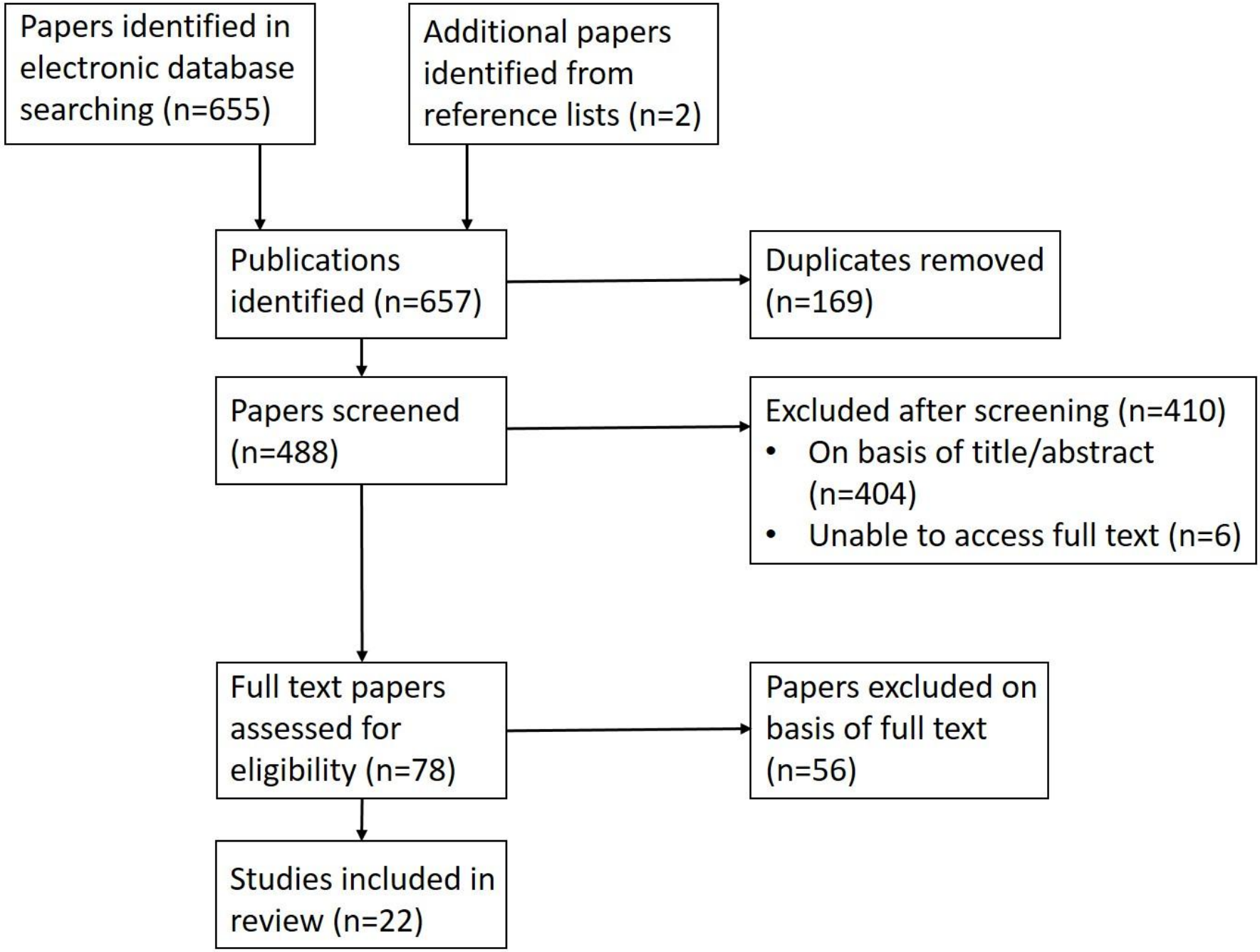
Figure 2: Quality assessment of included studies

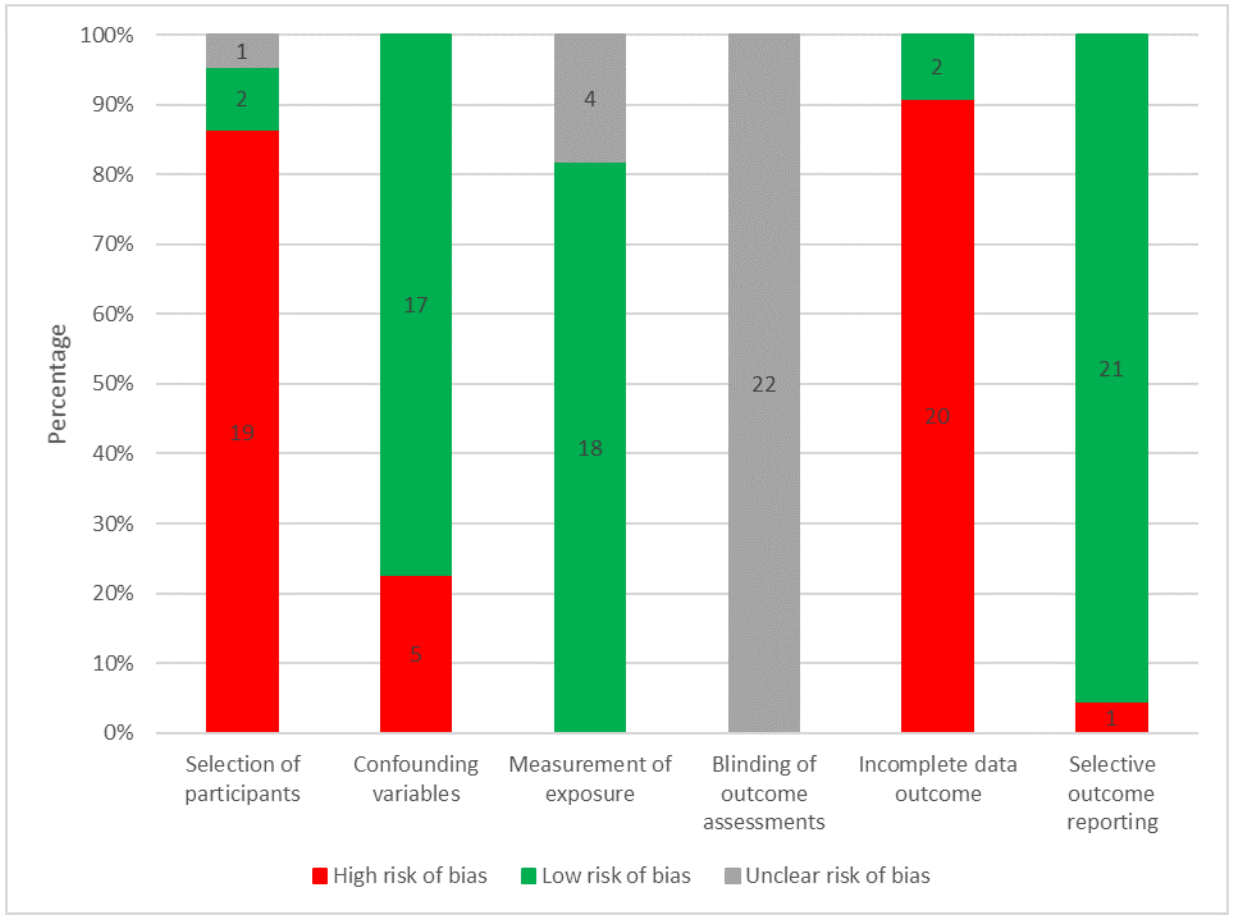
Figure 3: Screening cascade

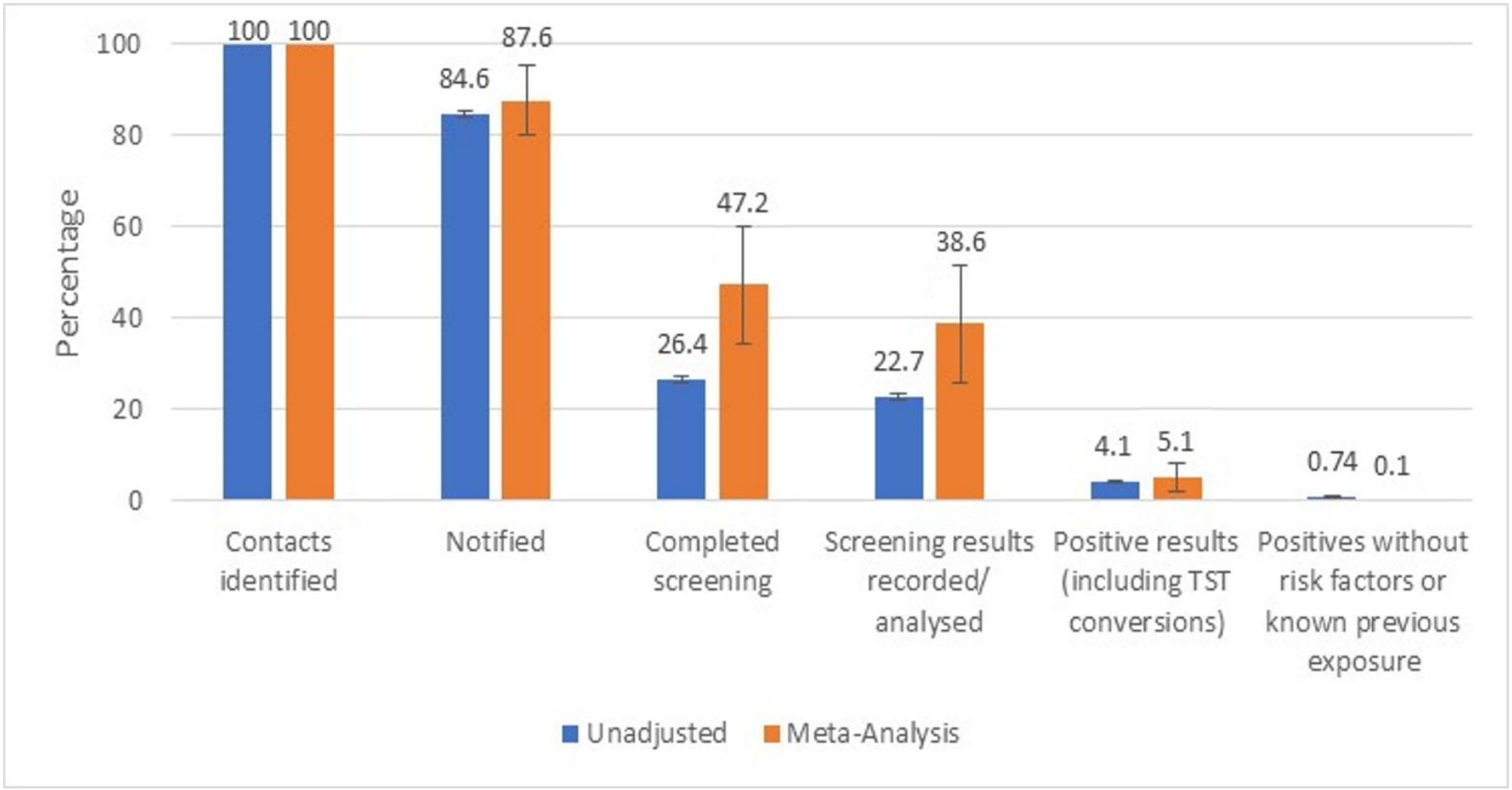
Figure 4: Screening results stratified by flight time

Annex: Forrest plots of meta-analysis

(see attached files)


Papers identified in electronic database searching (n=655)
Additional papers identified from reference lists (n=2)
Publications identified (n=657)
Duplicates removed (n=169)
Papers screened (n=488)
Excluded after screening (n=410)
• On basis of title/abstract (n=404)
• Unable to access full text (n=6)
Full text papers assessed for eligibility (n=78)
Papers excluded on basis of full text (n=56)
Studies included in review (n=22)


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage
1
2
19
17
5
4
18
22
2
20
21
1
Selection of participants
Confounding variables
Measurement of exposure
Blinding of outcome assessments
Incomplete data outcome
Selective outcome reporting
High risk of bias
Low risk of bias
Unclear risk of bias


Percentage
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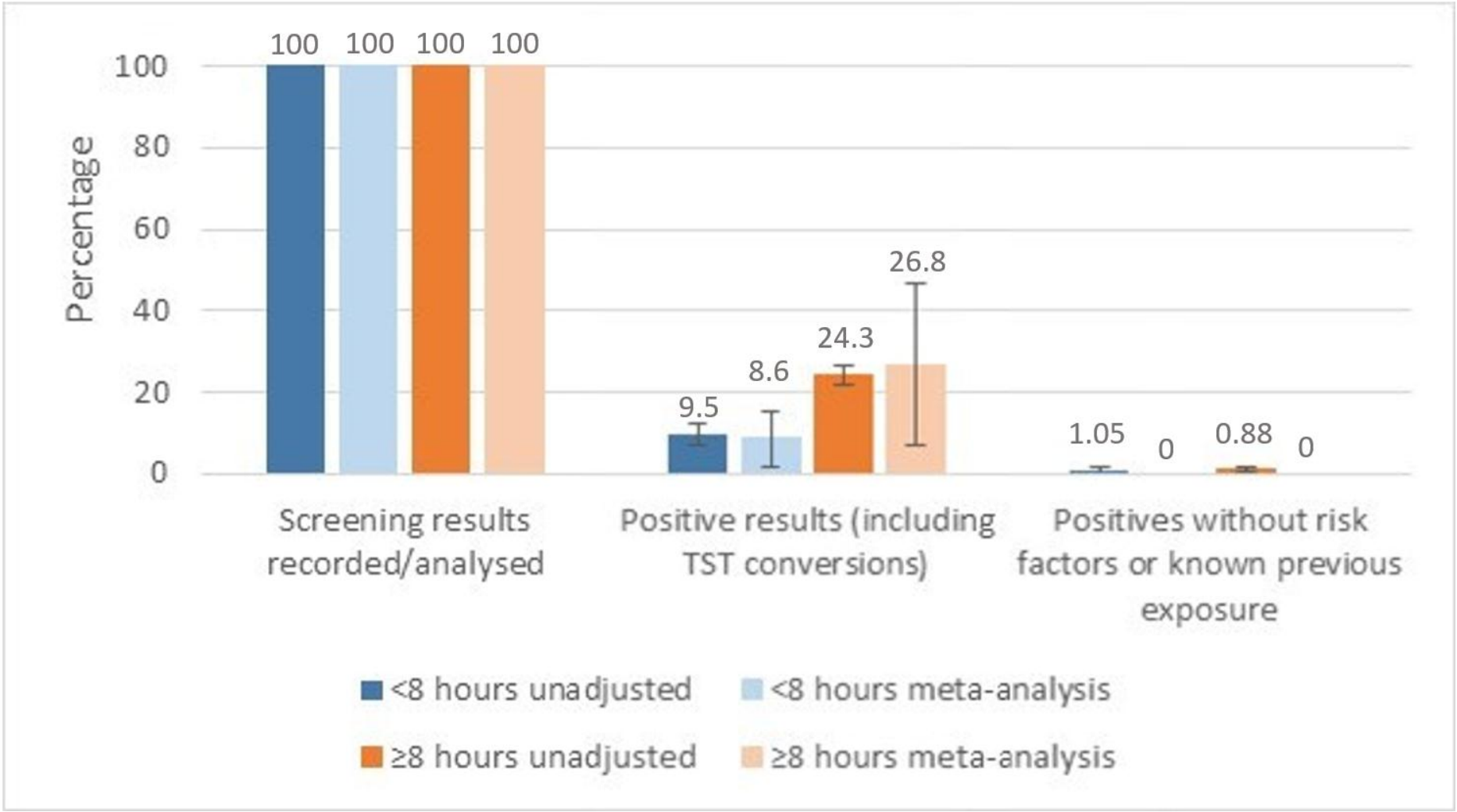
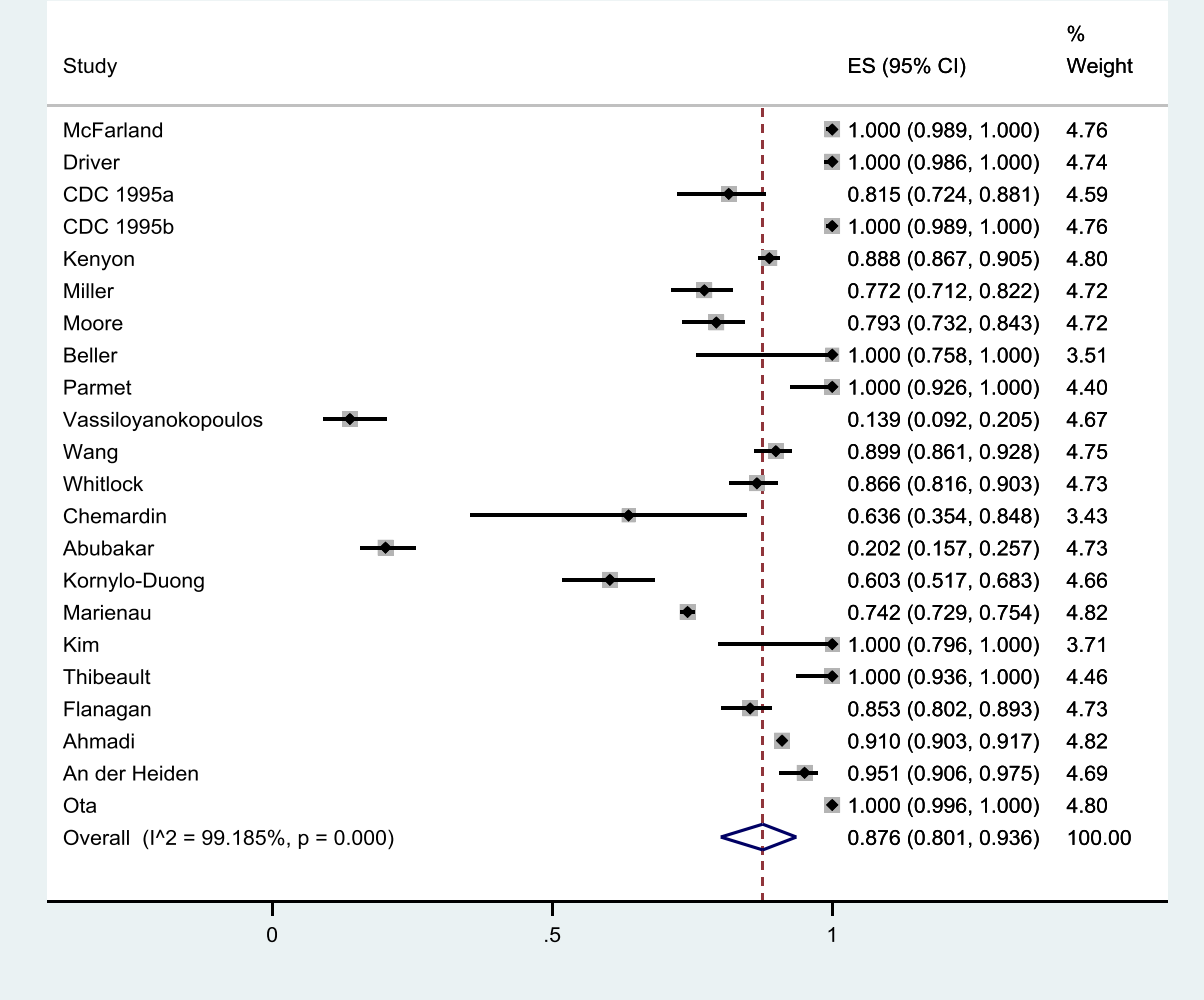
80
60
40
20
0
100
100
84.6
87.6
26.4
47.2
22.7
38.6
4.1
5.1
0.74
0.1
Contacts identified
Notified
Completed screening
Screening results recorded/ analysed
Positive results (including TST conversions)
Positives without risk factors or known previous exposure
Unadjusted
Meta-Analysis

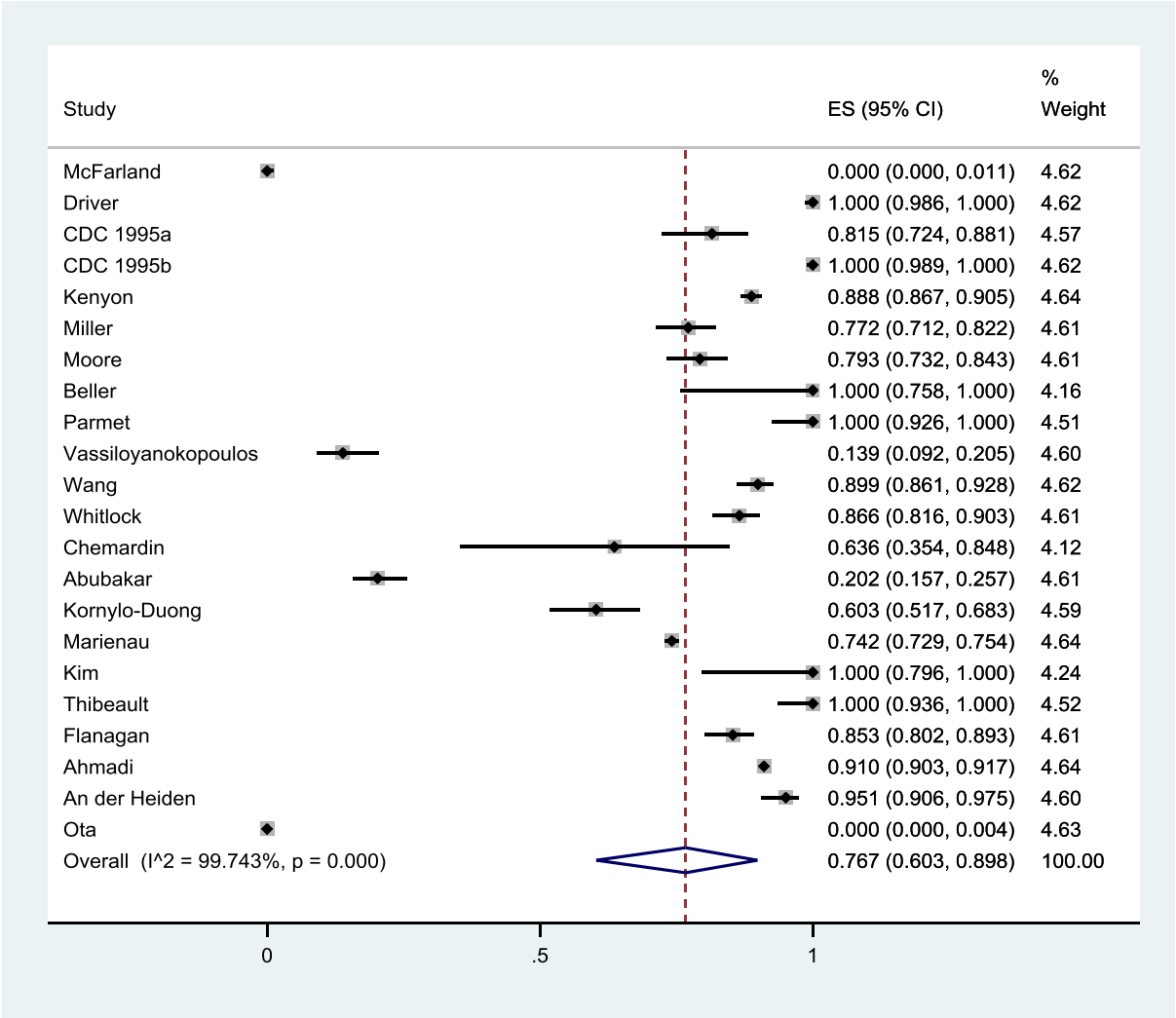

100
80
60
40
20
0
Percentage
100
100
100
100
9.5
8.6
24.3
26.8
1.05
0
0.88
0
Screening results recorded/analysed
Positive results (including TST conversions)
Positives without risk factors or known previous exposure
<8 hours unadjusted
<8 hours meta-analysis
≥8 hours unadjusted
≥8 hours meta-analysis

Annex: Forrest plots of meta-analysis

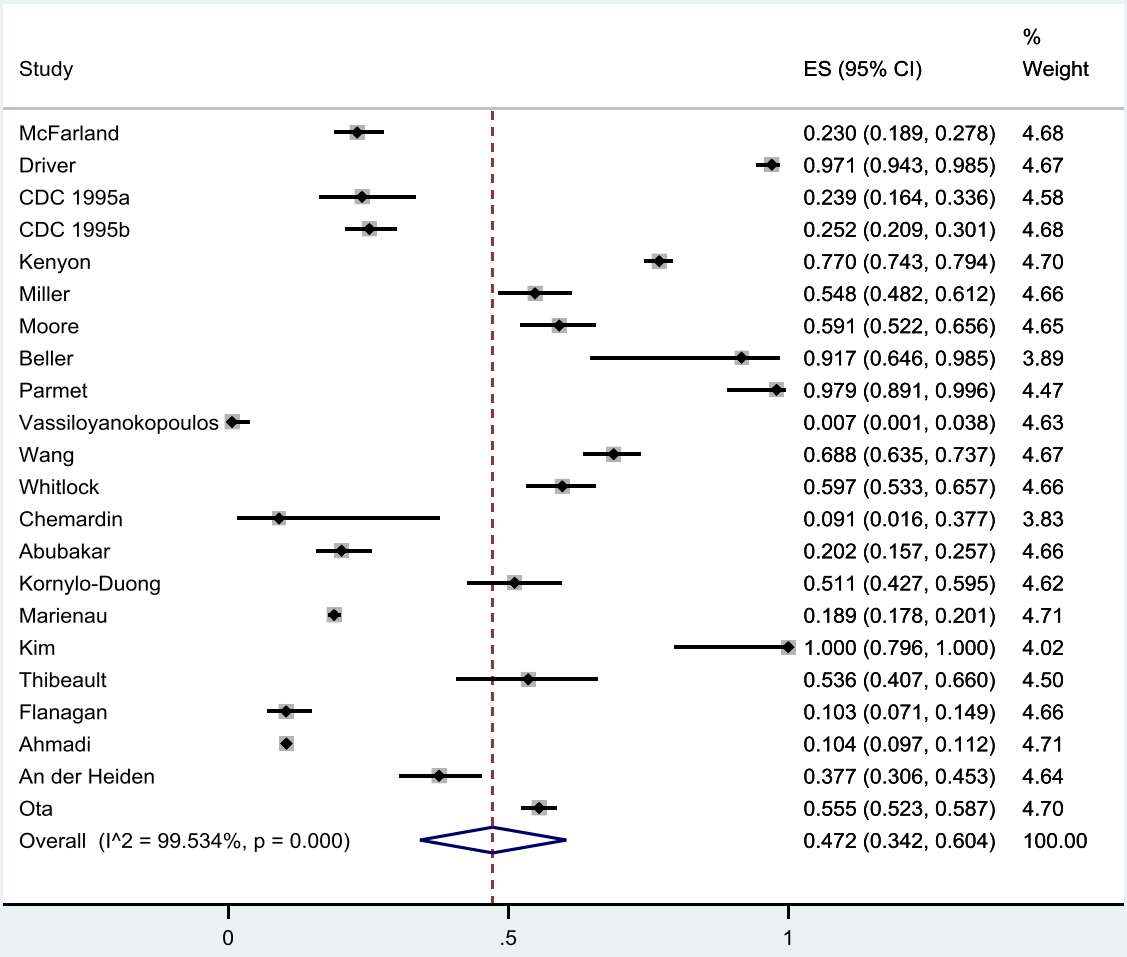
A: Proportion of total contacts identified who were notified (upper estimate)



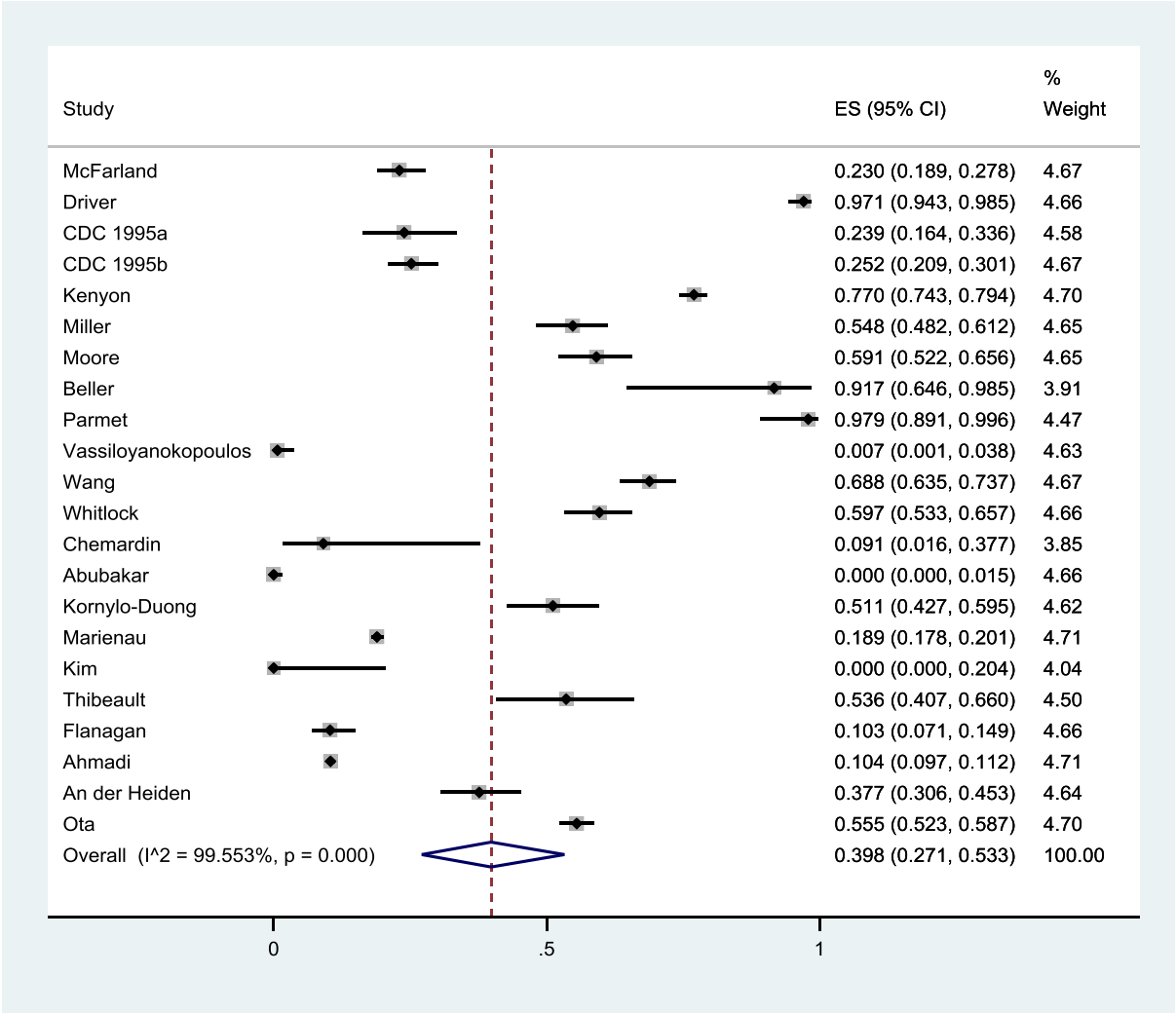
B: Proportion of total contacts identified who were notified (lower estimate)



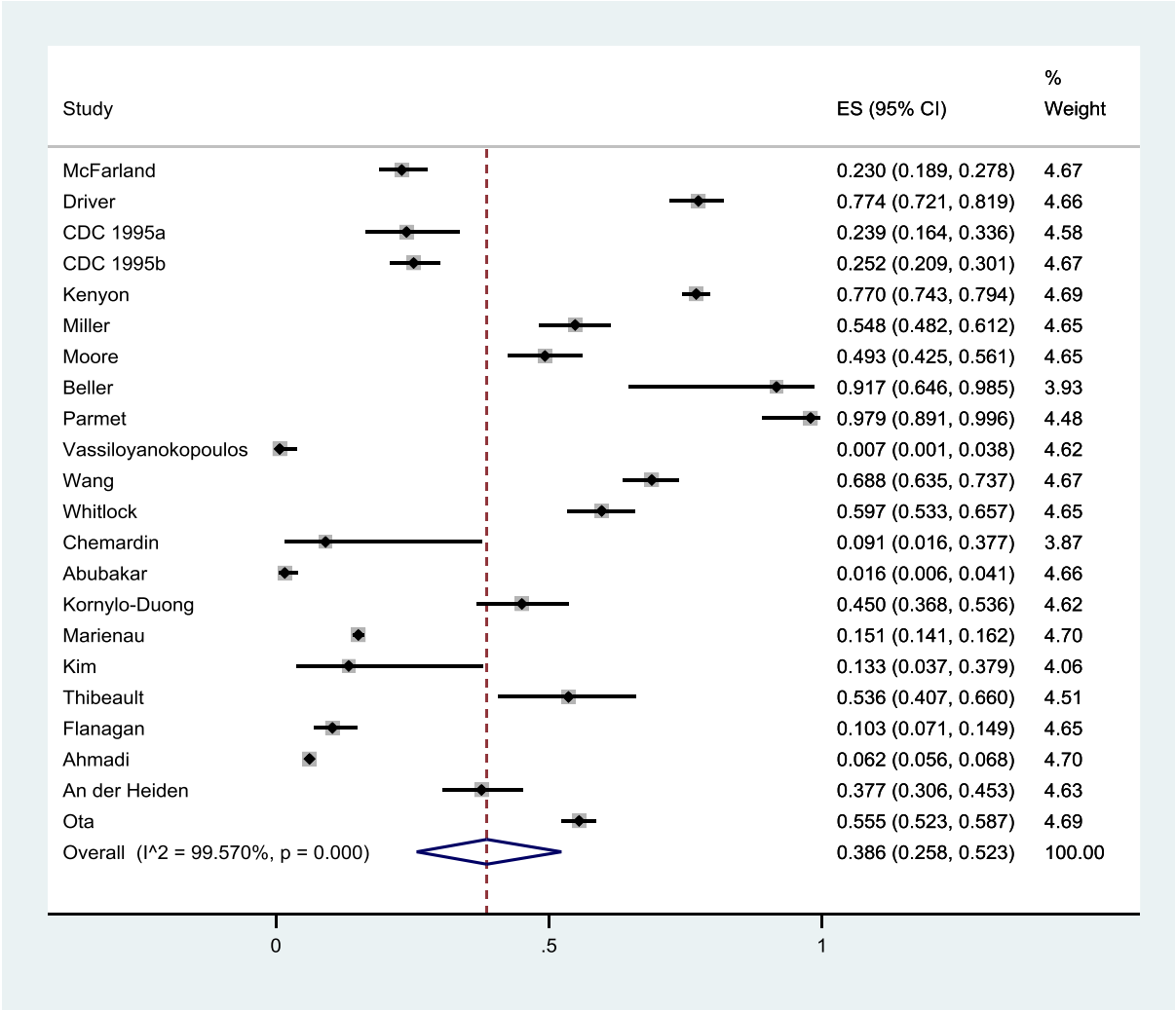
C: Proportion of total contacts identified who were screened (upper estimate)



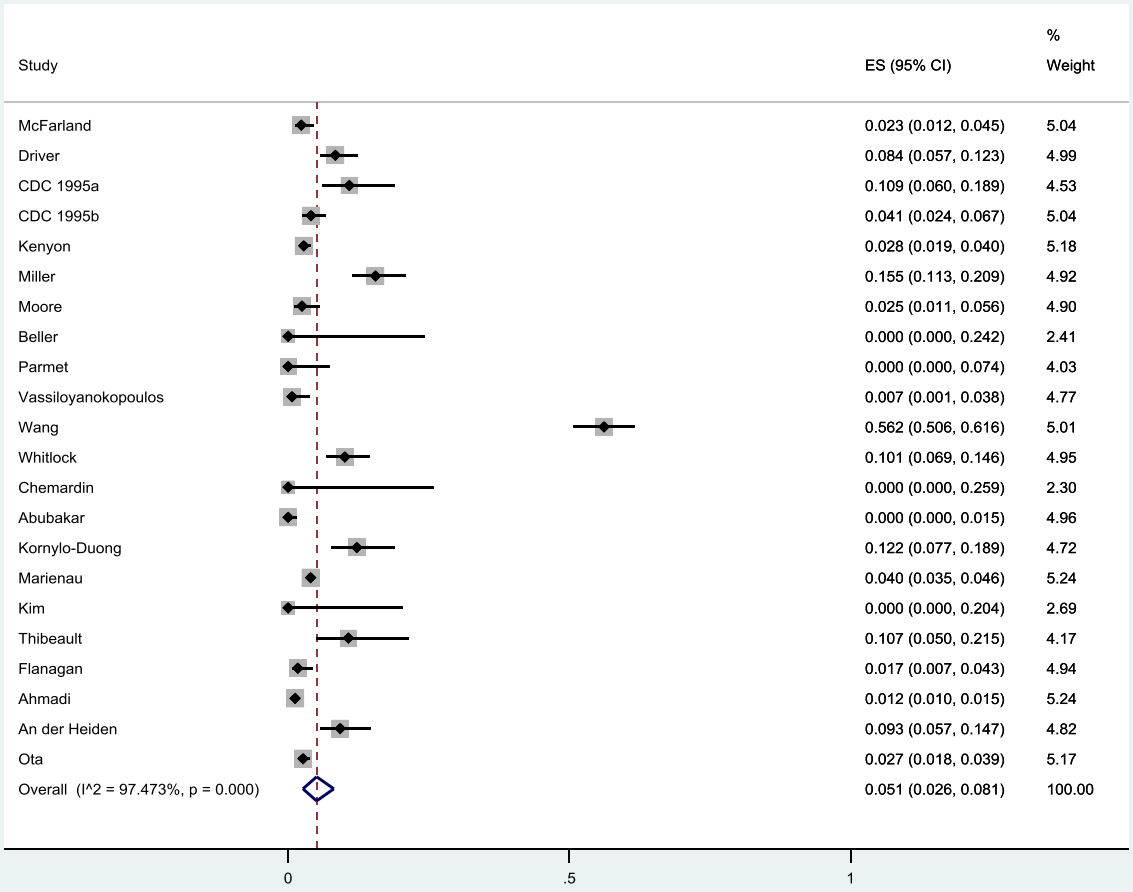
D: Proportion of total contacts identified who were screened (lower estimate)



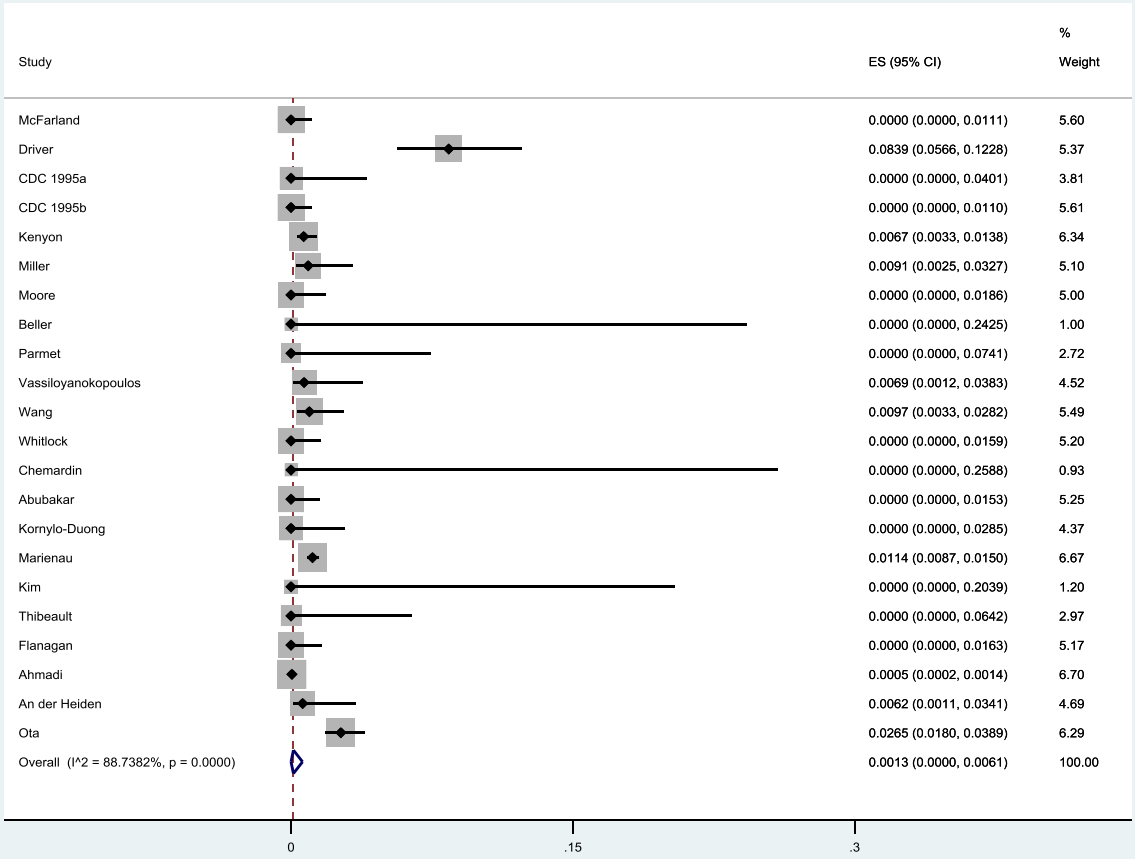
E: Proportion of total contacts identified who have results available



F: Proportion of total contacts identified who had a positive test



G: Proportion of total contacts identified who had a positive test with no risk factors (upper estimate)



H: Proportion of total contacts identified who had a positive test with no risk factors (lower estimate)