Systematic review for evidence of administrative infection control interventions to reduce TB transmission and three related background questions

Background question 1

Final report

01 October 2018 (revised report)

Authors: Katherine Fielding, Aaron Karat, Rebecca Harris, Dave Moore

Contributors: Jane Falconer, Maria Calderon, Nicky McCreesh, Akira Endo

Enquiries to: katherine.fielding@lshtm.ac.uk

Contents

List of tables

List of figures

1. Executive summary

This review addressed whether healthcare workers (HCWs) working in the settings outlined below are at higher risk of tuberculosis (TB) infection or active TB disease than the general population from which they are drawn, who are not working in healthcare settings.

1.1. Methods

The population included HCWs in hospitals (including TB hospital/wards and multidrug-resistant (MDR)-TB wards) and outpatient clinics. The comparator was the general population (outside of the healthcare setting) reported within the same publication. Outcomes were incidence or prevalence of latent TB infection (LTBI) or TB disease. The search strategy was constructed and implemented by a professional librarian, using relevant subject headings, and search terms in the title and abstract fields where possible. Searches were restricted to papers written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese, published after 1946. Bibliographic databases searched included MEDLINE, EMBASE, CINAHL Plus, and Global Health. Two independent reviewers screened publications for eligibility for inclusion using a two-stage sifting process: (1) at title and abstract; and (2) at full text level. Citations and references of selected papers were also reviewed and screened for eligibility. For systematic reviews all the source manuscripts identified by our search and deemed eligible for inclusion at screening were included; data from the systematic review itself were not extracted. Data were extracted, in duplicate, from those papers selected for final inclusion into a standardised database. Quality assessment at the study level was conducted using standardised Newcastle-Ottawa Scale tools. Extracted data were synthesised using a narrative approach and, where appropriate, fixed-effects and random-effects meta-analyses. When comparing HCWs versus the general population, odds ratios (ORs) were used for TB infection prevalence, risk/rate differences were used for TB infection incidence and rate ratios (RRs) were used for TB disease incidence. Study settings were defined as low or high TB burden using the post-2015 WHO definition.

1.2. Results

In total, 3,256 records were assessed at the title and abstract phase after removal of duplicates. After full text sifting, reference and citation tracking 49 papers were included in the review, of which 41 were primary research articles eligible for data extraction and eight were systematic reviews. Of the included primary research studies, 12 measured latent TB infection prevalence (10 using the tuberculin skin test [TST] and two using interferon-gamma release assays [IGRAs]), two measured TB infection incidence (by TST conversion) and 28 measured TB disease incidence.

A total of 10 studies (six in high TB burden countries) contributed to the meta-analysis for TB infection prevalence measured by TST using unadjusted effect estimates. The summary OR using random-effects was 2.04 (95% confidence interval [CI] 1.73–2.40; I^2 = 39.3%). Results were similar for fixed-effects meta-analysis and when stratified by low and high TB disease burden countries. Three studies in high TB burden countries reported an adjusted OR and using random effects meta-analysis the summary adjusted OR was 1.61 (95% CI 1.35–1.93; I^2 = 0%).

Two studies from high TB burden countries reported TB infection incidence, both using two-step TST. Using a cut-off of ≥10 mm increase in TST induration diameter one study reported conversion in 1.1% of healthcare students compared to none in the comparator population (percentage difference 1.1%, 95% CI −1.0–3.2), and the other reported a rate difference of an additional 13.2 conversions per 1000 person-years at risk (95% CI 6.5–20.0) for nursing students over the comparator.

Of the 28 studies that measured TB disease incidence, 20 studies (eight in high TB burden countries) contributed to the meta-analysis of unadjusted RRs. There was extreme heterogeneity across studies overall (I^2 = 99.5%) and when stratified by high (I^2 = 98.6%) or low (I^2 = 99.4%) TB burden countries. For studies from eight high TB burden countries, study-level RRs varied from 1.96 to 11.90 and the summary RRs, using random and fixed effects, were 4.32 (95% CI 2.36–7.91) and 3.00 (95% CI 2.83–3.17), respectively. For studies from the 12 low TB burden countries, study-level RRs varied from 0.35 to 11.00 (5 of 12 unadjusted study-level RRs were <1.0) and the summary RR, using random effects, was 1.28 (95% CI 0.67–2.42). Four studies, all in low TB burden countries, reported an adjusted RR; the summary estimate using random effects was 1.29 (95% CI 0.82–2.03; I^2 = 77.1%).

For the 31 cohort studies the median quality total score was 4 (range 1-7; maximum possible total score 10) and for 10 cross-sectional studies the median quality total score was 2 (range 0-4; maximum possible total score 9).

1.3. Discussion

The systematic review identified 41 articles that reported data on TB infection prevalence, incidence and TB disease incidence in HCWs versus a comparator population. Studies were conducted in low and high burden countries and few reported adjusted effect estimates. Overall HCWs had twice the odds of TB infection compared with the general population and this was similar when stratified by high or low TB burden countries. Heterogeneity across these studies was low. Summary RRs for TB disease incidence from the meta-analyses need to be interpreted with extreme caution as heterogeneity across studies was very large.

For high TB burden countries, the random and fixed effects summary RRs were 4.32 and 3.00, respectively. For low TB burden countries, the summary RR using random effects was 1.28, with the 95% CI crossing 1.

Study quality using the modified Newcastle-Ottawa scale was low for both cohort and cross-sectional studies.

2. Background and question

This review aims to quantify whether healthcare workers (HCWs) working in general hospitals (including those working on an infectious disease or respiratory wards), TB hospital/ward, Multi-drug-resistant (MDR)-TB ward and out-patient clinics are at higher risk of TB infection prevalence/incidence or active TB disease than the general population from which they are drawn, who are not working in healthcare settings.

3. Methods

3.1. Population, comparator and outcomes

Population

HCWs, including community health workers (CHWs), in the following settings:

- General hospital, including those working on an infectious disease or respiratory ward
- TB hospital/ward,
- Multi-drug-resistant (MDR)-TB ward,
- Out-patient clinic

Comparator

General population (outside of healthcare setting)

Outcomes

Compared between HCW population and general population in the same study:

- Difference in latent TB infection (LTBI) incidence/prevalence or
- Difference in TB disease incidence/ prevalence or
- Incidence/prevalence (of TB or LTBI) ratio (or other measures of relative difference)

3.2. Search strategy

Search strategies for the background questions were constructed and run by a professional librarian with experience of systematic review literature searching. The search strategy was compiled and tested on the OvidSP Medline database before being edited, as required, and run across other relevant information sources.

The search strategies used subject headings where available, and search terms in the title and abstract fields where possible. Due to language skills available in the research team, searches were limited to papers written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese. No date limits or publication type limits were added to the search.

The following search was constructed in OvidSP Medline and was adapted, as appropriate, for the other search sources.

1. respiratory care units/
2. hospitals/
3. hospitals, community/

4. hospitals, general/
5. hospitals, group practice/
6. hospitals, high-volume/
7. hospitals, low-volume/
8. exp hospitals, private/
9. exp hospitals, public/
10. hospitals, rural/
11. hospitals, satellite/
12. hospitals, isolation/
13. exp hospitals, teaching/
14. exp hospitals, urban/
15. secondary care centers/
16. tertiary care centers/
17. Intensive Care Units/
18. ambulatory care facilities/
19. outpatient clinics, hospital/
20. hospital*.ti,ab.
21. (secondary adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
22. (tertiary adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
23. (acute adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
24. (sub-acute adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
25. (subacute adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? Or unit? or theatre? or theater?)).ti,ab.
26. (intensive care adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
27. icu.ti,ab.
28. (respiratory adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
29. (pulmonary adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
30. (outpatient? adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
31. (out-patient? adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
32. (infectious adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
33. (communicable adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
34. or/1-33
35. exp tuberculosis/
36. mycobacterium tuberculosis/
37. tuberculosis.ti,ab.

38. tb.ti,ab.
39. ltbi.ti,ab.
40. or/35-39
41. 34 and 40 [HOSPITALS AND TB]
42. (tuberculosis adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
43. (tb adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit?or theatre? or theater?)).ti,ab.
44. (mdr-tb adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
45. (mdrtb adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
46. (xdr-tb adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
47. (xdrtb adj3 (clinic or facil* or centre? or center? or institut* or ward? or setting? or service? or room? or unit? or theatre? or theater?)).ti,ab.
48. or/42-47 [TB WARDS]
49. 41 or 48
50. prevalence/
51. incidence/
52. prevalence.ti,ab.
53. incidence.ti,ab.
54. epidemiol*.ti,ab.
55. survey.ti,ab.
56. rapid assessment?.ti,ab.
57. situation assessment?.ti,ab.
58. situational assessment?.ti,ab.
59. rar.ti,ab.
60. cohort.ti,ab.
61. surveillance.ti,ab.
62. screening.ti,ab.
63. or/50-62 [PREVALENCE]
64. exp administrative personnel/
65. emergency responders/
66. exp health personnel/
67. medical laboratory personnel/
68. staff*.ti,ab.
69. healthcare worker?.ti,ab.
70. health-care worker?.ti,ab.
71. hcw.ti,ab.
72. nurse?.ti,ab.
73. doctor?.ti,ab.
74. physician?.ti,ab.
75. surgeon?.ti,ab.

76. (anaesthetist? or anesthetist? or anesthesiologist?).ti,ab.
77. dentist?.ti,ab.
78. physiotherapist?.ti,ab.
79. physical therapist?.ti,ab.
80. dietician?.ti,ab.
81. occupational therapist?.ti,ab.
82. psychiatrist?.ti,ab.
83. mortician?.ti,ab.
84. coroner?.ti,ab.
85. (orderly or orderlies).ti,ab.
86. contractor?.ti,ab.
87. or/64-86 [STAFF]
88. 49 and 63 and 87
89. Humans/
90. Animals/
91. 89 and 90
92. 90 not 91 [ANIMAL STUDIES ONLY]
93. 88 not 92
94. (chinese or english or french or japanese or portuguese or russian or spanish).lg.
95. 93 and 94
96. remove duplicates from 95

3.3. Bibliographic databases

The following bibliographic databases were used: OvidSP MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE; Daily and Ovid MEDLINE 1946 to present; OvidSP EMBASE Classic + Embase 1947 to present; EBSCO CINAHL Plus; and OvidSP Global Health 1910 to present.

3.4. Eligibility criteria

3.4.1. Inclusion criteria

Types of participants

Studies on HCWs (including community health workers) working in healthcare settings or other staff working in a healthcare setting in the following settings: general hospital, TB hospital/ward, MDR-TB ward, out-patient clinic.

Types of study

Any consecutive case series, case control study, cohort study, randomised controlled study, systematic review, or meta-analysis including a comparator group reporting on the outcomes listed below.

Types of comparator

Studies also reporting data from the general population.

Types of outcome measures

- Studies reporting data on at least one of the outcome measures of interest: difference in LTBI incidence/cumulative incidence/prevalence; or difference in TB incidence/cumulative incidence/prevalence; or incidence rate ratio or prevalence ratio or odds ratio for active TB or LTBI
- LTBI incidence and prevalence based on tuberculin skin tests (TST) (using any method) or interferon-gamma release assays (IGRAs, including QuantiFERON-TB (QFT) Plus, QFT Gold, QFT Gold In-Tube, and TSPOT.TB)
- TB disease based on microbiological (smear microscopy, culture, or molecular diagnostic), radiological, or clinical diagnosis

3.4.2. Exclusion criteria

- Any study not in humans
- Any study that did not report any of the above-stated outcomes of interest
- Any study reporting solely on primary outcomes of interest without a control or comparator group
- Any systematic review superseded by an updated systematic review
- Narrative reviews not adding new data or new analysis of data to existing knowledge
- Commentaries and mathematical modelling studies
- Studies with fewer than 10 participants per comparator arm
- Any study not written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese
- Any study published before 1946

3.5. Data extraction

A two-stage sifting process was employed to screen publications: (1) at title and abstract; and (2) at full text level for eligibility for inclusion using the criteria listed. Articles identified from the reference lists and citations of all included articles were also sifted. Sifting was performed in duplicate independently by two reviewers and any unresolved disagreements in sifting were resolved by a third, independent reviewer. Data were extracted from papers included after full text sifting in duplicate using a standardised Excel database. Any unresolved disagreements in extraction were resolved by a third, independent reviewer. For systematic reviews, data from all the source manuscripts identified by our search were included; data were not extracted from the systematic review itself.

3.6. Quality assessment

Assessment of bias was conducted at the study level, as prescribed in the PRISMA statement for reporting of systematic reviews.[1] Assessment of bias at the study level was assessed using the Newcastle-Ottawa Scale

for assessing the quality of non-randomised studies for case-control and cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). For cross-sectional studies, a published adapted Newcastle-Ottawa Scale for cross sectional studies was employed.[2] Data used from conference abstracts meeting the inclusion criteria, were not assessed for risk of bias.

3.7. Data synthesis

Extracted data were synthesised using a narrative approach and meta-analyses. TB infection prevalence was summarised by the percentage (and n/N) with the outcome and an odds ratio (OR) and 95% confidence interval (CI) for the comparison of health care workers (HCW) versus the comparator group(s). Analyses were stratified by type of TB infection measure (TST vs. QFT/TSPOT). The unadjusted OR and 95% CI were calculated directly from the available data and used in the meta-analysis. TB infection incidence was summarised a risk (and n/N) or rate (events/person-years [pyrs]), and a risk/rate difference for the comparison of health care workers (HCW) versus the comparator group(s).

TB disease incidence was summarised by a rate per 100,000 pyrs (events/pyrs where reported) and a rate ratio (RR) and 95% CI for the comparison of health care workers versus the comparator group(s). If the RR and/or 95% CI were not reported in an included publication, the RR and standard error (SE) for the natural logarithm of the RR (lnRR) were calculated from the available data. For studies where a CI was not reported and a SE for the lnRR could not be calculated were summarised in the descriptive tables only.

Extracted data from all comparisons, across all studies were first displayed using a Forest plot, without calculation of a summary measure, displaying data stratified by high and low TB burden countries,[3] based on unadjusted effect estimates. For the meta-analysis, each study contributed one effect estimate, with the primary analysis based on unadjusted effect estimates. Both fixed and random effects models were presented alongside the I^2 statistic measuring between-study heterogeneity. A second analysis was conducted restricted to studies which reported an adjusted effect estimate. For studies where there was more than one effect estimate, we adopted the approach described in Table 1 to define the effect estimate used in the meta-analysis.

A sensitivity analysis was conducted restricting data from HCWs to those working in high TB risk health care settings, including, though not restricted to, TB wards.

4. Results

4.1. Articles identified

In total, after duplicates were removed, 3,256 records were assessed at the title and abstract phase. Of these, 49 went to full text sifting and 29 were selected for data extraction. Following reference and citation review, a total of eight review articles and 41 primary research articles were selected. (Figure 1, Table 2).

Of the 41 primary research articles identified, 12 measured TB infection prevalence (10 using TST and two using interferon-gamma release assays), two measured TB infection incidence (both using TST conversion), and 28 measured TB disease incidence. Table 17 lists the figures in the report showing forest plots of the extracted data.

4.2. TB infection prevalence – data summaries and meta-analysis

Twelve studies (8 from high TB burden countries) measured TB infection prevalence in health care workers compared to a general population group (see Table 9). Ten studies used tuberculin skin tests and two used IFN-ɣ release assays (QuantiFERON–TB Gold and T-SPOT.TB). From these 12 studies, 19 unadjusted effect estimates and their associated 95% CIs were obtained (Table 3, Figure 2- no summary measure). One study (Agaya 2015)[4] reported an adjusted OR for the HIV-negative subgroup and an unadjusted OR could not be calculated with the available data (see Table 9).

A meta-analysis was conducted, restricted to studies using TST to measure TB infection prevalence and using one unadjusted comparison per study. For Silva[5] and Nikokar[6] the outcome of TST response (not using the 2-step procedure) was used, for Golchin,[7] TST ≥10 mm outcome was used and for Maciel,[8] medical and nursing students were combined and compared with economics students. Results from the meta-analysis using random effects are presented in Figure 3 (Figure 10 for fixed effects meta-analysis), overall and stratified by low or high TB burden setting. Summary measures are presented in Table 4, using both fixed and random effects.

Four studies (three high TB burden countries) also reported an adjusted effect of the HCW versus general population (Figure 4). Hohmuth[9] adjusted for age, sex, number in household not having electricity, running water and sewer access in home and history of BCG, Powell[10] adjusted for age and sex, Agaya[4] adjusted for sex, HIV status, active TB contact and persons/room in household, and Rutanga[11] adjusted for age, sex HIV status, active TB contact and persons/room in household.

4.3. TB infection incidence

Two studies (both in high TB burden countries) reported TB infection incidence, as measured by TST conversion, and compared heath care workers with the general population using a risk and rate differences (Table 5 and Table 6).

4.4. TB disease incidence – data summaries and meta-analyses

A total of 28 studies (10 in high burden TB settings) that measured TB disease incidence in HCWs and a comparator population were identified (see Table 10). It was not possible to calculate the CI for the RR for six studies. Of the remaining 22 studies (eight in high burden TB settings) an unadjusted RR and 95% CI were reported or could be calculated from the data extracted for 20 studies (eight in high burden TB setting) (Table 7). For two studies (Pan 2015[12] and Riley 1997[13]) only an adjusted RR and 95% CI were reported and an unadjusted RR and 95% CI could not be calculated from the available data.

Of the 20 studies, the number of comparisons within a study ranged from 1 to 36 and overall there were a total of 107 comparisons (Table 7).

Figure 5 and Figure 6 show the Forest plots for all available comparisons for high and low TB burden countries, respectively. Figure 7 and Figure 8 show the Forest plots and summary RR and 95% CI, after collapsing the data so that each study contributes one effect estimate, for high and low TB burden countries, respectively. Twenty studies, eight and 12 in high and low burden TB countries, respectively, contributed to these analyses. Heterogeneity across studies was very large; overall the I^2 was 99.5%. For studies from the eight high TB burden countries, the I^2 was 98.6% and the study-level RRs varied from 1.96 to 11.90. For studies from the 12 low TB burden countries, the I^2 was 99.4%; study-level RRs varied from 0.35–11.00; and 5/12 unadjusted study-level RRs were <1.0.

Results from the fixed effects meta-analysis are shown in Table 8, Figure 11, and Figure 12. Table 14 summarises the data used and how the study-level RR and 95% CI were calculated. Five studies reported adjusted effect estimates (four in low TB burden countries) and these are summarised in Figure 9. Riley,[13] Pan,[12] and Classens[14] adjusted for age and sex using indirect standardisation, Raitio[15,16] adjusted for age, and Chu[17] adjusted for age and Charlson Comorbidity Index score. For studies conducted in low TB burden countries the summary estimate using random effects was 1.29 (95% CI 0.82–2.03; I^2 = 77.1%). Results from fixed effects meta-analysis are in Figure 13. The original data are listed in Table 11, which includes data from Burrill[18] (1985), which reported an adjusted RR with no confidence interval.

4.5. Quality assessment

Quality assessments using the modified Newcastle-Ottawa scale (maximum possible total score is 10) for the 31 cohort studies are summarised in Table 12. The overall score ranged from 1 to 7 with a median of 4. Most studies scored well for the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of outcome and length of follow-up for outcomes to occur; and scored poorly for ascertainment of exposure, demonstration that outcome was not present at start, non-response rate for retrospective cohorts and adequacy of follow up of cohorts for prospective studies.

Quality assessments using the modified Newcastle-Ottawa scale (maximum possible total score is nine) for the 10 cross-sectional studies are summarised in Table 13. The overall score ranged from 0 to 4 with a median of 2. Most studies scored poorly for sample size, ascertainment of exposure, management of non-respondents, assessment of outcome and statistical tests.

4.6. Sensitivity analysis – high TB risk health care settings

A sensitivity analysis was conducted restricting data from HCWs to those working in high TB risk health care settings.

4.6.1. TB infection prevalence

Table 15 summarises the studies contributing to this sensitivity analysis, including the description of the high TB risk health care setting. Overall, seven of the 10 studies using TST to measure TB infection prevalence were included in this sensitivity analysis.

Four of six studies conducted in high TB burden settings contributed data to the sensitivity analysis, either as the health care setting overall was defined as high-risk (Chaudhry, Maciel) or the authors reported data stratified by high/low-TB risk in their health care setting (Agaya, Powell). Results from the meta-analysis using random effects are presented in Figure 14. The I^2 was 67.4%, and the study-level ORs varied from 1.34 to 3.66 giving a summary OR, using random effects, of 2.04 (95% CI 1.34 to 3.11).

Three of four studies conducted in low TB burden settings contributed data to the sensitivity analysis, either as the health care setting overall was defined as high-risk (Nikokar) or the authors reported data stratified by high/low-TB risk in their health care setting (El Houssine, Rutanga). Results from the meta-analysis using random effects are presented in Figure 14. The I^2 was 58.5%, and the study-level ORs varied from 2.03 to 3.78 giving a summary OR, using random effects, of 2.30 (95% CI 1.76 to 3.01).

4.6.2. TB disease incidence

Table 16 summarises the studies contributing to this sensitivity analysis, including the description of the high TB risk health care setting. Overall, four of the 20 studies measuring TB disease incidence were included in this sensitivity analysis.

Four of eight studies conducted in high TB burden settings contributed data to the sensitivity analysis, as either the health care setting overall was defined as high-risk (Claassens, Eyob, Harries) or the authors reported data stratified by high/low-TB risk in their health care setting (Pazin-Filho). Results from the meta-analysis using random effects are presented in Figure 15. The I^2 was 88.7%, and the study-level RRs varied from 2.34 to 12.60 giving a summary RR, using random effects, of 6.75 (95% CI 2.45 to 18.58).

None of the 12 studies conducted in low TB burden settings reported TB incidence rates in high TB risk health care setting and so a sensitivity analysis was not conducted.

5. Discussion

The systematic review identified 41 articles that reported data on at least one of TB infection prevalence, TB infection incidence and TB disease incidence in HCWs and in a suitable comparator population. Studies were conducted in low and high burden countries and the minority reported adjusted effect estimates. Overall HCWs had twice the odds of TB infection compared with the general population without exposure to a healthcare setting and this was similar when stratified by high or low TB burden countries. Heterogeneity across these studies was low. Three studies from low TB burden settings reported adjusted ORs for TB infection prevalence; the summary OR indicated HCWs were associated with a 60% increase in odds of TB infection compared to the general population.

Summary RRs from the meta-analyses for TB disease incidence need to be interpreted with extreme caution as heterogeneity across studies was very large. For high TB burden countries (eight studies), the random and fixed effects summary RRs were 4.32 and 3.00 respectively. For low TB burden countries (12 studies), the summary RR using random effects was 1.28, with the 95% CI crossing 1. Five of 12 unadjusted study-level RRs were <1.0.

6. Annexes

6.1. Main tables

Table 1. Definition of effect estimate used in meta-analysis when there are multiple effect estimates within a study

	Scenario – data as reported in publication	Analytic approach for the meta-analysis to obtain a single effect estimate per study
1a	Separate effect estimates for subgroups of the exposed and unexposed and where no overall effect estimate is reported and cannot be calculated from the available data	Conducted a random effects meta-analysis within the study to obtain a study-level summary effect estimate & 95% CI.
1b	Separate effect estimates for subgroups of the exposed and unexposed and where no overall effect estimate was reported but can be calculated from the available data	Data were collapsed across the subgroups and a study-level effect estimate & 95% CI was calculated.
2a.	There are ≥2 exposed groups compared to the same unexposed group, within a study and no overall effect estimate is reported.	Data were collapsed access the exposed groups (into a single exposed group) and a study-level effect estimate & 95% CI was calculated. One caveat with this approach was that equal probability of being sampled for each exposed subgroup was assumed.
2b.	There are ≥2 exposed groups compared to the same unexposed group, within a study and no overall effect estimate is reported. Further, only the effect estimates and 95% CIs are reported, and therefore we cannot adopt approach 2a.	Conducted a random effects meta-analysis within the study to obtain a study-level summary effect estimate & 95% CI. One caveat with this approach was that the same comparator group was used for each exposed subgroup.
3.	There are ≥2 “unexposed” groups compared to the same exposed group, within a study.	One of the unexposed groups was chosen for the comparison and a study-level effect estimate and 95% CI was calculated
4	Multiple outcomes within a study.	One outcome was chosen, based on being most consistent with the outcomes used in other studies.
5	Overall and subgroup comparisons within a study (eg., overall and then among males and females)	The “overall” comparison was used.

Table 2. List of 41 primary research articles selected and their outcomes

First author	Year	Title	Country	Low/high TB burden	TB infection prev.	TB infection incid.	TB disease incid.
Agaya[4]	2015	Tuberculosis and latent tuberculosis infection among healthcare workers in Kisumu, Kenya.	Kenya	high	y		
Burrill[18]	1985	Tuberculosis in female nurses in British Columbia: implications for control programs.	Canada	low			y*
Chaudhry[19]	2017	Prevalence of latent tuberculosis among exposed population of medical students as compared with unexposed population of non-medical students and its relation with duration of exposure.	India	high	y		
Chen[20]	2014	Tuberculosis among healthcare workers in Southeastern China: A retrospective study of 7-year surveillance data 2014	China	high			y
Chu[17]	2014	Risk of tuberculosis among healthcare workers in an intermediate-burden country: A nationwide population study.	Taiwan	low			y
Claassens[14]	2010	Tuberculosis among community-based health care researchers.	South Africa	high			y
Corbett[21]	2007	Nursing and community rates of *Mycobacterium tuberculosis* infection among students in Harare, Zimbabwe.	Zimbabwe	high		y	
Cuhadaroglu[22]	2002	Increased risk of tuberculosis in health care workers: a retrospective survey at a teaching hospital in Istanbul, Turkey.	Turkey	low			y*
Dimitrova[23]	2005	Increased risk of tuberculosis among health care workers in Samara Oblast, Russia: analysis of notification data.	Russia	high			y*
Driver[24]	2005	Tuberculosis in health care workers during declining tuberculosis incidence in New York State.	USA	low			y
Drobniewski[25]	2007	Rates of latent tuberculosis in health care staff in Russia.	Russia	high	y		
El Houssine[26]	2004	Assessment of the risk of tuberculosis among health care personnel in Meknes.	Morocco	low	y		

First author	Year	Title	Country	Low/high TB burden	TB infection prev.	TB infection incid.	TB disease incid.
Eyob[27]	2002	Increase in tuberculosis incidence among the staff working at the Tuberculosis Demonstration and Training Centre in Addis Ababa, Ethiopia: a retrospective cohort study (1989–1998).	Ethiopia	high			y
Golchin[7]	2005	Tuberculin test in nursing and human-sciences students.	Iran	low	y		
Harries[28]	1999	Tuberculosis in health care workers in Malawi.	Malawi	high			y
Hill[29]	1997	Tuberculosis in National Health Service hospital staff in the west Midlands region of England, 1992–5.	United Kingdom	low			y
Hohmuth[9]	2006	Latent tuberculosis infection: risks to health care students at a hospital in Lima, Peru.	Peru	high	y	y	
Klimuk[30]	2014	Tuberculosis in health care workers in Belarus.	Belarus	high			y
Krüüner[31]	2001	Tuberculosis as an occupational hazard for health care workers in Estonia.	Estonia	low			y*
Marena[32]	1996	Occupational tuberculosis infection among health care personnel. Eleven years' experience in a large university hospital.	Italy	low			y
Maciel[8]	2007	Nosocomial *Mycobacterium tuberculosis* transmission among healthcare students in a high incidence region in Vitoria, State of Espirito Santo.	Brazil	high	y		
Nikokar[6]	2015	A comparison of two-step tuberculin skin test between health-care workers and nonhospital employees.	Iran	low	y		
O'Donnell[33]	2010	High incidence of hospital admissions with multidrug-resistant and extensively drug-resistant tuberculosis among South African health care workers.	South Africa	high			y
O'Hara[34]	2017	Infection control and tuberculosis in health care workers: an assessment of 28 hospitals in South Africa.	South Africa	high			y

First author	Year	Title	Country	Low/high TB burden	TB infection prev.	TB infection incid.	TB disease incid.
Ohmori[35]	2007	Current epidemiological situation of tuberculosis in the workplace: considering the risk of tuberculosis among nurses.	Japan	low			y
Ong[36]	2006	Tuberculosis in Healthcare workers: A molecular epidemiologic study in San Francisco	USA	low			y
Pan[12]	2015	Tuberculosis in Healthcare Workers: A Matched Cohort Study in Taiwan.	Taiwan	low			y
Pazin-Filho[37]	2008	Tuberculosis among health care workers in a Brazilian tertiary hospital emergency unit.	Brazil	high			y
Pleszewski[38]	1998	Tuberculosis among health care workers in British Columbia.	Canada	low			y
Powell[10]	2011	Prevalence and risk factors for tuberculosis infection among personnel in two hospitals in Viet Nam.	Viet Nam	high	y		
Raitio[15]	2000	Tuberculosis among health care workers during three recent decades.	Finland	low			y
Raitio[16]	2003	Is the risk of occupational tuberculosis higher for young health care workers?	Finland	low			y
Reis[39]	2012	Tuberculosis in health-care workers: 5-year, multi-institutional analysis of the northern region of Portugal.	Portugal	low			y
Riley[13]	1997	Tuberculosis in health service employees in Northern Ireland.	Northern Ireland	low			y
Rutanga[11]	2015	Latent tuberculosis infection and associated factors among Health Care Workers in Kigali, Rwanda.	Rwanda	low	y		
Shimouchi[40]	2007	Discussion on incidence of tuberculosis patients among nurses in Osaka city.	Japan	low			y
Silva[5]	2000	Medical students at risk of nosocomial transmission of *Mycobacterium tuberculosis.*	Brazil	high	y		
Skodric-Trifunovic[41]	2009	The risk of occupational tuberculosis in Serbian health care workers.	Serbia	low			y*
Sotgiu[42]	2008	High risk of tuberculosis in health care workers in Romania.	Romania	low			y

First author	Year	Title	Country	Low/high TB burden	TB infection prev.	TB infection incid.	TB disease incid.
Wilkinson[43]	1998	Increasing frequency of tuberculosis among staff in a South African district hospital: impact of the HIV epidemic on the supply side of health care.	South Africa	high			y*
Zhu[44]	2014	The performance and limitation of T-SPOT.TB for the diagnosis of TB in a high prevalence setting.	China	high			

*data do not contribute to meta-analysis as a confidence interval for the effect estimate could not be calculated with the available data.

TB dis incid.: TB disease incidence; TB infection incid.: TB infection incidence; TB infection prev.: TB infection prevalence.

Table 3. Summary of 12 studies (8 in high TB burden countries) contributing to data summaries, based on unadjusted effect estimates, comparing TB infection prevalence in healthcare workers versus the general population

First author	Year	Country	Low/high burden	Measure used for latent TB infection	Number of comparisons*
Silva	2000	Brazil	high	TST ≥10mm; and 2-step TST	2
Hohmuth	2006	Peru	high	TST ≥10mm	1
Drobniewski	2007	Russia	high	QuantiFERON–TB Gold	3
Maciel	2007	Brazil	high	TST ≥10mm using 2-step TST	2
Powell	2011	Viet Nam	high	TST ≥10mm	1
Zhu	2014	China	high	TSPOT.TB	1
Agaya	2015	Kenya	high	TST ≥10mm (≥5mm for HIV+)	1
Chaudhry	2017	India	high	TST ≥10mm	1
ElHoussine	2004	Morocco	low	TST ≥10mm	2
Golchin	2005	Iran	low	TST ≥10mm; and ≥15mm	2
Nikokar	2015	Iran	low	TST ≥10mm; and 2-step TST	2
Rutanga	2015	Rwanda	low	TST ≥10mm (≥5mm for HIV+)	1

* for unadjusted comparisons

TST tuberculin skin test; mm millimetre; HIV+ HIV positive; QuantiFERON–TB Gold and TSPOT.TB are interferon-gamma release assays

Table 4. Summary of meta-analyses based on unadjusted ORs (10 studies) comparing TB infection prevalence (using TST) in healthcare workers versus the general population

Low/high TB burden setting	Number of studies	Fixed effects		Random effects		I^2
		OR	95% CI	OR	95% CI	
All	10	2.04	(1.81-2.30)	2.04	(1.73-2.40)	39.3%
High	6	1.93	(1.6502.25)	2.01	(1.62-2.50)	42.9%
Low	4	2.22	(1.84-2.67)	2.08	(1.60-2.71)	37.8%

CI: confidence interval; I^2: percentage of variation across studies that is due to heterogeneity and not chance; OR: odds ratio TB: tuberculosis

Table 5. Summary of two studies (both high TB burden countries) with data on TB infection conversion (based on TST) among healthcare workers and the general population

First author	Year of publication	Country	Low/high TB burden setting	Number of comparisons	HCW definition	General population definition	TB infection conversion definition
Hohmuth	2006	Peru	high	2	Health care students (included medical, pharmacy, and laboratory technician students)	Non-health care students	(1) Initial two-step TSTs both <10 mm, with an increase of at ≥10 mm on the subsequent TST* (2) Similar definition for 6mm cut-off.
Corbett	2007	Zimbabwe	high	2	Nursing students	Polytechnic School students	(3) Initial two-step reaction sizes Were ≤9 mm and an increase of ≥10 mm over the two-step reaction size on a subsequent TST in follow-up (up to 18 months)* (4) Initial two-step reaction sizes were ≤9 mm and an increase of ≥10 mm over the two-step reaction size on a subsequent TST in follow-up to a final induration ≥15mm

* American Thoracic Society criteria (Joint Statement of the American Thoracic Society and the Centers for Diseases Control and Prevention Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000; 161:221S–47S.)

TST: tuberculin skin test

Table 6. Summary comparing TB infection conversion (based on TST) between healthcare workers and the general population (two studies in high TB burden countries)

		HCW			General population						
First author	**Outcome definition**	**N**	**n**	**%**	**N**	**n**	**%**	**% difference**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Hohmuth	(1) 10mm defn	93	1	1.08	127	0	0.00	1.1	-1.0[1]	3.2[1]	0.423
Hohmuth	(2) 6mm defn	93	11	11.83	127	0	0.00	11.8	4.8[1]	18.8[1]	<0.0001

First author	**Outcome definition**	**Pyrs**	**n**	**Rate/ 100 pyrs**	**pyrs**	**n**	**Rate/ 100 pyrs**	**Rate difference (/100 pyrs)**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Corbett	(3) 10mm defn	213	41	19.3	216	13	6.0	13.2	6.5	20.0	Not reported
Corbett	(4) Induration size ≥15mm & increase of ≥10mm	225	28	12.5	218	6	2.8	9.7	4.6	14.8	Not reported

[1]Calculated from available data. CI: confidence interval, defn: definition; pyrs person-years

Table 7. Summary of 20 studies (eight in high TB burden countries) contributing to the meta-analysis using the unadjusted RR comparing TB disease incidence between healthcare workers and the general population

First author	Year of publication	Country	Low/high TB burden setting	Number of comparisons
Chu	2014	Taiwan	low	3
Driver	2005	USA	low	1
Hill	1997	United Kingdom	low	4
Marena	1996	Italy	low	2
Ohmori	2007	Japan	low	36
Ong	2006	USA	low	1
Pleszewski	1998	Canada	low	4
Raitio	2000	Finland	low	6
Raitio	2003	Finland	low	6
Reis	2012	Portugal	low	1
Shimouchi	2007	Japan	low	1
Sotgiu	2008	Romania	low	1
Chen	2014	China	high	14
Claassens	2010	South Africa	high	1
Eyob	2002	Ethiopia	high	1
Harries	1999	Malawi	high	4
Klimuk	2014	Belarus	high	5
O'Donnell	2010	South Africa	high	3
O'Hara	2017	South Africa	high	11
Pazin-Filho	2008	Brazil	high	2

TB: tuberculosis

Table 8. Summary of meta-analyses (20 studies) Summary of meta-analyses based on unadjusted RRs (20 studies) comparing TB disease incidence in healthcare workers versus the general population

Low/high TB burden setting	Number of studies	Fixed effects		Random effects		I^2
		Unadj RR	95% CI	Unadj RR	95% CI	
Overall	20	1.34	(1.29, 1.39)	2.05	(1.22, 3.46)	99.5%
High	8	3.00	(2.83, 3.17)	4.32	(2.36, 7.91)	98.6%
Low	12	0.80	(0.76, 0.83)	1.28	(0.67, 2.42)	99.4%

CI: confidence interval; RR: rate ratio; Unadj: unadjusted; I^2 percentage of variation across studies that is due to heterogeneity

6.2. Main figures

Figure 1. Flow diagram showing databases searched, records found, sifted, and included, and reasons for exclusion at full text review

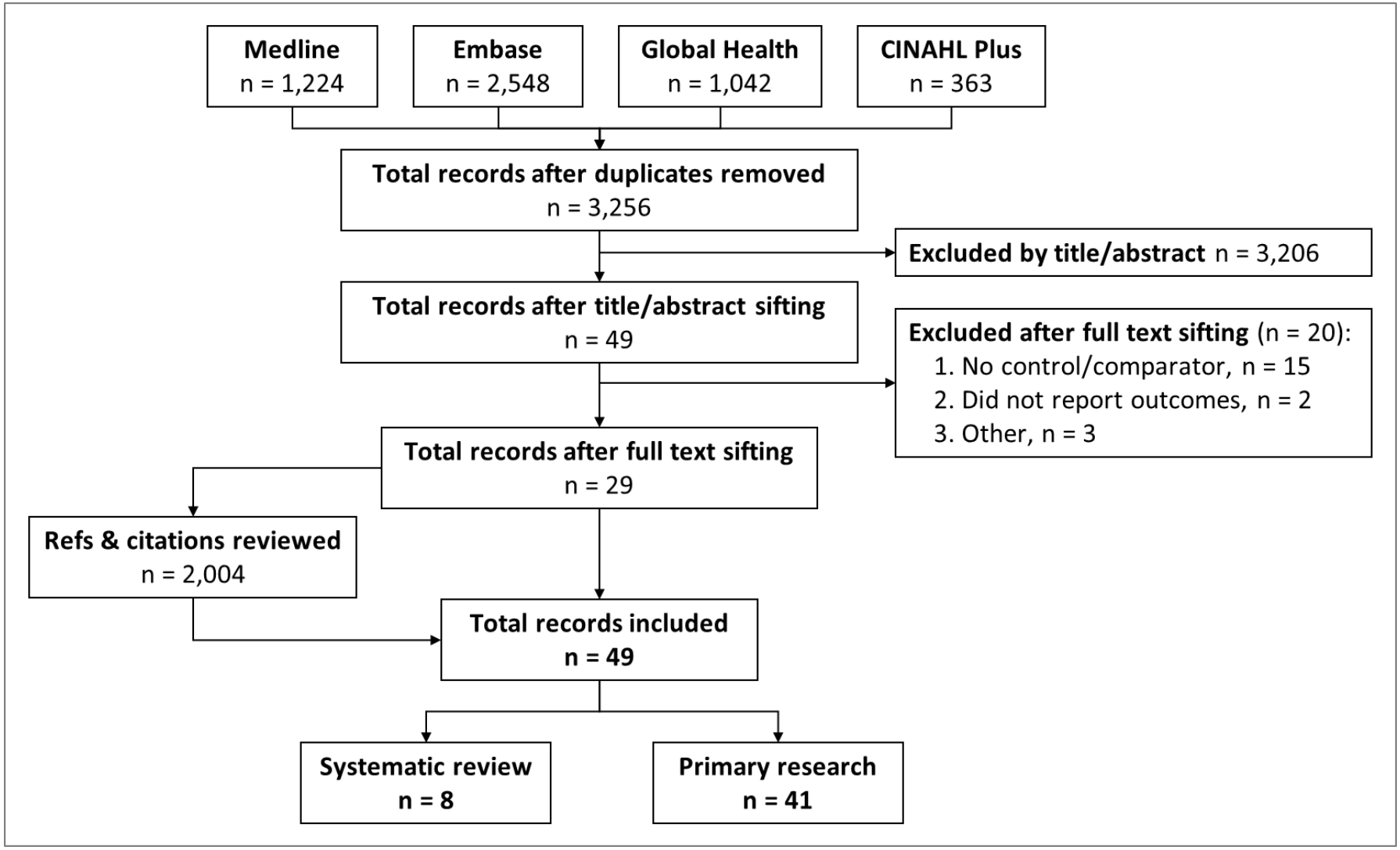
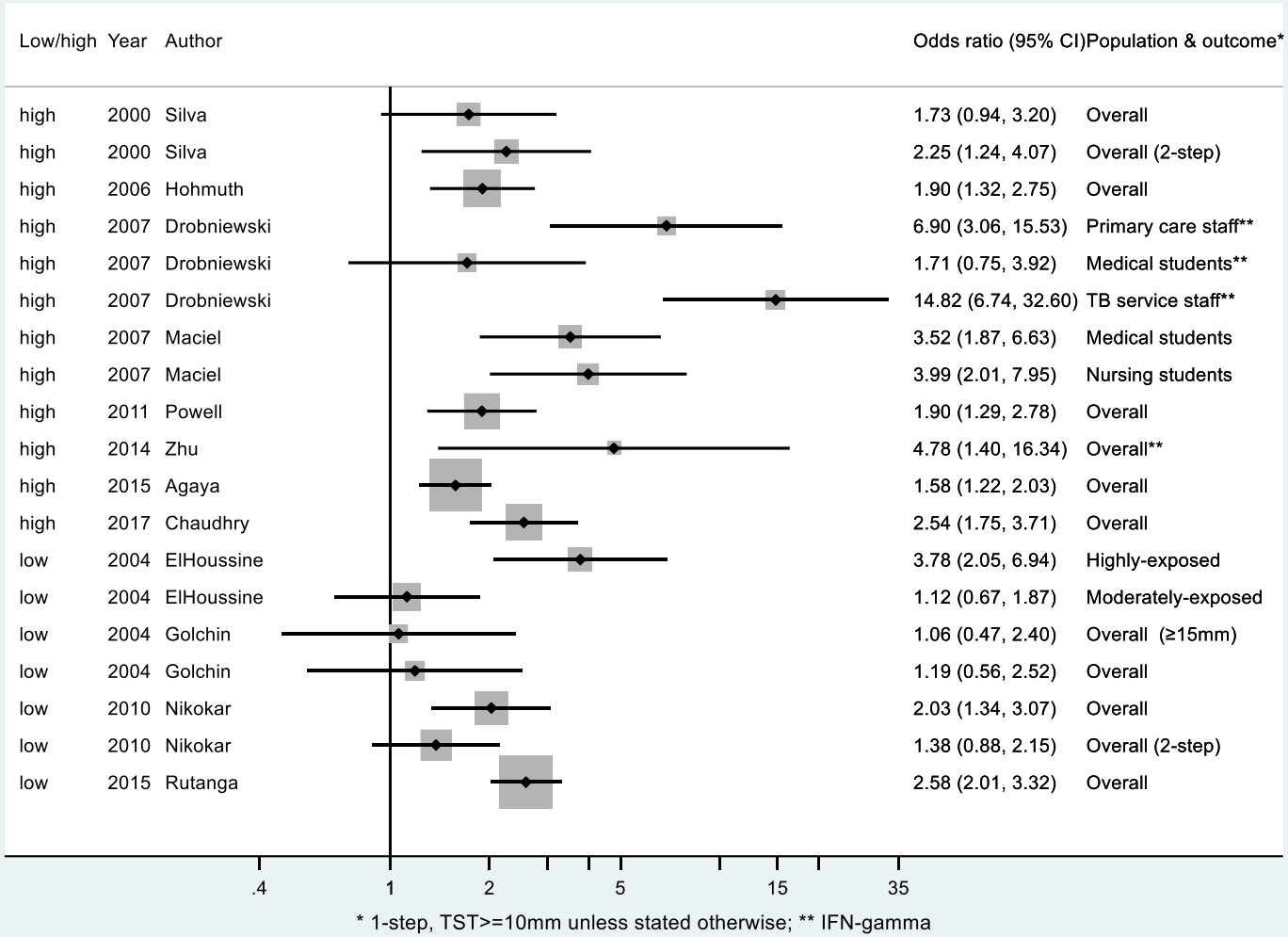
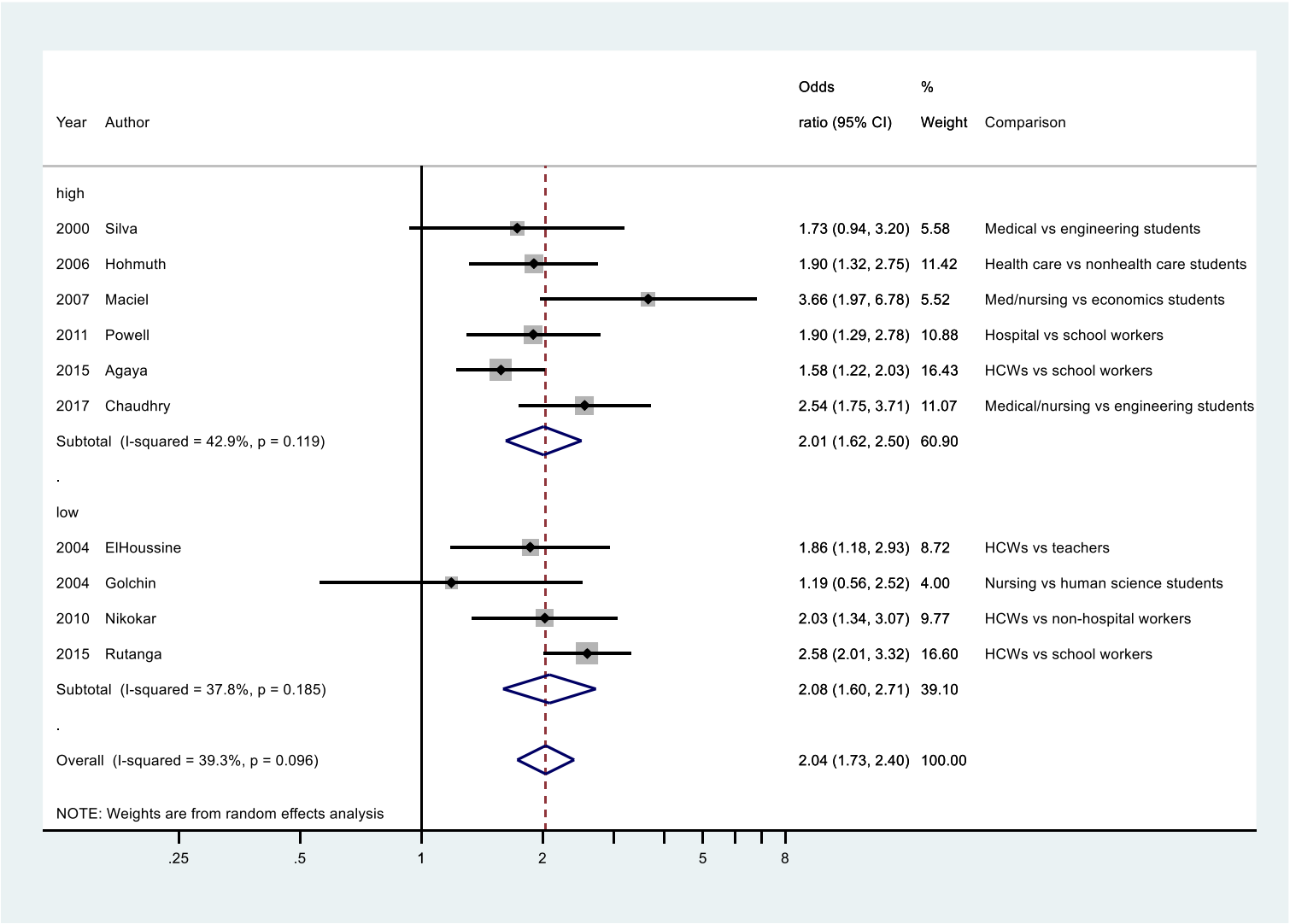


Figure 2. Forest plot for all studies (n = 19 effect estimates from 12 studies), no summary measure, comparing TB infection prevalence in healthcare workers versus the general population



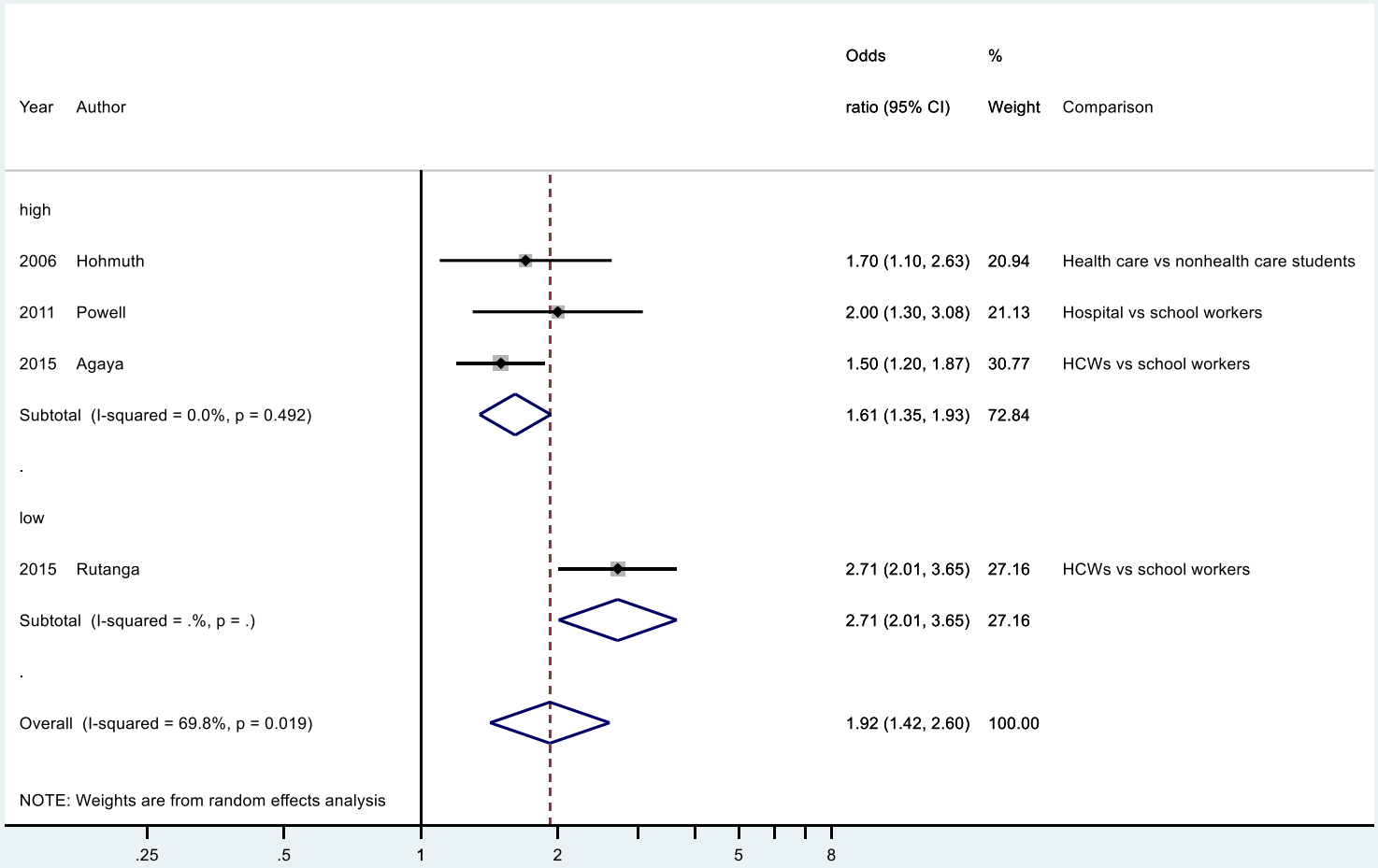
CI: confidence interval; IFN: interferon; TB: tuberculosis; TST: tuberculin skin test

Figure 3. Forest plot for 10 studies using TST to measure TB infection prevalence (6 in high TB burden countries), based on unadjusted ORs and 95% CI, and random effects meta-analysis, stratified by low/high TB burden setting, comparing TB infection prevalence in healthcare workers versus the general population



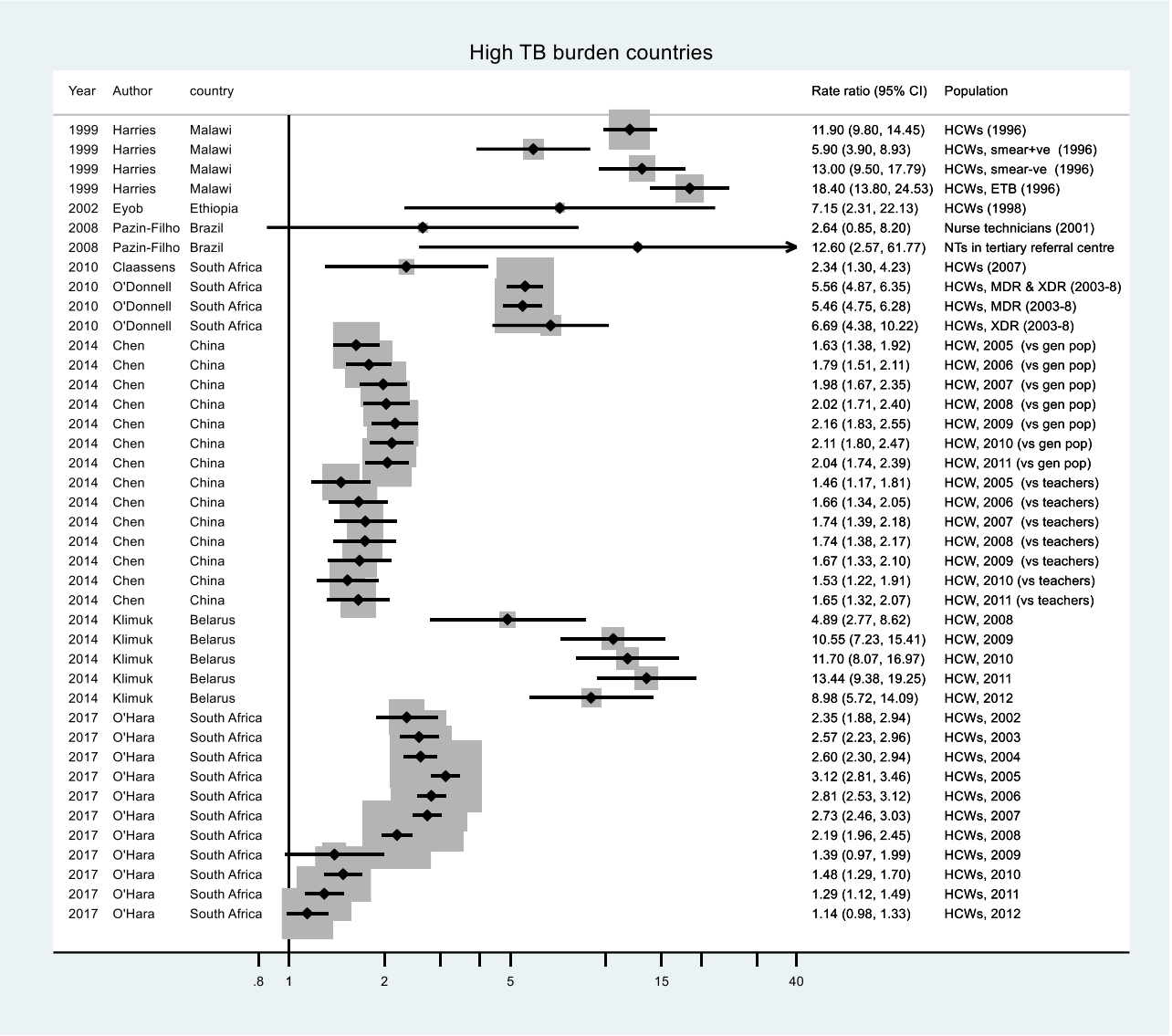
CI: confidence interval; HCW: health care worker; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test

Figure 4. Forest plot for 4 studies using TST to measure TB infection prevalence (3 in high TB burden countries), based on adjusted OR and 95% CI, and random effects meta-analysis, stratified by low/high TB burden setting, comparing TB infection prevalence (using TST) in healthcare workers versus the general population



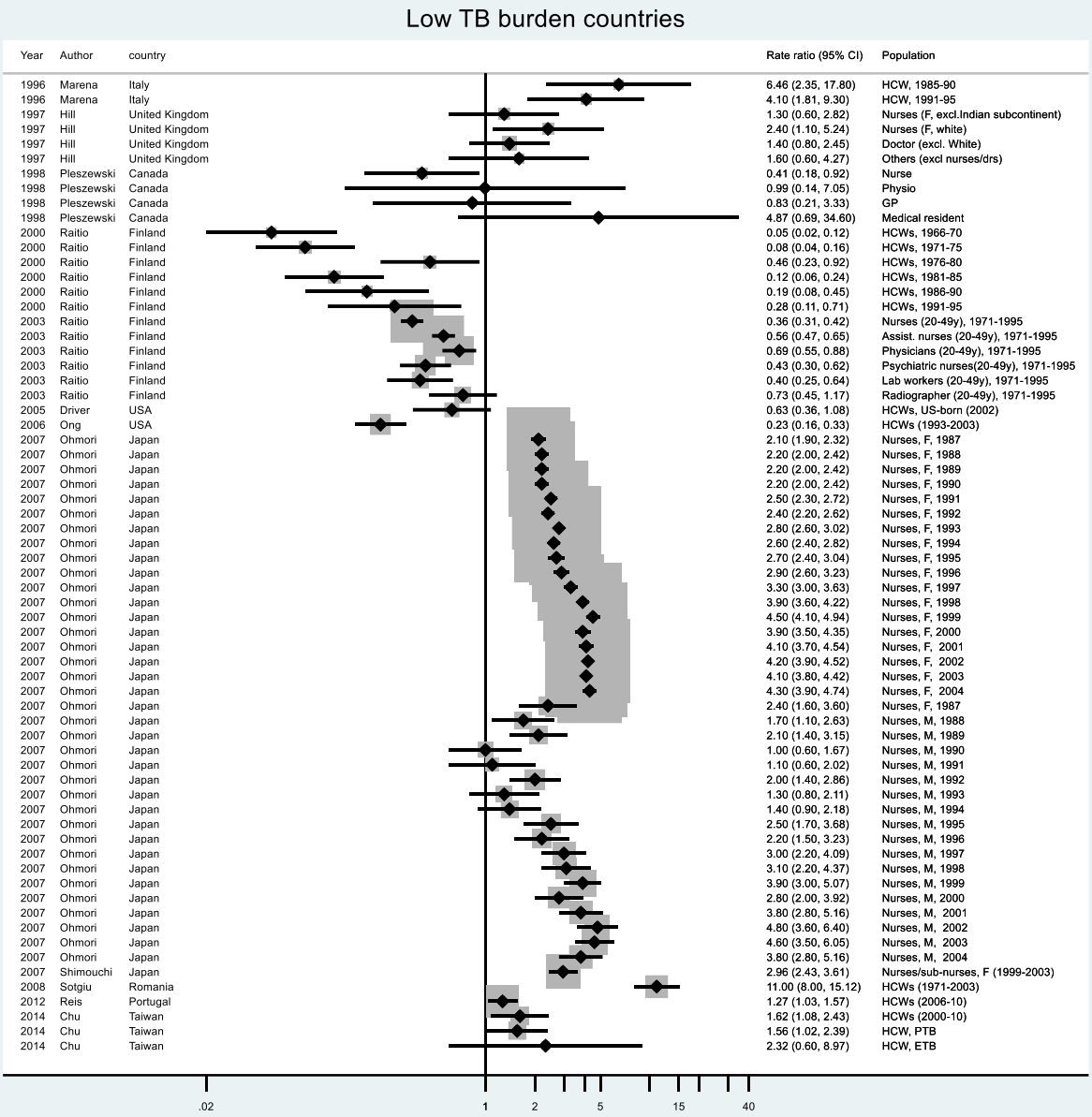
CI: confidence interval; HCW: health care worker; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test

Figure 5. Forest plots for eight studies (41 comparisons) conducted in high TB burden countries using the unadjusted RR and 95% CI for TB disease incidence amongst healthcare workers compared to the general population; no summary measure



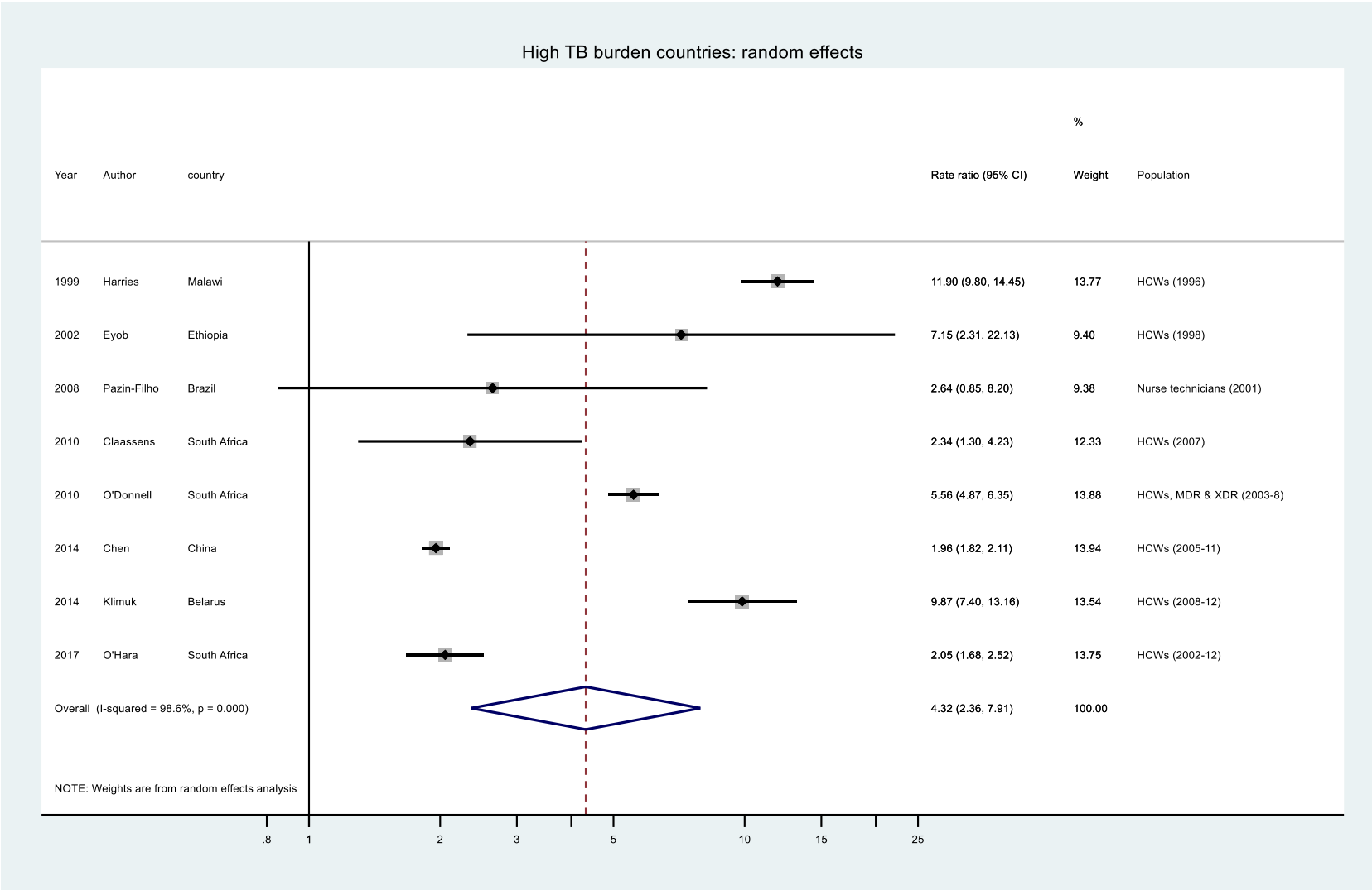
CI: confidence interval; ETB: extrapulmonary TB; gen pop: general population; HCW: health care worker; MDR: multidrug resistant; NT: nurse technician; RR: rate ratio; TB: tuberculosis; XDR: extensively drug resistant;

Figure 6. Forest plots for 12 studies (66 comparisons) conducted in low burden TB countries using the unadjusted RR and 95% CI for TB disease incidence amongst healthcare workers compared to the general population; no summary measure



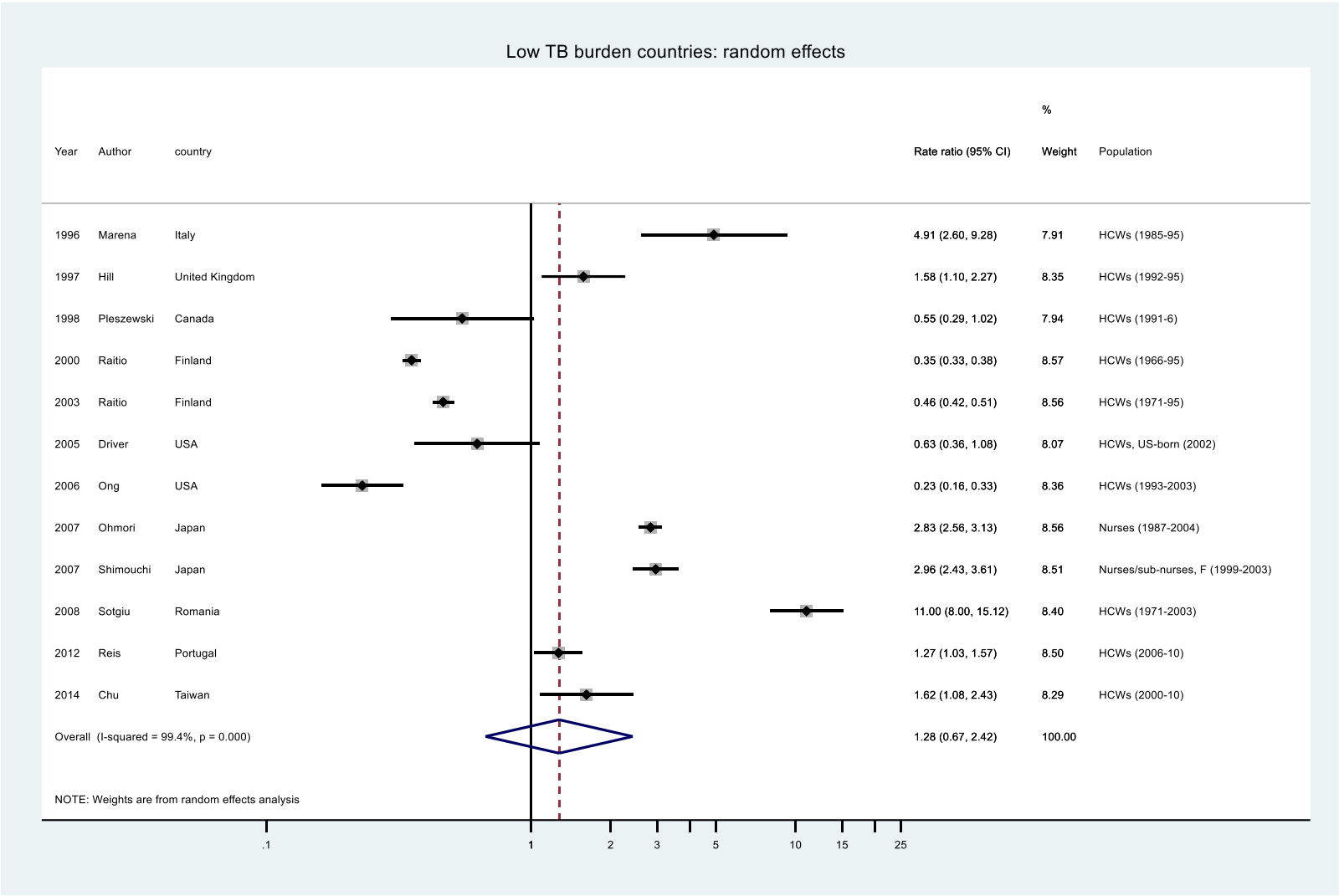
CI: confidence interval; excl.: excluding; ETB: extrapulmonary TB; F: female; GP: general practitioner; HCW: health care worker; M: male; NT: nurse technician; PTB: pulmonary TB; RR: rate ratio; TB: tuberculosis

Figure 7. Forest plot for 8 studies conducted in high TB burden countries, using unadjusted RR and 95% CI, and random effects meta-analysis, for TB disease incidence amongst healthcare workers compared to the general population



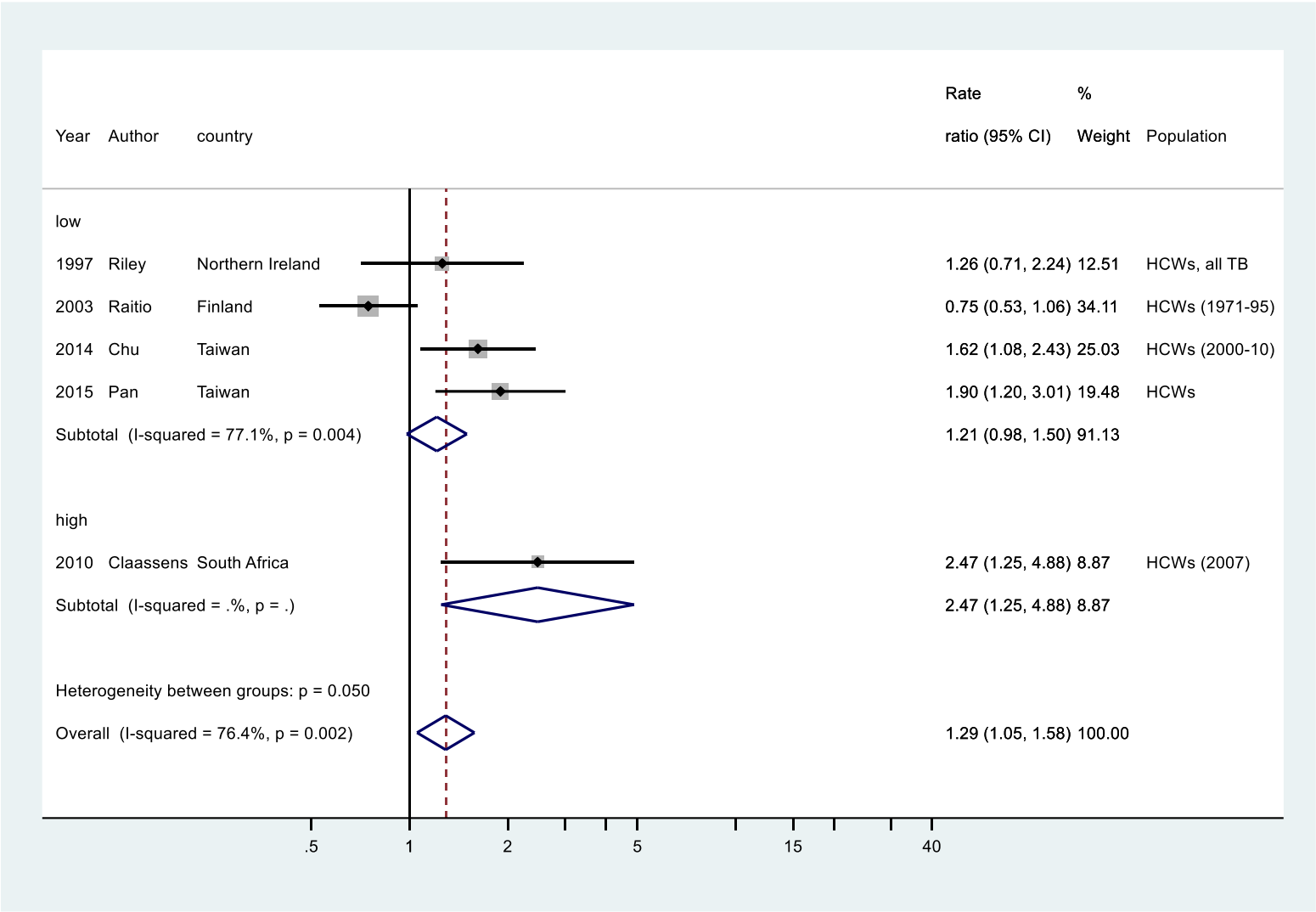
CI: confidence interval; HCW: health care worker; MDR: multidrug-resistant; RR: rate ratio; TB: tuberculosis; XDR: extensively drug-resistant

Figure 8. Forest plot for 12 studies conducted in low TB burden countries, using unadjusted RR and 95% CI, and random effects meta-analysis, for TB disease incidence amongst healthcare workers compared to the general population



CI: confidence interval; HCW: health care worker; F: female; RR: rate ratio; TB: tuberculosis; US: United States

Figure 9. Forest plot for five studies (4 in low TB burden countries) using adjusted RR and 95% CI, and random effects meta-analysis, for TB disease incidence amongst healthcare workers compared to the general population



CI: confidence interval; HCW: health care worker; RR: rate ratio; TB: tuberculosis

6.3. Additional summary tables

Table 9. Summary of 20 effect estimates from 12 studies for TB infection prevalence in healthcare workers compared to the general population

First author	Year	Cou-ntry	Low/ high TB burden	Comparison	Outcome	HCWs			General population			Unadj OR	Lower 95% CI	Upper 95% CI	P-value	Adj OR	Lower 95% CI	Upper 95% CI
						n	N	%	n	N	%							
Agaya	2015	Kenya	high	HCW vs school workers, overall	TST prevalence (≥10 mm & ≥5 mm HIV+)	534	898	59%	160	332	48%	1.58	1.22	2.03	NR	1.5	1.2	2
Agaya	2015	Kenya	high	HCW vs school workers, HIV-ve	TST prevalence (≥10 mm)	48	259	19%	NR	211	NR	NR	NR	NR	NR	3.1	1.4	6.6
Chaudhry	2017	India	high	Medical/nursing vs engineering students	TST prevalence (≥10 mm)	155	522	30%	42	295	14%	2.54	1.75	3.71	NR	NR	NR	NR
Drobniewski	2007	Russia	high	Primary care staff vs nonmedical students	QuantiFERON–TB Gold	38	122	31%	8	130	6%	6.90	3.06	15.53	NR	NR	NR	NR
Drobniewski	2007	Russia	high	Medical vs nonmedical students	QuantiFERON–TB Gold	24	238	10%	8	130	6%	1.71	0.75	3.92	NR	NR	NR	NR
Drobniewski	2007	Russia	high	TB service staff vs nonmedical students	QuantiFERON–TB Gold	69	140	49%	8	130	6%	14.82	6.74	32.60	NR	NR	NR	NR
Hohmuth	2006	Peru	high	Health care vs non-health care students	TST prevalence (≥10 mm)	117	559	21%	47	385	12%	1.90	1.32	2.75	0.0005	1.7	1.1	2.6
Maciel	2007	Brazil	high	Prevalence of TB infection in medical vs.	TST prevalence (≥10 mm), 2-step	78	427	18%	12	201	6%	3.52	1.87	6.63	0.0001	NR	NR	NR

First author	Year	Country	Low/ high TB burden	Comparison	Outcome	HCWs			General population			Unadj OR	Lower 95% CI	Upper 95% CI	P-value	Adj OR	Lower 95% CI	Upper 95% CI
						n	N	%	n	N	%							
				economics students														
Maciel	2007	Brazil	high	Prevalence of TB infection in nursing vs. economics students	TST prevalence (≥10 mm), 2-step	36	178	20%	12	201	6%	3.99	2.01	7.95	0.0001	NR	NR	NR
Powell	2011	Viet Nam	high	Hospital vs school workers	TST prevalence (≥10 mm)	380	956	40%	40	155	26%	1.90	1.29	2.78	<0.01	2	1.3	3
Silva	2000	Brazil	high	Medical vs engineering students	TST prevalence (≥10 mm)	33	455	7%	16	370	4%	1.73	0.94	3.20	NR	NR	NR	NR
Silva	2000	Brazil	high	Medical vs engineering students, 2-step	TST prevalence (≥10 mm), 2-step	42	455	9%	16	370	4%	2.25	1.24	4.07	NR	NR	NR	NR
Zhu	2014	China	high	HCW vs gen pop	TSPOT.TB	6	20	30%	7	85	8%	4.78	1.40	16.34	NR	NR	NR	NR
ElHoussine	2004	Morocco	low	HCW (high exp) vs teachers	TST prevalence (≥10 mm)	90	109	83%	69	124	56%	3.78	2.05	6.94	NR	NR	NR	NR
ElHoussine	2004	Morocco	low	HCW (moderate exp) vs teachers	TST prevalence (≥10 mm)	69	118	58%	69	124	56%	1.12	0.67	1.87	NR	NR	NR	NR
Golchin	2004	Iran	low	Nursing vs human science students	TST prevalence (≥15 mm)	14	123	11%	12	111	11%	1.06	0.47	2.40	NR	NR	NR	NR
Golchin	2004	Iran	low	Nursing vs human science students	TST prevalence (≥10 mm)	18	123	15%	14	111	13%	1.19	0.56	2.52	NR	NR	NR	NR

First author	Year	Cou-ntry	Low/ high TB burden	Comparison	Outcome	HCWs			General population			Unadj OR	Lower 95% CI	Upper 95% CI	P-value	Adj OR	Lower 95% CI	Upper 95% CI
						n	N	%	n	N	%							
Nikokar	2010	Iran	low	HCW vs non-hospital workers, 2-step	TST prevalence (≥10 mm), 2-step	125	178	70%	108	171	63%	1.38	0.88	2.15	NR	NR	NR	NR
Nikokar	2010	Iran	low	HCW vs non-hospital workers	TST prevalence (≥10 mm)	113	185	61%	79	181	44%	2.03	1.34	3.07	0.001	NR	NR	NR
Rutanga	2015	Rwanda	low	HCW vs school workers	TST prevalence (≥10 mm & ≥5 mm HIV+)	635	1023	62%	135	348	39%	2.58	2.01	3.32	NR	2.71	2.01	3.67

adj.: adjusted; CI: confidence interval; HCW: health care worker; HIV+: HIV-positive; HIV-ve: HIV-negative; mm: millimetres; NR: not reported; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test; unadj.: unadjusted; vs: versus

Table 10. Summary of data contributing to TB disease in healthcare workers compared to the general population, unadjusted rate ratios

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Wilkinson	1998	South Africa	high	HCWs	2328	13	NR	NR	NR	NR	NR	<0.0001			
Wilkinson	1998	South Africa	high	Ancillary staff	2022	9	NR	NR	NR	NR	NR	<0.0001			
Harries	1999	Malawi	high	HCWs (1996)	3042	108	5714946	17554	11.9	9.8	14.4	<0.05	11.9	9.8	14.4
Harries	1999	Malawi	high	HCWs, ETB (1996)	3042	46	5714946	4711	18.4	13.8	24.6	<0.05	18.4	13.8	24.5
Harries	1999	Malawi	high	HCWs, smear -ve (1996)	3042	40	5714946	5835	13	9.5	17.7	<0.05	13.0	9.5	17.8
Harries	1999	Malawi	high	HCWs, smear +ve (1996)	3042	22	5714946	7008	5.9	3.9	9	<0.05	5.9	3.9	8.9
Eyob	2002	Ethiopia	high	HCWs (1998)	90	5	59304	461	7.15	2.31	16.8	NR	7.1	2.3	22.1
Dimitrova	2005	Russia	high	TB facilities	10787.4	80	NR	NR	NR	NR	NR	NR			
Pazin-Filho	2008	Brazil	high	NTs in tertiary referral centre	570	3	514160	215	12.6	2.57	37.23	NR	12.6	2.6	61.8
Pazin-Filho	2008	Brazil	high	Nurse technicians (2001)	4520	5	514160	215	2.64	0.85	6.27	NR	2.6	0.8	8.2
Claassens	2010	South Africa	high	HCWs (2007)	250.4	11	343197	6436	NR	NR	NR	NR	2.3	1.3	4.2
O'Donnell	2010	South Africa	high	HCWs, MDR & XDR (2003–8)	NR	231	NR	4151	5.56	4.87	6.35	<0.001	5.6	4.9	6.3
O'Donnell	2010	South Africa	high	HCWs, XDR (2003–8)	NR	23	NR	344	6.69	4.38	10.2	<0.001	6.7	4.4	10.2
O'Donnell	2010	South Africa	high	HCWs, MDR (2003–8)	NR	208	NR	3807	5.46	4.75	6.28	<0.001	5.5	4.8	6.3
Chen	2014	China	high	HCW, 2007 (vs gen pop)	NR	131		41234	NR	NR	NR	NR	2.0	1.7	2.4
Chen	2014	China	high	HCW, 2011 (vs teachers)	NR	153		146	NR	NR	NR	NR	1.7	1.3	2.1
Chen	2014	China	high	HCW, 2008 (vs gen pop)	NR	135		41087	NR	NR	NR	NR	2.0	1.7	2.4

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Chen	2014	China	high	HCW, 2005 (vs gen pop)	NR	138		41473	NR	NR	NR	NR	1.6	1.4	1.9
Chen	2014	China	high	HCW, 2006 (vs gen pop)	NR	142		45208	NR	NR	NR	NR	1.8	1.5	2.1
Chen	2014	China	high	HCW, 2008 (vs teachers)	NR	135		170	NR	NR	NR	NR	1.7	1.4	2.2
Chen	2014	China	high	HCW, 2006 (vs teachers)	NR	142		211	NR	NR	NR	NR	1.7	1.3	2.0
Chen	2014	China	high	HCW, 2009 (vs teachers)	NR	140		151	NR	NR	NR	NR	1.7	1.3	2.1
Chen	2014	China	high	HCW, 2011 (vs gen pop)	NR	153		36792	NR	NR	NR	NR	2.0	1.7	2.4
Chen	2014	China	high	HCW, 2007 (vs teachers)	NR	131		172	NR	NR	NR	NR	1.7	1.4	2.2
Chen	2014	China	high	HCW, 2005 (vs teachers)	NR	138		206	NR	NR	NR	NR	1.5	1.2	1.8
Chen	2014	China	high	HCW, 2010 (vs gen pop)	NR	157		37037	NR	NR	NR	NR	2.1	1.8	2.5
Chen	2014	China	high	HCW, 2010 (vs teachers)	NR	157		148	NR	NR	NR	NR	1.5	1.2	1.9
Chen	2014	China	high	HCW, 2009 (vs gen pop)	NR	140		38604	NR	NR	NR	NR	2.2	1.8	2.6
Klimuk	2014	Belarus	high	HCW, 2010	NR	28	NR	4178	NR	NR	NR	<0.001	11.7	8.1	17.0
Klimuk	2014	Belarus	high	HCW, 2012	NR	19	NR	3744	NR	NR	NR	<0.001	9.0	5.7	14.1
Klimuk	2014	Belarus	high	HCW, 2008	NR	12	NR	4393	NR	NR	NR	<0.001	4.9	2.8	8.6
Klimuk	2014	Belarus	high	HCW, 2011	NR	30	NR	3900	NR	NR	NR	<0.001	13.4	9.4	19.2
Klimuk	2014	Belarus	high	HCW, 2009	NR	27	NR	4441	NR	NR	NR	<0.001	10.6	7.2	15.4
O'Hara	2017	South Africa	high	HCWs, 2003	NR	198	NR	NR	2.57	2.23	2.95	<0.001	2.6	2.2	3.0
O'Hara	2017	South Africa	high	HCWs, 2006	NR	362	NR	NR	2.81	2.53	3.11	<0.001	2.8	2.5	3.1
O'Hara	2017	South Africa	high	HCWs, 2008	NR	326	NR	NR	2.19	1.96	2.44	<0.001	2.2	2.0	2.4
O'Hara	2017	South Africa	high	HCWs, 2011	NR	191	NR	NR	1.29	1.12	1.49	<0.001	1.3	1.1	1.5
O'Hara	2017	South Africa	high	HCWs, 2007	NR	371	NR	NR	2.73	2.46	3.02	<0.001	2.7	2.5	3.0

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
O'Hara	2017	South Africa	high	HCWs, 2002	NR	80	NR	NR	2.35	1.88	2.91	<0.001	2.3	1.9	2.9
O'Hara	2017	South Africa	high	HCWs, 2010	NR	203	NR	NR	1.48	1.29	1.7	<0.001	1.5	1.3	1.7
O'Hara	2017	South Africa	high	HCWs	NR		NR	NR	NR	NR	NR	NR			
O'Hara	2017	South Africa	high	HCWs, 2009	NR	157	NR	NR	1.39	0.97	1.33	0.106	1.4	1.0	2.0
O'Hara	2017	South Africa	high	HCWs, 2004	NR	255	NR	NR	2.6	2.3	2.94	<0.001	2.6	2.3	2.9
O'Hara	2017	South Africa	high	HCWs, 2005	NR	365	NR	NR	3.12	2.81	3.45	<0.001	3.1	2.8	3.5
O'Hara	2017	South Africa	high	HCWs, 2012	NR	169	NR	NR	1.14	0.98	1.32	0.084	1.1	1.0	1.3
Burrill	1985	Canada	low	Nurses, F, European	29163	6	NR	NR	NR	NR	NR	NR			
Burrill	1985	Canada	low	All HCWs	218797	57	NR	NR	NR	NR	NR	NR			
Burrill	1985	Canada	low	Nurses, F, Canadian born, 18–24yrs	56870	7	NR	NR	2.05	NR	NR	NR			
Burrill	1985	Canada	low	Nurses, F, Canadian born, >45yrs	43071	13	NR	NR	1.71	NR	NR	NR			
Burrill	1985	Canada	low	Nurses, F, Canadian born, 25–44yrs	76307	15	NR	NR	2.03	NR	NR	NR			
Burrill	1985	Canada	low	Nurses, F, Asian	6446	16	NR	NR	NR	NR	NR	NR			
Burrill	1985	Canada	low	Nurses, F, other birthplace	6940	0	NR	NR	NR	NR	NR	NR			
Burrill	1985	Canada	low	Nurses, F, Canadian born	176248	35	NR	NR	NR	NR	NR	NR			
Marena	1996	Italy	low	HCW, 1985–90	NR	4	NR	58	nr	nr	nr	nr	6.5	2.3	17.8
Marena	1996	Italy	low	HCW, 1991–95	NR	6	NR	128	nr	nr	nr	nr	4.1	1.8	9.3
Hill	1997	United Kingdom	low	Nurses (F, white)	NR	7	NR	NR	2.4	1.1	5.5	NR	2.4	1.1	5.2

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Hill	1997	United Kingdom	low	Nurses (F, excl. Indian subcontinent)	NR	8	NR	NR	1.3	0.6	2.7	NR	1.3	0.6	2.8
Hill	1997	United Kingdom	low	Others (excl. nurses/Drs)	NR	4	NR	NR	1.6	0.6	4.4	NR	1.6	0.6	4.3
Hill	1997	United Kingdom	low	Doctor (excl. White)	NR	13	NR	NR	1.4	0.8	2.7	NR	1.4	0.8	2.4
Riley	1997	Northern Ireland	low	HCWs, PTB	521656	28	NR	NR	NR	NR	NR	NR			
Riley	1997	Northern Ireland	low	HCWs, all TB	521656	42	NR	NR	NR	NR	NR	NR			
Riley	1997	Northern Ireland	low	HCWs, non-PTB	521656	14	NR	NR	NR	NR	NR	NR			
Pleszewski	1998	Canada	low	Medical resident	430	1	3518913	1680	NR	NR	NR	0.51	4.9	0.7	34.6
Pleszewski	1998	Canada	low	GP	5038	2	3518913	1680	NR	NR	NR	0.79	0.8	0.2	3.3
Pleszewski	1998	Canada	low	Nurse	30604	6	3518913	1680	NR	NR	NR	0.03	0.4	0.2	0.9
Pleszewski	1998	Canada	low	Physio	2111	1	3518913	1680	NR	NR	NR	>0.99	1.0	0.1	7.0
Raitio	2000	Finland	low	HCWs, 1966–70	45029	76	3022971	23697	0.05	0.02	0.13	0.001	0.1	0.0	0.1
Raitio	2000	Finland	low	HCWs, 1976–80	80384	158	3134816	8612	0.46	0.23	0.92	0.001	0.5	0.2	0.9
Raitio	2000	Finland	low	HCWs, 1971–75	63541	184	3076659	14649	0.08	0.04	0.17	0.001	0.1	0.0	0.2
Raitio	2000	Finland	low	HCWs, 1986–90	157920	69	3190940	2646	0.19	0.08	0.49	0.001	0.2	0.1	0.5
Raitio	2000	Finland	low	HCWs, 1991–95	184708	56	3213420	1469	0.28	0.11	0.72	0.003	0.3	0.1	0.7
Raitio	2000	Finland	low	HCWs, 1981–85	93473	115	3218001	5073	0.12	0.06	0.26	0.001	0.1	0.1	0.2
Krüüner	2001	Estonia	low	HCWs	73650	67	NR	NR	NR	NR	NR	NR			

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Cuhadaroglu	2002	Turkey	low	Doctors	8	NR	NR	NR	2.2	NR	NR	NR			
Cuhadaroglu	2002	Turkey	low	Nurses	1	NR	NR	NR	NR	NR	NR	NR			
Cuhadaroglu	2002	Turkey	low	All HCWs	31	NR	NR	NR	2.71	NR	NR	NR			
Cuhadaroglu	2002	Turkey	low	Other professional	22	NR	NR	NR	3.4	NR	NR	NR			
Raitio	2003	Finland	low	Psychiatric nurses(20–49y), 1971–1995	33776	30	1.28E+07	26308	NR	NR	NR	NR	0.4	0.3	0.6
Raitio	2003	Finland	low	Lab workers (20–49y), 1971–1995	21867	18	1.28E+07	26308	NR	NR	NR	NR	0.4	0.3	0.6
Raitio	2003	Finland	low	Nurses (20–49y), 1971–1995	220830	163	1.28E+07	26308	NR	NR	NR	NR	0.4	0.3	0.4
Raitio	2003	Finland	low	Physicians (20–49y), 1971–1995	48407	69	1.28E+07	26308	NR	NR	NR	NR	0.7	0.5	0.9
Raitio	2003	Finland	low	Radiographer (20–49y), 1971–1995	11324	17	1.28E+07	26308	NR	NR	NR	NR	0.7	0.5	1.2
Raitio	2003	Finland	low	Assist. nurses (20–49y), 1971–1995	131189	150	1.28E+07	26308	NR	NR	NR	NR	0.6	0.5	0.7
Driver	2005	USA	low	HCWs, US-born (2002)		13	NR	1381	NR	NR	NR	NR	0.6	0.4	1.1
Ong	2006	USA	low	HCWs (1993–2003)		31	NR	2479	NR	NR	NR	NR	0.2	0.2	0.3
Ohmori	2007	Japan	low	Nurses, F, 2000	NR	NR	NR	NR	3.9	3.5	4.2	NR	3.9	3.5	4.3
Ohmori	2007	Japan	low	Nurses, M, 1995	NR	NR	NR	NR	2.5	1.7	3.6	NR	2.5	1.7	3.7
Ohmori	2007	Japan	low	Nurses, F, 2004	NR	NR	NR	NR	4.3	3.9	4.8	NR	4.3	3.9	4.7
Ohmori	2007	Japan	low	Nurses, M, 1993	NR	NR	NR	NR	1.3	0.8	2.2	NR	1.3	0.8	2.1
Ohmori	2007	Japan	low	Nurses, F, 1998	NR	NR	NR	NR	3.9	3.6	4.2	NR	3.9	3.6	4.2

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Ohmori	2007	Japan	low	Nurses, F, 2002	NR	NR	NR	NR	4.2	3.9	4.6	NR	4.2	3.9	4.5
Ohmori	2007	Japan	low	Nurses, F, 1991	NR	NR	NR	NR	2.5	2.3	2.8	NR	2.5	2.3	2.7
Ohmori	2007	Japan	low	Nurses, F, 1996	NR	NR	NR	NR	2.9	2.6	3.2	NR	2.9	2.6	3.2
Ohmori	2007	Japan	low	Nurses, M, 2001	NR	NR	NR	NR	3.8	2.8	5.2	NR	3.8	2.8	5.2
Ohmori	2007	Japan	low	Nurses, F, 2001	NR	NR	NR	NR	4.1	3.7	4.5	NR	4.1	3.7	4.5
Ohmori	2007	Japan	low	Nurses, F, 1989	NR	NR	NR	NR	2.2	2	2.4	NR	2.2	2.0	2.4
Ohmori	2007	Japan	low	Nurses, F, 1992	NR	NR	NR	NR	2.4	2.2	2.7	NR	2.4	2.2	2.6
Ohmori	2007	Japan	low	Nurses, M, 1996	NR	NR	NR	NR	2.2	1.5	3.2	NR	2.2	1.5	3.2
Ohmori	2007	Japan	low	Nurses, M, 1992	NR	NR	NR	NR	2	1.4	3.1	NR	2.0	1.4	2.9
Ohmori	2007	Japan	low	Nurses, M, 1988	NR	NR	NR	NR	1.7	1.1	2.7	NR	1.7	1.1	2.6
Ohmori	2007	Japan	low	Nurses, M, 1991	NR	NR	NR	NR	1.1	0.6	1.9	NR	1.1	0.6	2.0
Ohmori	2007	Japan	low	Nurses, M, 1999	NR	NR	NR	NR	3.9	3	5.2	NR	3.9	3.0	5.1
Ohmori	2007	Japan	low	Nurses, M, 2000	NR	NR	NR	NR	2.8	2	3.9	NR	2.8	2.0	3.9
Ohmori	2007	Japan	low	Nurses, F, 1990	NR	NR	NR	NR	2.2	2	2.5	NR	2.2	2.0	2.4
Ohmori	2007	Japan	low	Nurses, M, 1997	NR	NR	NR	NR	3	2.2	4.2	NR	3.0	2.2	4.1
Ohmori	2007	Japan	low	Nurses, M, 2004	NR	NR	NR	NR	3.8	2.8	5.2	NR	3.8	2.8	5.2
Ohmori	2007	Japan	low	Nurses, F, 2003	NR	NR	NR	NR	4.1	3.8	4.5	NR	4.1	3.8	4.4
Ohmori	2007	Japan	low	Nurses, M, 2003	NR	NR	NR	NR	4.6	3.5	6.1	NR	4.6	3.5	6.0
Ohmori	2007	Japan	low	Nurses, M, 1990	NR	NR	NR	NR	1	0.6	1.8	NR	1.0	0.6	1.7
Ohmori	2007	Japan	low	Nurses, F, 1988	NR	NR	NR	NR	2.2	2	2.5	NR	2.2	2.0	2.4
Ohmori	2007	Japan	low	Nurses, F, 1995	NR	NR	NR	NR	2.7	2.4	2.9	NR	2.7	2.4	3.0

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Ohmori	2007	Japan	low	Nurses, F, 1993	NR	NR	NR	NR	2.8	2.6	3.1	NR	2.8	2.6	3.0
Ohmori	2007	Japan	low	Nurses, M, 1994	NR	NR	NR	NR	1.4	0.9	2.3	NR	1.4	0.9	2.2
Ohmori	2007	Japan	low	Nurses, F, 1999	NR	NR	NR	NR	4.5	4.1	4.8	NR	4.5	4.1	4.9
Ohmori	2007	Japan	low	Nurses, F, 1987	NR	NR	NR	NR	2.1	1.9	2.3	NR	2.1	1.9	2.3
Ohmori	2007	Japan	low	Nurses, M, 2002	NR	NR	NR	NR	4.8	3.6	6.3	NR	4.8	3.6	6.4
Ohmori	2007	Japan	low	Nurses, M, 1998	NR	NR	NR	NR	3.1	2.2	4.3	NR	3.1	2.2	4.4
Ohmori	2007	Japan	low	Nurses, F, 1997	NR	NR	NR	NR	3.3	3	3.6	NR	3.3	3.0	3.6
Ohmori	2007	Japan	low	Nurses, F, 1987	NR	NR	NR	NR	2.4	1.6	3.4	NR	2.4	1.6	3.6
Ohmori	2007	Japan	low	Nurses, F, 1994	NR	NR	NR	NR	2.6	2.4	2.9	NR	2.6	2.4	2.8
Ohmori	2007	Japan	low	Nurses, M, 1989	NR	NR	NR	NR	2.1	1.4	3.1	NR	2.1	1.4	3.1
Shimouchi	2007	Japan	low	Nurses/sub-nurses, F (1999–2003)	86790	104	4608820	1866	3	NR	NR	NR	3.0	2.4	3.6
Sotgiu	2008	Romania	low	HCW, 2002	NR	6	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1984	NR	1	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 2001	NR	2	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 2000	NR	1	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1996	NR	2	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1988	NR	1	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1989	NR	4	NR	NR	33	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1992	NR	2	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1976	NR	1	NR	NR	NR	NR	NR	NR			

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Sotgiu	2008	Romania	low	HCW, 1993	NR	2	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1987	NR	1	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1980	NR	2	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1995	NR	2	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1997	NR	5	NR	NR	19	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1973	NR	2	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCWs (1971–2003)		50	NR	NR	11	8	14	<0.001	11.0	8.0	15.1
Sotgiu	2008	Romania	low	HCW, 1994	NR	1	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1971	NR	3	NR	NR	9	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1999	NR	3	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1998	NR	3	NR	NR	NR	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1986	NR	2	NR	NR	18	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 2003	NR	3	NR	NR	5	NR	NR	NR			
Sotgiu	2008	Romania	low	HCW, 1990	NR	1	NR	NR	NR	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	Inf dis HCW, all TB	NR	4	NR	NR	4.6	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	Pulmon. HCW, all TB	3146	13	NR	NR	12.2	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	Neuropsyc. HCW, all TB	NR	2	NR	NR	1.6	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	Surgery HCWs, all TB	NR	2	NR	NR	1.1	NR	NR	NR			

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Skodric-Trifunovic	2009	Serbia	low	Intern. Med, all TB	NR	2	NR	NR	0.9	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	Nurse/tech. HCW, all TB	NR	23	NR	NR	1.6	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	Dr, all TB	NR	1	NR	NR	0.2	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	HCW, all TB, 1992–2004	57330	24	NR	NR	1.2	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	Gynaec. HCW, all TB	NR	1	NR	NR	0.6	NR	NR	NR			
Skodric-Trifunovic	2009	Serbia	low	Non-pulmon. HCW, all TB	`	11	NR	NR	0.6	NR	NR	NR			
Reis	2012	Portugal	low	HCWs (2006–10)	213565	90	NR	NR	1.27	1.03	1.56	NR	1.3	1.0	1.6
Chu	2014	Taiwan	low	HCWs (2000–10)	101505	62	100493	38	1.62	1.08	2.42	0.02	1.6	1.1	2.4
Chu	2014	Taiwan	low	HCW, Charlson = 1	2086	8	2102	5	NR	NR	NR	NR	1.6	0.5	4.9
Chu	2014	Taiwan	low	HCW, ETB	101505	7	100493	3	2.32	0.6	8.95	0.224	2.3	0.6	9.0
Chu	2014	Taiwan	low	HCW, <30y	6997	42	6847	7	NR	NR	NR	NR	5.9	2.6	13.1
Chu	2014	Taiwan	low	HCW, PTB	101505	55	100493	35	1.56	1.02	2.38	0.041	1.6	1.0	2.4
Chu	2014	Taiwan	low	HCW, low risk TB	9152	52	9152	29	NR	NR	NR	NR	1.8	1.1	2.8
Chu	2014	Taiwan	low	HCW, Charlson = 0	8679	50	8734	31	NR	NR	NR	NR	1.6	1.0	2.5
Chu	2014	Taiwan	low	HCW, Charlson >= 2	1046	4	975	2	NR	NR	NR	NR	1.9	0.3	10.2
Chu	2014	Taiwan	low	HCW, >= 30y	4814	20	4964	31	NR	NR	NR	NR	0.7	0.4	1.2
Chu	2014	Taiwan	low	Other emp. Clinic	3602	10	3602	21	NR	NR	NR	NR	0.5	0.2	1.0

First author	Year	Country	Low/ high TB	HCW description	HCWs		Comparator		Reported RR & 95% CI, P-value				Calculated RR & 95% CI		
					pyears	TB	pyears	TB	Unadj RR	lower 95% CI	upper 95% CI	P-value	Unadj RR*	lower 95% CI*	upper 95% CI*
Chu	2014	Taiwan	low	HCW, M	2974	19	2974	21	NR	NR	NR	NR	0.9	0.5	1.7
Chu	2014	Taiwan	low	Other emp. Hosp	5877	37	5877	13	NR	NR	NR	NR	2.8	1.5	5.4
Chu	2014	Taiwan	low	Lab tech	2303	7	2303	9	NR	NR	NR	NR	0.8	0.3	2.1
Chu	2014	Taiwan	low	Nurses	6936	36	6936	14	NR	NR	NR	NR	2.6	1.4	4.8
Chu	2014	Taiwan	low	Other emp. Medical Centre	2332	15	2332	4	NR	NR	NR	NR	3.8	1.2	11.3
Chu	2014	Taiwan	low	Physicians	2347	19	2347	15	NR	NR	NR	NR	1.3	0.6	2.5
Chu	2014	Taiwan	low	HCW, F	8837	43	8837	17	NR	NR	NR	NR	2.5	1.4	4.4
Chu	2014	Taiwan	low	SW & therapists	225	0	225	0	NR	NR	NR	NR			
Chu	2014	Taiwan	low	HCW, high risk TB	2659	10	2659	9	NR	NR	NR	NR	1.1	0.5	2.7
Pan	2015	Taiwan	low	HCWs		41	NR	NR	NR	NR	NR	NR			

-ve: negative; +ve: positive; CI: confidence interval; Drs: doctors; emp.: employee; ETB: extrapulmonary TB; excl.: excluding; F: female; gynaec.: gynaecology; HCW: health care worker; Inf dis: infectious disease; intern.: internal; lab: laboratory; M: male; MDR: multidrug-resistant; NR: not reported; NT: nurse technician; pulmon.: pulmonology; PTB: pulmonary TB; pyrs: person-years; RR: rate ratio; TB: tuberculosis; tech: technician; unadj: unadjusted; XDR: extensively drug-resistant; y: years

Table 11. Summary of data contributing to TB disease in healthcare workers compared to the general population, adjusted rate ratios

First author	Year	Country	Low/ high TB burden	HCW description	Adjusted RR	Lower 95% CI	Upper 95% CI	P-value
Claassens	2010	South Africa	high	HCWs (2007)	2.47	1.25	4.32	NR
Burrill	1985	Canada	low	Nurses, F, European	1.11	NR	NR	NR
Burrill	1985	Canada	low	All HCWs	0.91	NR	NR	NR
Burrill	1985	Canada	low	Nurses, F, Asian	0.41	NR	NR	NR
Burrill	1985	Canada	low	Nurses, F, Canadian born	1.9	NR	NR	NR
Riley	1997	Northern Ireland	low	HCWs, PTB	1.17	0.78	1.69	NR
Riley	1997	Northern Ireland	low	HCWs, all TB	1.26	0.71	1.7	NR
Riley	1997	Northern Ireland	low	HCWs, non-PTB	1.49	0.81	2.5	NR
Raitio	2003	Finland	low	Psychiatric nurses(20–49y), 1971–1995	0.48	0.34	0.69	<0.0001
Raitio	2003	Finland	low	Lab workers (20–49y), 1971–1995	0.8	0.52	1.24	0.3173
Raitio	2003	Finland	low	Nurses (20–49y), 1971–1995	0.45	0.39	0.53	<0.0001
Raitio	2003	Finland	low	Physicians (20–49y), 1971–1995	0.94	0.74	1.19	0.6085
Raitio	2003	Finland	low	Radiographer (20–49y), 1971–1995	1.38	0.88	2.16	0.1632
Raitio	2003	Finland	low	Assist. nurses (20–49y), 1971–1995	0.86	0.73	1.01	0.0612
Chu	2014	Taiwan	low	HCWs (2000–10)	1.62	1.08	2.43	0.019
Chu	2014	Taiwan	low	HCW, Charlson = 1	1.62	0.53	4.95	NR
Chu	2014	Taiwan	low	HCW, ETB	2.33	0.6	9	0.221
Chu	2014	Taiwan	low	HCW, <30y	5.84	2.62	13.01	NR
Chu	2014	Taiwan	low	HCW, PTB	1.56	1.02	2.39	0.039
Chu	2014	Taiwan	low	HCW, low risk TB	1.78	1.13	2.81	NR
Chu	2014	Taiwan	low	HCW, Charlson = 0	1.61	1.03	2.51	NR
Chu	2014	Taiwan	low	HCW, Charlson >= 2	1.75	0.32	9.62	NR

First author	Year	Country	Low/ high TB burden	HCW description	Adjusted RR	Lower 95% CI	Upper 95% CI	P-value
Chu	2014	Taiwan	low	HCW, >= 30y	0.65	0.37	1.13	NR
Chu	2014	Taiwan	low	Other emp. Clinic	0.5	0.22	1	NR
Chu	2014	Taiwan	low	HCW, M	0.89	0.48	1.66	NR
Chu	2014	Taiwan	low	Other emp. Hosp	2.84	1.51	5.34	NR
Chu	2014	Taiwan	low	Lab tech	0.76	0.28	2.04	NR
Chu	2014	Taiwan	low	Nurses	2.55	1.37	4.72	NR
Chu	2014	Taiwan	low	Other emp. Medical Centre	3.74	1.24	11.27	NR
Chu	2014	Taiwan	low	Physicians	1.27	0.64	2.5	NR
Chu	2014	Taiwan	low	HCW, F	2.5	1.43	4.39	NR
Chu	2014	Taiwan	low	HCW, high risk TB	1.12	0.45	2.75	NR
Pan	2015	Taiwan	low	HCWs	1.9	1.2	2.9	NR

assist.: assistant; CI: confidence interval; Drs: doctors; emp.: employee; ETB: extrapulmonary TB; excl.: excluding; F: female; HCW: health care worker; hosp.: hospital; lab: laboratory; M: male; NR: not reported; PTB pulmonary TB; pyrs: person-years; RR: rate ratio; TB: tuberculosis; tech: technician; unadj: unadjusted

Table 12. Summary of quality assessments for cohort studies using a modified Newcastle-Ottawa scale* (n = 31 studies)

First author	Year published	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of exposed and non-exposed on the basis of the design or analysis	Ascertainment of outcome	Was follow-up long enough for outcomes to occur	Non-response rate for retrospective cohorts	Adequacy of follow up of cohorts for prospective studies	Total score
Burrill	1985	1	1	0	0	1	1	1	0	0	**5**
Chen	2014	1	1	0	0	0	0	0	0	0	**2**
Chu	2014	1	1	0	0	2	1	1	0	0	**6**
Claassens	2010	1	1	0	1	2	1	1	0	0	**7**
Corbett	2007	1	0	0	1	2	0	1	0	0	**5**
Cuhadaroglu	2002	1	1	0	0	0	1	1	0	0	**4**
Dimitrov	2005	1	0	0	0	0	1	1	0	0	**3**
Driver	2005	1	1	0	0	0	1	1	0	0	**4**
Eyob	2002	1	1	0	0	0	1	1	0	0	**4**
Golchin	2005	0	0	0	0	2	0	1	0	0	**3**
Harries	1999	1	1	0	0	0	1	1	0	0	**4**
Hill	1997	1	1	1	0	1	1	1	0	0	**6**
Hohmuth	2006	0	0	0	1	0	0	0	0	0	**1**
Klimuk	2014	1	1	0	0	0	1	1	0	0	**4**
Krüüner	2001	1	1	0	0	0	1	1	0	0	**4**
Marena	1996	1	1	0	0	0	1	1	0	0	**4**
O'Donnell	2010	1	1	0	0	0	1	1	0	0	**4**
O'Hara	2017	1	1	1	0	0	1	1	0	0	**5**

First author	Year pub-lished	Represen-tativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demon-stration that outcome of interest was not present at start of study	Comparability of exposed and non-exposed on the basis of the design or analysis	Ascertainment of outcome	Was follow-up long enough for outcomes to occur	Non-response rate for retrospective cohorts	Adequacy of follow up of cohorts for prospective studies	Total score
Ohmori	2007	1	1	0	0	2	0	1	0	0	**5**
Ong	2006	0	1	0	0	0	1	1	0	0	**3**
Pan	2015	1	0	0	0	2	1	1	0	0	**5**
Pazin-Filho	2008	0	1	0	0	0	1	1	0	0	**3**
Pleszewski	1998	1	1	0	0	0	1	1	0	0	**4**
Raitio	2000	1	1	0	0	1	1	1	0	0	**5**
Raitio	2003	1	1	1	0	1	1	1	0	0	**6**
Reis	2012	1	1	0	0	0	1	1	0	0	**4**
Riley	1997	1	1	0	0	2	1	1	0	0	**6**
Shimouchi	2007	1	1	0	0	2	0	1	0	0	**5**
Skodric-Trifunovic	2009	1	1	0	0	0	1	1	0	0	**4**
Sotgiu	2008	1	1	0	0	0	1	1	0	0	**4**
Wilkinson	1998	1	1	0	0	2	1	1	0	0	**6**

*A study can be awarded a maximum of one point for each category, except for comparability which has a maximum of two points. Maximum possible total score is 10.

Table 13. Summary of quality assessment scores for cross-sectional studies using a modified Newcastle-Ottawa scale* (n = 10 studies)

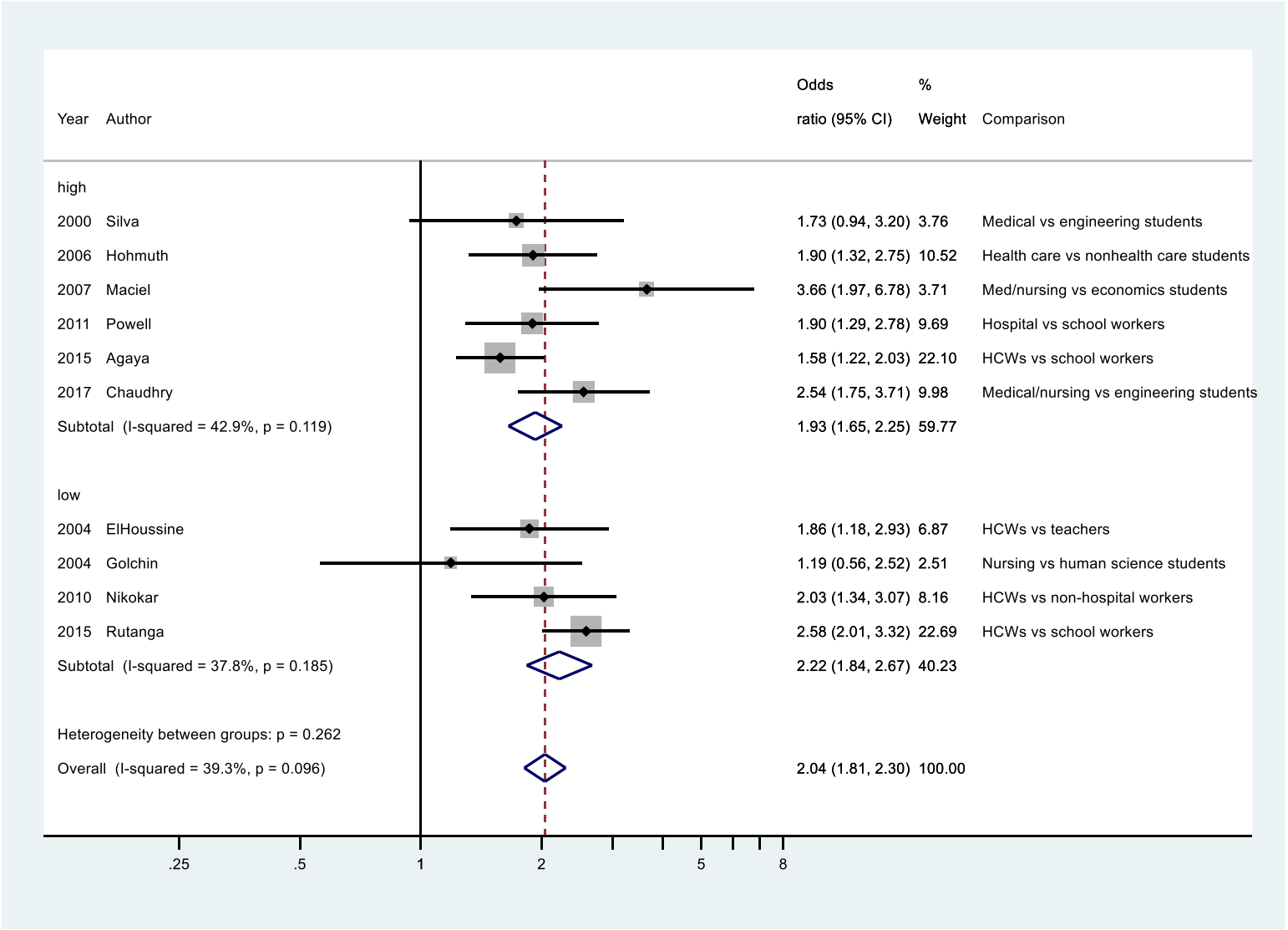
First author	Year pub-lished	Represen-tativeness of the HCW study group	Represen-tativeness of the general population study group	Sample size	Ascertainment of exposure	Management of non-respondents	Comparability of exposed and non-exposed on the basis of the design or analysis	Assessment of outcome	Statistical test	Total
Agaya	2015	1	0	0	1	0	2	0	0	**4**
Chaudhry	2017	0	0	0	0	0	0	0	0	**0**
Drobniewski	2007	1	1	0	0	1	0	0	0	**3**
El Houssine	2004	0	0	0	1	0	0	0	0	**1**
Maciel	2007	1	0	0	0	0	0	0	1	**2**
Nikokar	2015	0	0	1	0	0	0	0	0	**1**
Powell	2011	1	1	0	0	0	2	0	0	**4**
Rutanga	2015	1	1	0	0	0	2	0	0	**4**
Silva	2000	1	1	0	0	0	0	0	0	**2**
Zhu	2014	0	1	0	0	1	0	0	0	**2**

HCW: healthcare worker.

*A study can be awarded a maximum of one point for each category, except for comparability which has a maximum of two points. Maximum possible total score is 9.

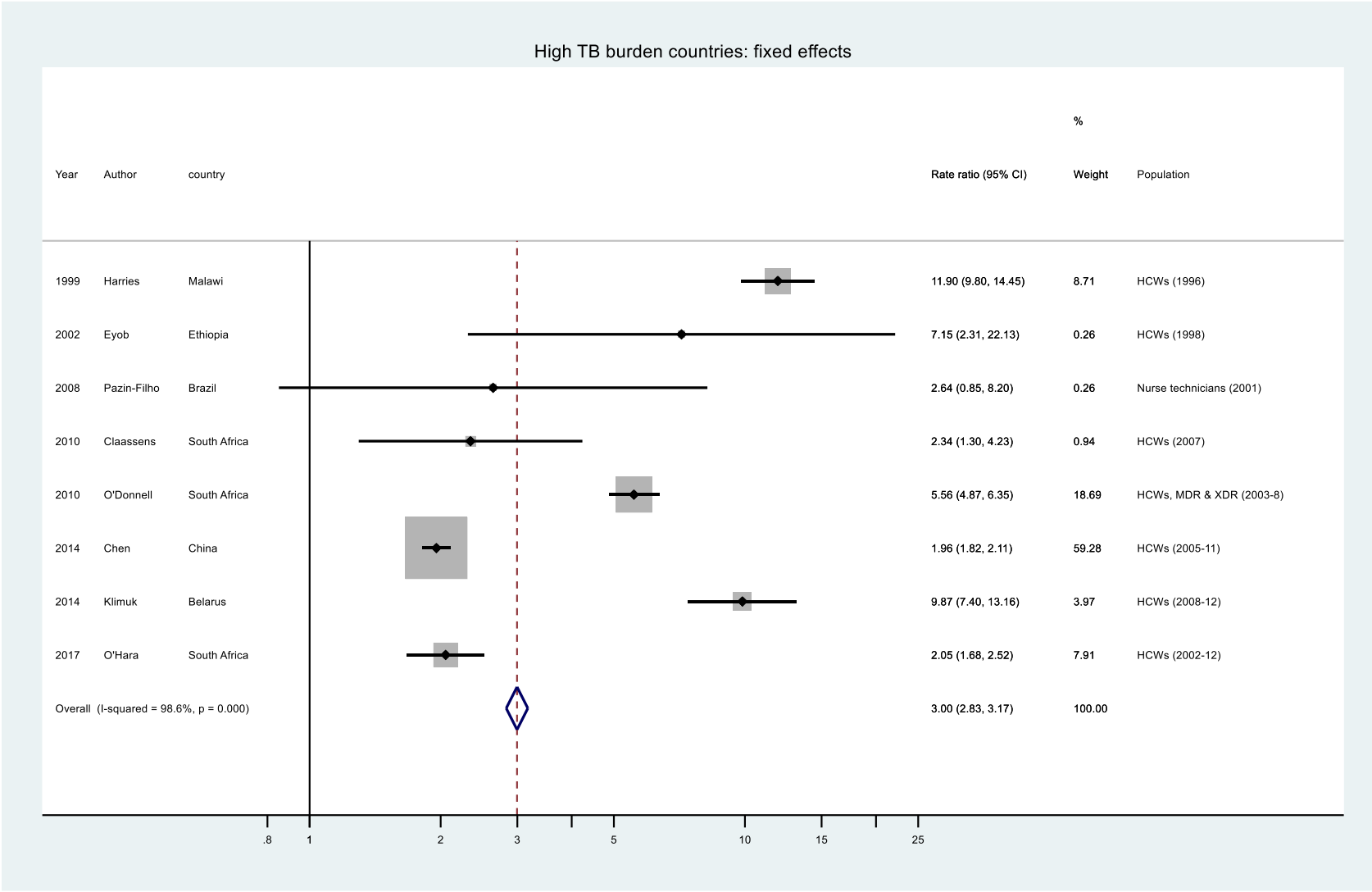
6.4. Additional figures

Figure 10. Ten studies (6 in high TB burden countries) using unadjusted OR and 95% CI, and fixed effect meta-analysis for TB infection prevalence in healthcare workers compared to the general population



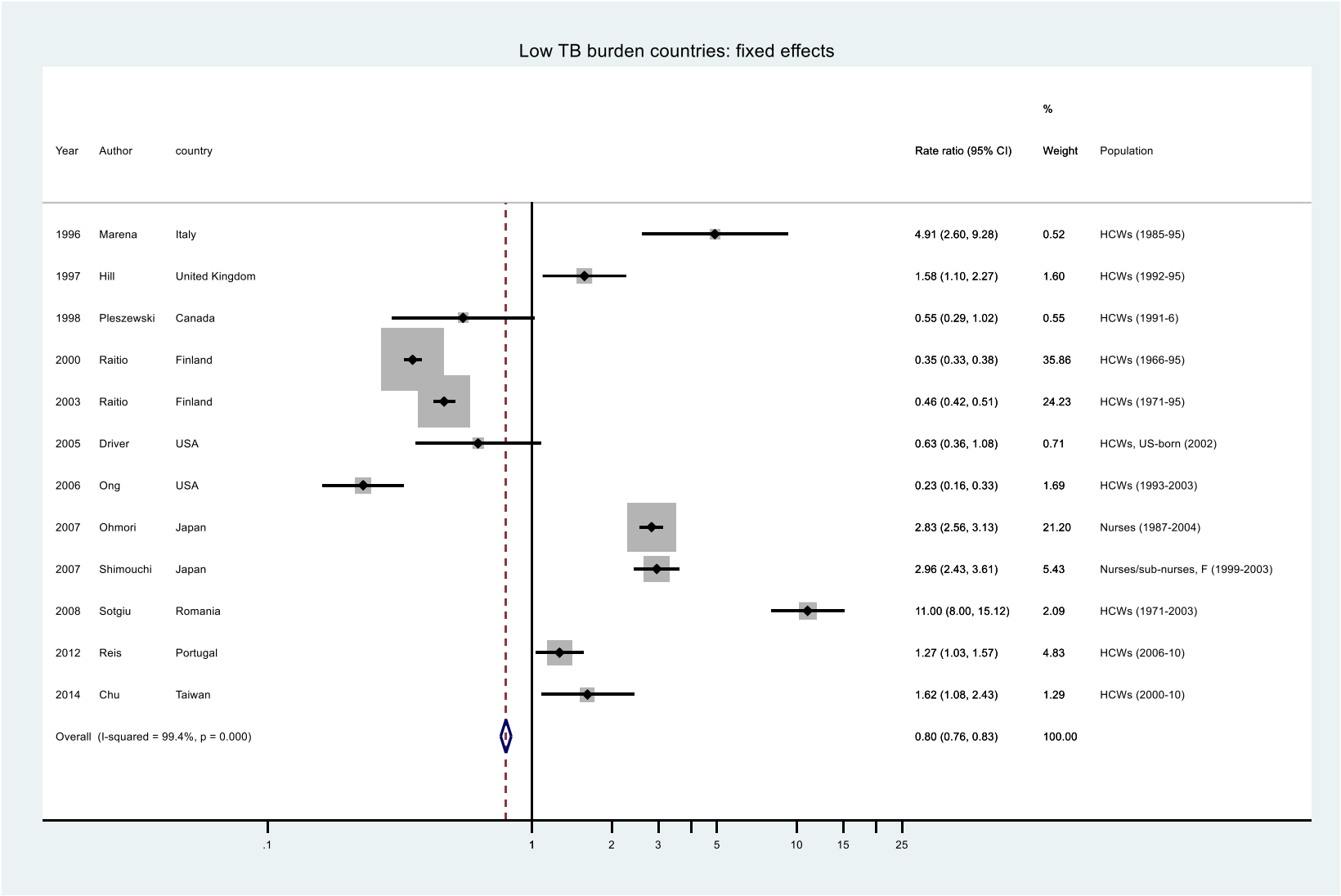
CI: confidence interval; HCW: health care worker; OR: odds ratio; TB: tuberculosis; vs: versus

Figure 11. Eight studies conducted in high TB burden countries, using unadjusted RR and 95% CI, and fixed effect meta-analysis for TB disease incidence in healthcare workers compared to the general population



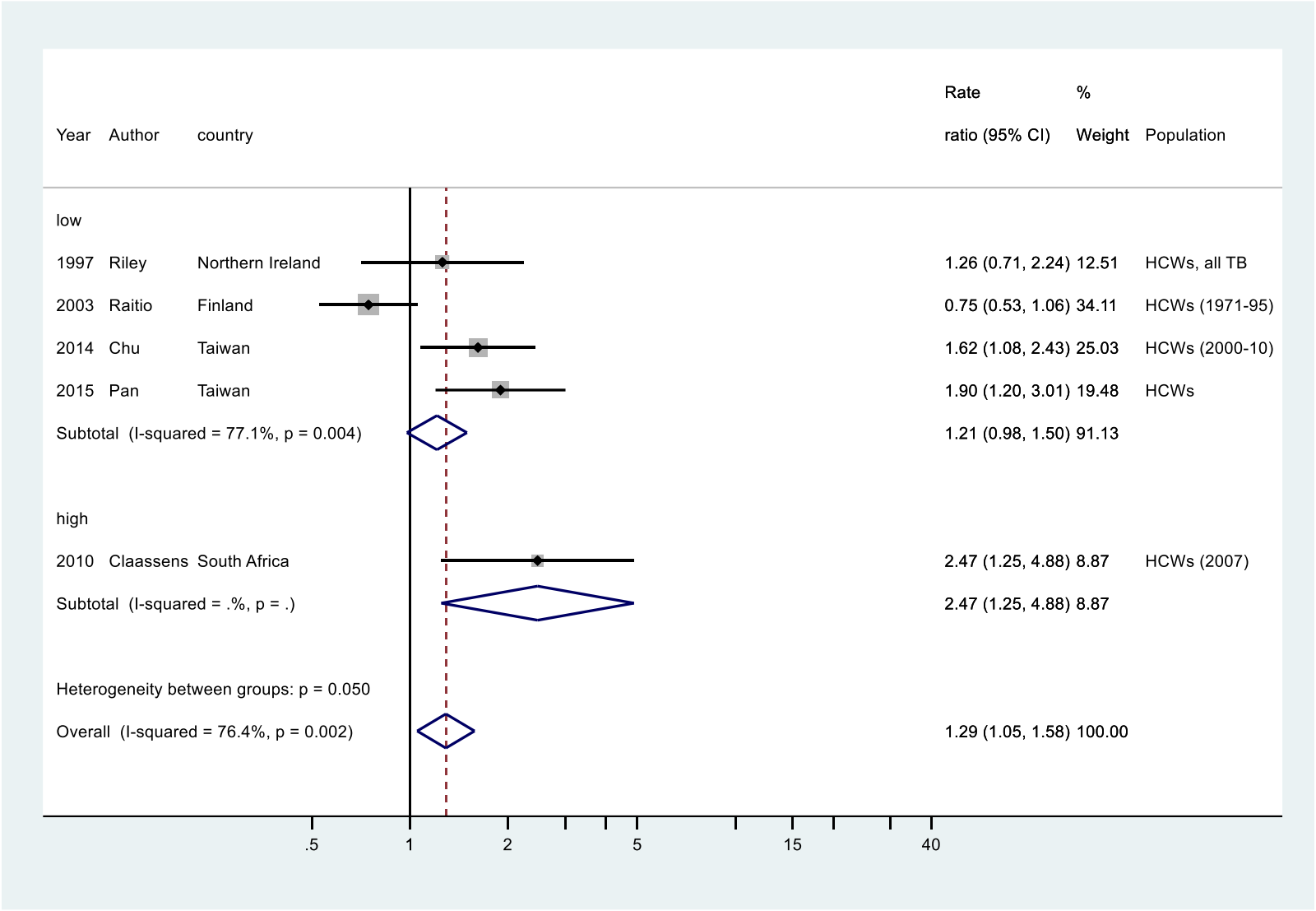
CI confidence interval; HCW: health care worker; MDR: multidrug-resistant; RR: rate ratio; TB: tuberculosis; XDR: extensively drug-resistant

Figure 12. Twelve studies conducted in low TB burden countries, using unadjusted RR and 95% CI, and fixed effect meta-analysis for TB disease incidence in healthcare workers compared to the general population



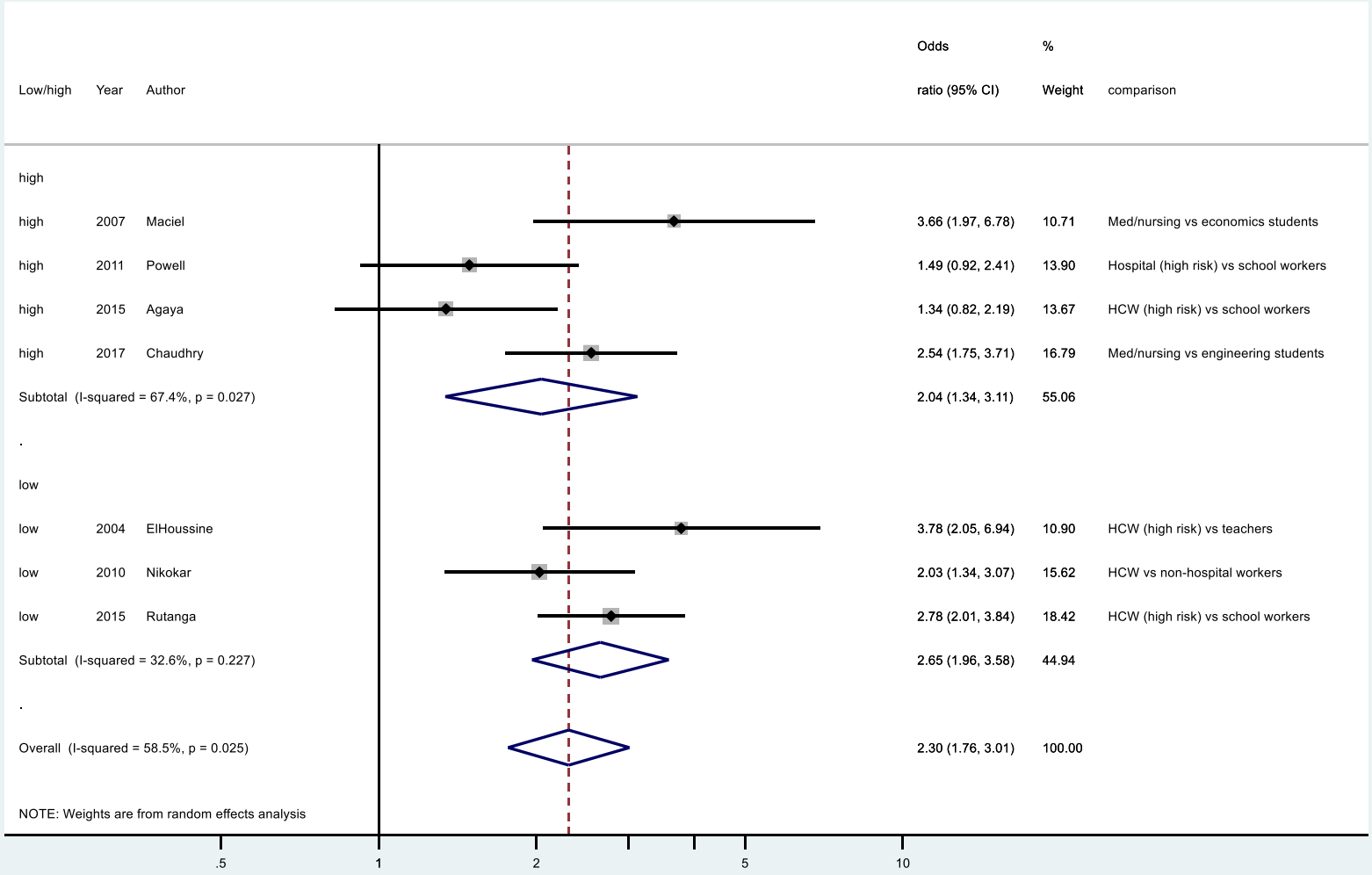
CI: confidence interval; HCW: health care worker; F: female; RR: rate ratio; TB: tuberculosis

Figure 13. Forest plot for five studies (4 in low TB burden countries) using adjusted RR and 95% CI, and fixed effects meta-analysis, for TB disease incidence amongst healthcare workers compared to the general population



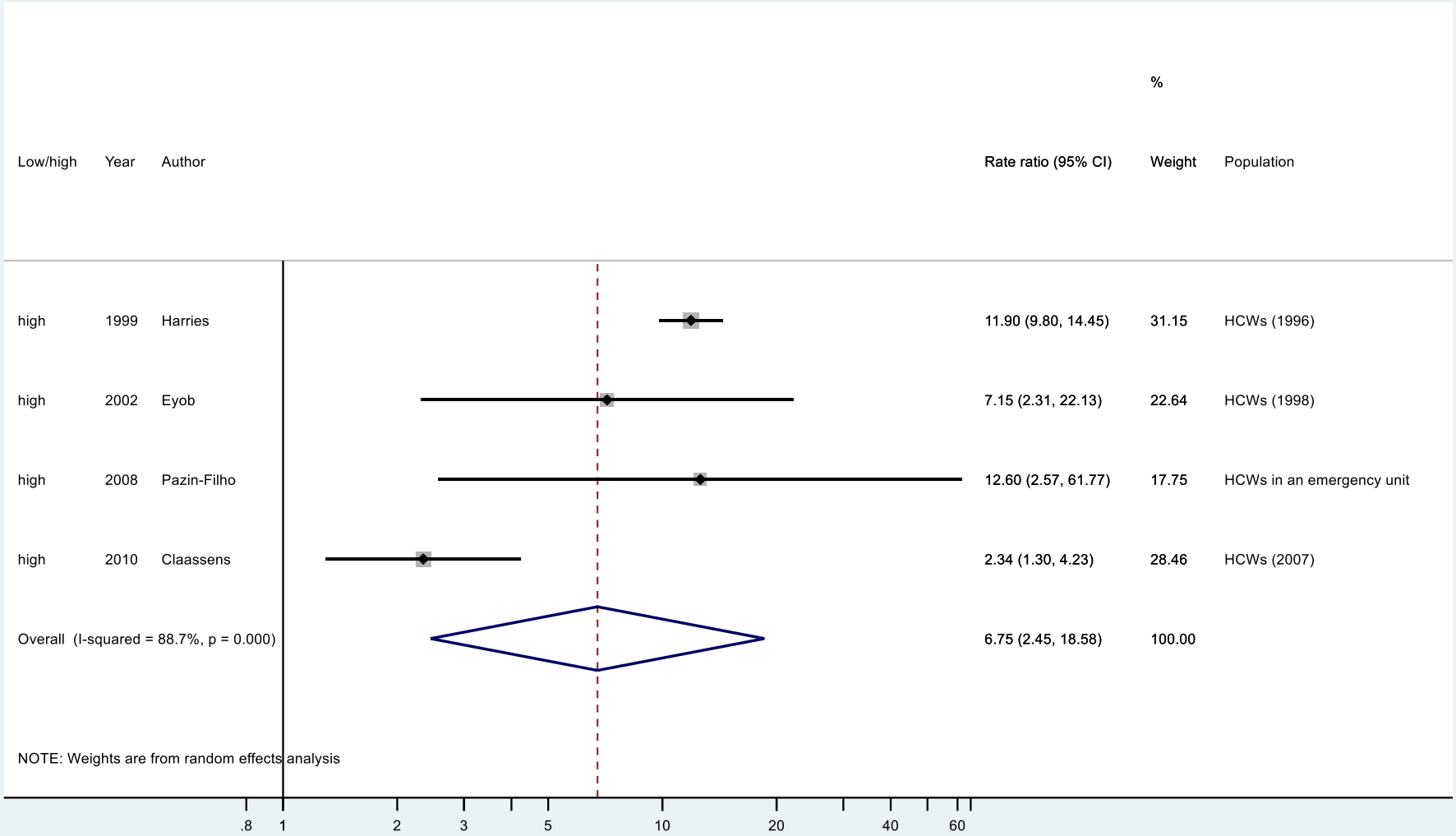
CI: confidence interval; HCW: health care worker; RR: rate ratio; TB: tuberculosis

Figure 14. Forest plot for seven studies using TST to measure TB infection prevalence (four in high TB burden countries), based on unadjusted ORs and 95% CI, and random effects meta-analysis, stratified by low/high TB burden setting, comparing TB infection prevalence in health care workers versus the general population, and restricted to high TB risk health care settings



CI: confidence interval; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test

Figure 15. Forest plot for four studies (all in high TB burden countries) comparing TB disease incidence in health care workers versus the general population, and restricted to high TB risk health care settings, based on unadjusted RRs and 95% CI and random effects meta-analysis



CI: confidence interval; HCW: health care worker; RR: rate ratio; TB: tuberculosis

6.5. Additional information on analysis of TB disease incidence

Table 14. 20 studies contributing to unadjusted RR and 95% CI for TB disease incidence outcome, single study-level estimate

Author, year	Country	Low/ high	HCW population	Unadj RR	Lower 95% CI	Upper 95% CI	How study-level RR and 95% CI was calculated
Harries, 1999	Malawi	high	HCWs (1996)	11.90	9.80	14.45	From publication
Eyob, 2002	Ethiopia	high	HCWs (1998)	7.15	2.31	22.13	From publication
Pazin-Filho, 2008	Brazil	high	Nurse technicians (2001)	2.64	0.85	8.20	From publication
Claassens, 2010	South Africa	high	HCWs (2007)	2.34	1.30	4.23	Calculated from reported data
O'Donnell, 2010	South Africa	high	HCWs, MDR & XDR (2003–8)	5.56	4.87	6.35	From publication
Chen, 2014	China	high	HCWs (2005–11)	1.96	1.82	2.11	From publication, using general population comparator
Klimuk, 2014	Belarus	high	HCWs (2008–12)	9.87	7.40	13.16	Estimate from within-study meta-analysis of reported data
O'Hara, 2017	South Africa	high	HCWs (2002–12)	2.05	1.68	2.52	Estimate from within-study meta-analysis of reported data
Marena, 1996	Italy	low	HCWs (1985–95)	4.91	2.60	9.28	Estimate from within-study meta-analysis of reported data
Hill, 1997	United Kingdom	low	HCWs (1992–95)	1.58	1.10	2.27	Estimate from within-study meta-analysis of reported data
Pleszewski, 1998	Canada	low	HCWs (1991–6)	0.55	0.29	1.02	Calculated from reported data, collapsed across subgroups*
Raitio, 2000	Finland	low	HCWs (1966–95)	0.35	0.33	0.38	Calculated from reported data, collapsed across subgroups
Raitio, 2003	Finland	low	HCWs (1971–95)	0.46	0.42	0.51	Calculated from reported data, collapsed across subgroups*
Driver, 2005	USA	low	HCWs, US-born (2002)	0.63	0.36	1.08	Calculated from reported data
Ong, 2006	USA	low	HCWs (1993–2003)	0.23	0.16	0.33	Calculated from reported data
Ohmori, 2007	Japan	low	Nurses (1987–2004)	2.83	2.56	3.13	Estimate from within-study meta-analysis of reported data
Shimouchi, 2007	Japan	low	Nurses/sub-nurses, F (1999–2003)	2.96	2.43	3.61	Calculated from reported data

Author, year	Country	Low/ high	HCW population	Unadj RR	Lower 95% CI	Upper 95% CI	How study-level RR and 95% CI was calculated
Sotgiu, 2008	Romania	low	HCWs (1971–2003)	11.00	8.00	15.12	From publication
Reis, 2012	Portugal	low	HCWs (2006–10)	1.27	1.03	1.57	From publication
Chu, 2014	Taiwan	low	HCWs (2000–10)	1.62	1.08	2.43	From publication

* only for HCW data

CI confidence interval; F: female; HCW: health care worker; MDR: multidrug resistant; RR: rate ratio; TB: tuberculosis; unadj: unadjusted; US: United States; XDR: extensively drug resistant;

6.6. Additional information on sensitivity analysis of high TB risk health care settings

Table 15. Seven studies (four from high TB burden countries) contributing to the sensitivity analysis of high TB risk health care settings for TB infection prevalence.

First author	Year	Country	Low/high TB burden	Description of high TB risk health care setting
Maciel[8]	2007	Brazil	high	Medical/nursing students working at referral hospital for TB patients.
Powell[10]	2011	Viet Nam	high	Authors stratified places of work into high- and low-risk. High-risk defined as TB ward, communicable disease ward, internal medicine wards, casualty departments, and microbiology departments.
Agaya[4]	2015	Kenya	high	Authors stratified places of work into high- and low-risk. High-risk included internal medicine, emergency room, and laboratory departments.
Chaudhry[19]	2017	India	high	All health care workers were from a department of pulmonary & critical care medicine.
El Houssine[26]	2004	Morocco	low	Authors stratified places of work into high- and low-risk. High-risk defined as in permanent contact with TB patients and practicing in TB hospitals or in specialised diagnostic centres for TB.
Nikokar[6]	2015	Iran	low	All health care workers were in high-risk wards defined as infectious diseases, thorax surgery, haemodialysis, and radiology.
Rutanga[11]	2015	Rwanda	low	Authors stratified places of work into high- and low-risk. High-risk defined as clinical departments providing services to a patient population known to have a high prevalence of TB disease that included HIV care and treatment and TB services.

TB: tuberculosis

Table 16. Four studies (all from high TB burden countries) contributing to the sensitivity analysis of high TB risk health care settings for TB disease incidence

First author	Year	Country	Low/high TB burden	Description of high TB risk health care setting
Claassens[14]	2010	South Africa	high	All health care workers were all researchers working on a TB case-finding study
Eyob[27]	2002	Ethiopia	high	All health care workers worked at the TB Demonstration and Training Centre
Harries[28]	1999	Malawi	high	All health care workers worked in hospitals that diagnose and care for TB patients.
Pazin-Filho[37]	2008	Brazil	high	Authors stratified places of work, which included the Emergency Unit at a University hospital, considered high TB risk.

TB: tuberculosis

6.7. Summary table of figures showing forest plots

Table 17. Summary table describing figures in report showing Forest plots

Figure number	Number of studies	Outcome	Summary estimate	Fixed/random effects	High/low TB burden setting	Sensitivity analysis
2	12	TB infection prevalence	No summary estimate	NA	NA	NA
3	10	TB infection prevalence	Unadjusted	Random effects	Stratified	No
4	4	TB infection prevalence	Adjusted	Random effects	Stratified	No
5	8	TB disease incidence	No summary estimate	NA	NA	NA
6	12	TB disease incidence	No summary estimate	NA	NA	NA
7	8	TB disease incidence	Unadjusted	Random effects	High	No
8	12	TB disease incidence	Unadjusted	Random effects	Low	No
9	5	TB disease incidence	Adjusted	Random effects	Stratified	No
10	10	TB infection prevalence	Unadjusted	Fixed effect	Stratified	No
11	8	TB disease incidence	Unadjusted	Fixed effect	High	No
12	12	TB disease incidence	Unadjusted	Fixed effect	Low	No
13	5	TB disease incidence	Adjusted	Fixed effect	Stratified	No
14	7	TB infection prevalence	Unadjusted	Random effects	Stratified	Restricted to high TB risk health care settings
15	4	TB disease incidence	Unadjusted	Random effects	High	Restricted to high TB risk health care settings

NA: not applicable; TB: tuberculosis

7. References

1 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;**6**(7):e1000097.

2 Modesti PA, Reboldi G, Cappuccio FP, et al. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. *PLoS One*. 2016;**11**(1):e0147601.

3 World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. 2015. p. 19. http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf?ua=1 (accessed 2018 Jan 10)

4 Agaya J, Nnadi CD, Odhiambo J, et al. Tuberculosis and latent tuberculosis infection among healthcare workers in Kisumu, Kenya. *Trop Med Int Health*. 2015;**20**(12):1797–804.

5 Silva VM, Cunha AJ, Oliveira JR, et al. Medical students at risk of nosocomial transmission of Mycobacterium tuberculosis. *Int J Tuberc Lung Dis*. 2000;**4**(5):420–6.

6 Nikokar I, Dadgran A, Mafozei L. A comparison of two-step tuberculin skin test between health-care workers and nonhospital employees. *Iran J Med Sci*. 2010;**35**(3):201–4.

7 Golchin M, Rostami M. Tuberculin test in nursing and human-sciences students. *J Res Med Sci*. 2005;**10**(3):172–6.

8 Maciel EL, Meireles W, Silva AP, Fiorotti K, Dietze R. Nosocomial Mycobacterium tuberculosis transmission among healthcare students in a high incidence region, in Vitoria, State of Espirito Santo. *Rev Soc Bras Med Trop*. 2007;**40**(4):397–9.

9 Hohmuth BA, Yamanija JC, Dayal AS, Nardell E, Salazar JJ, Smith Fawzi MC. Latent tuberculosis infection: risks to health care students at a hospital in Lima, Peru. *Int J Tuberc Lung Dis*. 2006;**10**(10):1146–51.

10 Powell K, Han D, Hung N V, et al. Prevalence and risk factors for tuberculosis infection among personnel in two hospitals in Viet Nam. *Int J Tuberc Lung Dis*. 2011;**15**(12):1643–9.

11 Rutanga C, Lowrance DW, Oeltmann JE, et al. Latent Tuberculosis Infection and Associated Factors among Health Care Workers in Kigali, Rwanda. *PLoS ONE [Electronic Resour*. 2015;**10**(4):e0124485.

12 Pan SC, Chen YC, Wang JY, et al. Tuberculosis in Healthcare Workers: A Matched Cohort Study in Taiwan. *PLoS ONE [Electronic Resour*. 2015;**10**(12):e0145047–e0145047.

13 Riley M, Loughrey CM, Wilkinson P, Patterson CC, Varghese G. Tuberculosis in health service employees in Northern Ireland. *Respir Med*. 1997;**91**(9):546–50.

14 Claassens MM, Sismanidis C, Lawrence KA, et al. Tuberculosis among community-based health care researchers. *Int J Tuberc Lung Dis*. 2010;**14**(12):1576–81.

15 Raitio M, Tala E. Tuberculosis among health care workers during three recent decades. *Eur Respir J*. 2000;**15**(2):304–7.

16 Raitio M, Helenius H, Tala E. Is the risk of occupational tuberculosis higher for young health care workers? *Int J Tuberc Lung Dis*. 2003;**7**(6):556–62.

17 Chu H, Shih C-J, Lee Y-J, et al. Risk of tuberculosis among healthcare workers in an intermediate-burden country: a nationwide population study. *J Infect*. 2014;**69**(6):525–32.

18 Burrill D, Enarson DA, Allen EA, Grzybowski S. Tuberculosis in female nurses in British Columbia: implications for control programs. *Can Med Assoc J*. 1985;**132**(2):137–40.

19 Chaudhry D, Jain N, Singh S, Prajapat B, Agarwal A. Prevalence of latent tuberculosis among exposed population of medical students as compared with unexposed population of non-medical students and its relation with duration of exposure. *Am J Respir Crit Care Med Conf Am Thorac Soc Int Conf ATS*. 2017;**195**(no pagination).

20 Chen B, Wang X, Zhong J, et al. Tuberculosis among healthcare workers in southeastern China: A retrospective study of 7-year surveillance data. *Int J Environ Res Public Health*. 2014;**11**(11):12042–52.

21 Corbett EL, Muzangwa J, Chaka K, et al. Nursing and community rates of Mycobacterium tuberculosis infection among students in Harare, Zimbabwe. *Clin Infect Dis*. 2007;**44**(3):317–23.

22 Cuhadaroglu C, Erelel M, Tabak L, Kilicaslan Z. Increased risk of tuberculosis in health care workers: a retrospective survey at a teaching hospital in Istanbul, Turkey. *BMC Infect Dis*. 2002;**2**:14.

23 Dimitrova B, Hutchings A, Atun R, et al. Increased risk of tuberculosis among health care workers in Samara Oblast, Russia: analysis of notification data. *Int J Tuberc Lung Dis*. 2005;**9**(1):43–8.

24 Driver CR, Stricof RL, Granville K, et al. Tuberculosis in health care workers during declining tuberculosis incidence in New York State. *Am J Infect Control*. 2005;**33**(9):519–26.

25 Drobniewski F, Balabanova Y, Zakamova E, Nikolayevskyy V, Fedorin I. Rates of latent tuberculosis in health care staff in Russia. *PLoS Med / Public Libr Sci*. 2007;**4**(2):e55.

26 El Houssine Laraqui C, Laraqui O, El Kabouss Y, et al. [Assessment of the risk of tuberculosis among health care personnel in Meknes]. *Sante*. 2004;**14**(3):167–71.

27 Eyob G, Gebeyhu M, Goshu S, Girma M, Lemma E, Fontanet A. Increase in tuberculosis incidence among the staff working at the Tuberculosis Demonstration and Training Centre in Addis Ababa, Ethiopia: a retrospective cohort study (1989-1998). *Int J Tuberc Lung Dis*. 2002;**6**(1):85–8.

28 Harries AD, Nyirenda TE, Banerjee A, Boeree MJ, Salaniponi FM. Tuberculosis in health care workers in Malawi. *Trans R Soc Trop Med Hyg*. 1999;**93**(1):32–5.

29 Hill A, Burge A, Skinner C. Tuberculosis in National Health Service hospital staff in the west Midlands region of England, 1992-5. *Thorax*. 1997;**52**(11):994–7.

30 Klimuk D, Hurevich H, Harries AD, et al. Tuberculosis in health care workers in Belarus. *Public Heal Action*. 2014;**4**(Suppl 2):S29-33.

31 Kruuner A, Danilovitsh M, Pehme L, Laisaar T, Hoffner SE, Katila ML. Tuberculosis as an occupational hazard for health care workers in Estonia. *Int J Tuberc Lung Dis*. 2001;**5**(2):170–6.

32 Marena C, Mangairotti P, Manara G, et al. Occupational tuberculosis infection among health care personnel. Eleven years experience in a large university hospital. In: *European Respiratory Society*. 1996. p. #P1139.

33 O'Donnell MR, Jarand J, Loveday M, et al. High incidence of hospital admissions with multidrug-resistant and extensively drug-resistant tuberculosis among South African health care workers.[Summary for patients in Ann Intern Med. 2010 Oct 19;153(8):I-62; PMID: 20956693]. *Ann Intern Med*. 2010;**153**(8):516–22.

34 O'Hara LM, Yassi A, Bryce EA, et al. Infection control and tuberculosis in health care workers: an assessment of 28 hospitals in South Africa. *Int J Tuberc Lung Dis*. 2017;**21**(3):320–6.

35 Ohmori M, Hoshino H, Yamauchi Y, Uchimura K. [Current epidemiological situation of tuberculosis in the workplace: considering the risk of tuberculosis among nurses]. *Kekkaku*. 2007;**82**(2):85–93.

36 Ong A, Rudoy I, Gonzalez LC, Creasman J, Kawamura LM, Daley CL. Tuberculosis in healthcare workers: a molecular epidemiologic study in San Francisco. *Infect Control Hosp Epidemiol*. 2006;**27**(5):453–8.

37 Pazin-Filho A, Soares CS, Ferrais Ada S, et al. Tuberculosis among health care workers in a Brazilian tertiary hospital emergency unit. *Am J Emerg Med*. 2008;**26**(7):796–8.

38 Pleszewski B, FitzGerald JM. Tuberculosis among health care workers in British Columbia. *Int J Tuberc Lung Dis*. 1998;**2**(11):898–903.

39 Reis R, Correia AM, Gomes M, Duarte R. Tuberculosis in healthcare workers: 5year, multiinstitutional analysis of the northern region of Portugal. *Eur Respir Journal Conf Eur Respir Soc Annu Congr*. 2012;**40**(no pagination).

40 Shimouchi A, Hirota S, Koda S, Mui K. [Discussion on incidence of tuberculosis patients among nurses in Osaka City]. *Kekkaku*. 2007;**82**(9):697–703.

41 Skodric-Trifunovic V, Markovic-Denic L, Nagorni-Obradovic L, Vlajinac H, Woeltje KF. The risk of occupational tuberculosis in Serbian health care workers. *Int J Tuberc Lung Dis*. 2009;**13**(5):640–4.

42 Sotgiu G, Arbore AS, Cojocariu V, et al. High risk of tuberculosis in health care workers in Romania. *Int J Tuberc Lung Dis*. 2008;**12**(6):606–11.

43 Wilkinson D, Gilks CF. Increasing frequency of tuberculosis among staff in a South African district hospital: impact of the HIV epidemic on the supply side of health care. *Trans R Soc Trop Med Hyg*. 1998;**92**(5):500–2.

44 Zhu C, Liu Z, Li Z, Mei S, Hu Z. The performance and limitation of T-SPOT.TB for the diagnosis of TB in a high prevalence setting. *J Thorac Dis*. 2014;**6**(6):713–9.

Systematic review for evidence of administrative infection control interventions to reduce TB transmission and three related background questions

Background question 2

Final report

1 June 2018

Authors: Katherine Fielding, Raoul Mansukhani, Aaron Karat, Rebecca Harris, Dave Moore

Contributors: Jane Falconer, Manisha Wadhwa, Carolin Bresges, Ed Monk, Maria Calderon, Marc Woodman, Natalia Castano-Villegas, Claire Calderwood, Jayne Ellis, Nicky McCreesh, Malin Bergstrom, Hannah Theodorou, Akira Endo, Meghann Gregg, Hannah Barton, Sarah Stokes, Maria Krutikov, James Wilson, Indira Govender

Enquiries to: katherine.fielding@lshtm.ac.uk

Contents

List of tables

List of figures

1. Executive summary

1.1. Question

This review addressed whether individuals living in TB-affected households or spending time in congregate settings at higher risk of tuberculosis (TB) infection or active TB disease than the general population from which they are drawn, who are not similarly exposed.

1.2. Methods

The population included individuals living in TB-affected households or residing in a congregate setting (e.g., correctional facility, nursing home). The comparator was the general population reported within the same publication. Outcomes were incidence or prevalence of latent TB infection (LTBI) or TB disease. The search strategy was constructed and implemented by a professional librarian, using relevant subject headings, and search terms in the title and abstract fields where possible. Searches were restricted to papers written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese, published after 1946. Bibliographic databases searched included MEDLINE, EMBASE, CINAHL Plus, and Global Health. Two independent reviewers screened publications for eligibility for inclusion using a two-stage sifting process: (1) at title and abstract; and (2) at full text level. Consensus was conducted at each stage, with a third reviewer for resolution of unresolved disagreements. Citations and references of selected papers were also reviewed and screened for eligibility. For included systematic reviews, all the source manuscripts identified by our search and deemed eligible for inclusion at screening were included; data from the systematic review itself were not extracted. Data were extracted from those papers selected for final inclusion, in duplicate by independent extractors into a piloted standardised database. Quality assessment at the study level was conducted using standardised Newcastle-Ottawa Scale tools. Extracted data were synthesised using a narrative approach and, where appropriate, fixed-effects and random-effects meta-analyses. When comparing residents of TB-affected households or those living in a congregate setting versus the general population, odds ratios (ORs) were used for TB infection prevalence, risk/rate differences were used for TB infection incidence and rate ratios (RRs) were used for TB disease incidence. Study settings were defined as low or high TB burden using the post-2015 WHO definition. For the congregate settings summary, estimates were stratified by low or high TB burden countries. For TB-affected household studies, summary estimates were stratified by high or low TB burden countries and by age as child, adult or combined (child and adult) populations.

1.3. Results

In total 5,236 records were assessed at the title and abstract phase after removal of duplicates. 164 papers were reviewed at full text. After full text sifting, reference and citation tracking 96 papers were included in

the review, of which 93 were primary research articles eligible for data extraction and 3 were systematic reviews. Twenty-one articles were identified from congregate settings: 12 from correctional facilities alone; five from nursing homes alone; one reported data from a correctional facility and nursing home; one reported data from a long-term care residential facility and shelter; one from social institute and psychiatric hospital; and one displaced persons camp. TB disease incidence was the most common outcome reported.

Five studies in correctional facilities reporting data allowing estimation of confidence intervals contributed to the meta-analysis for TB disease incidence, two studies from high TB burden countries and three studies from low TB burden countries. For high TB burden countries, using random effects, the summary RR was 6.48 (95% confidence interval [CI] 2.70-15.60) and I^2 was 80.1%. For low TB burden countries, the summary RR was 7.25 (95% CI 1.89-27.82) and I^2 was 99.6%. Three studies (all low TB burden settings) measured TB disease incidence among nursing homes residents and a general population. The summary RR using random effects meta-analysis was 1.40 (95% CI 0.89-2.22; I^2=88.8%). Overall, six studies from correctional facilities and three studies among nursing homes residents did not contribute to the analysis, as a 95% CI could not be calculated for the RR.

Three studies, all conducted in low TB burden countries, reported TB disease prevalence; two were in correctional facilities (unadjusted ORs were 15.7 and 7.7) and one in social institution and psychiatric hospital (among adults the OR were 3.77 and 15.6, respectively). One study (low burden setting) measured TB infection prevalence using QuantiFERON-TB Gold In-Tube interferon-gamma release assay (IGRA) and tuberculin skin test (TST), ≥10 mm, in two congregate settings; residents in a long-term care facility and a homeless shelter, compared to a general population. TB infection prevalence was higher among indivduals from the homeless shelter versus the comparator using IGRA (OR 1.87, 95% CI 1.10-3.22).

A total of 72 studies assessing the effect of TB-affected household contact on TB outcomes, were identified. The most common outcome was LTBI; measured in 35 studies by TST and 19 measured by IGRA, and contributing to the meta-analysis. In high TB burden countries with LTBI measured by TST and using random effects for unadjusted ORs, for children (18 studies) the summary OR was 3.86 (95% CI 2.60-5.72; I^2 95.2%), for adults (six studies) the summary OR was 3.02 (95% CI 1.66-5.47; I^2 96.1%), and for 10 studies that did not stratify data by age the summary OR was 2.18 (95% CI 1.70-2.80; I^2 84.9%). For low TB burden countries there were no studies enrolling children and measuring LTBI using TST. Among adults (three studies) and children/adults combined (three studies), the summary ORs using random effects were 4.18 (95% CI 2.59-6.72; I^2 0%) and 4.15 (95% CI 3.38-5.10; I^2 0%), respectively.

For studies assessing the impact of TB household contact in high TB burden countries with LTBI measured by IGRA and using random effects for unadjusted ORs, for children (six studies) the summary OR was 2.76 (95% CI 2.22-3.44; I^2 5.1%), for adults (four studies) the summary OR was 2.23 (95% CI 1.69-2.96; I^2 0%), and for four studies that did not stratify data by age the summary OR was 2.01 (95% CI 1.11-3.65; I^2 93.8%). For low TB burden countries among children alone (two studies) and children/adults combined (two studies) the summary ORs were 5.42 (95% CI 3.70-7.95; I^2 0%) and 2.39 (95% CI 0.31-18.17; I^2 76.2%), respectively.

Fifteen studies reported data assessing the effect of TB-affected households on TB disease prevalence (with 95% CIs reported); two cross-sectional, four unmatched case-control studies and nine matched case-control studies. Using random effects meta-analysis for unadjusted ORs, in high TB burden countries among children (two studies) the summary OR was 5.30 (95% CI 2.76-10.18; I^2=55.9%), among adults (six studies) the summary OR was 2.91 (95% CI 2.24-3.77; I^2=40.0%), and children/adults (three studies which did not report data stratified by age) the summary OR was 8.92 (95% CI 1.49-53.40; I^2=97.3%).

1.4. Discussion

The systematic review identified 93 primary research articles that reported data on TB infection prevalence, incidence or TB disease incidence in TB-affected households or congregate settings compared with comparator population. Studies were conducted in low and high burden countries and few reported adjusted effect estimates. Five studies reported TB disease incidence in correctional facilities, and stratified by TB disease burden, the summary RRs indicated higher TB disease rates compared to the general population. However I^2s were large (>80%) indicating huge study-heterogeneity making the summary estimates difficult to interpret. Many studies did not report sufficient data to calculate a CI for the RR.

For TB-affected households 72 primary research articles were identified of which the most common outcome was TB infection prevalence. For the outcome of TST positivity prevalence among children, adults and children/adults living in high TB burden settings, the summary ORs, using random-effects, were 3.9, 3.0 and 2.2, respectively, comparing TB-affected households with a comparator population. Study heterogeneity was extremely large (>84%) resulting in the summary estimates being difficult to interpret. Fewer studies contributed to the IRGA outcome. Study heterogeneity was low for children and adult populations, separately, in high TB burden settings, and summary estimates suggested around a three-fold increase in odds of TB infection for TB-affected households compared with a comparator. Case-control studies mainly contributed data for the outcome of TB disease prevalence and most studies were conducted in a high TB burden settings. Among children and adults separately the summary ORs were 5.3 and 2.9, respectively and study heterogeneity was less than 60%.

Study quality using the modified Newcastle-Ottawa scale was low for all study designs.

2. Background and question

A systematic review of the literature was conducted to answer the question: Are individuals living in TB-affected households or spending time in congregate settings at higher risk of TB infection or active TB disease than the general population from which they are drawn, who are not similarly exposed?

3. Methods

3.1. Population, comparator, and outcomes

Population

Individuals in the following settings:

- Household contacts of an index TB patient,
- Household contacts of an index MDR/extensively drug-resistant (XDR)-TB patient,
- Persons exposed in a congregate setting (as per glossary definition)

Comparator

General population without exposure to household TB or congregate setting

Outcomes

Compared between household or congregate setting exposed population and general population in the same study:

- Difference in latent TB infection (LTBI) incidence/cumulative incidence/prevalence or
- Difference in TB disease incidence/cumulative incidence/prevalence or
- Incidence rate ratio or prevalence ratio or odds ratio for TB disease or LTBI

Congregate setting

Defined as a mix of institutional (non-healthcare) settings where people reside long-term in close proximity to each other. Congregate settings range from correctional facilities (prisons), homeless shelters, refugee camps, army barracks, hospices, boarding school dormitories and nursing homes.

3.2. Search strategy

Search strategies for this background question was constructed and run by a professional librarian with experience of systematic review literature searching. The search strategy was compiled and tested on the OvidSP Medline database before being edited, as required, and run across other relevant information sources.

The search strategies used subject headings, where available, and search terms run in the title and abstract, where possible. Due to language skills available in the research team, literature was limited to papers written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese. No date limits or publication type limits were added to the search.

The following search was constructed in OvidSP Medline and was adapted, as appropriate, for the other search sources.

1. exp Residential Facilities/
2. exp Prisons/
3. Military Facilities/
4. Hospices/
5. Ships/
6. congregate setting?.ti,ab.
7. residential.ti,ab.
8. orphanage?.ti,ab.
9. children? home?.ti,ab.
10. (boarding adj2 school?).ti,ab.
11. (halls adj2 (residen* or student?)).ti,ab.
12. ((elderly or old age or aged or retirement or assisted living) adj2 (home? or house? or facilit* or residence?)).ti,ab.
13. ((nursing or care) adj1 (home? or house? or residence?)).ti,ab.
14. hostel*.ti,ab.
15. barrack?.ti,ab.
16. (military adj2 (facilit* or camp?)).ti,ab.
17. (refugee adj2 (facilit* or camp?)).ti,ab.
18. dormitor*.ti,ab.
19. work* camp?.ti,ab.
20. shelter?.ti,ab.
21. halfway house?.ti,ab.
22. rooming house?.ti,ab.
23. (group adj2 (home? or house? or residence?)).ti,ab.
24. (treatment adj2 (home? or house? or residence?)).ti,ab.
25. prison?.ti,ab.
26. (jail? or gaol?).ti,ab.
27. correctional facilit*.ti,ab.
28. (detention centre? or detention center?).ti,ab.
29. hospice?.ti,ab.
30. oil rig?.ti,ab.
31. ship?.ti,ab.
32. or/1-31 [CONGREGATE SETTINGS]

33. family characteristics/
34. household.ti,ab.
35. or/33-34 [HOUSEHOLDS]
36. exp tuberculosis/
37. mycobacterium tuberculosis/
38. tuberculosis.ti,ab.
39. tuberculin.ti,ab.
40. tb.ti,ab.
41. ltbi.ti,ab.
42. or/36-41 [TUBERCULOSIS]
43. 32 and 42
44. 35 and 42
45. 43 or 44
46. Humans/
47. Animals/
48. 46 and 47
49. 47 not 48 [ANIMAL STUDIES ONLY]
50. 45 not 49
51. (chinese or english or french or japanese or portuguese or russian or spanish).lg. (26984251)
52. 50 and 51
53. remove duplicates from 52

3.3. Databases searched

The following bibliographic databases were used: OvidSP MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE; Daily and Ovid MEDLINE 1946 to present; OvidSP EMBASE Classic + Embase 1947 to present; EBSCO CINAHL Plus; and OvidSP Global Health 1910 to present.

3.4. Eligibility criteria

3.4.1. Inclusion criteria

Types of participants:

Individuals in the following settings: household contacts of a TB patient; or household contacts of an MDR/XDR-TB patient; or congregate setting.

Types of study:

Any consecutive case series, case control study, cohort study, randomised controlled study, systematic review, or meta-analysis including a comparator group reporting on the outcomes listed below.

Types of comparator:

Studies also reporting data on the same outcome from the general population.

Types of outcome measures:

- Studies reporting data on at least one of the outcome measures of interest. Outcomes of interest are: difference in LTBI incidence/cumulative incidence/prevalence; or difference in TB incidence/cumulative incidence/prevalence; or incidence rate ratio or prevalence ratio or odds ratio for active TB or LTBI.
- LTBI incidence and prevalence will be based on tuberculin skin tests (TST) (using any method) or interferon-gamma release assays (IGRAs; including QFT Plus, QFT Gold, QFT Gold In-Tube, and TSPOT.TB)
- TB disease will be based on microbiological (smear microscopy, culture, or molecular diagnostic), radiological, or clinical diagnosis.

3.4.2. Exclusion criteria

- Any study not in humans
- Any study that does not report any of the above-stated outcomes of interest
- Any study reporting solely on primary outcomes of interest in the household or congregate setting group without a control or comparator group
- Any systematic review superseded by an updated systematic review
- Narrative reviews not adding new data or new analysis of data to existing knowledge
- Commentaries and mathematical modelling studies
- Studies with fewer than 10 participants per arm
- Any study not written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese
- Any study published before 1946

3.5. Data extraction

A two-stage sifting process was employed to screen publications: (1) at title and abstract; and (2) at full text level for eligibility for inclusion using the criteria listed. Sifting was performed in duplicate independently by two reviewers and any unresolved disagreements in sifting were resolved by a third, independent reviewer. Articles identified from the reference lists and citations of all included articles were also sifted. Data were extracted in duplicate from included papers using a piloted and standardised Excel database. Any unresolved

disagreements in extraction were resolved by a third, independent reviewer. For systematic reviews, data from all the source manuscripts identified by our search were included; data were not extracted from the systematic review itself.

3.6. Quality assessment

Assessment of bias was conducted at the study level, as prescribed in the PRISMA statement for reporting of systematic reviews.[1] Assessment of bias at the study level was assessed using the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies for case-control and cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). For cross-sectional studies, a published adapted Newcastle-Ottawa Scale for cross sectional studies was employed.[2] Data used from conference abstracts meeting the inclusion criteria, were not assessed for risk of bias.

3.7. Data synthesis

Extracted data were synthesised using a narrative approach and meta-analyses, where appropriate.

Data were analysed in four groups: correctional facilities, nursing homes, other congregate settings and TB-affected households. For all congregate settings (correctional facilities, nursing homes, other congregate settings) data were stratified by high and low TB burden countries[3] . For TB-affected household studies, data were stratified by high and low TB burden countries[3] and by age for studies reporting on children, adults and combined (child and adult) populations. We used the definition of child and adult as described in the original paper.

For the meta-analysis, each study contributed one effect estimate, with the primary analysis based on unadjusted effect estimates. Both fixed and random effects models were presented alongside the I^2 statistic measuring between-study heterogeneity. For studies where there was more than one effect estimate, we adopted the approach described in Table 1 to select the effect estimate for use in the meta-analysis.

TB disease incidence was summarised by a rate per 100,000 pyrs (events/pyrs where reported) and an unadjusted rate ratio (RR) and 95% confidence interval (CI) for the comparison of residents of TB-affected households or congregate settings versus the comparator group(s). If the unadjusted RR and/or 95% CI were not reported in an included publication, the RR and standard error (SE) for the natural logarithm of the RR (lnRR) were calculated from the available data. Studies where a CI was not reported and a SE for the lnRR could not be calculated are summarised in the descriptive tables only.

TB infection prevalence was summarised by the percentage (and n/N) with the outcome and an unadjusted odds ratio (OR) and 95% CI for the comparison of those in the TB-affected household/congregate setting versus the comparator group(s). We analyse outcomes separately for TST and IGRA, and used the definition of a positive TST response of ≥10mm. We allowed studies that used ≥10mmfor those HIV-negative or unknown status and ≥5mm for those HIV-positive. Studies using an alternative definition of TST positivity were summarised in the descriptive tables only.

TB disease prevalence was summarised by the percentage (and n/N) with the outcome and an unadjusted OR and 95% CI for the comparison of those in congregate setting versus the comparator group(s). For TB-affected household studies we also summarise data from cross-sectional studies and (unmatched and matched) case-control studies where cases were individuals with TB disease and the exposure was living in a household with a TB patient, using unadjusted ORs and 95% CIs. Studies where a CI was not reported and the SE for the log (unadjusted OR) could not be calculated were summarised in the descriptive tables only.

4. Results

4.1. Articles identified

In total, after duplicates were removed, 5,236 records were assessed at the title and abstract phase. Of these, 164 were assessed at full text. After full text review and reference and citation checking, 93 primary research articles were included, of which 21 reported data from congregate settings and 72 reported data from TB-affected households. (Figure 1, Table 2, Table 3).

Of the 21 primary research articles identified from congregate settings, 15 were from low burden TB settings, one reported TB infection prevalence, 17 reported TB disease incidence and three reported TB disease prevalence (Table 2).

Of the 72 primary research articles identified from TB-affected households, 15 were from low burden TB settings, 52 reported TB infection prevalence, two reported TB infection incidence, 21 reported TB disease prevalence and three reported TB disease incidence (Table 3). Some studies contributed more than one outcome.

4.2. Congregate settings

The congregate settings for the 21 primary research articles were as follows: 12 from correctional facilities alone; five from nursing homes alone; one reported data from a correctional facility and nursing home; one reported data from a long-term care residential facility and shelter; one from social institute and psychiatric hospital; and one displaced persons camp. Eleven papers did not contribute to any analysis as a confidence interval for the effect estimate could not be calculated with the available data (see * in Table 2). Studies reported outcomes of TB infection prevalence, TB disease prevalence (mainly a period prevalence) and TB disease incidence (the most common outcome reported). No study reported TB infection incidence.

4.2.1. TB infection prevalence – data summaries

One study (low burden setting (Poland); Kruczak, 2014[4]) measured TB infection prevalence using QuantiFERON-TB Gold In-Tube assay and TST (≥10 mm) in two congregate settings, residents in a long-term care facility and a homeless shelter, compared to a general population (Table 4). The same comparator was used for both congregate settings. TB infection prevalence was higher among indivduals from the homeless shelter versus the comparator using the QuantiFERON-TB Gold In-Tube assay (OR 1.87, 95% CI 1.10–3.22), though such a difference was not observed when measured using TST (OR 1.37, 95% CI 0.81–2.33), and was similar for those in the long-term care facility versus the comparator.

4.2.2. TB disease prevalence – data summaries

Three studies (Story 2007,[5] Karabela 2010,[6] Pannier 1954[7]) reported TB disease prevalence; all conducted in low TB burden countries (Table 5).

Two of the studies were from correctional facilities. Karabela et al.[6] measured a TB prevalence in the prison population in Greece of 250 per 100,000 prisoners, and reported an OR compared to the general population of 15.66 (95% CI 9.44–25.96). Story et al.[5] measured prevalence in the prison population in UK (London) of 208 per 100,000 prisoners, in comparison with the population in London (including prisoners) of 27 per 100,000. Adjusted comparisons were not reported.

The third study (Pannier, 1954[7]) compared TB disease prevalence of children and adults in a social institution to school children and the general adult population, respectively. Adults and children had higher prevalence of disease than the relevant general population comparator. Based upon their reported data, we estimated the OR for adults as 3.77 (95% CI, 1.58–9.03) and for children as 3.29 (95% CI 1.99–5.43). Pannier also estimated TB prevalence among patients in a psychiatric hospital, and found that patients had a higher prevalence of disease than the general population (OR 15.62; 95% CI 10.04–24.31).

4.2.3. TB disease incidence – data summaries and meta-analyses

Seventeen studies reported TB disease incidence: 11 from correctional facilities (five contributing to meta-analysis and six not); six from a nursing home setting (three contributing to meta-analysis and three not); and one study measured TB incidence among males living in displaced persons' camp in the UK in 1946. One study measured TB disease incidence in both correctional facilities and nursing home setting, data from neither setting contributed to the meta-analysis.

Of the five studies in correctional facilities contributing to the analysis, two were conducted in high TB burden settings and three were in low TB burden settings (see Table 6 and Figure 2), and all reported unadjusted RRs only. In random effects meta-analysis in high TB burden settings, where each study contributed one effect estimate, the RRs were 3.78 (Castandeda-Hernandez, Brazil[8]) and 9.40 (Noeske, Cameroon[9]) giving a summary RR of 6.48 (95% CI 2.70–15.60; Figure 3, Table 7). The I^2 was 80.1%. For low TB burden countries, the study-specific RRs were 3.90 and 3.96 (Hutton[10] and MacNeil,[11] respectively, both USA) and 24.59 (Alavi, Iran[12]), giving a summary RR of 7.25 (95% CI 1.89–27.82; I^2 of 99.6%; Figure 4, Table 7). Summary RRs using fixed effects are reported in Table 7.

Table 8 shows the six studies from correctional facilities not contributing to the analysis, as sufficient data were not available to allow calculation of a 95% CI for the RR. For two studies, conducted in low TB burden

countries, the RR (calculated from the rates reported) were 11.50 (Chevallay,[13] all TB) and 2.6 (Wong,[14] all TB from 1999–2005, age- and sex-adjusted). For the latter study, after excluding illegal immigrants and drug addicts the RR was 1.08. For the four studies conducted in high TB burden countries the RRs were 0.03–0.04 (Sacramento,[15] study conducted in Brazil), 2.41 (Kanyerere,[16] Malawi), 24–27 (Jenkins,[17] Moldova, MDR-TB) and 28 (Russkikh,[18] Russia).

Posner[19] (1952) measured TB disease incidence in Polish and Latvian Displaced Persons' camps (all male) and found a rate of 3.13/100,000/year (using numerator data estimated from graph) compared with local male workers (combined light engineering and carpet factory workers) who had a rate of 0.64/100,000/year (using numerator data estimated from graph).

Three studies, all from low TB burden settings, measured TB disease incidence among nursing homes residents and a general population (Table 9 and Figure 5 and Figure 6). Using unadjusted RRs, the summary RR using random effects meta-analysis was 1.40 (95% CI 0.89–2.22; I^2 = 88.8%) and fixed effects meta-analysis was 1.67 (95% CI 1.53–1.82). MacArthur[20] reported an adjusted RR (adjusting for age, sex, and excluding Native Americans) for all TB of 1.09 (95% CI 0.38–1.6) compared with the unadjusted RR of 1.48 (95% CI 0.64-2.32) (Table 9).

Three studies not contributing to the meta-analysis due to lack of reported numerators are summarised in Table 10.

4.3. TB-affected households

4.3.1. TB infection prevalence – data summaries and meta-analyses

Forty-three studies (33 from high TB burden countries and 59 effect estimates) contributed data to the meta-analyses (Table 11). LTBI was measure by TST in 35 studies and by IGRA in 19 studies.

For LTBI measured by TST in high TB burden countries, 18, six, and 10 studies in children, adults and combined, respectively, contributed to the meta-analysis (Table 12). For studies in children, the summary OR using random effects was 3.86 and 95% CI 2.60–5.72 (Figure 7). Among adults, the summary OR using random effects was 3.02 and 95% CI 1.66–5.47 (Figure 8). For the 10 studies that did not stratify data by age the summary OR using random effects was 2.18 and 95% CI 1.70–2.80 (Figure 9). I^2s for these three analyses were 95.2%, 96.1% and 84.9% respectively (Table 12).

Fourteen studies conducted in high TB burden countries measured LTBI using IGRA (12 studies used QuantiFERON-TB Gold and two studies used T SPOT). For six studies in children, the summary OR using

random effects was 2.76 and 95% CI 2.22–3.44 (Figure 10). Among four studies conducted in adults, the summary OR using random effects was 2.23 and 95% CI 1.69–2.96 (Figure 11). For the four studies that did not stratify data by age the summary OR using random effects was 2.01 and 95% CI 1.11–3.65 (Figure 12). I^2 for the child/adult combined population was 93.8%, and 5.1% and 0.0% for the separate children and adults populations, respectively.

Ten studies contributed data from low TB burden countries; five measured TST alone, four measured IGRA alone and one measured both TST and IGRA. For the outcome of TST, three studies each in adults and children/adults combined contributed to the meta-analysis (Table 12). There were no studies conducted in children only. Among adults and children/adults combined, the summary ORs using random effects were 4.18 (95% CI 2.59–6.72; Figure 13) and 4.15 (95% CI 3.38–5.10; Figure 14), respectively.

For the outcome of LTBI based on IGRA, two studies each, in children alone and children and adults combined, contributed to the meta-analysis (Table 12). There was one study conducted in adults. Among these five studies, four used QuantiFERON-TB Gold and one study used T SPOT. For children alone and adults/children combined, the summary ORs, using random effects, were 5.42 (95% CI 3.70–7.95; Figure 15) and 2.39 (95% CI 0.31–18.17; Figure 15), respectively.

Table 12 also shows the summary OR and 95% CIs for a fixed-effects meta-analysis. Table 13 lists nine studies which satisfied the inclusion criteria and which did contribute to the meta-analyses. Reasons for non-inclusion in the meta-analyses were a different definition of TST positivity (six studies), no definition of TST positivity (one study), use of the Heaf test (one study) and combined IGRA/TST test (one study).

4.3.2. TB infection incidence – data summaries

Two studies compared TB infection incidence in TB-affected households and a comparator population. One study in a low TB burden setting (Druszczynska, 2016[31]) followed up IGRA-negative household contacts of a TB patient and community controls and measured IGRA results two years later. Four out of 10 household TB contacts were IGRA positive at follow-up compared with 1/16 of community controls. The second study (Middelkoop, 2014[39]), conducted in a high TB burden setting, followed-up 67 TST-negative (<10mm) adolescents for two years and measured incident TB infection, defined as positive result (≥10mm) at follow-up and with an absolute increase of at least 6mm. In an adjusted analysis, controlling for sex, the OR for TB infection was 1.9 (95% CI 0.5-7.3) for exposure to a household adult TB patient and 1.5 (95% CI 0.3-8.4) for exposure to smear-positive TB patient, both versus no exposure to a TB patient.

4.3.3. TB disease prevalence – data summaries and meta-analyses

Fifteen studies reported data, including 95% CIs of the effect estimate, assessing the effect of TB-affected households on TB disease prevalence; two cross-sectional, four unmatched case-control studies and nine matched case-control studies (Table 14 and Table 15). Overall, fourteen studies were conducted in high-TB burden countries. Three studies (labelled * and *** in Table 14) did not contribute to the meta-analysis for high TB burden countries as a 95% CI for the unadjusted ORs was not reported. Unadjusted ORs from unmatched case-control and cross-sectional studies, and for matched case-control studies, ORs controlling for matching variables only, were used in the meta-analysis.

Using random effects meta-analysis, in high TB burden countries among children (two studies) the summary OR was 5.30 (95% CI 2.76–10.18; I^2 = 55.9%). Among six studies conducted in adults the summary OR was 2.91 (95% CI 2.24–3.77; I^2 = 40.0%). Among three studies conducted in children/adults (where studies did not report data stratified by age) the summary OR was 8.92 (95% CI 1.49–53.40; I^2 = 97.3%). Figure 16 and Figure 17 show analyses based on random effects and fixed effects meta-analysis, respectively. Table 16 shows summary estimates for random effects and fixed effects meta-analysis.

One matched case-control study conducted in The Gambia (low TB burden) among adults (Hill, 2006[62]) reported an OR controlling for matching variables of 6.02 (95% CI 3.23–11.25) and OR controlling for matching variables and ethnic group, smoking status, occupation, ceiling and crowding index of 7.55 (95% CI 3.43–16.6, p <0.0001).

Nine studies in high TB burden countries reported an adjusted OR (Table 15). One study in children (Kumar, 2005[84]) reported an adjusted OR of 4.26 (95% CI 2.26–8.04) controlling for BCG scar and residence. Among five studies conducted in adults (Crampin[83], Lienhardt[85], Coker[86], Corbett[88], Alemu[94]) the adjusted ORs ranged from 1.6 to 3.25, and three studies conducted in adults (Chelleng[89], Stevens[90], Aldridge[93]) the adjusted ORs ranged from 1.82 to 32.0.

A further six studies, measuring TB disease prevalence in TB-affected households and a comparator population, did not contribute to the meta-analysis as a 95% CI for the OR was not reported in the article and could not calculated, primarily because of clustering in the study design. (Table 17).

4.3.4. TB disease incidence – data summaries

Three studies measured TB disease incidence in TB-affected households and a comparator population. The first study (Narain, 1973[79]), conducted in high TB burden setting, looked at incident TB disease stratified by whether household had (i) culture positive TB patient(s); (ii) culture negative and with a photofluorogram

consistent with active/possibly active TB or inactive TB or non-tuberculous pulmonary TB patient(s); or (iii) household members with normal photofluorograms, at baseline. The incidence of pulmonary TB was 9.6/1000 person-years [pyrs] (13 TB events, 491 individuals), 1.2/1000pyrs (37 TB events, 11,124 individuals), and 1.3/1000pyrs (70 TB events, 19,301 individuals), in these three groups respectively. The second study (Mwale, 2003[25]), conducted in Malawi, measured TB incidence over a 35 month follow-up period among household members of a TB patient and households where no TB had been previously diagnosed. In TB-affected and control households 8/229 and 0/218 developed TB, respectively, (RR 1.99, 95% CI 1.81–2.18). The third study (Radhakrishna, 2007[96]) conducted in India followed-up household contacts of smear-positive/culture-positive, smear-negative/culture-positive and household members with no exposure to TB patient at home for 15 years for incident TB disease. Annual culture-positive TB incidence was 526/100,000 (adjusted RR [aRR] 3.4, 95% CI 3.0–3.9, vs no exposure) and 271/100,000 (aRR 1.7, 95% CI 1.4–2.0, vs no exposure) for contacts of smear-positive, smear-negative TB patients, respectively, and 198/100,000 for household members with no exposure to TB patient at home.

4.4. Quality assessment

Quality assessments for congregate settings are summarised in Table 18 and Table 19 and for TB-affected households in Table 20, Table 21 and Table 22.

For cross-sectional congregate studies (maximum score of 7) 3/5 studies scored one or less. For cohort congregate studies (16 studies) quality assessments using the modified Newcastle-Ottawa scale (maximum total score of 9) had a median score was 4.5 and interquartile range (IQR) 4 to 5 (range 2-7). Studies scored poorly on items “Demonstration that outcome of interest was not present at start of study”, “non-response rate for retrospective cohorts” and “adequacy of follow up of cohorts for prospective cohorts”.

For 34 TB-affected household studies, assessed using the case-control modified Newcastle-Ottawa scale quality assessment tool, the median score was 5 and IQR 4 to 6 (range 1-8). Studies scored poorly on items “ascertainment of exposure” and “non-response rate”. Quality assessments for 36 cross-sectional studies were conducted, giving a median score of 3 and IQR 1 to 5 (range 0-7). Studies scored poorly on items “ascertainment of exposure” and “assessment of outcome”.

5. Discussion

The systematic review identified 93 primary research articles that reported data on TB infection prevalence, incidence or TB disease incidence in TB-affected households (72 articles) or congregate settings (21 articles) compared with a comparator population. Studies were conducted in low and high burden countries and few reported adjusted effect estimates.

For congregate settings most data came from correctional facilities. Five studies reported TB disease incidence in correctional facilities, and stratified by TB disease burden, the summary RRs indicated higher TB disease rates compared to the general population. However I^2s were large (>80%) indicating huge study heterogeneity making the summary estimates difficult to interpret. Six studies did not contribute data to the meta-analysis as sufficient data to calculate a CI for the effect estimate were not reported. Three studies conducted in nursing homes in low TB burden settings were included in a meta-analysis for TB disease incidence. The summary estimate indicates similar rates for nursing home residents versus the general population, though huge study heterogeneity was large.

For TB-affected households the most common outcome was TB infection prevalence, measured using TST or IGRA. For the latter, QuantiFERON-TB Gold and T SPOT assays were used. Study heterogeneity was extremely large (>84%) for the outcome of TST positivity prevalence among children, adults and children/adults living in high TB burden settings. Summary ORs, using random-effects, were 3.9, 3.0 and 2.2, for children, adults and combined populations, respectively, comparing TB-affected households with a comparator population. Extreme caution must be taken in interpreting these summary estimates due to very large study heterogeneity resulting in the summary estimates being difficult to interpret. Fewer studies contributed to the IRGA outcome. Study heterogeneity was low for children and adult populations, separately, in high TB burden settings, and summary estimates suggested around a three-fold increase in odds of TB infection for TB-affected households with a comparator. Case-control studies mainly contributed data for the outcome of TB disease prevalence and most studies were conducted in a high TB burden setting. Among children and adults separately the summary ORs were 5.3 and 2.9, respectively and study heterogeneity was less than 60%. Meta-analyses were based on unadjusted ORs, though we also included ORs from matched case-control studies, controlling for the matching variables only.

Study quality using the modified Newcastle-Ottawa scale was low for all study designs.

6. Annexes

6.1. Tables

Table 1. Definition of effect estimate used in meta-analysis when there are multiple effect estimates within a study

	Scenario – data as reported in publication	Analytic approach for the meta-analysis to obtain a single effect estimate per study
1a	Separate effect estimates for subgroups of the exposed and unexposed and where no overall effect estimate is reported and cannot be calculated from the available data	Conducted a random effects meta-analysis within the study to obtain a study-level summary effect estimate & 95% CI.
1b	Separate effect estimates for subgroups of the exposed and unexposed and where no overall effect estimate was reported but can be calculated from the available data	Data were collapsed across the subgroups and a study-level effect estimate & 95% CI was calculated.
2a.	There are ≥2 exposed groups compared to the same unexposed group, within a study and no overall effect estimate is reported.	Data were collapsed access the exposed groups (into a single exposed group) and a study-level effect estimate & 95% CI was calculated. One caveat with this approach was that equal probability of being sampled for each exposed subgroup was assumed.
2b.	There are ≥2 exposed groups compared to the same unexposed group, within a study and no overall effect estimate is reported. Further, only the effect estimates and 95% CIs are reported, and therefore we cannot adopt approach 2a.	Conducted a random effects meta-analysis within the study to obtain a study-level summary effect estimate & 95% CI. One caveat with this approach was that the same comparator group was used for each exposed subgroup.
3.	There are ≥2 “unexposed” groups compared to the same exposed group, within a study.	One of the unexposed groups was chosen for the comparison and a study-level effect estimate and 95% CI was calculated
4	Multiple outcomes within a study.	One outcome was chosen, based on being most consistent with the outcomes used in other studies.
5	Overall and subgroup comparisons within a study (eg., overall and then among males and females)	The “overall” comparison was used.

Table 2. List of 21 primary research articles selected, their outcomes and congregate setting

First author	Year	Title	Country	Low/ high	Outcome	Congregate setting
Posner*[19]	1951	Pulmonary Tuberculosis amongst displaced persons	England	low	TB disease incidence	Displaced persons camps
Pannier[7]	1954	Results and reflections on the systematic pulmonary radiologic examination	Belgium	low	TB disease prevalence	Social Institute and Psychiatric Hospital
Chevallay*[13]	1983	[Epidemiology of pulmonary tuberculosis in the prison environment]	Switzerland	low	TB disease incidence	correctional facility
Bentley*[21]	1990	Tuberculosis in long-term care facilities	USA	low	TB disease incidence	nursing home
MacArthur[20]	1992	Tuberculosis among institutionalized elderly in Alberta, Canada	Canada	low	TB disease incidence	nursing home
Hutton[10]	1993	Results of a 29-state survey of tuberculosis in nursing homes and correctional facilities.	USA	low	TB disease incidence	correctional facility; nursing home
Shishido*[22]	2002	[Investigation on preventive measures of tuberculosis infection and onset of tuberculosis in nursing homes for the aged]	Japan	low	TB disease incidence	nursing home
Ohmori[23]	2003	[Factors related to early case detection of tuberculosis in health service facilities for the elderly]	Japan	low	TB disease incidence	nursing home
MacNeil[11]	2005	An unanswered health disparity: tuberculosis among correctional inmates, 1993 through 2003	USA	low	TB disease incidence	correctional facility
Story*[5]	2007	Tuberculosis in London: the importance of homelessness, problem drug use and prison	UK	low	TB disease prevalence	correctional facility
Wong*[14]	2008	TB surveillance in correctional institutions in Hong Kong, 1999-2005	Hong Kong	low	TB disease incidence	correctional facility
Karabela[6]	2010	Epidemiological monitoring of pulmonary tuberculosis in a correctional facility population, Athens, Greece, 2005-2009.	Greece	low	TB disease prevalence	correctional facility
Kanyerere*[16]	2012	Surveillance of tuberculosis in Malawian prisons.	Malawi	high	TB disease incidence	correctional facility
Jenkins*[17]	2013	Assessing spatial heterogeneity of multidrug-resistant tuberculosis in a high-burden country	Moldova	high	TB disease incidence	correctional facility

First author	Year	Title	Country	Low/ high	Outcome	Congregate setting
Alavi[12]	2014	A comparative study on the prevalence and risk factors of tuberculosis among the prisoners in Khuzestan, South-west Iran	Iran	low	TB disease incidence	correctional facility
Kruczak[4]	2014	Comparison of IGRA tests and TST in the diagnosis of latent tuberculosis infection and predicting tuberculosis in risk groups in Krakow, Poland	Poland	low	TB infection prevalence	long-term care facility residents; homeless shelter
Noeske[9]	2014	Tuberculosis incidence in Cameroonian prisons: a 1-year prospective study	Cameroon	high	TB disease incidence	correctional facility
Chitnis*[24]	2015	Trends in Tuberculosis Cases Among Nursing Home Residents, California, 2000 to 2009.	USA	low	TB disease incidence	nursing home
Russkikh*[18]	2007	[Comparative analysis of tuberculosis morbidity trends in the penitentiary and civil health care systems of the Udmurt Republic over 10 years]	Russia	high	TB disease incidence	correctional facility
Castaneda-Hernandez[8]	2013	Differences in TB incidence between prison and general populations, Pereira, Colombia, 2010-2011	Brazil	high	TB disease incidence	correctional facility
Sacramento*[15]	2017	Situation of tuberculosis in people deprived of freedom in the period 2007 to 2012	Brazil	high	TB disease incidence	correctional facility

*data do not contribute to analysis as a confidence interval for the effect estimate could not be calculated with the available data.

Table 3. List of 72 primary research articles selected, their outcomes for TB-affected households

First Author	Year	Title	Country	Low/ High	Outcome(s)
Aspin[80]	1953	Tuberculin-sensitivity among child contacts in Leeds, 1948-1949.	UK	low	LTBI Prevalence*
Egsmose[71]	1961	An investigation of household contacts of open cases of pulmonary tuberculosis amongst the Kikuyu in Kiambu, Kenya	Kenya	high	LTBI Prevalence,TB Disease Prevalence
Narain[70]	1966	Obtain a representative picture of the distribution of infection and disease in households can be obtained only from a tuberculosis prevalence survey.	India	high	LTBI Prevalence
Narain[79]	1973	Incidence of pulmonary tuberculosis	India	high	LTBI Prevalence*,TB Disease Incidence*
Gilpin[78]	1987	Active case-finding - for the whole community or for tuberculosis contacts only?, 1987	South Africa	high	LTBI Prevalence*,TB Disease Prevalence*
Sirinavin[81]	1991	Protective efficacy of neonatal Bacillus Calmette-Guerin vaccination against tuberculosis.	Thailand	low	TB Disease Prevalence
Madico[69]	1995	Community infection ratio as an indicator for tuberculosis control	Peru	high	LTBI Prevalence
Mudido[68]	1999	The effect of bacille Calmette-Guerin vaccination at birth on tuberculin skin test reactivity in Ugandan children	Uganda	high	LTBI Prevalence
Lutong[77]	2000	Association of prevalence of tuberculin reactions with closeness of contact among household contacts of new smear-positive pulmonary tuberculosis patients.	China	high	LTBI Prevalence*
Almeida[67]	2001	Use of purified protein derivative to assess the risk of infection in children in close contact with adults with tuberculosis in a population with high Calmette-Guérin bacillus coverage.	Brazil	high	LTBI Prevalence
Claessens[82]	2002	High frequency of tuberculosis in households of index TB patients.	Malawi	low	TB Disease Prevalence
Kenyon[66]	2002	Risk factors for transmission of mycobacterium tuberculosis from HIV-infected tuberculosis patients, Botswana.	Botswana	high	LTBI Prevalence
Lienhardt[64]	2003	Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in The Gambia	The Gambia	low	LTBI Prevalence

First Author	Year	Title	Country	Low/ High	Outcome(s)
Olender[65]	2003	To test whether high altitude lowers infection by Mycobacterium tuberculosis, the prevalence of tuberculin skin test (TST) positivity was compared between two high altitude villages (3,340 meters [10,960 feet] and 3,500 meters [11,480 feet]) and three sea-level sites in Peru.	Peru	high	LTBI Prevalence
Mwale[25]	2003	High frequency of Tuberculosis in households of patients with Pulmonary Tuberculosis in Mzimba, Malawi.	Malawi	high	TB disease incidence*
Crampin[83]	2004	Tuberculosis and gender: exploring the patterns in a case control study in Malawi.	Malawi	low	TB Disease Prevalence
Lienhardt[85]	2005	Investigation of the risk factors for tuberculosis: a case-control study in three countries in West Africa	Guinea, Guinea Bissau and The Gambia	low	TB Disease Prevalence*
Kumar[84]	2005	Protective role of BCG vaccination against tuberculous meningitis in Indian children: a reappraisal.	India	high	TB Disease Prevalence
Coker[86]	2006	Risk factors for pulmonary tuberculosis in Russia: case-control study.	Russia	high	TB Disease Prevalence
Nakaoka[63]	2006	Risk for tuberculosis among children	Nigeria	high	LTBI Prevalence
Hill[87]	2006	Surprisingly High Specificity of the PPD Skin Test for M. tuberculosis Infection from Recent Exposure in The Gambia.	The Gambia	low	LTBI Prevalence
Hill[62]	2006	Risk factors for pulmonary tuberculosis: a clinic-based case control study in The Gambia	The Gambia	high	TB Disease Prevalence*
Radhakrishna[96]	2007	Additional risk of developing TB for household members with a TB case at home at intake: a 15-year study	India	high	TB Disease incidence*
den Boon[61]	2007	Association between passive smoking and infection with Mycobacterium tuberculosis in children.	South Africa	high	LTBI Prevalence
Gustafson[60]	2007	Risk factors for positive tuberculin skin test in Guinea-Bissau.	Guinea-Bissau	high	LTBI Prevalence
Aziz[76]	2008	Risk to household contacts of tuberculous patients based on Mantoux test and antibody titre.	Pakistan	high	LTBI Prevalence*

First Author	Year	Title	Country	Low/ High	Outcome(s)
Lin[59]	2008	Dose-response relationship between treatment delay of smear-positive tuberculosis patients and intra-household transmission: a cross-sectional study.	China	high	LTBI Prevalence
Shalabi[58]	2009	Discrepancy between the tuberculin skin test and the levels of serum interferon-gamma in the diagnosis of tubercular infection in contacts.	Egypt	low	LTBI Prevalence
Corbett[88]	2009	Prevalent infectious tuberculosis in Harare, Zimbabwe: burden, risk factors and implications for control.	Zimbabwe	high	TB Disease Prevalence*
IMRC[75]	2011	Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases	India	high	LTBI Prevalence*
Mutsvangwa[57]	2010	Identifying recent Mycobacterium tuberculosis transmission in the setting of high HIV and TB burden.	Zimbabwe	high	LTBI Prevalence
Lee[56]	2010	Diagnosis of latent tuberculosis infection by using the QuantiFERON-TB Gold in-tube test in children whose household contact has contagious pulmonary tuberculosis disease	South Korea	low	LTBI Prevalence
Goletti[55]	2010	IFN-g, but not IP-10, MCP-2 or IL-2 response to RD1 selected peptides associates to active tuberculosis	India	high	LTBI Prevalence
Soborg[53]	2011	Risk factors for Mycobacterium tuberculosis infection among children in Greenland. Bull World Health Organ	Greenland	low	LTBI Prevalence
Crampin[50]	2011	Married to M. tuberculosis: risk of infection and disease in spouses of smear positive tuberculosis patients	Malawi	high	LTBI Prevalence
Preez[52]	2011	Environmental tobacco smoke exposure increases Mycobacterium tuberculosis infection risk in children.	South Africa	high	LTBI Prevalence
Abu-Taleb[49]	2011	Interferon-gamma release assay for detection of latent tuberculosis infection in casual and close contacts of tuberculosis cases.	Egypt	low	LTBI Prevalence
Mahomed[51]	2011	Predictive factors for latent tuberculosis infection among adolescents in a high-burden area in South Africa	South Africa	high	LTBI Prevalence
Whalen[54]	2011	Secondary Attack Rate of Tuberculosis in Urban Households in Kampala, Uganda.	Uganda	high	LTBI Prevalence

First Author	Year	Title	Country	Low/ High	Outcome(s)
Nkurunungi[45]	2012	Determining Mycobacterium tuberculosis Infection among BCG-Immunised Ugandan Children by T-SPOT.TB and Tuberculin Skin Testing	Uganda	high	LTBI Prevalence
Rutherford[46]	2012	To compare Quanti-FERON®-TB Gold In-Tube (QFT-GIT) and TST in Indonesian children.	Indonesia	high	LTBI Prevalence
Horne[44]	2012	Association between smoking and latent tuberculosis infection in the united states population.	USA	low	LTBI Prevalence
Wang[48]	2012	Evaluation of the diagnostic potential of IP-10 and IL-2 as biomarkers for the diagnosis of active and latent tuberculosis in BCG-vaccinated population.	China	high	LTBI Prevalence
Syed Ahamed Kabeer[47]	2012	Interferon gamma and interferon gamma inducible protein-10 in detecting tuberculosis infection.	India	high	LTBI Prevalence
Shapiro[26]	2012	Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa.	South Africa	high	TB Disease Prevalence*
Shakak[43]	2013	Prevalence of latent tuberculosis infection in Sudan: a case–control study comparing interferon-γ release assay and tuberculin skin test	Sudan	low	LTBI Prevalence
Rakotosamimanana[42]	2013	Expression of TNF-alpha-dependent apoptosis-related genes in the peripheral blood of Malagasy subjects with tuberculosis.	Madagascar	low	LTBI Prevalence
Hossain[74]	2013	To assess the prevalence of tuberculous infection and the annual risk of tuberculous infection (ARTI) for 2007–2009 in Bangladesh following countrywide implementation of the DOTS strategy	Bangladesh	high	LTBI Prevalence*
Jensen[41]	2013	The prevalence of latent Mycobacterium tuberculosis infection based on an interferon-gamma release assay: a cross-sectional survey among urban adults in Mwanza, Tanzania	Tanzania	high	LTBI Prevalence
Hoa[40]	2013	First national tuberculin survey in Viet Nam: characteristics and association with tuberculosis prevalence.	Vietnam	high	LTBI Prevalence
Chelleng[89]	2014	Risk factors of pulmonary tuberculosis in tea garden communities of Assam, India.	India	high	TB Disease Prevalence
Woldesemayat[91]	2014	Use of biomass fuel in households is not a risk factor for pulmonary tuberculosis in South Ethiopia.	Ethiopia	high	TB Disease Prevalence

First Author	Year	Title	Country	Low/ High	Outcome(s)
Middelkoop[39]	2014	Decreasing household contribution to TB transmission with age: a retrospective geographic analysis of young people in a South African township	South Africa	high	LTBI Prevalence, LTBI Incidence*
Stevens[90]	2014	Risk factors for tuberculosis in older children and adolescents: a matched case–control study in Recife, Brazil.	Brazil	high	TB Disease Prevalence
Lule[36]	2015	Factors associated with tuberculosis infection, and with anti-mycobacterial immune responses, among five year olds BCG-immunised at birth in Entebbe, Uganda	Uganda	high	LTBI Prevalence
Mumpe-Mwanja[38]	2015	Prevalence and risk factors of latent Tuberculosis among adolescents in rural Eastern Uganda	Uganda	high	LTBI Prevalence
Belay[35]	2015	Pro- and anti-inflammatory cytokines against Rv2031 are elevated during latent tuberculosis: a study in cohorts of tuberculosis patients, household contacts and community controls in an endemic setting.	Ethiopia	high	LTBI Prevalence
Mandalakas[37]	2015	Optimizing the detection of recent tuberculosis infection in children in a high tuberculosis-HIV burden setting	South Africa	high	LTBI Prevalence
Ephrem[92]	2015	Determinants of active pulmonary tuberculosis in Ambo Hospital, West Ethiopia	Ethiopia	high	TB Disease Prevalence
Elias[32]	2016	Risk of tuberculous infection in adolescents and adults in a rural community in Ethiopia	Ethiopia	high	LTBI Prevalence
Faisal[95]	2016	The risk factors associated with tuberculosis in children, 2016	Pakistan	high	TB Disease Prevalence*
Ferrarini[72]	2016	Rate of tuberculosis infection in children and adolescents with household contact with adults with active pulmonary tuberculosis as assessed by tuberculin skin test and interferon-gamma release assays, 2016	Brazil	high	LTBI Prevalence*, TB Disease Prevalence*
Aldridge[93]	2016	Prevalence of and risk factors for active tuberculosis in migrants screened before entry to the UK: a population-based cross-sectional study	Migrants screened** entry to the UK	high	TB Disease Prevalence
Druszczynska[31]	2016	Two-Year Follow-up Study of Mycobacterium tuberculosis Antigen-Driven IFN-c Responses and Macrophage sCD14 Levels After Tuberculosis Contact	Poland	low	LTBI Prevalence, LTBI Incidence*

First Author	Year	Title	Country	Low/ High	Outcome(s)
Ncayiyana[33]	2016	Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study	South Africa	high	LTBI Prevalence
Perez-Porcuna[34]	2016	Prevalence and diagnosis of latent tuberculosis infection in young children in the absence of a gold standard.	Brazil	high	LTBI Prevalence
Alemu[94]	2016	Determinants for tuberculosis in HIV-infected adults in Northwest Ethiopia: a multicentre case-control study.	Ethiopia	high	TB Disease Prevalence
Benson[27]	2016	Increasing tuberculosis yield from investigation of contacts of smear positive TB cases through engagement of civil society organizations: Active TB case finding in Mombasa, Kenya	Kenya	high	TB Disease Prevalence*
Khan[69]	2016	Risk factors for Mycobacterium tuberculosis infection in 2-4 year olds in a rural HIV-prevalent setting	Malawi	high	LTBI Prevalence
Khan[29]	2017	Challenges in the Estimation of the Annual Risk of Mycobacterium tuberculosis Infection in Children Aged Less Than 5 Years	Malawi	high	LTBI Prevalence
Narasimhan[30]	2017	High rates of latent TB infection in contacts and the wider community in South India.	India	high	LTBI Prevalence
McAllister[28]	2017	Feasibility of two active case finding approaches for detection of tuberculosis in Bandung city, Indonesia	Indonesia	high	TB Disease Prevalence*

* Outcome did not contribute to any meta-analysis. **Aldridge looks at migrants screened before entry in the UK. (applicants from Burkina Faso, Bangladesh, Cambodia, Cote d'Ivoire, Eritrea, Ghana, Kenya, Laos, Niger, Pakistan, Sudan, Somalia, Togo, Tanzania, Thailand)

Table 4. Summary of one study (low TB burden; Kruczak 2014) in long-term care facility and a homeless shelter reporting TB infection prevalence

Exposure	Congregate setting			Comparator			OR[1]	95% CI[1]
	N	n	%	N	n	%		
LTCF, QFT	152	32	21%	148	35	24%	0.86	(0.48-1.54)
LTCF, TST ≥10mm	148	64	43%	121	58	48%	0.83	(0.50-1.38)
Homeless shelter, QFT	147	54	37%	148	35	24%	1.87	(1.10-3.22)
Homeless shelter, TST ≥10mm	129	72	56%	121	58	48%	1.37	(0.81-2.33)

LTCF: long-term care facility; TST tuberculin skin test; QFT: QuantiFERON-TB Gold In-Tube assay

[1] calculated from the data. Confidence interval calculated using exact methods.

Table 5. Summary of three studies (all low TB burden settings) in correctional facilities, social institution and psychiatric hospital with data on TB disease prevalence

First author, year	Country	Congregate setting	Congregate setting			Comparator			Unadj OR	Lower 95% CI	Upper 95% CI	P-value
			N	n	Prev	N	n	Prev				
Story, 2007	UK	Prison (2003)	5278	11	208[1]	7172091	1941	27[1]	NR	NR	NR	NR
Karabela, 2010	Greece	Prison	NR	NR	250[1]	NR	NR	NR	15.66	9.44	25.96	NR
Pannier, 1954	Belgium	Social institution- children	3171	20	6.31[2]	34798	67	1.93[2]	3.29	1.99	5.43	<0.0001
Pannier, 1954	Belgium	Social institution- adults	862	6	6.96[2]	17797	33	1.85[2]	3.77	1.58	9.03	0.0029
Pannier, 1957	Belgium	Psychiatric hospital	1773	50	28.20[2]	17797	33	1.85[2]	15.62	10.04	24.31	<0.0001

[1]prevalence per 100,000 (as reported); [2]prevalence per 1000 (as reported)

Prev: prevalence; NR: not reported; OR: odds ratio; 95% CI: 95% confidence interval; Unadj: unadjusted

Table 6. Summary of five studies (two high TB burden and three low TB burden) in correctional facilities contributing to meta-analysis of TB disease incidence

First author, year	High/low TB burden	Outcome/population	Prison:			General population:			Unadj. RR	Lower 95% CI	Upper 95% CI	P-value
			Denom	TB	Rate*	Denom	TB	Rate*				
Castaneda-Hernandez, 2013[1]	High	All TB (2010)	NR	NR	213	NR	NR	67	4.55	1.46	14.22	0.02
Castaneda-Hernandez, 2013[1]	High	All TB (2011)	NR	NR	299	NR	NR	66	3.19	1.08	9.46	0.03
Hutton, 1993	Low	All TB	NR	181	30.6	NR	9483	7.9	3.9	3.35	4.49	NR
MacNeil, 2005[2]	Low	Federal (1993-2003)	NR	377	29.4	NR	200648	6.7	NR	NR	NR	NR
MacNeil, 2005[2]	Low	State (1993-2003)	NR	2648	24.2	NR	200648	6.7	NR	NR	NR	NR
Alavi, 2014[3]	Low	All TB (2005-10)	NR	363	403.3	NR	4199	16.4	NR	NR	NR	NR
Alavi, 2014	Low	All TB (2005)	12500	95	760	3438393	676	19.6	NR	NR	NR	NR
Alavi, 2014	Low	All TB (2006)	12500	88	704	3556002	681	19.1	NR	NR	NR	NR
Alavi, 2014	Low	All TB (2007)	12500	60	480	3581909	753	21	NR	NR	NR	NR
Alavi, 2014	Low	All TB (2008)	12500	37	296	3761251	642	17.1	NR	NR	NR	NR
Alavi, 2014	Low	All TB (2009)	12500	42	336	3799920	712	18.7	NR	NR	NR	NR
Alavi, 2014	Low	All TB (2010)	12500	41	328	3826396	735	19.2	NR	NR	NR	NR
Alavi, 2014♦	Low	New TB (2005)	12500	82	656	3438393	442	12.8	NR	NR	NR	NR
Alavi, 2014♦	Low	New TB (2006)	12500	74	592	3556002	465	13.1	NR	NR	NR	NR
Alavi, 2014♦	Low	New TB (2007)	12500	46	368	3581909	469	13.1	NR	NR	NR	NR
Alavi, 2014♦	Low	New TB (2008)	12500	27	216	3761251	396	10.5	NR	NR	NR	NR
Alavi, 2014♦	Low	New TB (2009)	12500	32	256	3799920	443	11.6	NR	NR	NR	NR
Alavi, 2014♦	Low	New TB (2010)	12500	30	240	3826396	425	11.1	NR	NR	NR	NR
Noeske, 2014	High	All TB (2011-12)	10468	178	1700	NR	NR	178	9.4	8.1	10.9	NR

* rate per 100,000 (as reported); Denom: denominator; RR: rate ratio; Unadj: unadjusted; CI: confidence interval; NR: not reported; ♦ For Alavi 2014 The outcome of New TB was not included in the meta analysis. It is shown in this table for completeness. For meta-analysis: [1] two effect estimates for 2010 and 2011 combined within study using random effects meta-analysis; [2] Effect estimates for federal and state prisons combined using random effects meta-analysis; [3] effect estimate for "All TB (2005-10)" used.

Table 7. Summary of meta-analyses based on unadjusted RR (five studies) comparing TB disease incidence in correctional facilities versus the general population

Low/high TB Setting	Number of Studies	Fixed effects		Random effects	95%CI	I^2
		Unadj RR	95% CI	Unadj RR		
Combined	5	10.38	(9.68,11.13)	6.82	(2.90,16.03)	99.20%
High	2	9.11	(7.87,10.54)	6.48	(2.70,15.60)	80.10%
Low	3	10.79	(9.96,11.68)	7.25	(1.89,27.82)	99.60%

Unadj RR unadjusted rate ratio; CI confidence interval

Table 8. Summary of six studies (two low TB burden and four high TB burden) in correctional facilities not contributing to analysis of TB disease incidence

First author, year	Country	High/low TB burden	Outcome/population	Correctional facilities			General population			Unadj P-value
				Denom	TB	Rate*	Denom	TB	Rate*	
Chevallay, 1983	Switzerland	Low	All TB	865	NR	230	36108	NR	20	NR
Wong, 2008	Hong Kong	Low	All TB (1999)	NR	NR	375	NR	NR	111.8	NR
Wong, 2008	Hong Kong	Low	All TB (2000)	NR	NR	331	NR	NR	113.7	NR
Wong, 2008	Hong Kong	Low	All TB (2001)	NR	NR	318	NR	NR	108	NR
Wong, 2008	Hong Kong	Low	All TB (2002)	NR	NR	238	NR	NR	97.3	NR
Wong, 2008	Hong Kong	Low	All TB (2003)	NR	NR	183	NR	NR	88.65	NR
Wong, 2008	Hong Kong	Low	All TB (2004)	NR	NR	178	NR	NR	90.46	NR
Wong, 2008	Hong Kong	Low	All TB (2005)	NR	NR	221	NR	NR	90.41	NR
Wong, 2008	Hong Kong	Low	All TB (age & sex adjusted)	NR	NR	280.6	NR	NR	108	<0.001

First author, year	Country	High/low TB burden	Outcome/population	Correctional facilities			General population			Unadj P-value
				Denom	TB	Rate*	Denom	TB	Rate*	
Wong, 2008	Hong Kong	Low	All TB (age, sex adj, excl. illegal immigrants & drug addicts)	NR	NR	117.1	NR	NR	108	0.52
Kanyerere, 2012	Malawi	High	All TB	33276	278	835	NR	NR	346	<0.0001
Kanyerere, 2012	Malawi	High	Smear+ PTB	33276	147	442	NR	NR	55	<0.0001
Jenkins, 2013	Moldova	High	Rest of Moldova (2007-10), notified MDR incidence		399	570		3447	20.9	NR
Jenkins, 2013	Moldova	High	Rest of Moldova (2007-10), estimated MDR-method 1	NR	NR	817 (95% CI 719, 916)	NR	NR	30.2 (95% CI 28.6, 31.8)	NR
Jenkins, 2013	Moldova	High	Rest of Moldova (2007-10), estimated MDR-method 2	NR	NR	1293 (95% CI 1138, 1451)	NR	NR	54.0 (95% CI 51.1, 56.9)	NR
Jenkins, 2013	Moldova	High	Transnistria (2007-10), notified MDR incidence		399	133		3447	20.9	NR
Jenkins, 2013	Moldova	High	Transnistria (2007-10), estimated MDR-method 1	NR	NR	959 (95% CI 517, 1401)	NR	NR	30.2 (95% CI 28.6, 31.8)	NR
Jenkins, 2013	Moldova	High	Transnistria (2007-10), estimated MDR-method 2	NR	NR	1346 (95% CI 726, 1966)	NR	NR	54.0 (95% CI 51.1, 56.9)	NR
Russkikh, 2007	Russia	High	All TB	NR	NR	1842.6[1]	NR	NR	64.8[1]	NR
Sacramento, 2017	Brazil	High	All TB (2007-9)	NR	NR	34.8	NR	NR	882.4	NR
Sacramento, 2017	Brazil	High	All TB (2010-12)	NR	NR	33.6	NR	NR	1011.9	NR

* rate per 100,000 (as reported);

[1] arithmetic mean of rates from 1996-2005

Denom: denominator; excl.: excluding; Unadj: unadjusted; adj: adjusted; CI: confidence interval; NR: not reported; MDR: multidrug resistant

Table 9. Summary of three studies (all low TB burden) in nursing home settings contributing to meta-analysis of TB disease incidence

First author, year	Outcome/ population	Nursing home			General population			Unadj RR	Lower 95% CI	Upper 95% CI	P-value	Adj RR	Lower 95% CI	Upper 95% CI	P-value
		Denom	TB	Rate*	Denom	TB	Rate*								
MacArthur, 1992	All TB	6454	12		147074	185		1.48	0.64	2.32	NR	1.09	0.38	1.6	NR
MacArthur, 1992	Cult+	6454	9		147074	142		NR	NR	NR	NR	1.22	0.37	2.07	NR
Hutton, 1993	All TB	NR	379	39.2	NR	4540	21.5	1.8	1.64	2.02	NR	NR	NR	NR	NR
Ohmori, 2003	All TB (1996-2000)	62160	65	104.57	1801000	1803	100.11	1.04	0.82	1.34	NR	NR	NR	NR	NR

* rate per 100,000 (as reported)

Denom: denominator; RR: rate ratio; Unadj: unadjusted; Adj: adjusted; CI: confidence interval; cult+: culture positive; NR: not reported

Table 10. Summary of three studies (all low TB burden) in nursing home settings not contributing to analysis of TB disease incidence

First author, year	Exposure	Nursing home			General population		
		Denom	TB	Rate*	Denom	TB	Rate*
Bentley, 1990	All TB	NR	NR	39.2	NR	NR	21.5
Chitnis, 2015	All TB (2000)	NR	NR	17.6	NR	NR	9.1
Chitnis, 2015	All TB(2009)	NR	NR	8.4	NR	NR	6.4
Chitnis, 2015	M, all TB (2000)	NR	NR	34.1	NR	NR	10.7
Chitnis, 2015	M, all TB (2009)	NR	NR	9.1	NR	NR	7.6
Chitnis, 2015	F, all TB (2000)	NR	NR	8.6	NR	NR	7.6
Chitnis, 2015	F, all TB (2009)	NR	NR	8	NR	NR	5.1
Chitnis, 2015	Hisp, all TB (2000)	NR	NR	16.8	NR	NR	10.2
Chitnis, 2015	Hisp, all TB (2009)	NR	NR	15	NR	NR	6.2
Chitnis, 2015	non-Hisp White, all TB (2000)	NR	NR	6.9	NR	NR	2.2
Chitnis, 2015	non-Hisp White, all TB (2009)	NR	NR	0.6	NR	NR	1.3
Chitnis, 2015	non-Hisp Black, all TB (2000)	NR	NR	19.7	NR	NR	12
Chitnis, 2015	non-Hisp Black, all TB (2009)	NR	NR	0	NR	NR	7.6
Chitnis, 2015	Asian/Pacific Islander , all TB (2000)	NR	NR	158.5	NR	NR	30.7
Chitnis, 2015	Asian/Pacific Islander , all TB (2009)	NR	NR	73.1	NR	NR	21.2
Chitnis, 2015	American Indian/Alaskan, all TB (2000)	NR	NR	0	NR	NR	3.4
Chitnis, 2015	American Indian/Alaska , all TB (2009)	NR	NR	0	NR	NR	1.1
Shishido, 2002	All TB, 60-69yrs	NR	4	54.7	NR	NR	61.2
Shishido, 2002	All TB, ≥70 yrs	NR	76	61.9	NR	NR	112.2

* rate per 100,000 (as reported)

Denom denominator; NR not reported; Hisp: Hispanic; M: male; F: female

Table 11. Summary of 43 studies (33 from high TB burden countries; 59 effect estimates) contributing to analysis of TB infection prevalence in TB-affected households versus the general population

Author, year	High/low TB burden	Outcome	Population	Age Range	TB-affected household		General population		Unadj OR	Lower 95% CI	Upper 95% CI	P-value
					N	Positive	N	Positive				
Khan, 2017[29]	high	TST	children	3m- 4y	152	56	4947	311	NR	NR	NR	NR
Narasimhan, 2017[30]	high	TST	combined	≥1y	329	193	334	179	1.22	0.9	1.67	p>0.05
Narasimhan, 2017[30]	high	IGRA (GIT)	combined	≥1y	323	143	319	140	1.01	0.74	1.38	NR
Druszczynska, 2016[31]	low	IGRA(GIT)	adults	≥18y	15	5	16	0	NR	NR	NR	NR
Elias, 2016[32]	high	TST	combined	≥13y	221	91	1657	496	NR	NR	NR	NR
Ncayiyana, 2016[33]	high	TST	combined	≥0y	24	14	365	129	2.33	1.03	5.28	NR
Perez-Porcuna, 2016[34]	high	TST	children	0-6y	80	33	25	0	NR	NR	NR	NR
Perez-Porcuna, 2016[34]	high	IGRA(GIT)	children	0-6y	80	31	25	3	NR	NR	NR	NR
Belay, 2015[35]	high	IGRA(GIT)	adults	18-60y	148	108	68	37	NR	NR	NR	NR
Lule, 2015[36]	high	IGRA(TSP)	children	5y	86	15	800	60	2.61	1.41	4.82	<0.01
Mandalakas, 2015[37]	high	TST	children	3m- 15y	824	378	501	151	N/A	NR	NR	<0.0001
Mandalakas, 2015[37]	high	IGRA(GIT)	children	3m- 15y	790	388	471	132	N/A	NR	NR	<0.0001
Mumpe-Mwanja, 2015[38]	high	TST	combined	12-18y	235	69	4746	734	1.9	1.54	2.34	<0.001
Middelkoop, 2014[39]	high	TST	children	5-14y	651	N/A	449	N/A	1.6	1.2	2	NR
Hoa, 2013[40]	high	TST	children	6-14y	432	111	21055	3699	1.6	1.3	2	NR
Jensen, 2013[41]	high	IGRA(GIT)	adults	>15y	245	145	192	78	NR	NR	NR	NR

Author, year	High/low TB burden	Outcome	Population	Age Range	TB-affected household		General population		Unadj OR	Lower 95% CI	Upper 95% CI	P-value
					N	Positive	N	Positive				
Rakotosamimanana, 2013[42]	low	IGRA(TSP)	combined	4-70y	53	27	37	19	NR	NR	NR	NR
Shakak, 2013[43]	low	TST	adults	≥15y	98	27	168	15	NR	NR	NR	<0.001
Horne, 2012[44]	low	TST	adults	≥20y	183	NR	3626	NR	4.41	1.87	10.37	NR
Nkurunungi, 2012[45]	high	TST	children	5y	35	4	284	20	NR	NR	NR	0.353
Nkurunungi, 2012[45]	high	IGRA(TSP)	children	5y	56	10	851	78	NR	NR	NR	0.045
Rutherford, 2012[46]	high	TST	children	6m-9y	299	144	72	7	NR	NR	NR	NR
Rutherford, 2012[46]	high	IGRA(GIT)	children	6m-9y	292	156	69	15	NR	NR	NR	NR
Syed Ahamed Kabeer, 2012[47]	high	TST	combined	≥0y	166	85	180	24	NR	NR	NR	NR
Syed Ahamed Kabeer, 2012[47]	high	IGRA(GIT)	combined	≥0y	200	128	186	46	NR	NR	NR	NR
Wang, 2012[48]	high	IGRA(GIT)	adults	≥18y	73	27	76	13	NR	NR	NR	NR
Abu-Taleb, 2011[49]	low	TST	combined	≥2y	27	8	26	3	3.2	0.6	8.1	0.1
Abu-Taleb, 2011[49]	low	IGRA(GIT)	combined	≥2y	24	8	34	2	8	1.3	62.4	0.01
Crampin, 2011[50]	high	TST	adults	≥15y	214	152	552	244	NR	NR	NR	NR
Mahomed, 2011[51]	high	TST	combined	12-18y	1332	NR	3911	NR	2.52	2.2	2.88	NR
Mahomed, 2011[51]	high	IGRA(GIT)	combined	12-18y	1332	NR	3911	NR	2.4	2.11	2.74	NR
Preez, 2011[52]	high	TST	children	0.3–15.9y	133	70	63	27				

Author, year	High/low TB burden	Outcome	Population	Age Range	TB-affected household		General population		Unadj OR	Lower 95% CI	Upper 95% CI	P-value
					N	Positive	N	Positive				
Soborg, 2011[53]	low	IGRA(GIT)	children	6 – 16y	180	48	1617	104	NR	NR	NR	NR
Whalen, 2011[54]	high	TST	adults	>15y	719	574	615	204	NR	NR	NR	NR
Whalen, 2011[54]	high	TST	children	≤15y	1199	795	564	78	NR	NR	NR	NR
Goletti, 2010[55]	high	TST	adults	≥18y	27	20	27	11	NR	NR	NR	<0.02
Goletti, 2010[55]	high	IGRA(GIT)	adults	≥18y	43	26	45	19	NR	NR	NR	0.087
Lee, 2010[56]	low	IGRA(GIT)	children	<15y	27	8	27	0	NR	NR	NR	NR
Mutsvangwa, 2010[57]	high	TST	combined	≥10y	222	161	176	132	N/A	NR	NR	0.58
Mutsvangwa, 2010[57]	high	IGRA(GIT)	combined	≥10y	222	79	176	53	N/A	NR	NR	0.25
Shalabi, 2009[58]	low	TST	adults	≥18y	118	55	31	5	NR	NR	NR	P<0.001
Lin, 2008[59]	high	TST	combined	≥0y	1360	317	308	30	NR	NR	NR	<0.001
Gustafson, 2007[60]	high	TST	adults	≥15y	577	303	380	142	NR	NR	NR	NR
Gustafson, 2007[60]	high	TST	children	0-14y	482	134	541	59	NR	NR	NR	NR
Gustafson, 2007[60]	high	TST	combined	≥0y	1059	437	921	201	1.48	1.37	1.6	NR
den Boon, 2007[61]	high	TST	children	0-14y	401	179	943	253	2.2	1.63	2.96	NR
Hill, 2006[62]	low	TST	combined	6m+	586	228	105	14	NR	NR	NR	NR
Nakaoka, 2006[63]	high	TST	children	<15y	158	51	48	6	N/A	NR	NR	NR
Nakaoka, 2006[63]	high	IGRA(GIT)	children	<15y	153	61	39	4	N/A	NR	NR	NR

Author, year	High/low TB burden	Outcome	Population	Age Range	TB-affected household		General population		Unadj OR	Lower 95% CI	Upper 95% CI	P-value
					N	Positive	N	Positive				
Lienhardt , 2003[64]	low	TST	combined	≥0y	2664	1165	2124	430	4.17	3.34	5.2	NR
Olender, 2003[65]	high	TST	combined	≥0y	118	NR	1123	NR	2.7	1.7	4.2	P≤0.05
Kenyon, 2002[66]	high	TST	children	<10y	107	13	697	43	NR	NR	NR	0.005
Almeida, 2001[67]	high	TST	children	<15y	141	67	505	18	NR	NR	NR	NR
Mudido, 1999[68]	high	TST	children	<5y	174	91	180	26	N/A	NR	NR	<0.02
Madico, 1995[69]	high	TST	children	6m-14y	175	97	382	129	2.48	1.11	1.57	3.92
Narain, 1966[70]	high	TST	adults	≥15y	945	620	14362	7756	NR	NR	NR	NR
Narain, 1966[70]	high	TST	children	0-14y	790	191	9186	1102	NR	NR	NR	NR
Egsmose, 1961[71]	high	TST	adults	≥15y	151	120	1956	1138	NR	NR	NR	NR
Egsmose, 1961[71]	high	TST	children	0-14t	247	128	2207	237	NR	NR	NR	NR

GIT refers to QuantiFERON Gold In Tube, TSP refers to the TSPOT TB test. Unadj unadjusted, CI confidence interval, NR not reported, TST tuberculin skin test, IGRA interferon-gamma release assay.

Lee, Perez-Porcuna and Druszczynska all report zeros for numbers infected with TB in the general population. To calculate an odds ratio the zeros have been replaced with 0.5.

Table 12. Summary of meta-analyses based on an unadjusted OR comparing TB infection prevalence in TB-affected households versus the general population for high and low TB burden countries, child, adult and combined populations and outcomes of TST (≥10 mm) and IGRA

Burden	Outcome	Population	Number of studies	Fixed			Random			
				OR	95% Lower CI	95% Upper CI	OR	95% Lower CI	95% Upper CI	I^2
High	IGRA	Child	6	2.716	2.226	3.312	2.759	2.216	3.435	5.1 %
High	IGRA	Combined	4	2.168	1.941	2.422	2.01	1.109	3.646	93.8 %
High	IGRA	Adult	4	2.235	1.687	2.96	2.235	1.687	2.96	0 %
Low	IGRA	Child	2	5.423	3.7	7.947	5.423	3.7	7.947	0 %
Low	IGRA	Combined	2	1.423	0.664	3.050	2.388	0.314	18.168	76.2 %
Low	IGRA	Adult	1[1]	-			-			
High	TST	Child	18	3.172	2.93	3.435	3.858	2.602	5.718	95.2 %
High	TST	Combined	10	2.255	2.070	2.457	2.183	1.701	2.802	84.9 %
High	TST	Adult	6	2.375	2.147	2.627	3.015	1.664	5.466	96.1 %
Low	TST	Child	0							
Low	TST	Combined	3	4.15	3.377	5.099	4.15	3.377	5.099	0 %
Low	TST	Adult	3	4.175	2.593	6.723	4.175	2.593	6.723	0 %

[1] OR = 15.5.0, 95% CI (0.8-315.7)

OR odds ratio, CI confidence interval, TST tuberculin skin test, IGRA interferon-gamma release assays. Combined children and adults combined (among studies not reporting data stratified by age)

Table 13. Summary of 9 studies (8 from high TB burden countries) not contributing to analysis of TB infection prevalence in TB-affected households versus the general population

Author, year	High/low TB burden	Outcome	Population	TB-affected household		General Population		Unadj OR	Lower 95% CI	Upper 95% CI	P-value
				N	Positive	N	Positive				
Ferrarini, 2016[72]	high	IGRA	children	59	38	42	4	NR	NR	NR	NR
Khan, 2016[73]	high	TST	children	20	1	3150	34	4.8	0.6	37.1	0.22
Hossain, 2013[74]	high	TST	children	19	9	17530	2934	4.5	1.7	11.9	NR
IMRC, 2011[75]	high	TST	combined	6341	3662	246845	114445	NR	NR	NR	NR
Aziz, 2008[76]	high	TST	combined	120	49	80	3	NR	NR	NR	NR
Lutong, 2000[77]	high	TST	combined	646	266	355	55	NR	NR	NR	NR
Gilpin, 1987[78]	high	TST	children	80	24	94	12	NR	NR	NR	<0.01
Narain, 1973[79]	high	TST	combined	11615	2759	19301	4452	NR	NR	NR	NR
Aspin, 1953[80]	low	TST	children	351	182	2921	751	NR	NR	NR	NR

*Note that Lutong, Aziz, Khan, Hossain, Narain and IMRC were excluded as they used a TST induration size different to 10mm to determine LTBI positivity. Gilpin is excluded as a Heaf test is used. Aspin is excluded because the induration size for TST positivity is not provided. Ferrarini is excluded because LTBI was based on TST and IGRA tests combined.

Unadj unadjusted, OR odds ratio, CI confidence interval, TST tuberculin skin test, IGRA interferon-gamma release assay, NR not reported, LTBI latent TB infection.

Table 14. Summary of 15 studies (14 from high TB burden countries) measuring the effect of living in a TB-affected household on TB disease prevalence

First author	Year	Country	Low/ high	Outcome (definition of case for case-control study or outcome for cross-sectional study)	Definition of exposure	Study type	Matching variables (for case-control studies)	Age range of study sample
Sirinavin[81]	1991	Thailand	high	Active TB (including microbiology, pathology, CXR)	HH member with TB disease	Case-control (matched)	age, district	Child: 3 months-14 years
Claessens[82]	2002	Malawi	high	Smear positive PTB (non-fee paying and receiving TB treatment)	HH member treated for TB in last 12 months	Case-control (unmatched)	NA	Adult: ≥15 years
Crampin[83]	2004	Malawi	high	Bacteriological or histological	HH/family member with TB disease	Case-control (matched)	age, sex, area	Adult: ≥15 years
Kumar[84]	2005	India	high	TB meningitis	Adult living in HH with: (i) TB diagnosis; or (ii) fever, cough & loss of weight ≥4 weeks	Case-control (unmatched)	NA	Child: ≤12 years
Lienhardt*[85]	2005	Guinea, Guinea Bissau and The Gambia	high[1]	Smear positive TB	HH member with TB disease	Case-control (matched)	age, neighbourhood	Adult: >15 years
Coker[86]	2006	Russia	high	Culture positive TB	HH member with TB disease	Case-control (matched)	age, sex	Adults
Hill**[87]	2006	The Gambia	low	Smear positive TB	HH member with TB disease	Case-control (matched)	age, sex	Adult: ≥15 years
Corbett*[88]	2009	Zimbabwe	high	Smear positive TB	HH member with TB in last 2 years (1 and ≥2 contacts)	Cross-sectional	NA	Adult: ≥16 years
Chelleng[89]	2014	India	high	Smear or culture positive PTB	HH/family member with TB disease	Case-control (matched)	age, sex	Combined: All ages
Stevens[90]	2014	Brazil	high	Newly diagnosed TB	HH member with TB disease	Case-control (matched)	age, neighbourhood	Combined: 7-19 years
Woldesemayat[91]	2014	Ethiopia	high	PTB (smear positive)	HH member with TB disease in past 5 years	Case-control (matched)	age	Adults

First author	Year	Country	Low/ high	Outcome (definition of case for case-control study or outcome for cross-sectional study)	Definition of exposure	Study type	Matching variables (for case-control studies)	Age range of study sample
Ephrem[92]	2015	Ethiopia	high	PTB (smear positive and negative)	Another HH member with TB disease	Case-control (unmatched)	NA	Adult: ≥15 years
Aldridge[93]	2016	Applicants to UK from multiple countries[2]	high	Smear or culture positive PTB	Close contact or HH member with TB disease	Cross-sectional	NA	Combined: All ages
Alemu[94]	2016	Ethiopia	high	Active TB (smear, culture, molecular CXR, histopathology) and on TB treatment	HH/family member with TB disease	Case-control (unmatched)	NA	HIV+ adults
Faisal***[95]	2016	Pakistan	high	Paediatric scoring chart system (modified Kenneth Jones criteria)	Adult living/frequently visiting HH with: (i) TB diagnosis; or (ii) taking treatment for TB; or (iii) >6m of cough with haemoptysis, in last 2 years	Case-control (matched)	age, sex, same body system affected	Child: <14 years

[1] defined as high due to Guinea-Bissau; [2]Burkina Faso, Bangladesh, Cambodia, Cote d'Ivoire, Eritrea, Ghana, Kenya, Laos, Niger, Pakistan, Sudan, Somalia, Togo, Tanzania, Thailand.

* Study did not contribute to meta-analysis for high TB burden countries as a 95% CI for the unadjusted OR was not reported

** single study conducted in low TB burden country

*** Study did not contribute to meta-analysis for high TB burden countries as an unadjusted OR and 95% CI were not reported

CXR chest radiograph, PTB pulmonary TB, HH household, NA not applicable

Table 15. Summary of 15 studies (14 from high TB burden countries) measuring the effect of living in a TB-affected household on TB disease prevalence, unadjusted and adjusted ORs and associated 95% CIs

First author	Year	Population	unadj OR^	Lower 95% CI	Upper 95% CI	adj OR**	Lower 95% CI	Upper 95% CI	**Adjusted for
Sirinavin	1991	child	7.4	4	15.1	NR	NR	NR	-
Claessens	2002	adult	5.97	2.99	12.21	NR	NR	NR	-
Crampin*	2004	adult	2.4	1.9	3.1	2.3	1.7	3.2	Matching variables (age, sex, area); and HIV
Kumar	2005	child	3.8	2.06	7	4.26	2.26	8.04	BCG scar, residence
Lienhardt	2005	adult	2.9[1]	1.96	4.29	NR	NR	NR	-
		adult	13.37[2]	4.1	43.61	NR	NR	NR	-
		adult	NR	NR	NR	3.25[3]	2.31	4.57	Matching variables (age, neighbourhood); and sex, HIV status
Coker	2006	adult	2.94	1.79	4.85	2.8	1.47	5.36	Matching variables (age, sex); and diabetes, drinking raw milk, assets, living space/person, employment status, financial security, illicit drug, history of incarceration
Hill*	2006	adult	6.02	3.23	11.25	7.55	3.43	16.6	Matching variables (age, sex); and ceiling, walls
Corbett*	2009	adult	1.87[4]	NR	NR	1.6	0.69	3.7	age, sex HIV status, history of TB (and their interaction), alcohol use, smoking status, beer hall and church attendance, crowding
		adult	2.76[5]	NR	NR	2.54	0.59	10.98	as above
Chelleng	2014	combined	1.8	1.34	2.42	1.82	1.25	2.65	Matching variables (age, sex); and literacy, regular family income, alcohol use, BMI
Stevens	2014	combined	27.72	10.79	71.21	32.05	10.92	94.05	Matching variables (age, neighbourhood); and sex, relationship to head of household, literacy, piped water and smoking status
Woldesemayat	2014	adult	3.05	1.89	4.94	2.25	1.34	3.78	Matching variable (age); and sex, history of TB treatment, smoking status, smoker currently in household, smoker previously in household
Ephrem	2015	adult	3.9	1.82	8.3	NR	NR	NR	-

First author	Year	Population	unadj OR^	Lower 95% CI	Upper 95% CI	adj OR**	Lower 95% CI	Upper 95% CI	**Adjusted for
Aldridge	2016	combined	15.7	9.6	25.5	11.6	7	19.3	age, sex, visa category & WHO prevalence of TB in country of screening
Alemu	2016	adult (HIV+)	1.99	1.11	3.57	2.66	1.25	5.66	ART, CPT, IPT, smoking status, Khat use, alcohol use, separate kitchen, CD4 count
Faisal*	2016	child	NR	NR	NR	NR	NR	NR	-

[1] one household member with TB vs none; [2] ≥ two household member with TB vs none; [3] ≥ one household member with TB vs none; [4] one household TB contact in last 2 years vs none; [5] ≥ two household TB contact in last 2 years vs none. * Study did not contribute to meta-analysis (see footnotes to Table 14 for reasons). ^ for matched case control studies this is the OR controlling for matching variables alone.

NR not reported; ART antiretroviral therapy; CPT cotrimoxazole preventive therapy; IPT isoniazid preventive therapy; unadj unadjusted; adj adjusted; BCG Bacillus Calmette-Guérin; OR odds ratio; CI confidence interval

Table 16. Summary of meta-analyses based on unadjusted OR (11 studies) measuring the effect of living in a TB-affected household on TB disease prevalence

Population	Number of Studies	Fixed effects		Random effects		I^2
		Unadj OR	95% CI	Unadj OR	95%CI	
Child	2	5.29	(3.43, 8.17)	5.30	(2.76, 10.18)	55.9%
Adult	6	2.71	(2.28, 3.22)	2.91	(2.24, 3.77)	40.0%
Combined*	3	3.69	(2.89, 4.71)	8.92	(1.49, 53.40)	97.3%

* children and adults combined (among studies not reporting data stratified by age); Unadj OR unadjusted odds ratio; CI confidence interval

Table 17. Summary of 6 studies (all from high TB burden countries) measuring TB prevalence in a TB-affected household and a general population, not contributing to the meta-analysis

Author	Year	High/low	Population	Outcome	TB affected household			General Population		
					N	TB	%	N	TB	%
Egsmose	1961	high	Combined	TB on chest x-ray	397	39	9.8%	3117	54	1.7%
Gilpin	1987	high	Adults	Sputum-positive	132	4	3.0%	148	2	1.4%
Shapiro	2012	high	Combined	Culture-positive	2166	169	7.8%	785	4	0.5%
Ferrarini	2016	high	Children & adolescents	TB on chest x-ray	59	0	0.0%	42	0	0.0%
Benson	2016	high	Combined	Not stated	1396	113	8.1%	13360	636	4.8%
McAllister	2017	high	Combined (>10years)	Smear-positive	5100	0	0.0%	88	0	0.0%

Table 18. Summary of quality scores for studies included in the congregate settings analysis that were assessed using the tool for cross-sectional studies (n = 5 studies)

First author, year published	Representative-ness of the 'intervention' study group	Representative-ness of the general population group	Sample size	Ascertainment of exposure	Management of non-respondents	Comparability of exposed and non-exposed	Assessment of outcome	Statistical test	Total
Bentley, 1990[21]	0	0	0	0	0	0	0	0	**0**
Jenkins, 2013[17]	1	1	1	0	0	0	1	0	**4**
Kruczak, 2014[4]	0	1	0	0	0	0	0	0	**1**
Posner, 1951[19]	1	0	0	0	0	0	0	0	**1**
Pannier, 1954[7]	1	1	1	1	1	0	0	0	**5**

Table 19. Summary of quality scores for studies included in the congregate settings analysis that were assessed using the tool for cohort studies (n = 16 studies)

First author, year published	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of exposed and non-exposed	Ascertainment of outcome	Was follow-up long enough for outcomes to occur?	Non-response rate for retrospective cohorts	Adequacy of follow up of cohorts for prospective cohorts	Total
Alavi, 2014[12]	0	0	1	1	0	1	1	0	0	**4**
Castaneda-Hernandez, 2013[8]	1	0	1	0	0	1	1	0	0	**4**
Chevallay, 1983[13]	1	1	0	1	0	0	1	0	1	**5**
Chitnis, 2015[24]	1	1	1	0	0	1	1	0	0	**5**
Hutton, 1993[10]	1	1	1	0	0	1	1	0	0	**5**
Kanyerere, 2012[16]	1	1	1	0	0	1	1	0	0	**5**
Karabela, 2010[6]	1	0	1	0	0	1	1	0	1	**5**
MacArthur, 1992[20]	1	1	1	0	2	1	1	0	0	**7**
MacNeil, 2005[11]	1	1	0	0	1	0	1	0	0	**4**
Noeske, 2014[9]	1	1	0	0	0	0	1	0	0	**3**
Ohmori, 2003[23]	1	1	0	0	1	0	1	0	0	**4**
Russkikh, 2007[18]	1	0	1	0	0	1	0	0	0	**3**
Shishido, 2002[22]	1	1	0	0	1	0	1	1	0	**5**
Sacramento, 2017[15]	1	1	0	0	0	0	1	1	0	**4**
Story, 2007[5]	0	1	0	0	1	0	0	0	0	**2**
Wong, 2008[14]	1	0	1	1	2	1	1	0	0	**7**

A study can be awarded a maximum of one point for each category, except for comparability which has a maximum of two points. Maximum possible total score is 9.

Table 20. Summary of quality scores for studies included in the TB-affected households analysis that were assessed using the tool for case-control studies (n = 34 studies, including probable exclusions)

First author, year published	Is the case definition adequate?	Representative-ness of the cases	Selection of Controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total
Alemu, 2016[94]	1	1	1	1	1	0	1	1	**7**
Chelleng, 2014[89]	1	1	0	0	2	0	1	0	**5**
Claessens, 2002[82]	0	1	1	1	0	0	1	0	**4**
Coker, 2006[86]	1	1	1	1	2	0	1	1	**8**
Crampin, 2004[83]	0	1	1	1	2	0	1	1	**7**
Crampin, 2011[50]	1	1	1	1	1	0	1	1	**7**
Ephrem, 2015[92]	1	1	1	1	0	0	1	0	**5**
Faisal, 2016[95]	1	1	1	1	2	0	1	0	**7**
Ferrarini, 2016[72]	1	0	0	1	2	1	1	0	**6**
Gilpin, 1987[78]	1	0	1	0	0	1	1	0	**4**
Goletti, 2010[55]	1	0	0	1	0	0	1	0	**3**
Gustafson, 2007[60]	1	0	1	1	1	0	1	0	**5**
Hill, 2006 (1) [62]	1	1	1	1	2	0	1	0	**7**
Hill, 2006 (2) [87]	1	1	1	1	2	1	1	0	**8**
Kumar, 2005[84]	1	1	1	1	2	0	1	0	**7**
Lee, 2010[56]	0	0	0	1	0	0	0	0	**1**
Lienhardt, 2005[85]	1	0	1	1	2	0	1	0	**6**
Lin, 2008[59]	1	1	1	0	0	0	1	0	**4**
Lutong, 2000[77]	1	0	1	1	0	0	1	1	**5**
Madico, 1995[69]	1	0	1	1	0	0	1	1	**5**
Mandalakas, 2015[37]	1	0	0	1	0	0	1	1	**4**

First author, year published	Is the case definition adequate?	Representative-ness of the cases	Selection of Controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total
McAllister, 2017[28]	1	1	1	0	0	0	1	0	**4**
Mutsvangwa, 2010[57]	1	0	1	1	0	0	1	1	**5**
Mwale, 2003[25]	0	0	1	1	0	0	1	1	**4**
Narasimhan, 2017[30]	0	0	1	0	0	0	1	0	**2**
Shakak, 2013[43]	1	0	0	1	0	0	0	0	**2**
Shalabi, 2009[58]	1	0	0	0	2	0	1	0	**4**
Shapiro, 2012[26]	1	0	1	1	0	0	1	0	**4**
Sirinavin, 1991[81]	1	1	1	1	1	0	1	0	**6**
Stevens, 2014[90]	1	0	1	1	2	0	1	0	**6**
Syed Ahmed Kabeer, 2012[47]	1	0	0	1	0	0	0	0	**2**
Wang, 2012[48]	1	0	0	1	1	0	1	0	**4**
Whalen, 2011[54]	1	0	1	1	1	0	0	0	**4**
Woldesemayat, 2014[91]	0	0	1	1	1	0	1	0	**4**

A study can be awarded a maximum of one point for each category, except for comparability which has a maximum of two points. Maximum possible total score is 9.

Table 21. Summary of quality scores for studies included in the TB-affected households analysis that were assessed using the tool for cohort studies (n = 3 studies)

First author, year published	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of exposed and non-exposed	Ascertainment of outcome	Was follow-up long enough for outcomes to occur?	Non-response rate for retrospective cohorts	Adequacy of follow up of cohorts for prospective cohorts	Total
Druszczynska, 2016[31]	0	0	0	1	0	0	1	0	1	3
Narain, 1973[79]	1	1	1	1	1	0	1	0	1	7
Radhakrishna, 2007[96]	1	1	0	1	2	0	1	0	1	7

A study can be awarded a maximum of one point for each category, except for comparability which has a maximum of two points. Maximum possible total score is 9.

Table 22. Summary of quality scores for studies included in TB-affected households analysis that were assessed using the tool for cross-sectional studies (n = 36 studies)

First author, year published	Representativeness of the HH/ congregate setting study group	Representativeness of the general population study group	Sample size	Ascertainment of exposure	Management of non-respondents	Comparability of exposed and non-exposed	Assessment of outcome	Statistical test	Total
Abu-Taleb, 2011[49]	0	0	0	0	0	0	0	0	**0**
Aldridge, 2016[93]	0	0	0	1	0	0	1	0	**2**
Almeida, 2001[67]	1	1	0	0	0	1	0	0	**3**
Aspin, 1953[80]	1	1	0	0	0	1	0	0	**3**
Aziz, 2008[76]	0	0	0	0	0	0	0	0	**0**
Belay, 2015[35]	0	1	0	1	0	0	0	0	**2**
Benson, 2016[27]	0	0	0	0	0	0	0	0	**0**
Corbett, 2009[88]	1	0	1	0	0	2	0	1	**5**
den Boon, 2007[61]	1	1	0	0	0	2	0	0	**4**
Egsmose, 1961[71]	1	0	0	0	0	0	0	0	**1**
Elias, 2016[32]	0	0	0	0	0	2	0	1	**3**
Hoa, 2013[40]	1	1	1	0	1	0	0	1	**5**
Horne, 2012[44]	1	1	1	0	0	2	0	1	**6**
Hossain, 2013[74]	1	0	0	0	0	0	0	0	**1**
IMRC, 2011[75]	1	1	0	0	0	2	0	1	**5**
Jensen, 2013[41]	1	0	0	1	0	1	1	1	**5**
Kenyon, 2002[66]	0	1	0	0	0	1	0	0	**2**
Khan, 2016[73]	1	1	1	0	0	2	1	1	**7**
Khan, 2017[29]	1	1	1	0	0	0	1	1	**5**
Lienhardt, 2003[64]	1	0	1	0	0	0	0	1	**3**
Lin, 2008[59]	1	0	1	0	1	2	0	1	**6**
Lule, 2015[36]	1	1	1	0	0	2	0	1	**6**

First author, year published	Representativeness of the HH/ congregate setting study group	Representativeness of the general population study group	Sample size	Ascertainment of exposure	Management of non-respondents	Comparability of exposed and non-exposed	Assessment of outcome	Statistical test	Total
Mahomed, 2011[51]	1	1	1	0	0	2	0	0	**5**
Middelkoop, 2014[39]	0	0	0	0	0	1	1	1	**3**
Mudido, 1999[68]	1	1	0	0	1	0	0	1	**4**
Mumpe-Mwanja, 2015[38]	1	0	0	0	1	1	0	0	**3**
Nakaoka, 2006[63]	1	0	0	0	1	0	0	0	**2**
Narain, 1966[70]	1	1	0	0	0	0	0	0	**2**
Ncayiyana, 2016[33]	0	0	0	0	0	2	0	1	**3**
Nkurunungi, 2012[45]	1	1	0	1	0	0	1	1	**5**
Olender, 2003[65]	0	0	0	0	0	0	0	0	**0**
Perez-Porcuna, 2016[34]	0	0	0	0	0	0	0	0	**0**
Preez, 2011[52]	0	0	0	0	0	0	1	0	**1**
Rakotosamimanana, 2013[42]	0	0	0	0	0	0	0	0	**0**
Rutherford, 2012[46]	0	0	0	0	0	0	0	0	**0**
Soborg, 2011[53]	1	1	0	0	0	2	0	1	**5**

6.2. Figures

Figure 1. Flow diagram showing databases searched, records found, sifted, and included, and reasons for exclusion at full text review

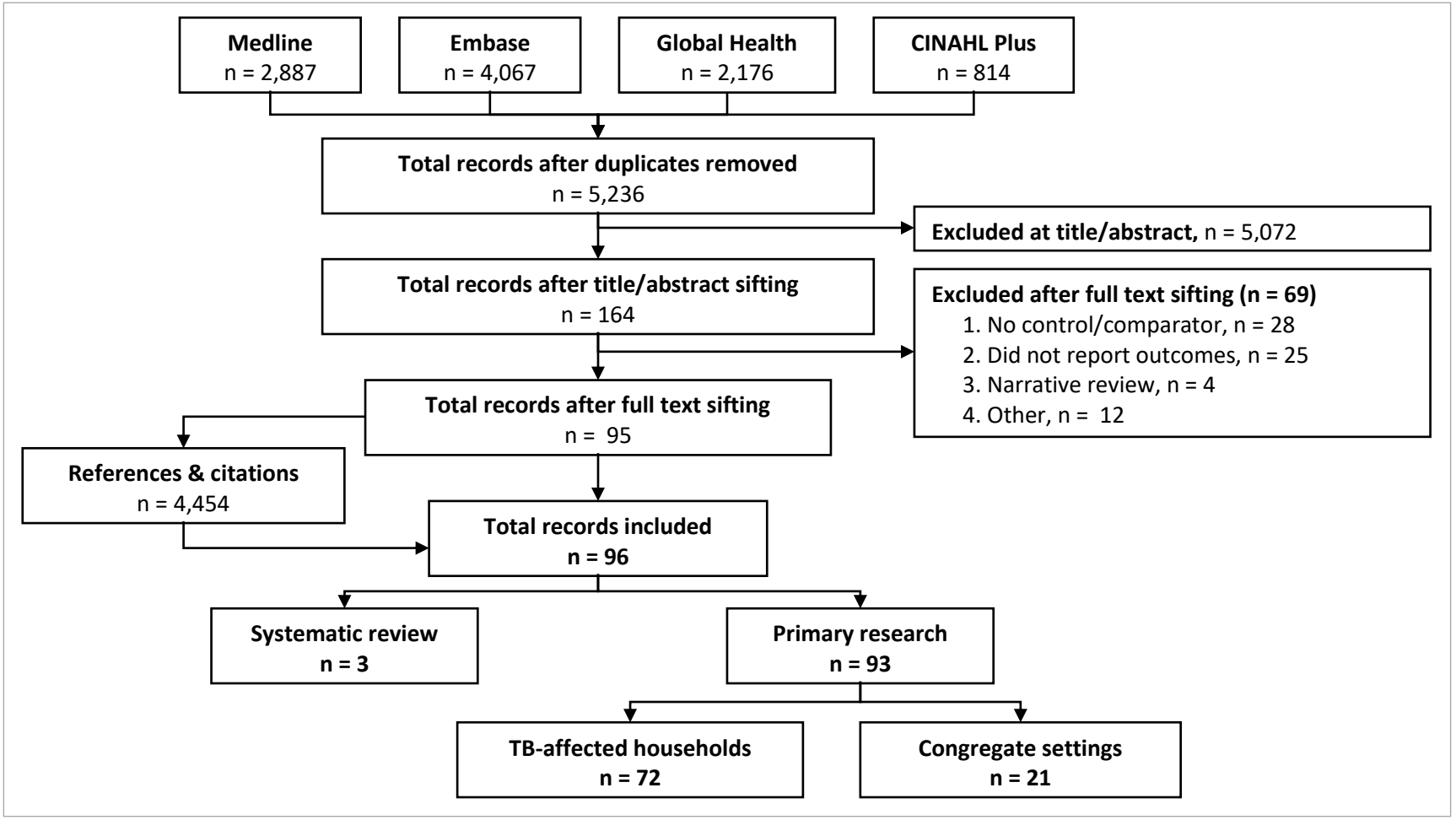
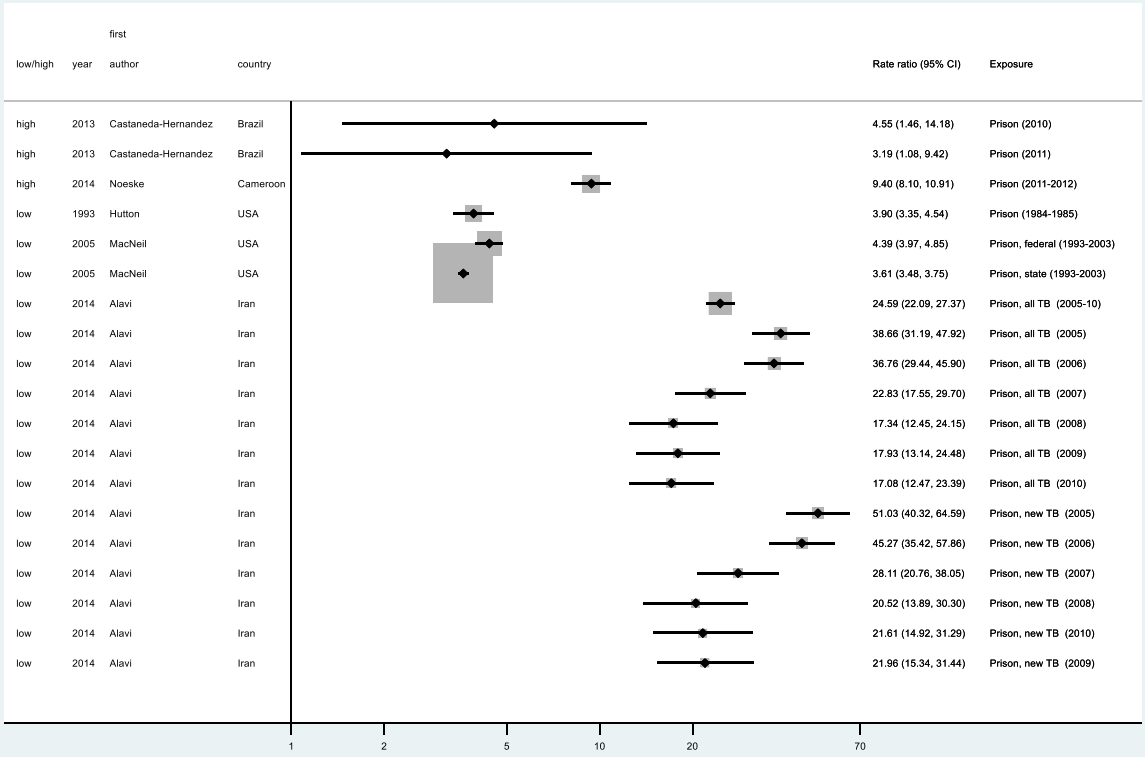
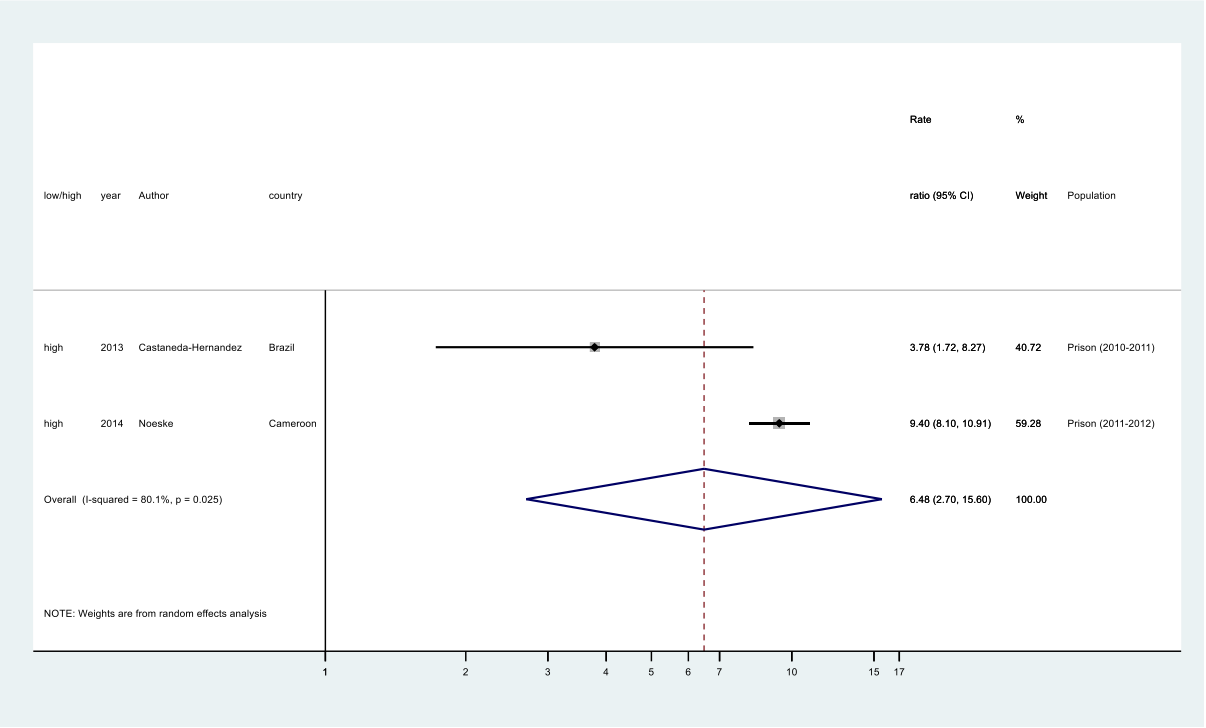


Figure 2. Forest plot for all studies (n = 19 effect estimates from 5 studies), no summary measure, comparing TB disease incidence in correctional facilities versus the general population



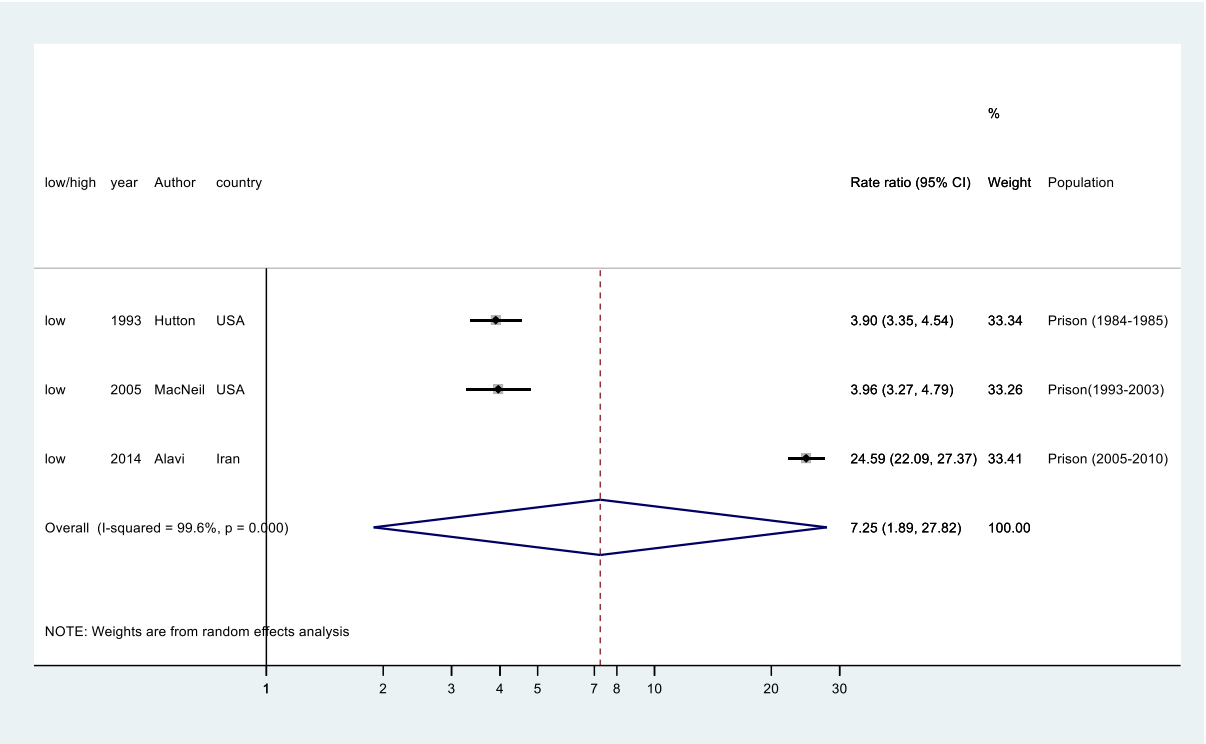
CI: confidence interval; TB: tuberculosis; USA: United States of America

Figure 3. Forest plot for all studies in high TB burden countries (2 studies) based on unadjusted RRs and 95% CIs, and using random effects, comparing TB disease incidence in correctional facilities versus the general population



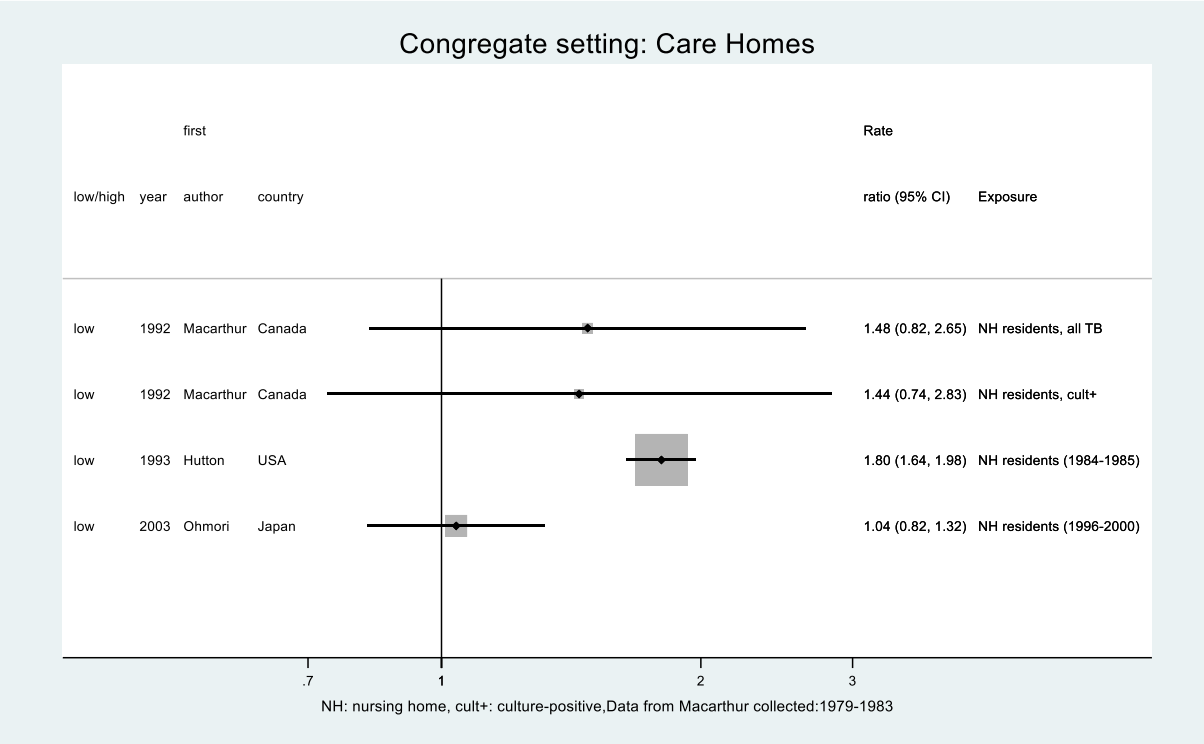
CI: confidence interval; RR: rate ratio; TB: tuberculosis

Figure 4. Forest plot for all studies in low TB burden countries (3 studies) based on unadjusted RRs and 95% CIs, and using random effects, comparing TB disease incidence in correctional facilities versus the general population



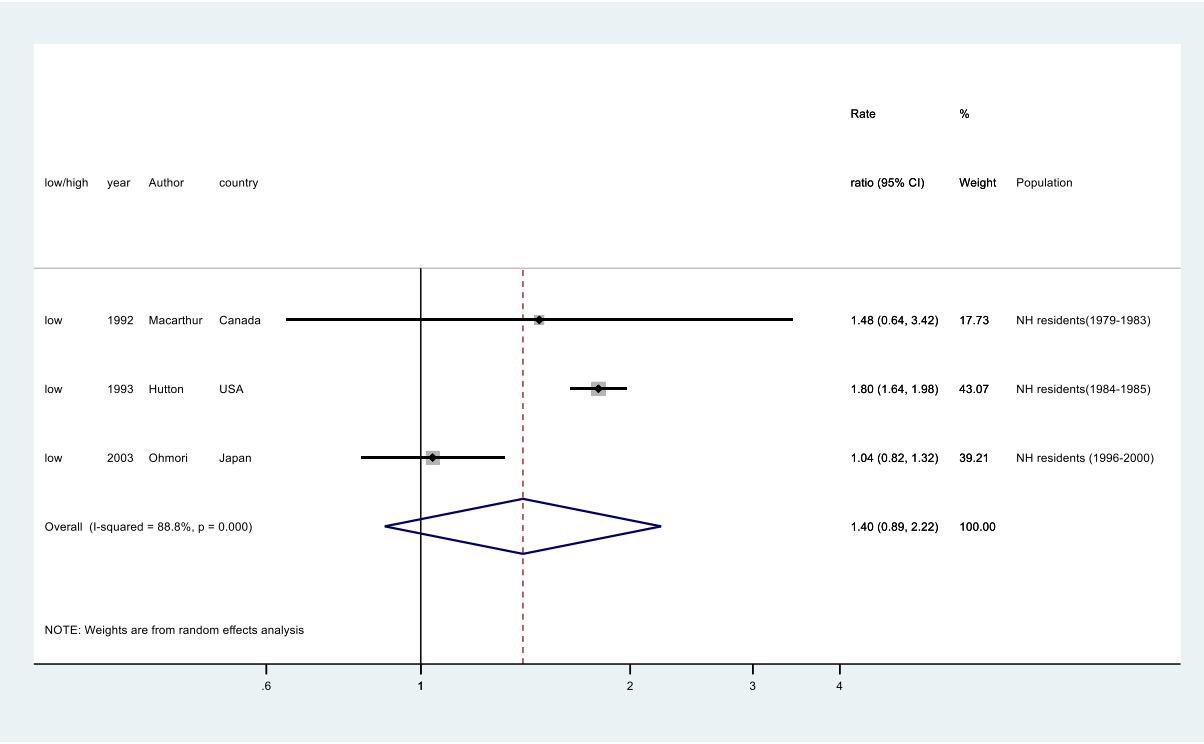
CI: confidence interval; RR: rate ratio; TB: tuberculosis; USA: United States of America

Figure 5. Forest plot for all studies (2 studies in low TB burden settings), no summary measure, comparing TB disease incidence in nursing care home residents versus the general population



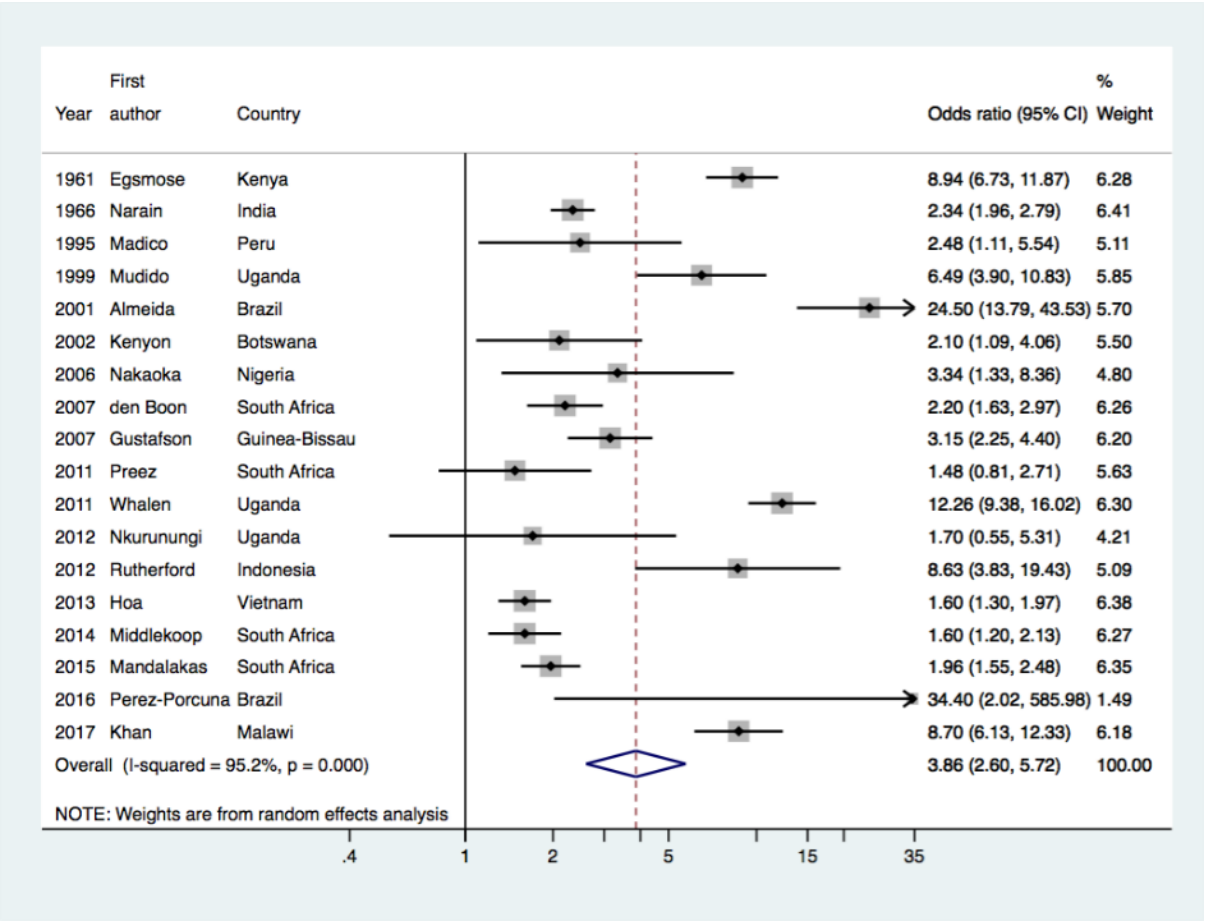
CI: confidence interval; cult+: culture-positive; NH: nursing home; TB: tuberculosis; USA: United States of America

Figure 6. Forest plot for all studies in low TB burden countries (3 studies) based on unadjusted RRs and 95% CIs, and using random effects, comparing TB disease incidence in nursing care home residents versus the general population



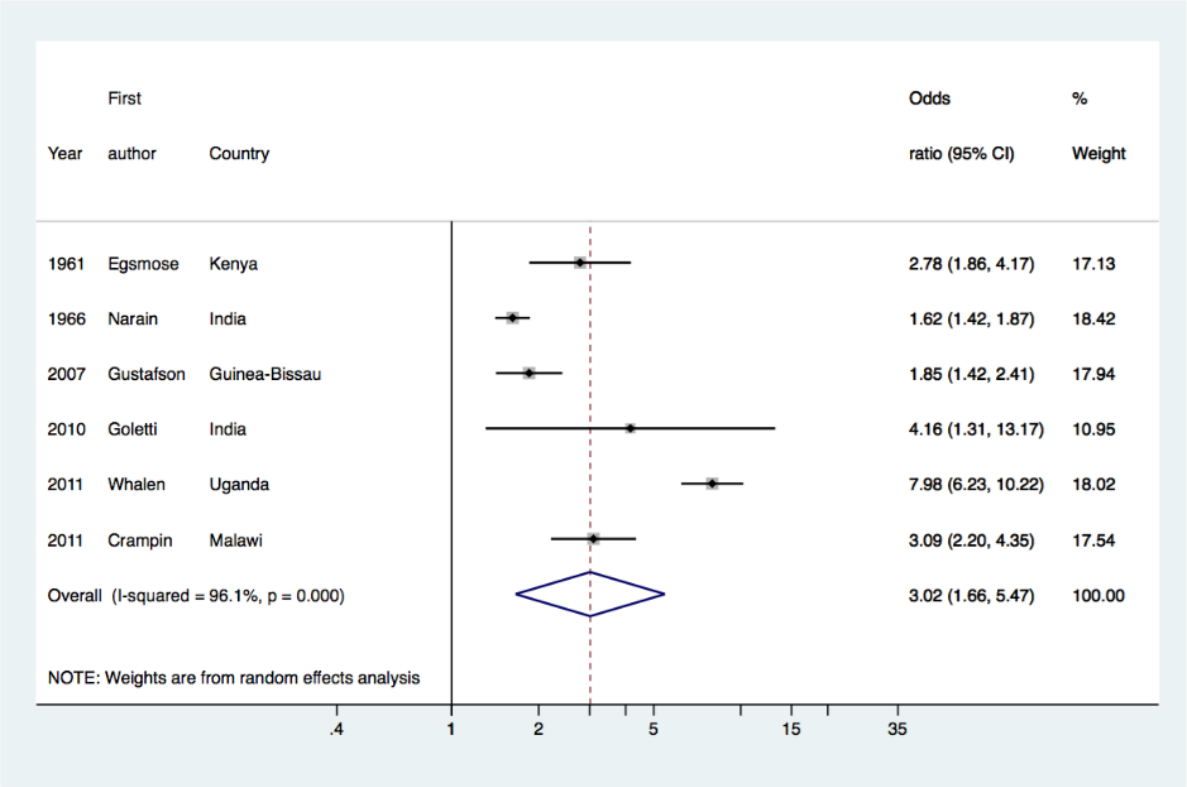
CI: confidence interval; NH: nursing home; RR: rate ratio; TB: tuberculosis; USA: United States of America

Figure 7. Forest plot for studies in high TB burden countries (19 studies) based on unadjusted ORs and 95% CIs, using random effects, comparing TB infection prevalence among children, measured by TST, in TB-affected households versus the general population



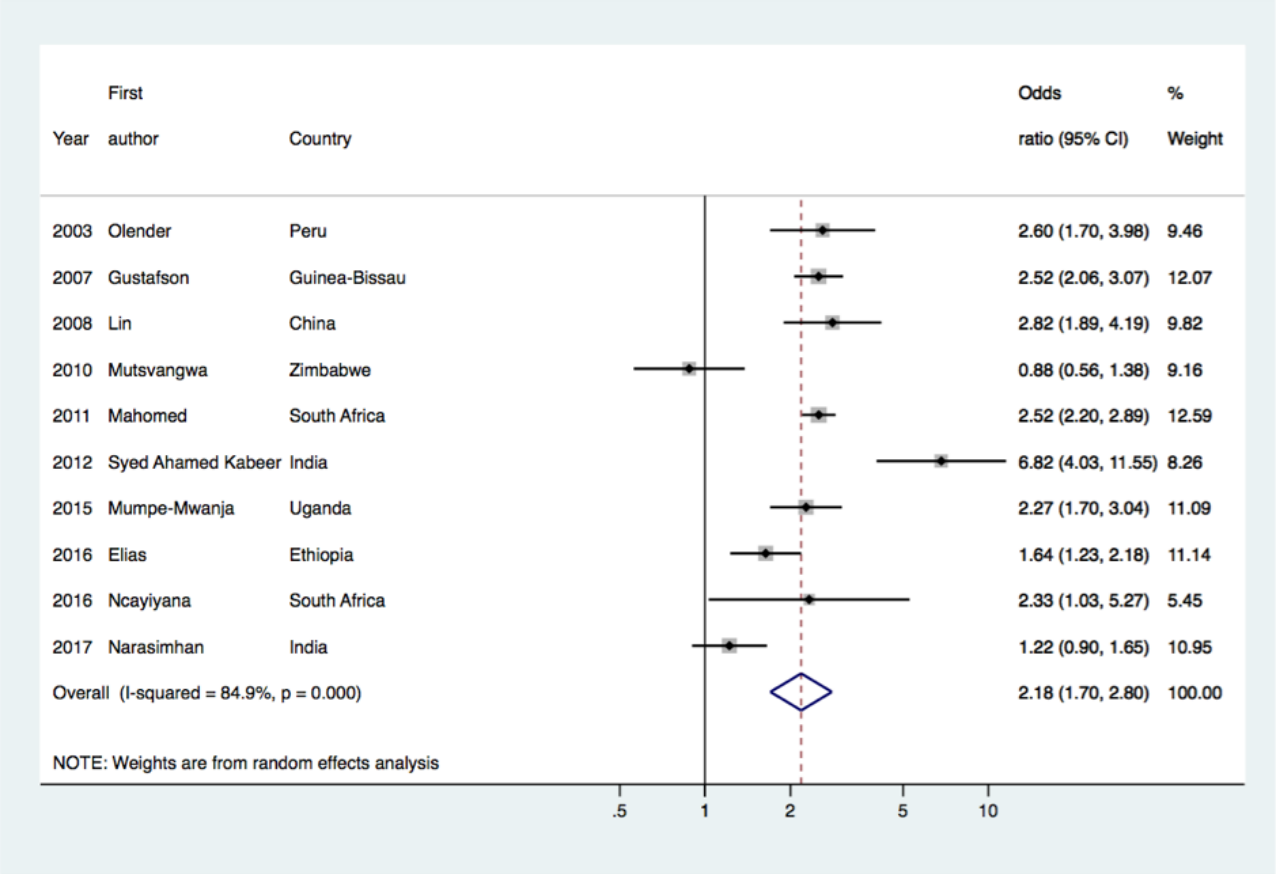
CI: confidence interval; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test

Figure 8. Forest plot for studies in high TB burden countries (6 studies) based on unadjusted ORs and 95% CIs, using random effects, and comparing TB infection prevalence among adults, measured by TST, in TB-affected households versus the general population



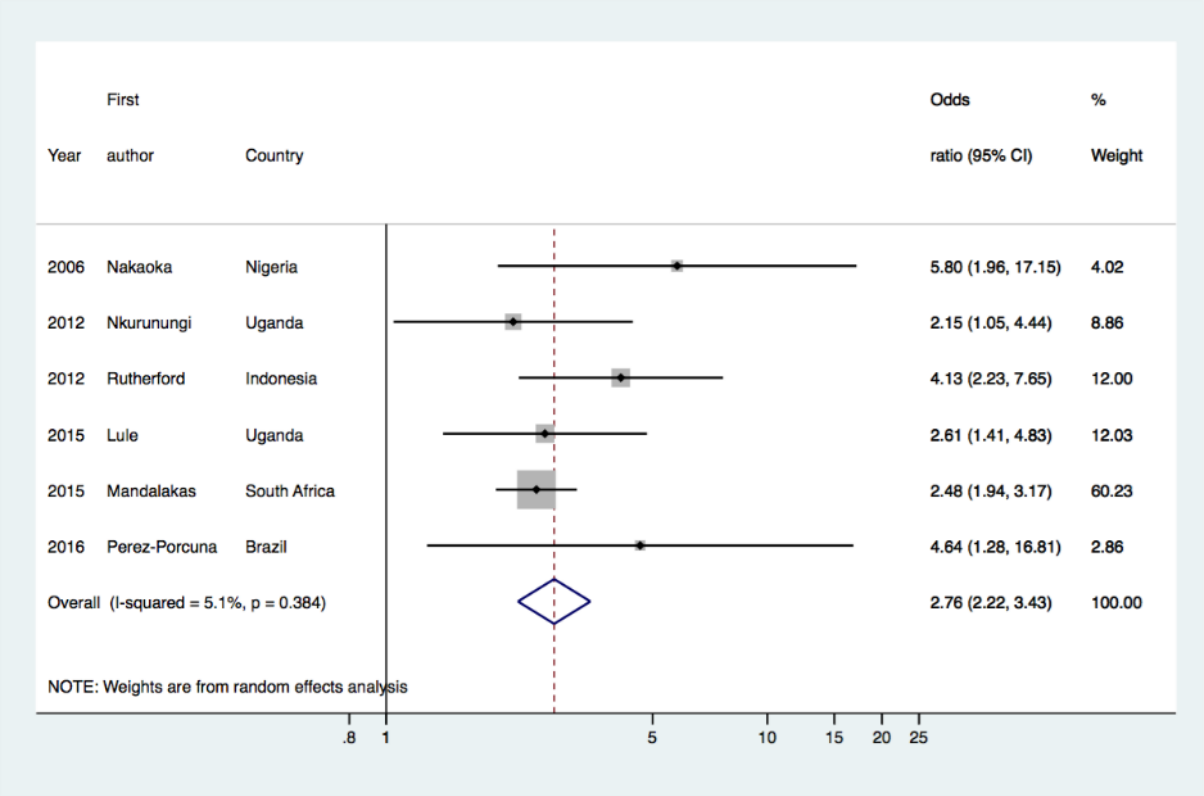
CI: confidence interval; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test

Figure 9. Forest plot for studies in high TB burden countries (10 studies) based on unadjusted ORs and 95% CIs, using random effects, comparing TB infection prevalence among children/adults combined, measured by TST, in TB-affected households versus the general population



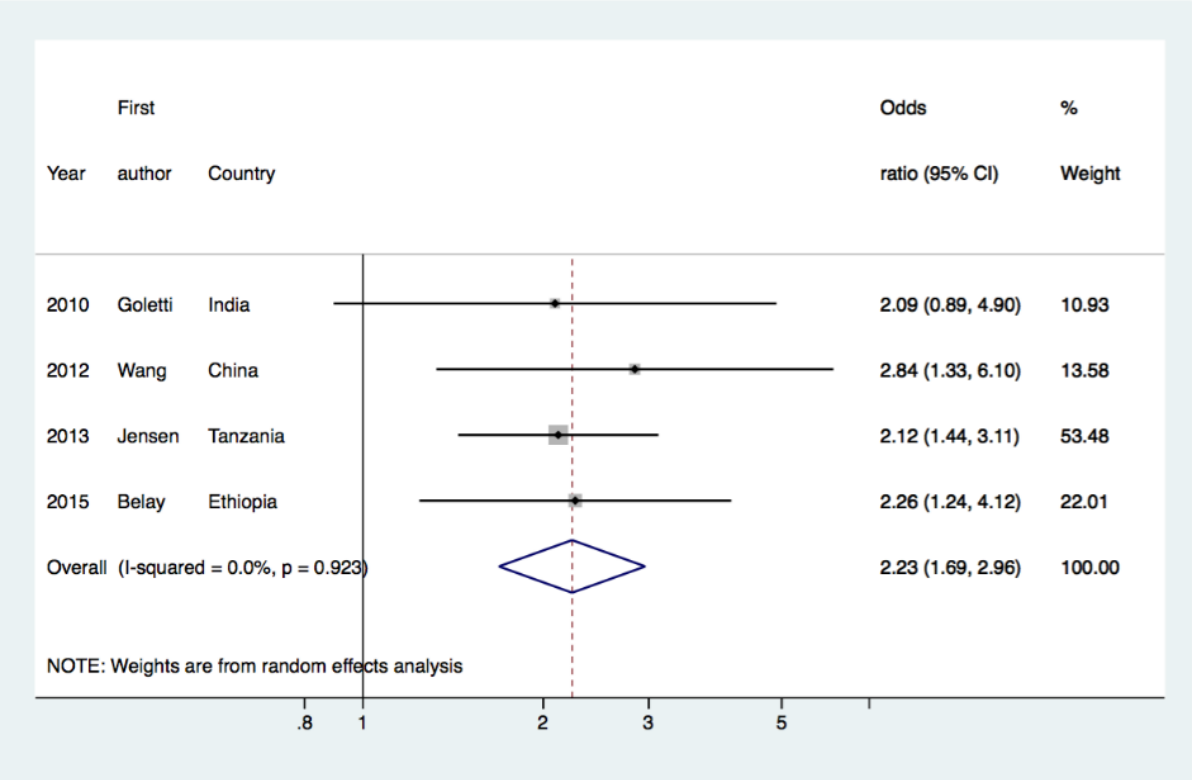
CI: confidence interval; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test

Figure 10. Forest plot for studies in high TB burden countries (6 studies) based on unadjusted ORs and 95% CIs, using random effects, comparing TB infection prevalence among children, measured by IGRA, in TB-affected households versus the general population



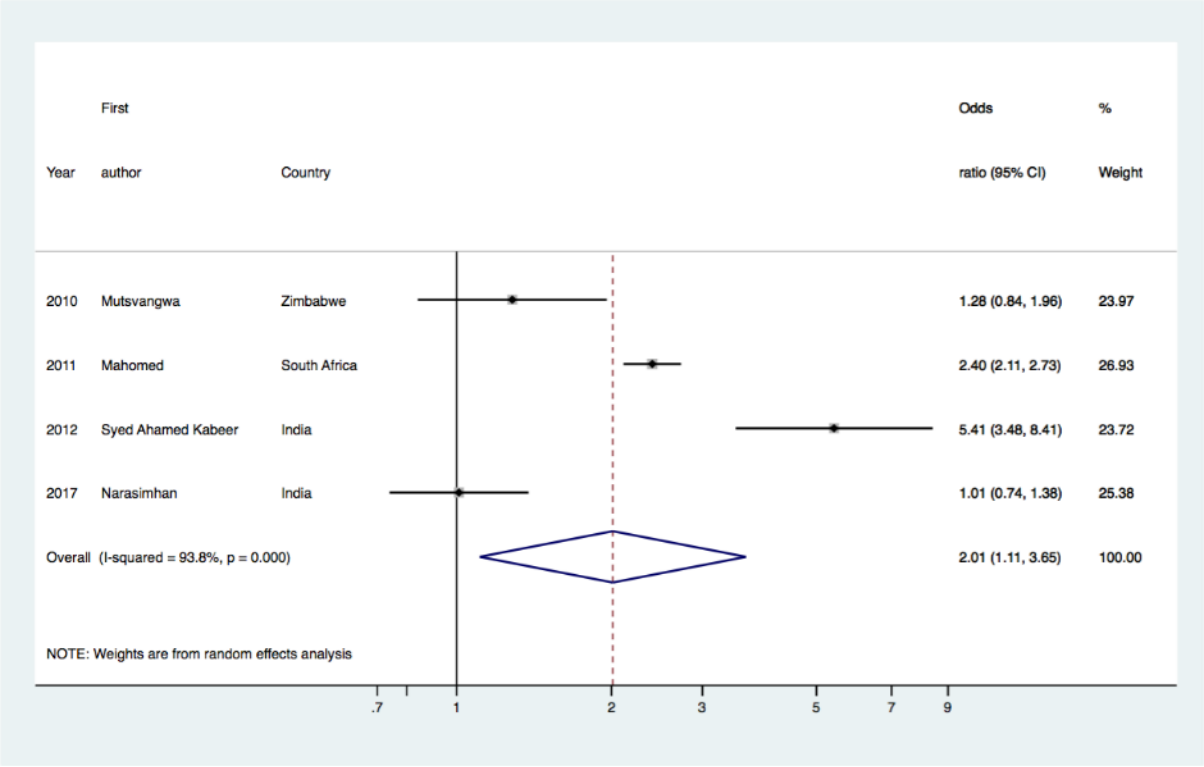
CI: confidence interval; IGRA: interferon gamma release-assay; OR: odds ratio; TB: tuberculosis

Figure 11. Forest plot for studies in high TB burden countries (4 studies) based on unadjusted ORs and 95% CIs, using random effects, comparing TB infection prevalence among adults, measured by IGRA, in TB-affected households versus the general population



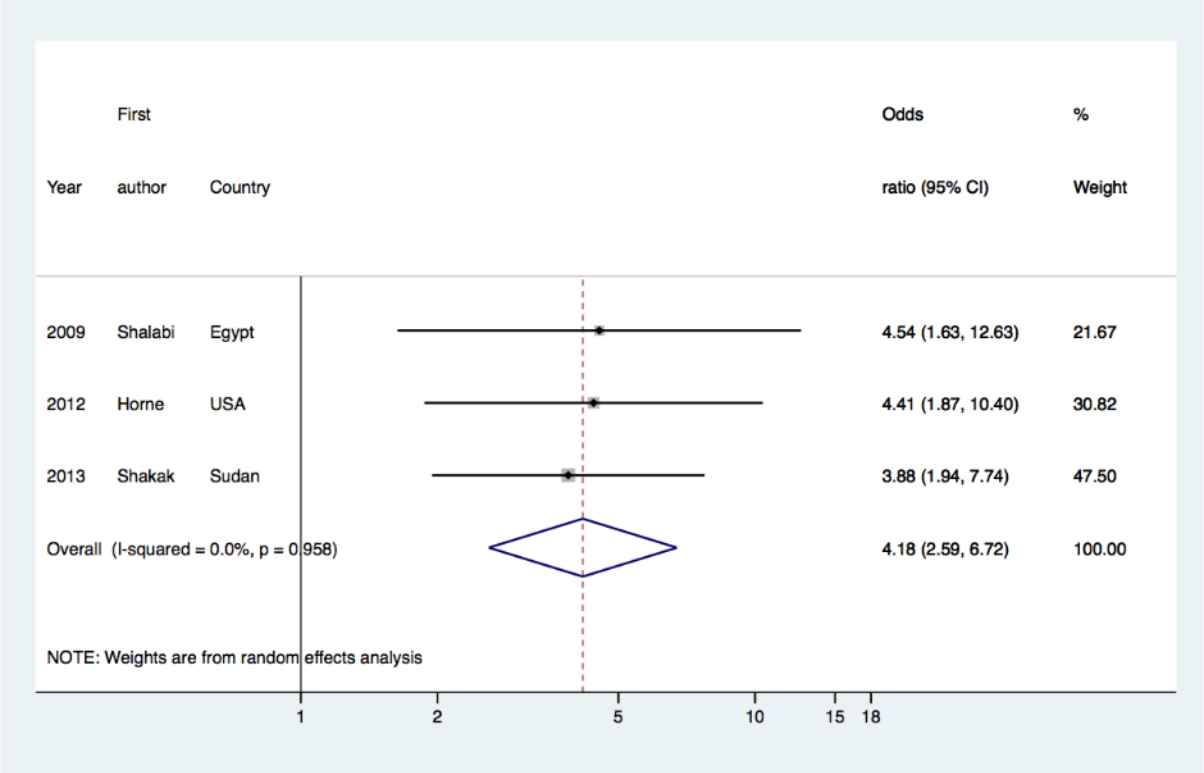
CI: confidence interval; IGRA: interferon gamma release-assay; OR: odds ratio; TB: tuberculosis

Figure 12. Forest plot for studies in high TB burden countries (4 studies) based on unadjusted ORs and 95% CIs, using random effects, comparing TB infection prevalence among children/adults combined, measured by IGRA, in TB-affected households versus the general population



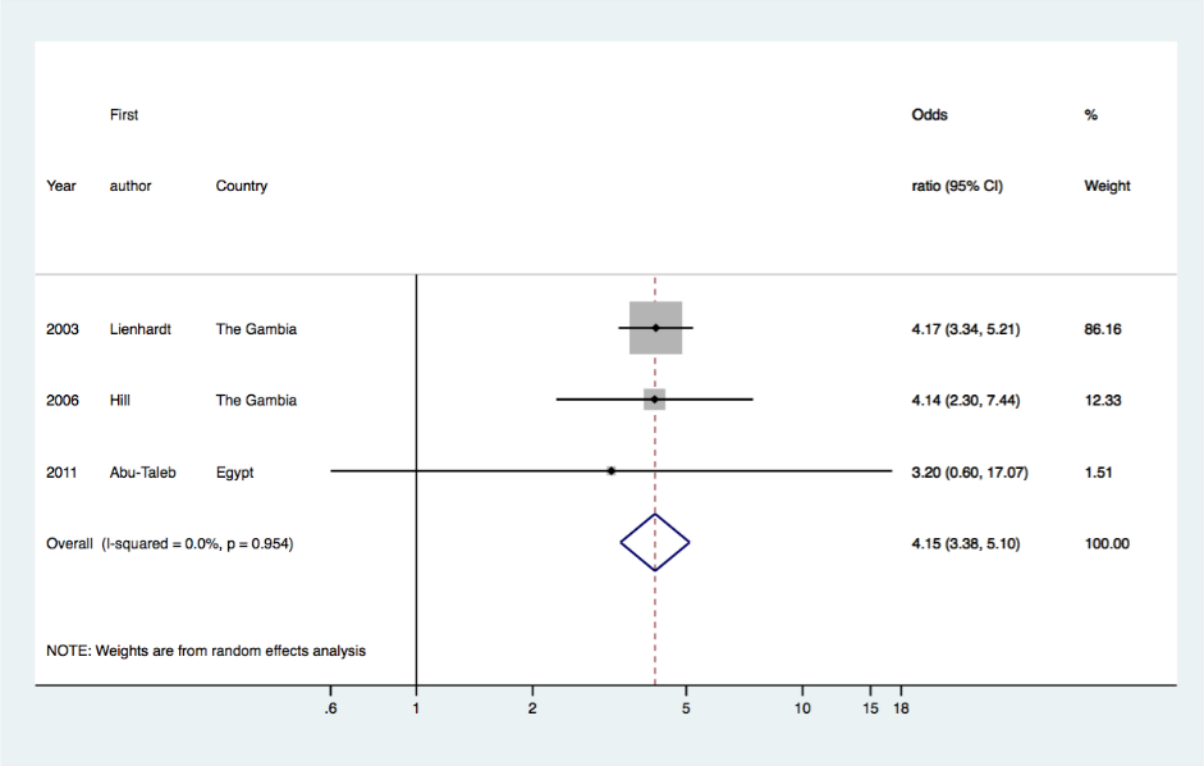
CI: confidence interval; IGRA: interferon gamma release-assay; OR: odds ratio; TB: tuberculosis

Figure 13. Forest plot for studies in low TB burden countries (3 studies) based on unadjusted ORs and 95% CIs, using random effects, comparing TB infection prevalence among adults, measured by TST, in TB-affected households versus the general population



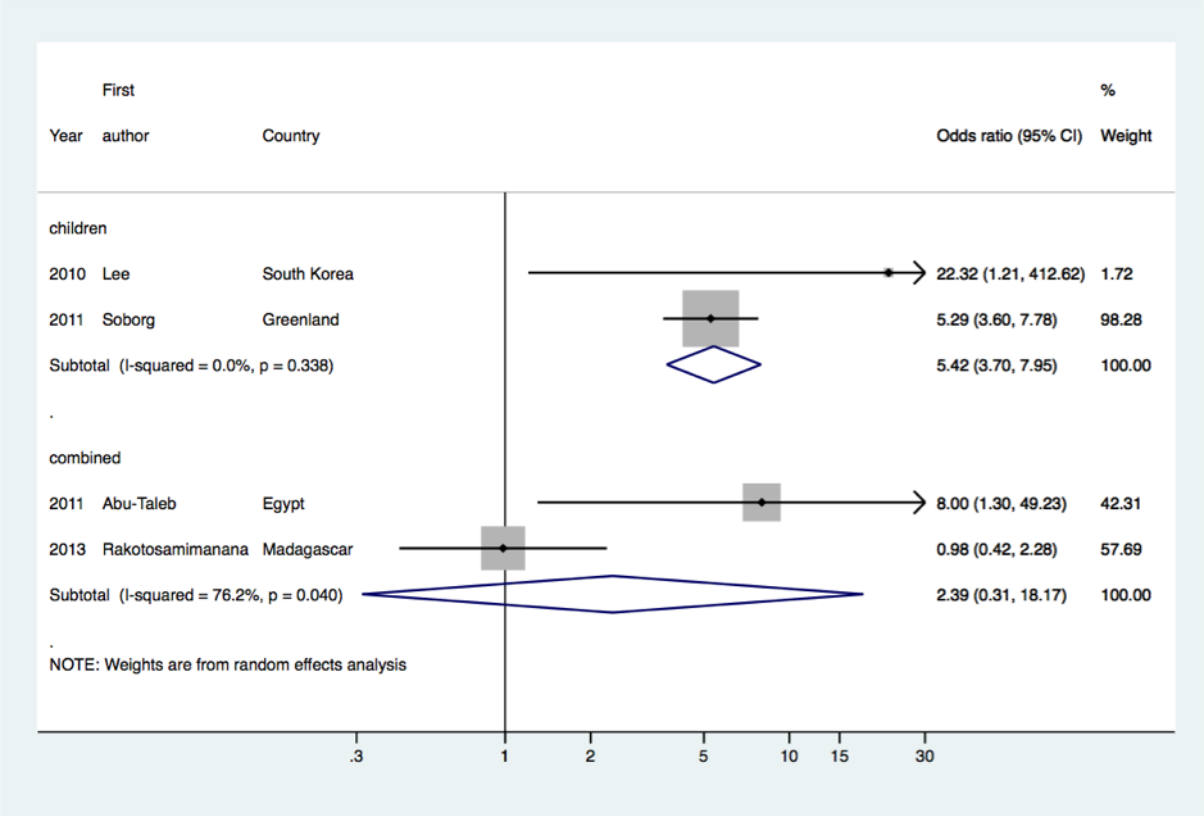
CI: confidence interval; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test; USA: United States of America

Figure 14. Forest plot for studies in low TB burden countries (3 studies) based on unadjusted ORs and 95% CIs, using random effects, comparing TB infection prevalence among children/adults, measured by TST, in TB-affected households versus the general population



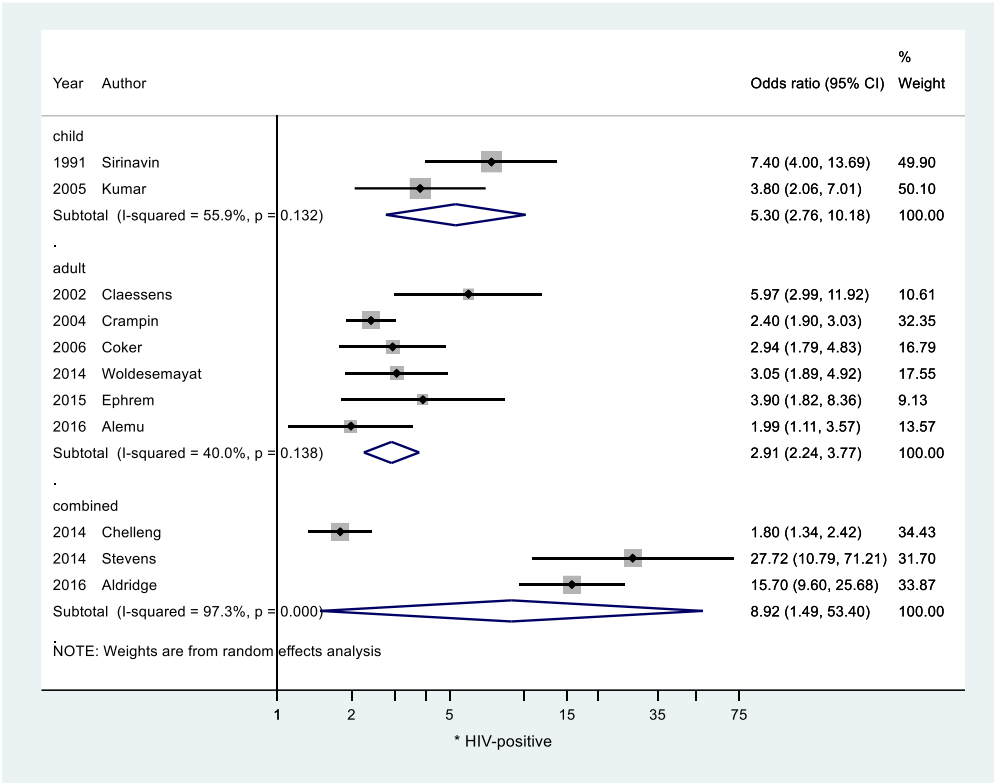
CI: confidence interval; OR: odds ratio; TB: tuberculosis; TST: tuberculin skin test

Figure 15. Forest plot for studies in low TB burden countries (4 studies) based on unadjusted ORs and 95% CIs, using random effects, comparing TB infection prevalence among children alone and adults/children combined, measured by IGRA, in TB-affected households versus the general population



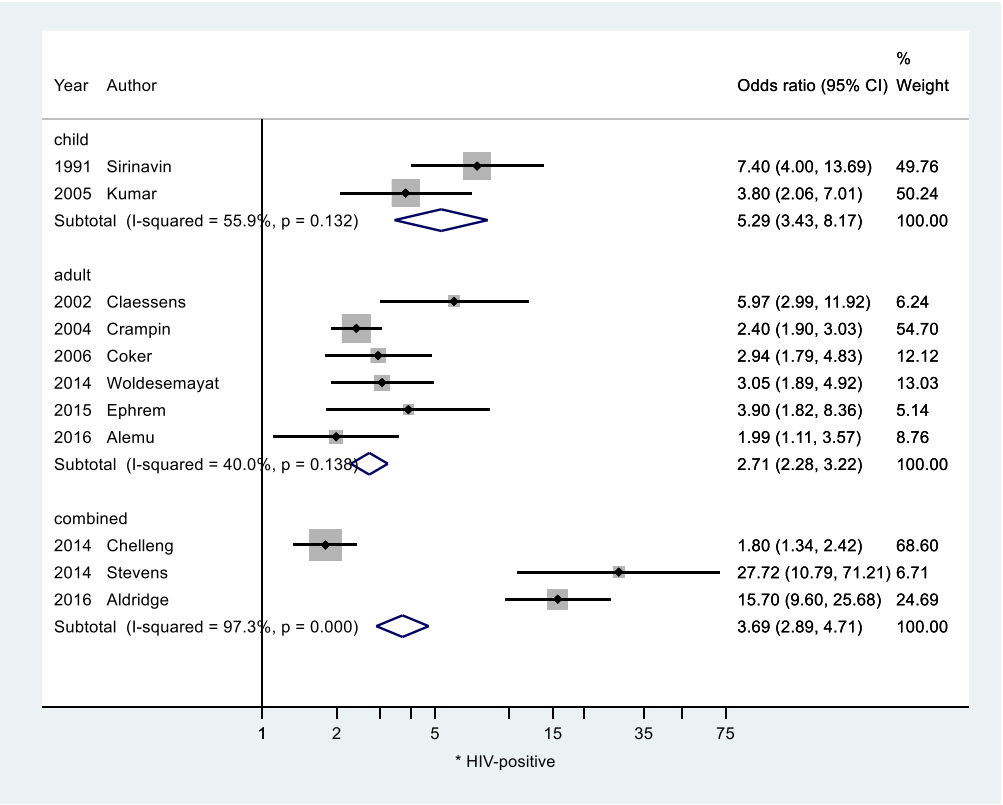
CI: confidence interval; IGRA: interferon gamma release-assay; OR: odds ratio; TB: tuberculosis

Figure 16. Forest plot for studies in high TB burden countries (11 studies) based on ORs and 95% CIs, using random effects, for TB disease prevalence, stratified by children alone, adults alone, and combined, assessing the exposure of household member with TB



CI: confidence interval; OR: odds ratio; TB: tuberculosis

Figure 17. Forest plot for studies in high TB burden countries (11 studies) based on ORs and 95% CIs, using fixed effects, for TB disease prevalence, stratified by children alone, adults alone, and combined, assessing the exposure of household member with TB



CI: confidence interval; OR: odds ratio; TB: tuberculosis

7. References

1 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;**6**(7):e1000097.

2 Modesti PA, Reboldi G, Cappuccio FP, et al. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. *PLoS One*. 2016;**11**(1):e0147601.

3 World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. 2015. p. 19. http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf?ua=1 (accessed 2018 Jan 10)

4 Kruczak K, Duplaga M, Sanak M, et al. Comparison of IGRA tests and TST in the diagnosis of latent tuberculosis infection and predicting tuberculosis in risk groups in Krakow, Poland. *Scand J Infect Dis*. 2014;**46**(9):649–55.

5 Story A, Murad S, Roberts W, Verheyen M, Hayward AC, London Tuberculosis Nurses N. Tuberculosis in London: the importance of homelessness, problem drug use and prison. *Thorax*. 2007;**62**(8):667–71.

6 Karabela S, Papaventsis D, Georgoulas S, et al. Epidemiological monitoring of pulmonary tuberculosis in a correctional facility population, Athens, Greece, 2005-2009. *Clin Microbiol Infect*. 2010;**16**:S620.

7 Pannier R. Results of and considerations on systematic X-ray examination of the lungs. [French] TT - Resultats et reflexions sur l'examen radiologique systematique des poumons. *Acta Tuberc Belg*. 1954;**45**(6):549–82.

8 Castaneda-Hernandez DM, Martinez-Ramirez JE, Bolivar-Mejia A, Rodriguez-Morales AJ. Differences in TB incidence between prison and general populations, Pereira, Colombia, 2010-2011. *Tuberculosis*. 2013;**93**(3):275–6.

9 Noeske J, Ndi N, Elo GA, Mfondih SM. Tuberculosis incidence in Cameroonian prisons: a 1-year prospective study. *South African Med Journal Suid-Afrikaanse Tydskr Vir Geneeskd*. 2014;**104**(3):209–11.

10 Hutton MD, Cauthen GM, Bloch AB. Results of a 29-state survey of tuberculosis in nursing homes and correctional facilities. *Public Health Rep*. 1993;**108**(3):305–14.

11 MacNeil JR, Lobato MN, Moore M. An unanswered health disparity: tuberculosis among correctional inmates, 1993 through 2003. *Am J Public Health*. 2005;**95**(10):1800–5.

12 Alavi SM, Bakhtiarinia P, Eghtesad M, Albaji A, Salmanzadeh S. A comparative study on the prevalence and risk factors of tuberculosis among the prisoners in khuzestan, South-west iran. *Jundishapur J Microbiol*. 2014;**7**(12):e18872.

13 Chevallay B, de Haller R, Bernheim J. [Epidemiology of pulmonary tuberculosis in the prison environment]. *Schweizerische Medizinische Wochenschrift J Suisse Med*. 1983;**113**(7):261–5.

14 Wong MY, Leung CC, Tam CM, Kam KM, Ma CH, Au KF. TB surveillance in correctional institutions in Hong Kong, 1999-2005. *Int J Tuberc Lung Dis*. 2008;**12**(1):93–8.

15 Souza Sacramento D, Ferreira Gonçalves MJ. SITUATION OF TUBERCULOSIS IN PEOPLE DEPRIVED OF FREEDOM IN THE PERIOD 2007 TO 2012. *J Nurs UFPE / Rev Enferm UFPE*. 2017;**11**(1):140–51.

16 Kanyerere HS, Banda RP, Gausi F, et al. Surveillance of tuberculosis in Malawian prisons. *Public Heal Action*. 2012;**2**(1):10–4.

17 Jenkins HE, Plesca V, Ciobanu A, et al. Assessing spatial heterogeneity of multidrug-resistant tuberculosis in a high-burden country. *Eur Respir J*. 2013;**42**(5):1291–301.

18 Russkikh OE. [Comparative analysis of tuberculosis morbidity trends in the penitentiary and civil health care systems of the Udmurt Republic over 10 years]. *Probl Tuberk I Bolezn Legk*. 2007;(8):38–9.

19 Posner E. Pulmonary tuberculosis amongst displaced persons. *Tubercle*. 1951;**32**(9):194–6.

20 Macarthur C, Enarson DA, Fanning EA, Hessel PA, Newman S. Tuberculosis among institutionalized elderly in Alberta, Canada. *Int J Epidemiol*. 1992;**21**(6):1175–9.

21 Bentley DW. Tuberculosis in long-term care facilities. *Infect Control Hosp Epidemiol*. 1990;**11**(1):42–6.

22 Shishido S, Mori T. [Investigation on preventive measures of tuberculosis infection and onset of tuberculosis in

nursing homes for the aged]. *Kekkaku*. 2002;**77**(4):341–6.

23 Ohmori M, Wada M, Yoshiyama T, Uchimura K. [Factors related to early case detection of tuberculosis in health service facilities for the elderly]. *Kekkaku*. 2003;**78**(6):435–42.

24 Chitnis AS, Robsky K, Schecter GF, Westenhouse J, Barry PM. Trends in tuberculosis cases among nursing home residents, California, 2000 to 2009. *J Am Geriatr Soc*. 2015;**63**(6):1098–104.

25 Mwale A, Harries AD, Hargreaves NJ, Salaniponi FM. High frequency of Tuberculosis in households of patients with Pulmonary Tuberculosis in Mzimba, Malawi. *Malawi Med J*. 2003;**15**(1):9–10.

26 Shapiro AE, Variava E, Rakgokong MH, et al. Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa. *Am J Respir Crit Care Med*. 2012;**185**(10):1110–6.

27 Benson UO, Mobegi D, Kiptai T, et al. Increasing tuberculosis yield from investigation of contacts of smear positive TB cases through engagement of civil society organizations: Active TB case finding in Mombasa, Kenya. *Int J Infect Dis*. 2016;**45**:293–4.

28 McAllister S, Lestari BW, Sujatmiko B, et al. Feasibility of two active case finding approaches for detection of tuberculosis in Bandung city, Indonesia. *Public Heal Action*. 2017;**7**(3):206–11.

29 Khan PY, Glynn JR, Mzembe T, et al. Challenges in the Estimation of the Annual Risk of Mycobacterium tuberculosis Infection in Children Aged Less Than 5 Years. *Am J Epidemiol*. 2017;**186**(8):1015–22.

30 Narasimhan P, MacIntyre CR, Mathai D, Wood J. High rates of latent TB infection in contacts and the wider community in South India. *Trans R Soc Trop Med Hyg*. 2017;**111**(2):55–61.

31 Druszczynska M, Wlodarczyk M, Kielnierowski G, Kawka M, Rudnicka W. Two-Year Follow-up Study of Mycobacterium tuberculosis Antigen-Driven IFN-gamma Responses and Macrophage sCD14 Levels After Tuberculosis Contact. *Indian J Microbiol*. 2016;**56**(2):205–13.

32 Elias D, Akuffo H, Abate E, Mekonnen Y, Aseffa A, Britton S. Risk of tuberculous infection in adolescents and adults in a rural community in Ethiopia. *Int J Tuberc Lung Dis*. 2016;**20**(2):218–22.

33 Ncayiyana JR, Bassett J, West N, et al. Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. *BMC Infect Dis*. 2016;**16**(1):661.

34 Perez-Porcuna TM, Pereira-da-Silva HD, Ascaso C, et al. Prevalence and Diagnosis of Latent Tuberculosis Infection in Young Children in the Absence of a Gold Standard. *PLoS ONE [Electronic Resour*. 2016;**11**(10):e0164181.

35 Belay M, Legesse M, Mihret A, et al. Pro- and anti-inflammatory cytokines against Rv2031 are elevated during latent tuberculosis: a study in cohorts of tuberculosis patients, household contacts and community controls in an endemic setting. *PLoS ONE [Electronic Resour*. 2015;**10**(4):e0124134.

36 Lule SA, Mawa PA, Nkurunungi G, et al. Factors associated with tuberculosis infection, and with anti-mycobacterial immune responses, among five year olds BCG-immunised at birth in Entebbe, Uganda. *Vaccine*. 2015;**33**(6):796–804.

37 Mandalakas AM, Kirchner HL, Walzl G, et al. Optimizing the detection of recent tuberculosis infection in children in a high tuberculosis-HIV burden setting. *Am J Respir Crit Care Med*. 2015;**191**(7):820–30.

38 Mumpe-Mwanja D, Verver S, Yeka A, et al. Prevalence and risk factors of latent Tuberculosis among adolescents in rural Eastern Uganda. *Afr Health Sci*. 2015;**15**(3):851–60.

39 Middelkoop K, Bekker L-G, Morrow C, Lee N, Wood R. Decreasing household contribution to TB transmission with age: a retrospective geographic analysis of young people in a South African township. *BMC Infect Dis*. 2014;**14**(1):221.

40 Hoa NB, Cobelens FG, Sy DN, Nhung N V, Borgdorff MW, Tiemersma EW. First national tuberculin survey in Viet Nam: characteristics and association with tuberculosis prevalence. *Int J Tuberc Lung Dis*. 2013;**17**(6):738–44.

41 Jensen A V, Jensen L, Faurholt-Jepsen D, et al. The prevalence of latent Mycobacterium tuberculosis infection based on an interferon-gamma release assay: a cross-sectional survey among urban adults in Mwanza,

Tanzania. *PLoS ONE [Electronic Resour*. 2013;**8**(5):e64008.

42 Rakotosamimanana N, Doherty TM, Andriamihantasoa LH, et al. Expression of TNF-alpha-dependent apoptosis-related genes in the peripheral blood of Malagasy subjects with tuberculosis. *PLoS ONE [Electronic Resour*. 2013;**8**(4):e61154.

43 Shakak AO, Khalil EA, Musa AM, et al. Prevalence of latent tuberculosis infection in Sudan: a case-control study comparing interferon-gamma release assay and tuberculin skin test. *BMC Public Health*. 2013;**13**:1128.

44 Horne DJ, Campo M, Arentz M, Oren E, Crothers KA, Narita M. Association between smoking and latent tuberculosis infection in the united states population. *Am J Respir Crit Care Med Conf Am Thorac Soc Int Conf ATS*. 2012;**185**(no pagination).

45 Nkurunungi G, Lutangira JE, Lule SA, et al. Determining Mycobacterium tuberculosis infection among BCG-immunised Ugandan children by T-SPOT.TB and tuberculin skin testing. *PLoS ONE [Electronic Resour*. 2012;**7**(10):e47340.

46 Rutherford ME, Nataprawira M, Yulita I, et al. QuantiFERON-TB Gold In-Tube assay vs. tuberculin skin test in Indonesian children living with a tuberculosis case. *Int J Tuberc Lung Dis*. 2012;**16**(4):496–502.

47 Syed Ahamed Kabeer B, Paramasivam P, Raja A. Interferon gamma and interferon gamma inducible protein-10 in detecting tuberculosis infection. *J Infect*. 2012;**64**(6):573–9.

48 Wang S, Diao N, Lu C, et al. Evaluation of the diagnostic potential of IP-10 and IL-2 as biomarkers for the diagnosis of active and latent tuberculosis in a BCG-vaccinated population. *PLoS ONE [Electronic Resour*. 2012;**7**(12):e51338.

49 Abu-Taleb AM, El-Sokkary RH, El Tarhouny SA. Interferon-gamma release assay for detection of latent tuberculosis infection in casual and close contacts of tuberculosis cases. *East Mediterr Heal J*. 2011;**17**(10):749–53.

50 Crampin A, Kasimba S, Mwaungulu NJ, et al. Married to M. tuberculosis: risk of infection and disease in spouses of smear-positive tuberculosis patients. *Trop Med Int Heal*. 2011;**16**(7):811–8.

51 Mahomed H, Hawkridge T, Verver S, et al. Predictive factors for latent tuberculosis infection among adolescents in a high-burden area in South Africa. *Int J Tuberc Lung Dis*. 2011;**15**(3):331–6.

52 du Preez K, Mandalakas AM, Kirchner HL, et al. Environmental tobacco smoke exposure increases Mycobacterium tuberculosis infection risk in children. *Int J Tuberc Lung Dis*. 2011;**15**(11):1490–6, i.

53 Soborg B, Andersen AB, Melbye M, et al. Risk factors for Mycobacterium tuberculosis infection among children in Greenland. *Bull World Health Org*. 2011;**89**(10):741–8.

54 Whalen CC, Zalwango S, Chiunda A, et al. Secondary attack rate of tuberculosis in urban households in Kampala, Uganda. *PLoS ONE [Electronic Resour*. 2011;**6**(2):e16137.

55 Goletti D, Alamelu R, Kabeer BSA, et al. IFN- gamma , but not IP-10, MCP-2 or IL-2 response to RD1 selected peptides associates to active tuberculosis. *J Infect*. 2010;**61**(2):133–43.

56 Lee T, Kim N, Kim J. Diagnosis of latent tuberculosis infection by using the QuantiFERON-TB Gold in-tube test in children whose household contact has contagious pulmonary tuberculosis disease. *Int J Infect Dis*. 2010;**14**:e307.

57 Mutsvangwa J, Millington KA, Chaka K, et al. Identifying recent Mycobacterium tuberculosis transmission in the setting of high HIV and TB burden. *Thorax*. 2010;**65**(4):315–20.

58 Shalabi NM, Houssen ME. Discrepancy between the tuberculin skin test and the levels of serum interferon-gamma in the diagnosis of tubercular infection in contacts. *Clin Biochem*. 2009;**42**(16–17):1596–601.

59 Lin X, Chongsuvivatwong V, Lin L, Geater A, Lijuan R. Dose-response relationship between treatment delay of smear-positive tuberculosis patients and intra-household transmission: a cross-sectional study. *Trans R Soc Trop Med Hyg*. 2008;**102**(8):797–804.

60 Gustafson P, Lisse I, Gomes V, et al. Risk factors for positive tuberculin skin test in Guinea-Bissau. *Epidemiology*. 2007;**18**(3):340–7.

61 Boon S den, Verver S, Marais BJ, et al. Association between passive smoking and infection with Mycobacterium

tuberculosis in children. *Pediatrics*. 2007;**119**(4):734–9.

62 Hill PC, Jackson-Sillah D, Donkor SA, Otu J, Adegbola RA, Lienhardt C. Risk factors for pulmonary tuberculosis: a clinic-based case control study in The Gambia. *BMC Public Health*. 2006;**6**:156.

63 Nakaoka H, Lawson L, Squire SB, et al. Risk for tuberculosis among children. *Emerg Infect Dis*. 2006;**12**(9):1383–8.

64 Lienhardt C, Fielding K, Sillah J, et al. Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in The Gambia. *Am J Respir Crit Care Med*. 2003;**168**(4):448–55.

65 Olender S, Saito M, Apgar J, et al. Low prevalence and increased household clustering of Mycobacterium tuberculosis infection in high altitude villages in Peru. *Am J Trop Med Hyg*. 2003;**68**(6):721–7.

66 Kenyon TA, Creek T, Laserson K, et al. Risk factors for transmission of Mycobacterium tuberculosis from HIV-infected tuberculosis patients, Botswana. *Int J Tuberc Lung Dis*. 2002;**6**(10):843–50.

67 Almeida LM, Barbieri MA, Da Paixao AC, Cuevas LE. Use of purified protein derivative to assess the risk of infection in children in close contact with adults with tuberculosis in a population with high Calmette-Guerin bacillus coverage. *Pediatr Infect Dis J*. 2001;**20**(11):1061–5.

68 Mudido PM, Guwatudde D, Nakakeeto MK, et al. The effect of bacille Calmette-Guerin vaccination at birth on tuberculin skin test reactivity in Ugandan children. *Int J Tuberc Lung Dis*. 1999;**3**(10):891–5.

69 Madico G, Gilman RH, Checkley W, et al. Community infection ratio as an indicator for tuberculosis control. *Lancet*. 1995;**345**(8947):416–9.

70 Narain R, Nair SS, Ramanatha Rao G, Chandrasekhar P. Distribution of tuberculous infection and disease among households in a rural community. *Bull World Health Org*. 1966;**34**(4):639–54.

71 WHO Tuberculosis Chemotherapy Centre. An investigation of household contacts of open cases of pulmonary tuberculosis amongst the Kikuyu in Kiambu, Kenya. *Bull World Health Org*. 1961;**25**(6):831–50.

72 Ferrarini MA, Spina FG, Weckx LY, Lederman HM, De Moraes-Pinto MI. Rate of tuberculosis infection in children and adolescents with household contact with adults with active pulmonary tuberculosis as assessed by tuberculin skin test and interferon-gamma release assays. *Epidemiol Infect*. 2016;**144**(4):712–23.

73 Khan PY, Glynn JR, Fielding KL, et al. Risk factors for Mycobacterium tuberculosis infection in 2-4 year olds in a rural HIV-prevalent setting. *Int J Tuberc Lung Dis*. 2016;**20**(3):342–9.

74 Hossain S, Zaman K, Banu S, et al. Tuberculin survey in Bangladesh, 2007-2009: prevalence of tuberculous infection and implications for TB control. *Int J Tuberc Lung Dis*. 2013;**17**(10):1267–72.

75 Tuberculosis Research Centre IC of MRCI. Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases. *Int J Tuberc Lung Dis*. 2011;**15**(6):782–8.

76 Aziz N, Hasan S, Munir M, Tayyab M, Chaudrhy NA. Risk to household contacts of tuberculous patients based on Mantoux test and antibody titre. *J Ayub Med Coll Abbottabad JAMC*. 2008;**20**(2):47–50.

77 Lutong L, Bei Z. Association of prevalence of tuberculin reactions with closeness of contact among household contacts of new smear-positive pulmonary tuberculosis patients. *Int J Tuberc Lung Dis*. 2000;**4**(3):275–7.

78 Gilpin TP, Hammond M. Active case-finding - for the whole community or for tuberculosis contacts only? *S Afr Med J*. 1987;**72**(4):260–2.

79 Narain R, Naganna K, Murthy SS. Incidence of pulmonary tuberculosis. *AmerRevRespDis*. 1973;**107**(6):992–1001.

80 Aspin J, Lotinga KHM. Tuberculin-sensitivity among child contacts in Leeds, 1948-1949. *Tubercle*. 1953;**34**(1):20–3.

81 Sirinavin S, Chotpitayasunondh T, Suwanjutha S, Sunakorn P, Chantarojanasiri T. Protective efficacy of neonatal Bacillus Calmette-Guerin vaccination against tuberculosis. *Pediatr Infect Dis J*. 1991;**10**(5):359–65.

82 Claessens NJ, Gausi FF, Meijnen S, Weismuller MM, Salaniponi FM, Harries AD. High frequency of tuberculosis in households of index TB patients. *Int J Tuberc Lung Dis*. 2002;**6**(3):266–9.

83 Crampin AC, Glynn JR, Floyd S, et al. Tuberculosis and gender: exploring the patterns in a case control study in Malawi. *Int J Tuberc Lung Dis*. 2004;**8**(2):194–203.

84 Kumar P, Kumar R, Srivastava KL, Kumar M. Protective role of BCG vaccination against tuberculous meningitis in Indian children: a reappraisal. *Natl Med J India*. 2005;**18**(1):7–11.

85 Lienhardt C, Fielding K, Sillah JS, et al. Investigation of the risk factors for tuberculosis: a case-control study in three countries in West Africa. *Int J Epidemiol*. 2005;**34**(4):914–23.

86 Coker R, McKee M, Atun R, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. *BMJ*. 2006;**332**(7533):85–7.

87 Hill PC, Brookes RH, Fox A, et al. Surprisingly High Specificity of the PPD Skin Test for M-tuberculosis Infection from Recent Exposure in The Gambia. *PLoS One*. 2006;**1**(1).

88 Corbett EL, Bandason T, Cheung YB, et al. Prevalent infectious tuberculosis in Harare, Zimbabwe: burden, risk factors and implications for control. *Int J Tuberc Lung Dis*. 2009;**13**(10):1231–7.

89 Chelleng PK, Devi KR, Debasish B, et al. Risk factors of pulmonary tuberculosis in tea garden communities of Assam, India. *Indian J Med Res*. 2014;**140**(1):138–41.

90 Stevens H, Ximenes RA, Dantas OM, Rodrigues LC. Risk factors for tuberculosis in older children and adolescents: a matched case-control study in Recife, Brazil. *Emerg Themes Epidemiol*. 2014;**11**(1):20.

91 Woldesemayat EM, Datiko DG, Lindtjorn B. Use of biomass fuel in households is not a risk factor for pulmonary tuberculosis in South Ethiopia. *Int J Tuberc Lung Dis*. 2014;**18**(1):67–72.

92 Ephrem T, Mengiste B, Mesfin F, Godana W. Determinants of active pulmonary tuberculosis in Ambo Hospital, West Ethiopia. *African J Prim Heal Care Fam Med*. 2015;**7**(1):e1–8.

93 Aldridge RW, Zenner D, White PJ, et al. Tuberculosis in migrants moving from high-incidence to low-incidence countries: a population-based cohort study of 519 955 migrants screened before entry to England, Wales, and Northern Ireland. *Lancet*. 2016;**388 North**(10059):2510–8.

94 Alemu YM, Awoke W, Wilder-Smith A. Determinants for tuberculosis in HIV-infected adults in Northwest Ethiopia: a multicentre case-control study.[Erratum appears in BMJ Open. 2016;6(4):e009058corr1; PMID: 27118281]. *BMJ Open*. 2016;**6**(4):e009058.

95 Faisal UA, Rubab A, Tahseen SA. The risk factors associated with tuberculosis in children. *Pakistan Paediatr J*. 2016;**40**(3):165–70.

96 Radhakrishna S, Frieden TR, Subramani R, Santha T, Narayanan PR, Indian Council of Medical R. Additional risk of developing TB for household members with a TB case at home at intake: a 15-year study. *Int J Tuberc Lung Dis*. 2007;**11**(3):282–8.

Systematic review for evidence of administrative infection control interventions to reduce TB transmission and three related background questions

Background question 3

How does the infectiousness of TB patients (ability to excrete viable bacteria and sustain transmission) change after having started on effective TB treatment?

Final report

31st May 2018

Authors: Claire Calderwood, Katherine Fielding, Rebecca Harris, Aaron Karat, Raoul Mansukhani, David Moore, James Wilson

Contributors: Jane Falconer, Malin Bergstrom, Akira Endo, Sarah-May Johnson, Maria Krutikov, Mengyun Liu, Nicky McCreesh, Ed Monk, Jasantha Odayar, Peter Scott, Sarah Stokes, Hannah Theodorou.

Enquiries to: katherine.fielding@lshtm.ac.uk

Contents

List of tables

List of figures

List of annex tables

1. Executive summary

1.1. Question

This document describes the systematic review undertaken specifically to determine smear and culture conversion times achieved by effective anti-tuberculosis therapy. It does not consider the other relevant published data pertaining to effect of therapy on cough frequency and duration. At the specific request of the Guideline Development Group an additional systematic review, also reported here, was undertaken to capture the literature examining the effect of tuberculosis treatment upon the infectiousness of TB patients to exposed laboratory animals.

1.2. Methods

A systematic review of the literature was conducted to answer to question: how does the infectiousness of TB patients (ability to excrete viable bacteria and sustain transmission) change after having started on effective TB treatment?

The focus of the main systematic review was time to smear and culture conversion; a second review undertaken at the subsequent request of the Guideline Development Group investigated the literature on the effect of TB treatment on infectiousness of TB patients to guinea pigs used as air samplers.

A literature search of relevant databases was undertaken to identify potentially relevant articles. Two-stage sifting, first by title and abstract and then by full text review was undertaken in duplicate by independent observers. Reference lists of included articles were reviewed and citations were checked to pick up any additional papers not captured by the original search. A secondary literature search focussed on randomised controlled trials was undertaken to capture additional papers. Data extraction was undertaken in duplicate by two independent researchers and consensus reached after discussion. Summary statistics were tabulated and Forest plots generated, with meta-analyses at time points where data permitted.

1.3. Results

After title and abstract sifting of 5,290 unique records identified through literature search and full text review of 180 articles, 47 papers were included for data extraction and analysis for time to smear and culture conversion. Considerable variation in smear and culture conversion times was seen across studies.

For the six studies reporting a summary estimate of time to smear conversion the median time to conversion ranged from 20–27 days and the mean time to conversion ranged from 29–61 days. The summary estimates across eight studies of the proportion of baseline smear-positive patients achieving smear conversion at the

1-, 2-, and 3-month time points were 0.3 (95% CI 0.27–0.34), 0.79 (95% CI 0.70–0.87), and 0.95 (95% CI 0.94–0.95) respectively.

For the five studies reporting a summary estimate of time to solid culture conversion the median time to conversion ranged from 35–49 days. For the five studies reporting a summary estimate of time to culture conversion where culture method was not specified the median time to conversion ranged from 32–48 days. For the five studies reporting a summary estimate of time to liquid culture conversion the median time to conversion ranged from 28–125 days.

The proportion of patients achieving culture conversion after two months of appropriate treatment for proven drug susceptible for solid culture, unspecified culture method and liquid culture was 0.84 (95% CI 0.80–0.88), 0.78 (95% CI 0.67–0.88), and 0.67 (95% CI 0.54–0.81) respectively.

Factors affecting time to culture conversion, such as the proportion of the study population with heavily smear-positive disease, were rarely reported and are likely to have accounted for some of the heterogeneity.

Four relevant papers were identified in the additional systematic review of the effect of TB treatment upon infectiousness of TB patients to experimental animals. All contained data suggesting that patients on TB treatment are less infectious to guinea pigs than patients not receiving effective TB treatment. However, there are no data indicating the time it takes for a patient receiving effective treatment to become non-infectious to guinea pigs.

1.4. Conclusion

There is significant variability in the time taken for patients with proven drug-susceptible pulmonary TB receiving appropriate first-line TB treatment to achieve smear and culture conversion. At the two-month time point around 21% of patients remain smear-positive and around 35% of patients remain sputum culture-positive by liquid culture.

2. Background and question

A systematic review of the literature was conducted to answer to question “how does the infectiousness of TB patients (ability to excrete viable bacteria and sustain transmission) change after having started on effective TB treatment?”

Diagnosis and effective treatment of patients with infectious tuberculosis (TB) interrupts TB transmission by reducing the production of infectious aerosols by TB patients. Regardless of whether coughing persists during treatment, microbiological sterilisation of spontaneously expectorated sputum renders patients non-infectious thus it is important to understand the dynamics of this process.

The time taken for the sputum of a TB patient to convert from microbiologically positive (by sputum smear or solid or liquid culture) to microbiologically negative (by the same methods) following initiation of a multiple drug regimen to which the TB strain is known to be susceptible, is the focus of this analysis.

An additional systematic review of the literature reporting the effect of TB treatment upon infectiousness of TB patients to experimental animals exposed to ambient air exhausted from patient isolation rooms is also included, at the request of the Guideline Development Group.

The presence of viable *Mycobacterium tuberculosis* in respiratory secretions is a necessary but not sufficient determinant of infectiousness of pulmonary TB. Microbiologically this presence is conventionally equated to detection of *M. tuberculosis* in sputum. However, it is recognised that in order for transmission to occur droplet nuclei containing viable infectious organisms must be generated; coughing Is a highly effective mechanism to achieve this. The reduction in cough frequency that is seen soon after initiation of effective TB treatment likely makes a significant contribution to reducing infectiousness; however, the Guideline Development Group were clear that effect of treatment upon cough was not to be considered in this review.

3. Methods – systematic review of time to smear and culture conversion

3.1. Overview

A literature search of relevant databases was undertaken to identify potentially relevant articles. Sifting of these articles by title and abstract was undertaken in duplicate by independent observers. The full text of each of the manuscripts retained after sifting was then retrieved and reviewed in duplicate by independent observers for eligibility. For each paper selected for inclusion after full text review the reference list was reviewed and citations were checked to pick up any additional papers not captured by the original search. Any newly included papers from this process were also subject to reference and citation checking. Data extraction was undertaken in duplicate by two independent researchers. Extracted data were compared and any discordance resolved through discussion to achieve a consensus result.

3.2. Population and outcomes

Population

Patients receiving effective treatment for drug-susceptible TB.

Outcomes

Infectiousness defined as bacteriological conversion (sputum smear, culture).

3.3. Initial search

The search strategy was constructed and run by a professional librarian with experience of systematic review literature searching. It was compiled and tested on the OvidSP Medline database before being edited, as required, and run across other relevant information sources.

The search strategies used subject headings, where available, and search terms run in the title and abstract, where possible. Due to language skills available in the research team, literature was limited to papers written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese. No date limits or publication type limits were added to the search.

The following databases were searched on 01 December 2017:
OvidSP Medline, 1946-present; OvidSP Embase, 1947 to November 30 2017; Global Health, 1910 to 2017 Week 47; and Ebsco CINAHL Plus, full database.

3.3.1. Search strategy of initial search

Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE
Date: 1946 to Present, search run on 01 December 2017.

1. carrier state/ (21766)

2. infectiousness.ti,ab. (1309)
3. infectivity.ti,ab. (25226)
4. ((transmis* or transmit*) adj2 (dynamic* or risk* or event? or reservoir? or less or more or remain or persist* or sustain* or probabilit*)).ti,ab. (16340)
5. (infection? adj2 (reservoir? or less or more or remain or persist* or sustain*)).ti,ab. (30172)
6. ((viable or live or infectious) adj2 (pathogen? or bacteria or bacterium)).ti,ab. (7132)
7. or/1-6 (99604)
8. exp tuberculosis/ (190560)
9. mycobacterium tuberculosis/ (47471)
10. tuberculosis.ti,ab. (176160)
11. tb.ti,ab. (43071)
12. or/8-11 (256157)
13. 7 and 12 (2452)
14. (chinese or english or french or japanese or portuguese or russian or spanish).lg. (26990357)
15. 13 and 14 (2332)
16. remove duplicates from 15 (2162)

The additional full search strategies for OvidSP Embase Classic+Embase, OvidSP Global Health and EBSCO CINAHL Plus can be found in Annex table 9.1.

3.3.2. Results of initial search

A total 6,395 records were retrieved; 3,558 remained after de-duplication (Table 3.1)

Table 3.1. Records retrieved from each database and number put forward for title and abstract sifting from original search (run 01 December 2017)

Database name	Date of search	Total number of references retrieved	Number of references after de-duplication
Medline	01/12/2017	2,162	2,158
Embase	01/12/2017	2,761	980
Global Health	01/12/2017	1,105	268
CINAHL Plus	01/12/2017	367	152
Total		**6395**	**3558**

CINAHL: Cumulative Index to Nursing and Allied Health Literature

3.4. Secondary search

After full text sifting and review of references following this primary search it became clear that several randomised treatment trials that contained time to conversion data in the standard treatment arms had not been captured by the initial search terms. A secondary search was thus undertaken.

The following databases were searched on 20th February 2018. OvidSP Medline, 1946-present; OvidSP Embase, 1974 to 2018 February 16; Global Health, 1910 to 2017 Week 47; and Ebsco CINAHL Plus, full database.

The literature search was constructed using concepts for pulmonary tuberculosis and drug-susceptible tuberculosis together with the four drugs used in treatment of drug-susceptible TB: isoniazid, rifampin, ethambutol, pyrazinamide. These were combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in Medline: sensitivity and precision maximizing version (2008 revision) (see box 6.4.d in http://handbook-5-1.cochrane.org/). A search in OvidSP Medline was constructed and search terms and syntax were updated as required by each new database. No language limits were applied. Dates were limited to 1990 onwards. The search strategy for Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE is provided below.

3.4.1. Search strategy of secondary search

Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE
Date: 1946 to Present, search run on 20 February 2018.

1 exp tuberculosis, pulmonary/ (72595)
2 tuberculosis/ (99245)
3 exp Tuberculosis, Multidrug-Resistant/ (6669)
4 tuberculosis.ti,ab. (169241)
5 tb.ti,ab. (40846)
6 mdr-tb.ti,ab. (2954)
7 xdr-tb.ti,ab. (853)
8 or/1-7 (226367)
9 randomized controlled trial.pt. (453810)
10 controlled clinical trial.pt. (92162)
11 randomized.ab. (393756)
12 placebo.ab. (183608)
13 clinical trials as topic.sh. (182599)
14 randomly.ab. (279733)
15 trial.ti. (174081)
16 or/9-15 (1116904)
17 exp animals/ not humans.sh. (4426664)
18 16 not 17 (1027253)
19 Isoniazid/ (17851)
20 isoniazid.ti,ab. (14060)

21 isonicotinic acid hydrazide.ti,ab. (1901)

22 phthivazid.ti,ab. (77)

23 phthivazide.ti,ab. (64)

24 tubazide.ti,ab. (16)

25 Rifampin/ (16499)

26 rifampin.ti,ab. (7525)

27 benemycin.ti,ab. (16)

28 rifadin.ti,ab. (46)

29 rifampicin.ti,ab. (14105)

30 rimactan.ti,ab. (26)

31 rimactane.ti,ab. (16)

32 Ethambutol/ (3721)

33 ethambutol.ti,ab. (4686)

34 myambutol.ti,ab. (42)

35 Pyrazinamide/ (3028)

36 pyrazinamide.ti,ab. (3413)

37 or/19-36 (45334)

38 8 and 18 and 37 (1339)

39 limit 38 to yr="1990 -Current" (814)

40 remove duplicates from 39 (808)

The additional full search strategies for OvidSP Embase Classic+Embase, OvidSP Global Health and EBSCO CINAHL Plus can be found in Annex table 9.2.

3.4.2. Results of secondary search

A total 2,870 references were retrieved; 1,732 remained after de-duplication (Table 3.2).

Table 3.2. Records retrieved from each database and number put forward for title and abstract sifting from secondary search (run 20 February 2018)

Database name	Date of search	Total number of references retrieved	Number of references after de-duplication
Medline	20/02/2018	808	801
Embase	20/02/2018	1,463	847
Global Health	20/02/2018	452	73
CINAHL Plus	20/02/2018	147	11
Total		**2870**	**1732**

CINAHL: Cumulative Index to Nursing and Allied Health Literature

3.5. Eligibility criteria

3.5.1. Inclusion criteria

Types of participants: TB patients on effective treatment

Types of study: Any consecutive case series, case control study, cohort study, randomised controlled study, systematic review or meta-analysis reporting on the outcomes listed below.

Types of outcome measures: bacteriological conversion (sputum smear, liquid or solid culture)

3.5.2. Exclusion criteria

1. Any study that does not report any of the above-stated outcomes of interest
2. Any systematic review superseded by an updated systematic review
3. Narrative reviews not adding new data or new analysis of data to the existing body of knowledge
4. Commentaries and mathematical modelling studies
5. Any study not written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese
6. Any study published before 1946

3.6. Data extraction

Data extraction was conducted in duplicate by two reviewers. Data was extracted from papers selected for final inclusion using a standardised database. Any unresolved disagreements in extraction were resolved by a third, independent reviewer. Data were not extracted from included systematic reviews as data were extracted from all the source manuscripts included by the original search, and from any additional manuscripts identified from reference checking of the systematic review itself.

3.7. Quality assessment

Assessment of quality was conducted at the study level, as prescribed in the PRISMA statement for reporting of systematic reviews[1]. An adapted NIH tool designed for quality assessment of case series was used https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

3.8. Data synthesis

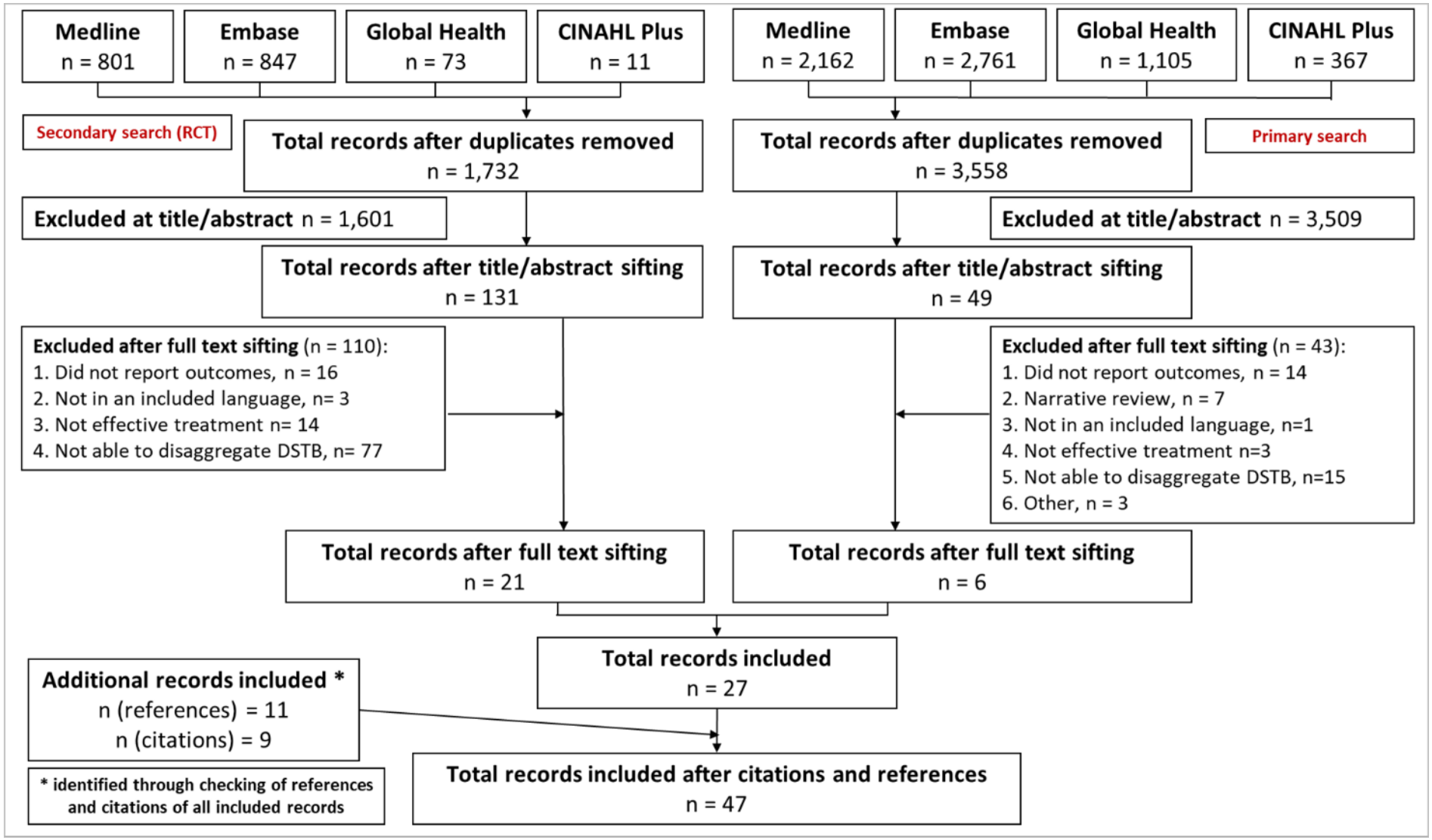
Extracted data have been synthesised using a narrative approach. Despite significant heterogeneity in study design, the Guideline Development Group were keen that summary statistics should be included where possible, so these are indicated in the Forest plots. The exact method was used for calculating confidence intervals. All meta- analyses are random-effects models.

4. Results – systematic review of time to smear and culture conversion

4.1. Articles identified

In total, after duplicates were removed, 5,290 records (3,558 + 1,732) were assessed at the title and abstract phase. Full text review of 180 papers resulted in selection of 27 papers, to which an additional 21 papers were finally added after review of all references and citations of included papers. Of these 47 included papers, 26 reported data from high burden settings. (Figure 4.1, Table 4.1).

Figure 4.1. Flow diagram showing databases searched, records found, sifted, and included, and reasons for exclusion at full text review



CINAHL: Cumulative Index to Nursing and Allied Health Literature; DSTB: drug-sensitive TB; RCT: randomised controlled trial; TB: tuberculosis:

Table 4.1. Articles selected for data extraction

First author	Year	Title	Country	Low/ high
Singapore TB Service / British MRC[2]	1979	Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis	Singapore	low
Hong Kong Chest Service / British MRC[3]	1981	Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis	Hong Kong	high
East and Central African / British MRC[4]	1983	Controlled clinical trial of 4 short course regimens of chemotherapy (three 6 month and one 8 month) for pulmonary tuberculosis	Kenya, Zambia, Tanzania and Uganda	high
Tuberculosis Research Centre[5]	1983	Study of chemotherapy regimens of 5 and 7 months' duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India	India	high
Combs[6]	1990	USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability. The report of final results	USA	low
Chaulet[7]	1995	Clinical trial of a combination of three drugs in fixed proportions in the treatment of tuberculosis	Algeria	low
Kennedy[8]	1996	Randomized controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis	Tanzania	high
Tanzania /British MRC Collaborative Investigation[9]	1996	A controlled trial of a 4-weekly supplement of rifampicin, pyrazinamide and streptomycin in the continuation phase of a 7-month daily chemotherapy regimen for pulmonary tuberculosis	Tanzania	high
Telzak[10]	1997	Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis	USA	low
Desjardin[11]	1999	Measurement of sputum *Mycobacterium tuberculosis* messenger RNA as a surrogate for response to chemotherapy	Brazil	high
Durban Immunotherapy Trial Group[12]	1999	Immunotherapy with *Mycobacterium vaccae* in patients with newly diagnosed pulmonary tuberculosis: a randomised controlled trial.	South Africa	high
Johnson[13]	2000	Randomized controlled trial of *Mycobacterium vaccae* immunotherapy in non-human immunodeficiency virus-infected Ugandan adults with newly diagnosed pulmonary tuberculosis	Uganda	high
Joloba[14]	2000	Quantitative sputum bacillary load during rifampin-containing short course chemotherapy in human immunodeficiency virus-infected and non-infected adults with pulmonary tuberculosis	Uganda	high
Hasegawa[15]	2002	Detection of mycobacteria in patients with pulmonary tuberculosis undergoing chemotherapy using MGIT and egg-based solid medium culture systems	Japan	low
Johnson[16]	2003	Randomized trial of adjunctive interleukin-2 in adults with pulmonary tuberculosis	Uganda	high

First author	Year	Title	Country	Low/ high
Domínguez-Castellano[17]	2003	Factors associated with time to sputum smear conversion in active pulmonary tuberculosis.	Spain	low
Singla[18]	2003	Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment	Saudi Arabia	low
Long[19]	2003	Relative versus absolute non-contagiousness of respiratory tuberculosis on treatment	Canada	low
Abal[20]	2005	Effect of cigarette smoking on sputum smear conversion in adults with active pulmonary tuberculosis	Kuwait	low
Dlugovitzky[21]	2006	Immunological consequences of three doses of heat-killed *Mycobacterium vaccae* in the immunotherapy of tuberculosis	Argentina	low
Babb[22]	2007	Vitamin D receptor gene polymorphisms and sputum conversion time in pulmonary tuberculosis patients	South Africa	high
Pheiffer[23]	2008	Time to detection of *Mycobacterium tuberculosis* in BACTEC systems as a viable alternative to colony counting	South Africa	high
Dawson[24]	2009	Immunomodulation with recombinant interferon-gamma1b in pulmonary tuberculosis	South Africa	high
Conde[25]	2009	Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial	Brazil	high
Dorman[26]	2009	Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis	North America, Brazil, South Africa, Spain, Uganda	mixed
Siddiqui[27]	2010	Smoking prolongs the infectivity of patients with tuberculosis	Ireland	low
Wang[28]	2010	Adding moxifloxacin is associated with a shorter time to culture conversion in pulmonary tuberculosis	Taiwan	low
Sajid[29]	2011	Addition of amikacin and levofloxacin is associated with higher culture conversion rate in pulmonary tuberculosis	Pakistan	high
Lienhardt[30]	2011	Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial.	Algeria, Colombia, Guinea, Vietnam, Nepal, Peru, Mozambique, Tanzania, Bolivia	mixed
Rathored[31]	2012	Risk and outcome of multidrug-resistant tuberculosis: vitamin D receptor polymorphisms and serum 25(OH)D	India	high
Dorman[32]	2012	Substitution of rifapentine for rifampin during intensive phase treatment of pulmonary tuberculosis: study 29 of the tuberculosis trials consortium	North America, Brazil, South Africa, Spain, Uganda, Peru, Vietnam	mixed
Ugarte-Gil[33]	2013	Induced sputum MMP-1,-3 &-8 concentrations during treatment of tuberculosis	Peru	high
Click[34]	2013	Association between *Mycobacterium tuberculosis* lineage and time to sputum culture conversion	USA	low

First author	Year	Title	Country	Low/ high
Lee[35]	2014	Culture conversion rate at 2 months of treatment according to diagnostic methods among patients with culture-positive pulmonary tuberculosis	South Korea	low
Stoffel[36]	2014	Treatment of pulmonary tuberculosis in a low-prevalence urban area. Compliance and sputum conversion	Argentina	low
Jindani[37]	2014	High-dose rifapentine with moxifloxacin for pulmonary tuberculosis	South Africa; Zimbabwe; Botswana; Zambia	high
Dorman[38]	2015	Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial	Uganda, Vietnam, South Africa, Kenya, China, USA, Peru, Brazil, Spain	mixed
Dawson[39]	2015	Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis	South Africa, Tanzania	high
Dawson[40]	2015	Two-stage activity-safety study of daily rifapentine during intensive phase treatment of pulmonary tuberculosis	South Africa, Tanzania	high
Kanda[41]	2015	Factors affecting time to sputum culture conversion in adults with pulmonary tuberculosis: a historical cohort study without censored cases	Japan	low
Ruan[42]	2016	Moxifloxacin and gatifloxacin for initial therapy of tuberculosis: a meta-analysis of randomized clinical trials	9 African countries, 4 Asian countries, USA, Mexico, Brazil, Spain	mixed
Conde[43]	2016	A phase 2 randomized trial of a rifapentine plus moxifloxacin-based regimen for treatment of pulmonary tuberculosis	Brazil	high
Jindani[44]	2016	A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis	Nepal, Bolivia, Uganda	low
Mechai[45]	2016	Active pulmonary tuberculosis: role for amikacin in early treatment	France	low
Scott[46]	2017	Comparison of sputum-culture conversion for *Mycobacterium bovis* and *M. tuberculosis*	USA	low
Leung[47]	2017	Effects of diabetes mellitus on the clinical presentation and treatment response in tuberculosis	China	high
Ko[48]	2017	Duration of pulmonary tuberculosis infectiousness under adequate therapy, as assessed using induced sputum samples	South Korea	low

4.2. Quality assessment

A summary table of the quality scores for studies included in this analysis is in Annex table 9.3. The quality tool for case series was not appropriate for the meta-analysis paper (Ruan 2016) so 46 studies are included.

Thirty-six (78%) studies were ranked as “good” quality by this scoring system (>7 out of 9), nine studies were ranked as “fair” (4–6 out of 9), and one as poor quality.

4.3. Data analysis

For data on the proportion of patients achieving microbiological conversion there were a total of 201 estimates; nine, 14, and five at weeks 1, 2, and 3, respectively; and 30, 87, 15, 23, six, and 12 at months 1, 2, 3, 4, 5, and 6, respectively (Table 4.2).

Table 4.2. Number of estimates contributing to analysis by time point and microbiological test

Visit	Smear	Solid culture	Culture, unspecified	Liquid culture	Total
Week 1	1	7	1	0	9
Week 2	1	6	2	5	14
Week 3	1	2	2	0	5
Month 1	3	11	6	10	30
Month 2	15	18	34	20	87
Month 3	4	3	5	3	15
Month 4	1	5	14	3	23
Month 5	0	3	0	3	6
Month 6	4	4	0	4	12
Total	**30**	**59**	**64**	**48**	**201**

If an estimate was 0% or 100% it was excluded from the summary (and displayed in the corresponding Forest plot as “Excluded”). Exact 95% confidence intervals were used. Where relevant, data in Forest plots data are stratified by type of test: solid culture, liquid culture, culture method unknown, and smear. Where data on subgroups could be extracted these are reported.

4.4. Conversion data

4.4.1. Time to smear conversion

Summary statistics for time to smear conversion were reported in six studies (median or mean with associated measures of spread - interquartile range, standard error, standard deviation or range), shown in Table 4.3.

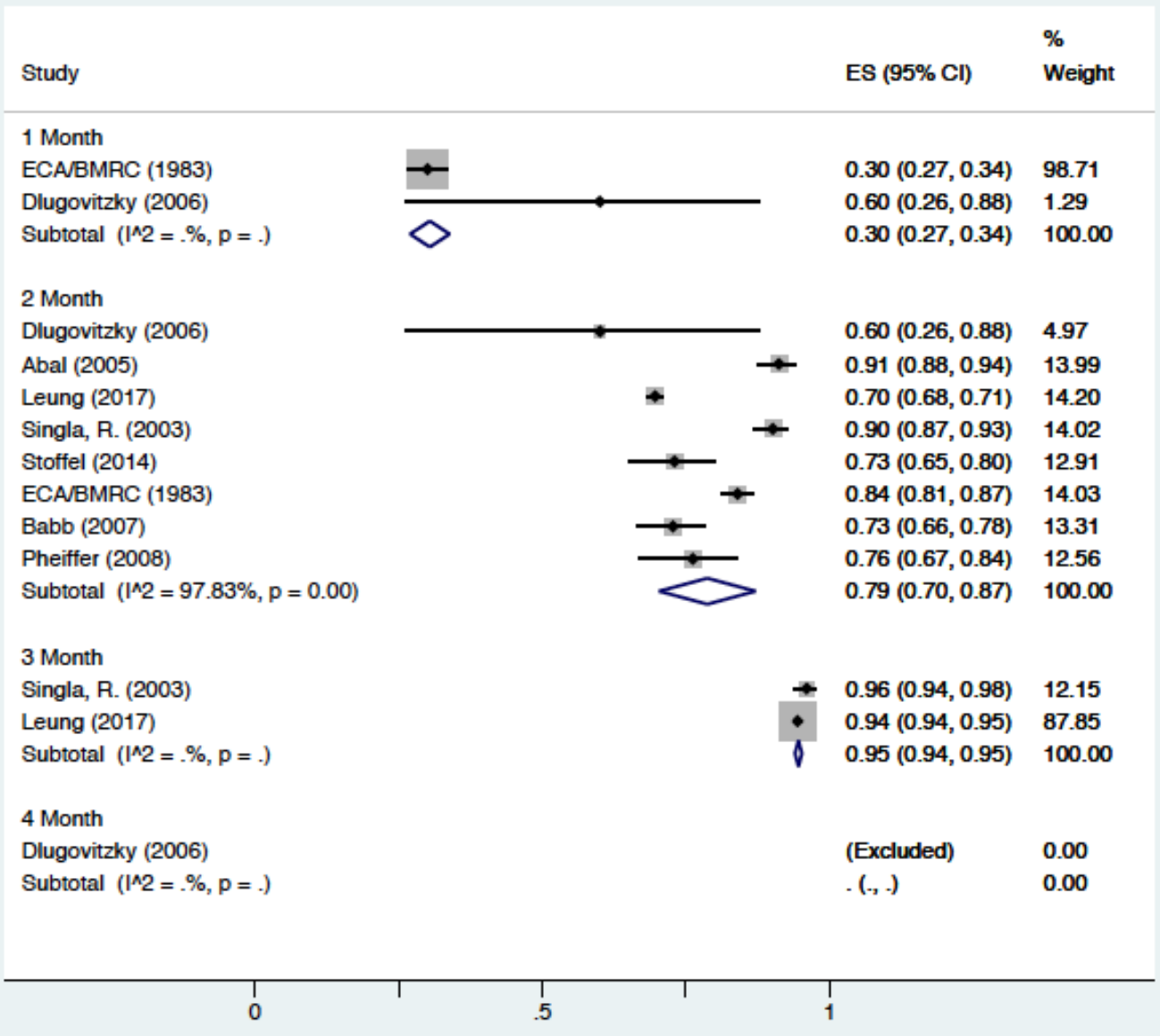
Table 4.3. Studies reporting a summary measure of time* to smear conversion

First author	Year	Country	N	Median (days)	IQR	Mean (days)	SD/range	High/low burden
Kennedy	1996	Tanzania	30 (HIV− 51 (HIV+)	-	-	61 49	30–120 30–90	High High
Dominguez-Castellano	2003	Spain	95	20	-	-	2 (SE)	Low
Telzak	1997	USA	77	-	-	33	± 6.2 (SE)	Low
Long	2003	Canada	32	-	-	46	± 27.9	Low
Rathored	2012	India	50	-	-	29	± 0.7	High
Mechai	2016	France	30	27	14–56	-	-	Low

*Where authors reported data in months these have been converted here to days to aid comparisons (using 30.4 days per month). Where both medians and means have been presented, medians have been selected for reporting here.
HIV−: HIV-negative; HIV+: HIV-positive; IQR: interquartile range; SD: standard deviation; SE: standard error; USA: United States of America

The proportion of treated patients with drug-susceptible TB achieving positive-to-negative smear conversion at months 1, 2, and 3 (12 estimates in total) are shown in Figure 4.2

Figure 4.2. Proportion of baseline smear-positive patients receiving effective treatment for drug-susceptible TB achieving smear conversion at 1, 2, and 3 months.



BMRC: British Medical Research Council; ECA: East and Central African; CI: confidence interval; ES: summary estimate; TB: tuberculosis

4.4.2. Time to culture conversion

Summary statistics for time to solid culture conversion were reported in five studies (median or mean with associated measures of spread - interquartile range, standard error, standard deviation or range), shown in Table 4.4.

Table 4.4. Studies reporting a summary measure of time* to solid culture conversion

First author	Year	Country	N	Median (days)	IQR	Mean (days)	SD/range	High/low burden
Dawson	2015	South Africa, Tanzania	59	35	-	60	± 32.2	High
Conde	2009	Brazil	72	49	41–56	33	± 6.2 (SE)	High
Dawson	2015	South Africa	36	43	29–52	46	± 27.9	High
Kanda	2015	Japan	86	39	25–55	-	-	Low
Rathored	2012	India	50	-	-	24	± 0.7	High

*Where authors reported data in months these have been converted here to days to aid comparisons (using 30.4 days per month). Where both medians and means have been presented, medians have been selected for reporting here.
IQR: interquartile range; SD: standard deviation

Summary statistics for time to culture conversion, in which culture method was not specified, were reported in five studies (median or mean with associated measures of spread - interquartile range, standard error, standard deviation or range), shown in Table 4.5.

Table 4.5. Studies reporting a summary measure of time* to culture conversion of unspecified culture method

First author	Year	Country	N	Median (days)	IQR	Mean (days)	SD/range	High/low burden
Wang	2010	Taiwan	72	32	-	-	-	Low
Kennedy	1996	Tanzania	30 (HIV−) 51 (HIV+)	-	-	52 55	30–90 30–120	High High
Click	2013	USA	10619	47	28–68	-	-	Low
Telzak	1997	USA	65	-	-	32	± 14 (SE)	Low
Mechai	2016	France	18	48	26–58	-	-	Low

*Where authors reported data in months these have been converted here to days to aid comparisons (using 30.4 days per month). Where both medians and means have been presented, medians have been selected for reporting here.
HIV−: HIV-negative; HIV+: HIV-positive; IQR: interquartile range; SD: standard deviation; USA: United States of America

Summary statistics for time to liquid culture conversion were reported in five studies (median or mean with associated measures of spread - interquartile range, standard error, standard deviation or range), shown in Table 4.6.

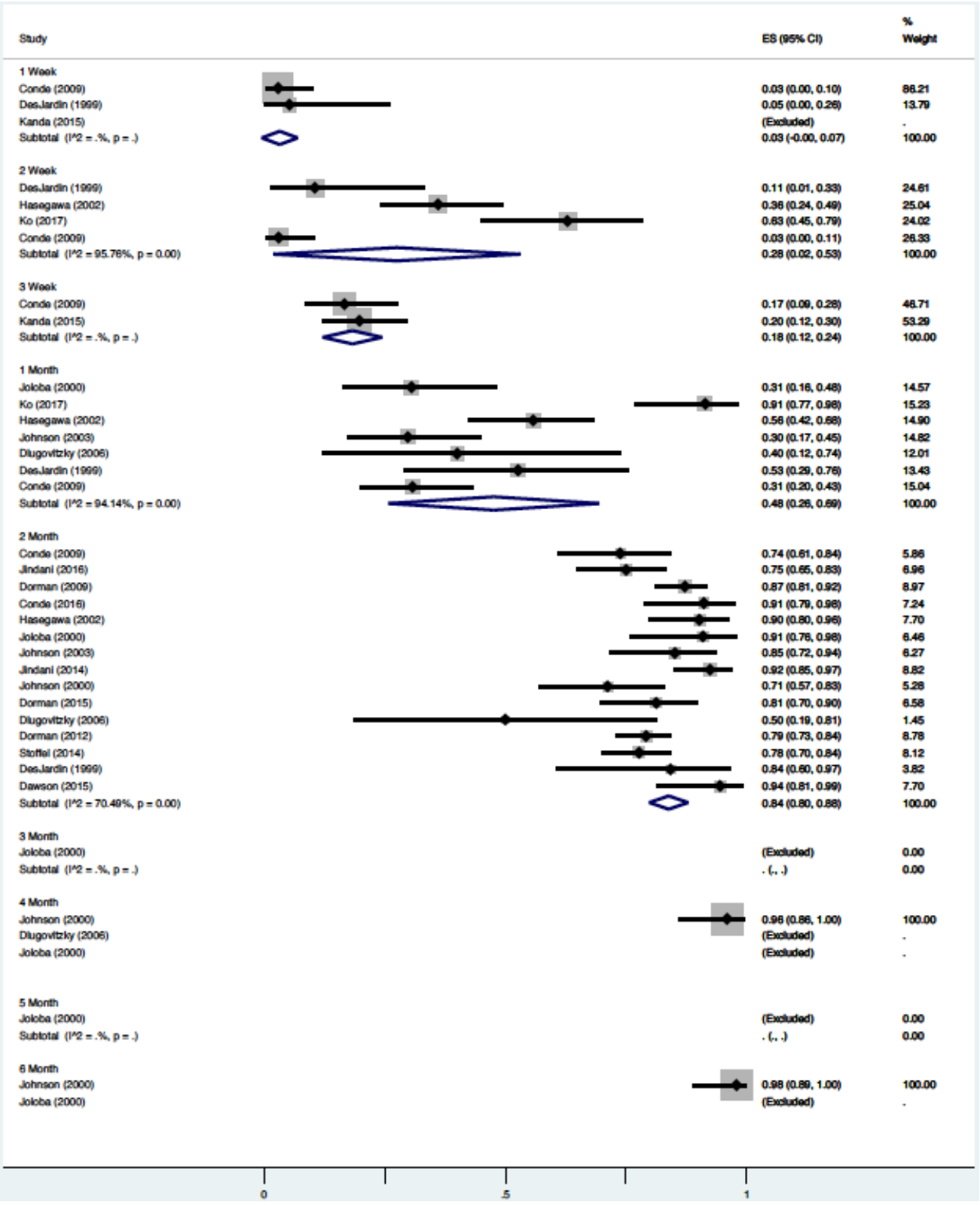
Table 4.6. Studies reporting a summary measure of time* to liquid culture conversion

First author	Year	Country	N	Median (days)	IQR	Mean (days)	SD/range	High/low burden
Dawson	2015	South Africa, Tanzania	59	56	-	-	-	High
Diacon	2014	Brazil, India, Latvia, Peru, Philippines, Russia, South Africa, Thailand	66	125	-	-	-	Mixed
Dawson	2015	South Africa	38	59	36–63	-	-	High
Ko	2017	South Korea	35	28	21–35 (range)	-	-	Low
Lee	2014	South Korea	61	40	28–61	-	-	Low

*Where authors reported data in months these have been converted here to days to aid comparisons (using 30.4 days per month). Where both medians and means have been presented, medians have been selected for reporting here.
IQR: interquartile range; SD: standard deviation

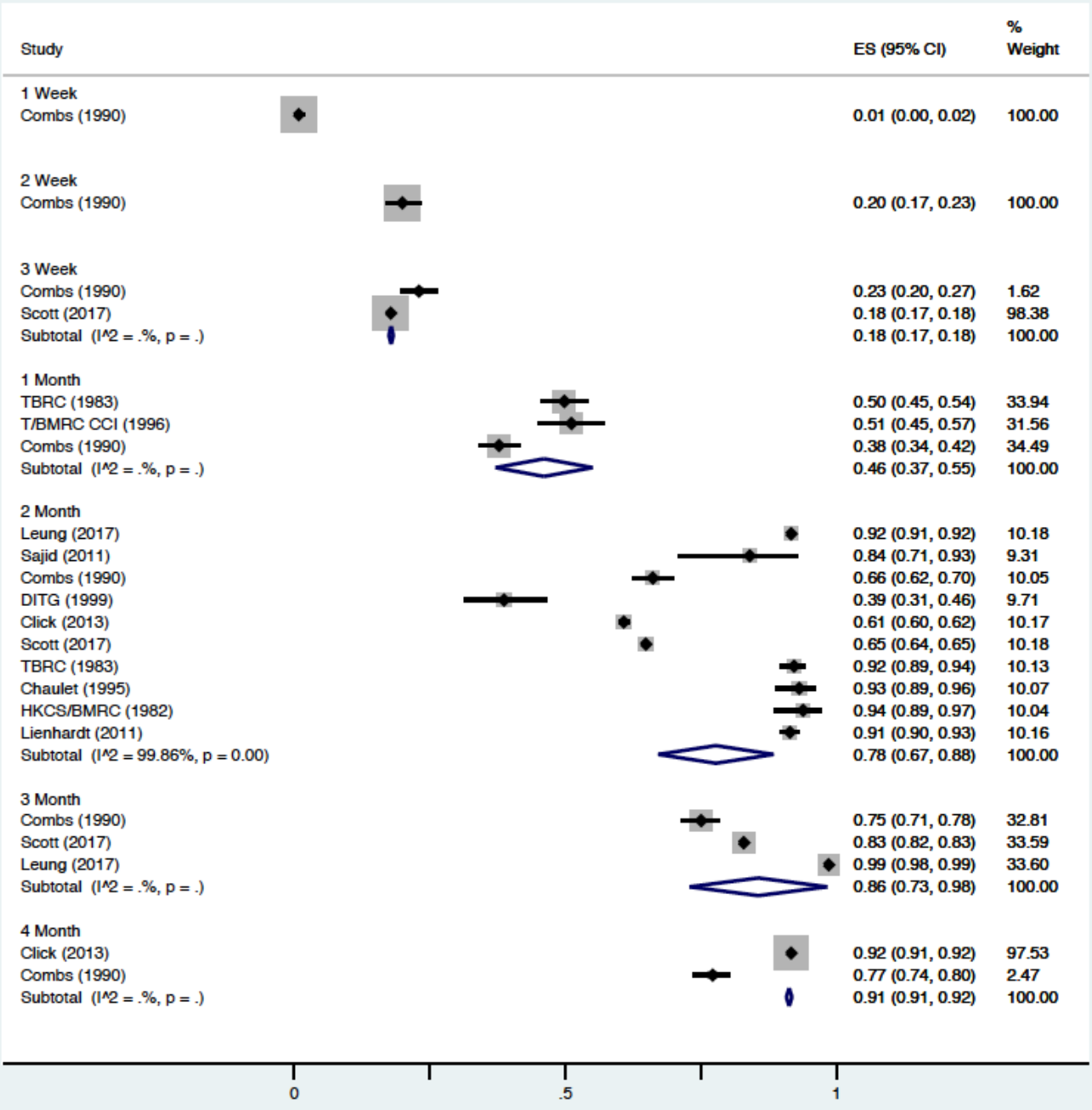
The proportion of treated patients with drug-susceptible TB achieving positive-to-negative culture conversion at weeks 1, 2, 3 and months 1, 2, 3, 4, and 6 (75 estimates in total) are shown in Figures 4.3–4.5 for solid, unspecified method, and liquid culture respectively.

Figure 4.3. Proportion of baseline culture-positive patients receiving effective treatment for drug-susceptible TB achieving solid-culture conversion at 1, 2 and 3 weeks, and at 1, 2, 4 and 6 months



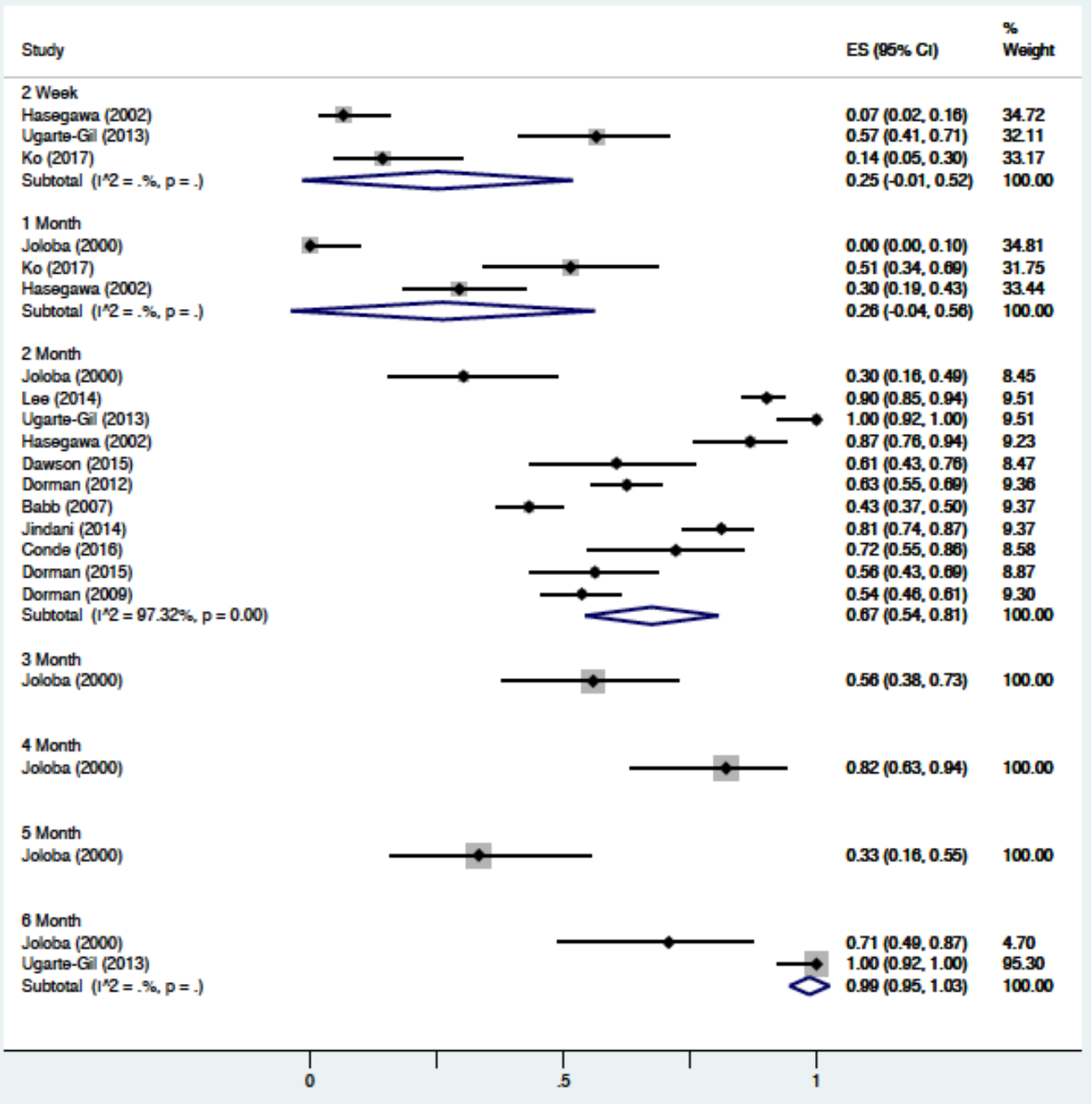
CI: confidence interval; ES: summary estimate; TB: tuberculosis

Figure 4.4. Proportion of baseline culture-positive patients receiving effective treatment for drug-susceptible TB achieving culture conversion (culture method unspecified) at 1, 2, and 3 weeks, and at 1, 2, 3, and 4 months



BMRC: British Medical Research Council; DITG: Durban Immunotherapy Trial Group; CI: confidence interval; ES: summary estimate; HKCS: Hong Kong Chest Services; T: Tanzania; TB: tuberculosis; TBRC: TB Research Centre

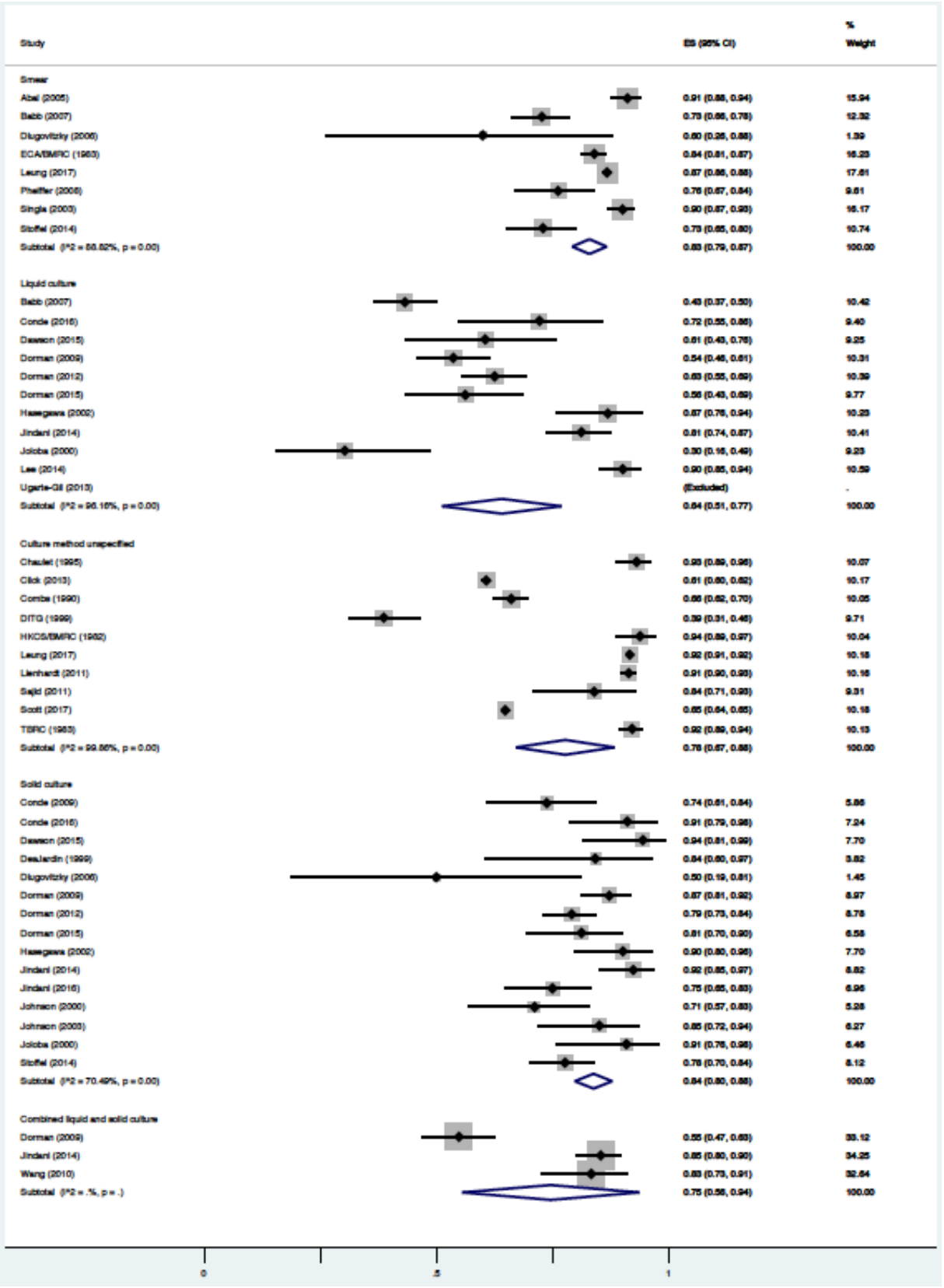
Figure 4.5. Proportion of baseline culture-positive patients receiving effective treatment for drug-susceptible TB achieving liquid culture conversion at 2 weeks, and at 1, 2, 3, 4, 5, and 6 months



CI: confidence interval; ES: summary estimate; TB: tuberculosis

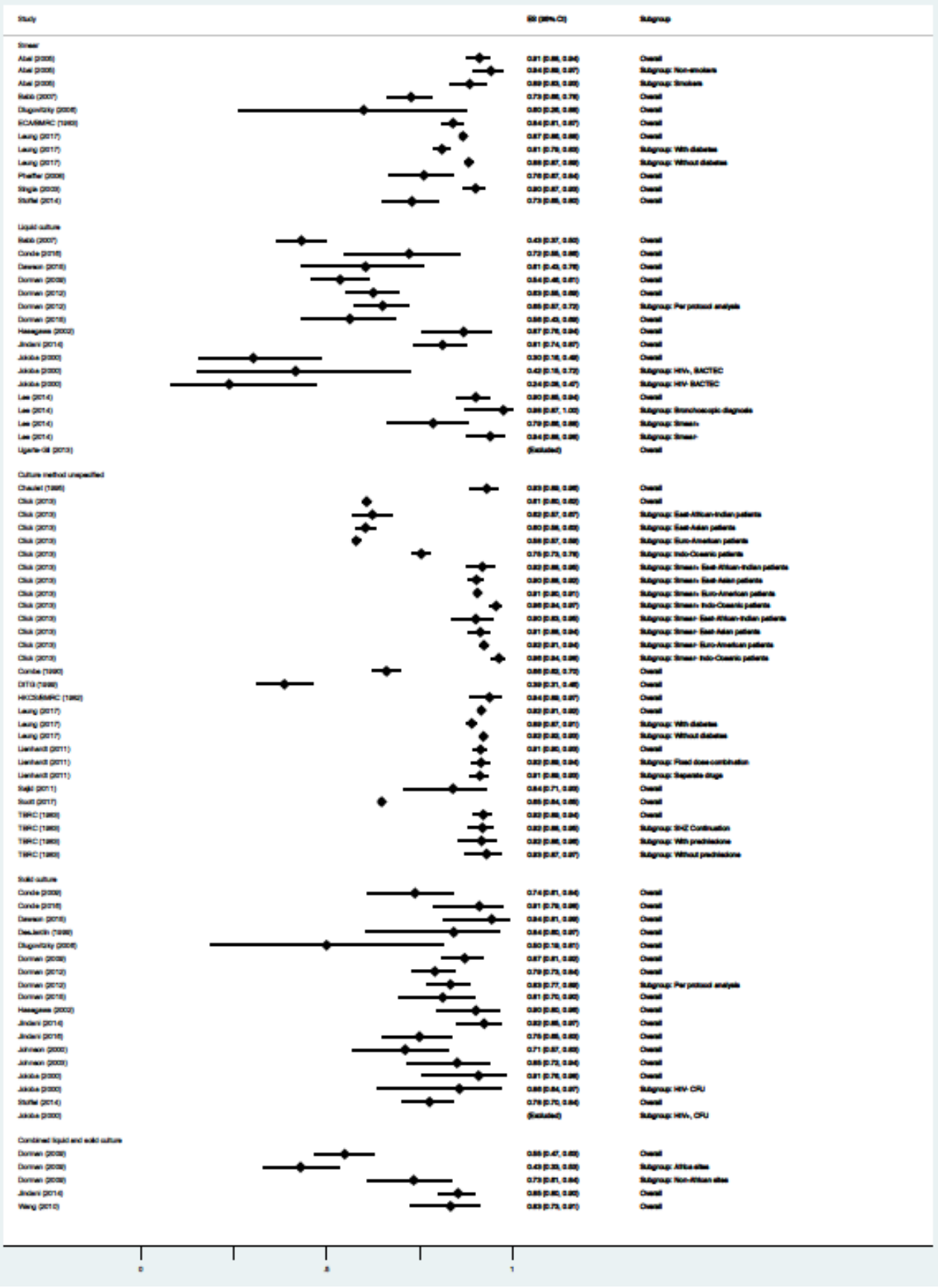
The two-month time point, at which treatment steps down from intensive to maintenance phase, is that for which the most data is available. Figures 4.6 and 4.7 collate data (already included in Figures 4.3–4.5 above) to illustrate the proportion of patients achieving conversion of smear, solid culture, and liquid culture at two months (unless otherwise indicated the data for solid and liquid culture conversion include patients who were either smear-negative or smear-positive at baseline). Figure 4.6 includes only overall data for clarity; Figure 4.7 includes subgroup data for completeness.

Figure 4.6. Proportion of patients receiving effective treatment for drug-susceptible TB achieving smear, solid culture and liquid culture conversion at 2 months (overall data)



BMRC: British Medical Research Council; ECA: East and Central African; DITG: Durban Immunotherapy Trial Group; CI: confidence interval; ES: summary estimate; HKCS: Hong Kong Chest Services; T: Tanzania; TB: tuberculosis; TBRC: TB Research Centre.

Figure 4.7. Proportion of patients receiving effective treatment for drug-susceptible TB achieving smear, solid culture and liquid culture conversion at 2 months, with inclusion of sub-group data



CI: confidence interval; ES: summary estimate; TB: tuberculosis

4.5. Summary of smear and culture conversion data

For the six studies reporting a summary estimate of time to smear conversion the median time to conversion ranged from 20–27 days and the mean time to conversion ranged from 29–61 days. The summary estimates across eight studies of the proportion of baseline smear-positive patients achieving smear conversion at the 1-, 2-, and 3-month time points were 0.3 (95% CI 0.27–0.34), 0.79 (95% CI 0.70–0.87) and 0.95 (95% CI 0.94–0.95) respectively.

For the five studies reporting a summary estimate of time to solid culture conversion the median time to conversion ranged from 35–49 days and the mean time to conversion ranged from 24–60 days. For the five studies reporting a summary estimate of time to culture conversion where culture method was not specified the median time to conversion ranged from 32–48 days and the mean time to conversion ranged from 32–55 days. For the five studies reporting a summary estimate of time to liquid culture conversion the median time to conversion ranged from 28–125 days. The proportion of patients treated for drug susceptible TB achieving culture conversion at each time point is summarised in Table 4.7. The number of studies contributing to each estimate can be seen on the corresponding Figures 4.3, 4.4, and 4.5 above

Table 4.7. Summary of proportion of patients achieving culture conversion at each time point, by culture detection method

Duration of treatment	Solid culture		Culture method not specified		Liquid culture	
	Proportion	95% CI	Proportion	95% CI	Proportion	95% CI
1 week	0.03	-0.00–0.07	0.01	0.00–0.02	-	-
2 weeks	0.28	0.02–0.53	0.2	0.17–0.23	0.25	0.26–0.69
3 weeks	0.18	0.12–0.24	0.18	0.17–0.18	-	-
1 month	0.48	0.26–0.69	0.46	0.37–0.55	0.26	-0.04–0.56
2 months	0.84	0.80–0.88	0.78	0.67–0.88	0.67	0.54–0.81
3 months	-	-	0.86	0.73–0.98	0.56	0.38–0.73
4 months	0.98	0.86–1.00	0.91	0.91–0.92	0.82	0.63–0.94
5 months	-	-	-	-	0.33	0.16–0.55
6 months	0.98	0.89–1.00	-	-	0.71	0.49–0.87

CI: confidence interval

5. Methods – systematic review of effect of TB treatment upon infectiousness of TB patients to experimental animals

This section describes the additional review undertaken at the explicit request of the Guideline Development Group to report data from animal studies that might shed light upon the dynamics of infectiousness of TB patients after having started on effective TB treatment. More specifically the guidance was to report upon studies evaluating the effect of anti-tuberculosis therapy upon infectiousness to susceptible animals of air exhausted from isolation facilities containing TB patients.

5.1. Population and outcomes

Population: patients receiving effective treatment for drug-susceptible or drug-resistant TB.

Outcomes: infectiousness to exposed experimental animals, defined as tuberculin skin test conversion or development of active TB disease in exposed animals

5.2. Search strategy

The following search strategy was run in PubMed on 27/03/2018:

(infectiousness [All Fields] OR ("transmission"[Subheading] OR "transmission"[All Fields])) AND (("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND "animals"[MeSH Terms: noexp]

5.3. Manuscript selection and data extraction

The titles of papers identified by the search were screened for relevance and the full texts of potentially relevant papers were reviewed. The diverse nature of study methodologies was not expected to lend itself to a standardized data extraction tool, so all relevant data were extracted from included papers for presentation in a narrative format.

6. Results – systematic review of effect of TB treatment upon infectiousness of TB patients to experimental animals

6.1. Articles identified

After sifting of 646 hits by title three[49–51] primary research papers were identified. A fourth[52] was identified after reference and citation searching as indicated in table 6.1. The two Escombe papers report different aspects of data from the same series of experiments so will be described together.

Table 6.1. Articles included in systematic review of effect of TB treatment upon infectiousness of TB patients to experimental animals

First author	Journal, year	Title	Untreated patients (n)	Treated patients (n)	Treatment duration	References (additional papers)	Citations (additional papers)
Riley	Am Rev Respir Dis, 1962	Infectiousness of air from a tuberculosis ward—ultraviolet irradiation of infected air: comparative infectiousness of different patients	67	40	Not clear	12 (0)	69 (0)
Escombe	Clin Infect Dis, 2007	The detection of airborne transmission of tuberculosis from HIV-infected Patients, using an in vivo air sampling model	17% of patient-days	83% of patient-days	Not clear	42 (1) (Riley 1962)	26 (0)
Escombe	PLoS Med, 2008	The infectiousness of tuberculosis patients coinfected with HIV			Not clear	43 (0)	49 (0)
Dharmadhikari	IJTLD, 2014	Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis	11 unrecognised XDR	mixed	Not clear	32 (0)	20 (0)

TB: tuberculosis; XDR: extensively drug-resistant

6.2. Data analysis

The four papers describe experimental data from studies in which groups of guinea pigs, used as air samplers, were exposed to air exhausted from dedicated isolation rooms in which human patients with TB were treated. The focus of this report, the effect upon infectiousness of anti-TB treatment, was not the primary objective for any of the original studies, though it was the purpose of the retrospective lookback at data from previous experiments in the Dharmadhikari paper. As such the available data are opportunistically available and incomplete, for some indices to a magnitude that it is not possible to determine, and thus not suitable to be combined. The extractable data pertaining to the effect of treatment for each individual dataset will thus be described separately in the narrative report below.

6.2.1. Riley, Am Rev Respir Dis (1962)

From 1959–1961 monthly tuberculin skin testing was performed on 120 guinea pigs (approximately 2,880 TSTs) that were breathing air exhausted from a purpose-designed six-bedded isolation unit. Of all those admitted through the unit during this period, 107 patients, representing 61% of total bed-days, were identified as having culture-positive pulmonary TB. Some patients were not treated, though it is not clear whether this was for the entire period of their admission.

It is stated that "*Treated patients were admitted to the ward at the time treatment was initiated*".

In total 63 guinea pigs were defined as having been infected (tuberculin skin test conversion), from 51 of which a positive *M. tuberculosis* culture was obtained. 50 of these isolates were matched to an index patient on the basis of drug susceptibility profile and temporal relationship; 15 of these matched to a single patient with laryngeal TB. The number of guinea-pigs infected by patients with drug-susceptible TB is shown in Table 6.2.

Table 6.2. Number of guinea pigs infected by patients with drug-susceptible TB.

	category	Number of patients	Percentage of total patient-days	Number of infected guinea pigs
untreated	non-infectors	53	6	0
	infectors	8	1	29
treated	non-infectors	28	14.7	0
	infectors	1	0.3	1

TB: tuberculosis

As the authors state ""*Evaluation of the effects of drug therapy on the transmission of tuberculosis is beset with a number of difficulties. Only 8 of 61 patients in the "untreated, susceptible organism" category infected any guinea pigs at all…and the patient with tuberculous laryngitis infected half of the total by himself (15 of 29)*".

The presented data suggest that patients on treatment are less able to infect guinea pigs than patients not receiving treatment. However this study provides no data to inform the question of the timing of when this reduction in/interruption of infectiousness occurs.

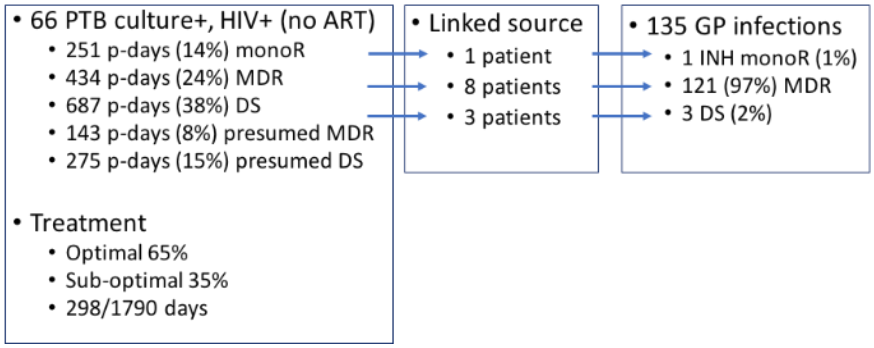
6.2.2. Escombe, Clin Infect Dis (2007), PLoS Med (2008)

The experiments reported in these two papers describe the findings in a guinea pig population exposed to 66 HIV-infected patients (not receiving antiretroviral therapy) with culture-positive pulmonary TB. Twelve (or possibly 11) of the 66 patients transmitted *M. tuberculosis* to the guinea pigs, with 108 of the 135 guinea pig infections attributed to a single individual patient with AFB 3+ smear-positive multidrug-resistant TB who spent 11 of 32 ward-days awaiting initiation of second line TB treatment. Though 38% of the inpatient bed-

days were accounted for by patients with drug-susceptible disease, only 2% of guinea pig infections were drug-susceptible.

Treatment is described as “sub-optimal” for 298/1790 (35%) patient bed-days (and “optimal” for 65%), though these categories are not clearly defined. Figure 6.1 summarizes the entirety of the data presented; it is not possible to disentangle which patients infected which guinea pigs and when. Most patients linked to a transmission event had periods both on and off treatment so it is not posssible to attribute transmission to an on-treatment or off-treatment moment. There are no data to inform the question of the speed of the effect of treatment upon infectiousness from time of initiation.

Figure 6.1. Summary of data from Escombe 2007 and 2008.



ART: antiretroviral therapy; DS: drug-susceptible; GP: guinea pig; HIV+: HIV-positive; INH: isoniazid; MDR: multidrug-resistant; monoR: mono-resistance; PTB: pulmonary tuberculosis

6.2.3. Dharmadhikari, Int J Tuberc Lung Dis (2014)

In this paper the data from five earlier experiments are scrutinised with the specific purpose of exploring the effectiveness of TB treatment upon infectiousness. Studies 1–4 were all intervention studies in which separated groups of guinea pigs were exposed either to air exhausted from isolation rooms where an intervention was being applied (either to the patient or the room or the air) or to control air which was exhausted from non-intervention rooms; only the control arm data are included in the analysis in this paper. The data reported is presented in Table 6.3 below which combines data from the text and several tables.

Table 6.3. Summary of data presented in Dharmadhikari 2014

study ID	patients (n)	DST available	% XDR	median duration treatment pre-entry (days)	duration of GP exposure (months)	% GPs infected
pilot	26	11	27.3	24.5	4	74
1	24	10	50.0	0	3	10
2	15	11	18.2	0	2	54
3	27	21	0.0	0	3	1
4	17	10	20.0	0	3	77

DST: drug sensitivity testing; GP: guinea pig; XDR: extensively drug-resistant

The authors indicate that study groups with a higher proportion of patients subsequently identified as having had XDR-TB (which was unrecognised and thus inadequately treated at the time) were associated with a higher percentage of TB infections amongst the guinea pigs. However TB culture from guinea pigs was only performed in the pilot study and drug susceptibility testing was only available for 13 of 216 guinea pig infections (5% of total, 18% of pilot study), all of which were XDR.

Attribution of guinea pig infection to periods on or off effective treatment is not possible from the available data. The speed of the effect of treatment cannot be elucidated.

6.3. Summary of data on the effect of TB treatment upon infectiousness of TB patients to experimental animals

Four relevant papers were identified. A small proportion of culture-positive TB patients are capable of transmitting *M. tuberculosis* infection to guinea pigs. All four papers contain data suggesting that patients on TB treatment are less infectious to guinea pigs than patients not receiving effective TB treatment. However, there are no data indicating the time it takes for a patient receiving effective treatment to become non-infectious to guinea pigs.

7. Discussion

In the main analysis of this review, examination of smear and culture conversion times during TB treatment, data have been presented on the proportion of subjects achieving conversion at specific time points, as well as on the median time to conversion for the population studied.

There was significant variability in the time taken for patients with proven drug-susceptible pulmonary TB receiving appropriate first-line TB treatment to achieve smear and culture conversion. Though the meaningfulness of summary estimates is questionable and the generalisability is clearly poor, it may be useful to note that at the two month time point, at step down from intensive to continuation phase treatment, overall around 21% of patients remain smear-positive and around 35% of patients remain sputum culture-positive by liquid culture.

Point estimates of median times to conversion, whether of sputum AFB smear, liquid culture, or solid culture, are heavily influenced by the frequency of sampling, a parameter often not clearly reported in published studies. Similarly, for the estimates of the proportion of conversions at specific time points, the denominator presented is generally the number of patients tested rather than the number initiating treatment; in such studies, the same denominator is not used throughout due to incomplete sampling at each time point.

For culture conversion, the profile of the population under study is important. Thus, when compared to study populations characterised by many individuals with advanced disease, for populations with a relatively smaller number of patients with heavily smear-positive disease at baseline, the median time to culture conversion will be shorter, and the proportion achieving culture conversion, particularly at earlier time points, will be greater.

For the reporting of data for this review some technical comments warrant mention. For most studies data have been extracted for a subgroup of the study population – those with proven drug-susceptible disease who received standard therapy with at least daily RHZ in the intensive phase and only daily RH in the continuation phase. The demographics of the entire study population are usually presented but very rarely are the demographics of the subgroup of interest for whom data has been extracted presented separately.

Assumptions have been made about adherence to therapy; some studies report mechanisms for adherence support but no studies report absolute number or proportion of doses taken. The estimates should thus be considered as analogous to an intention-to-treat rather than an on-treatment analysis.

A potential alternative source of information on the speed at which TB treatment renders treated patients non-infectious is studies using experimental animals as air samplers. In these studies, the air extracted from isolation rooms housing TB patients is exhausted over susceptible animals, exposing them to infectious droplet nuclei. Modification of patient conditions, including use of effective treatment, can be exploited to determine the effect of interventions upon infectiousness.

Some of the included studies are often cited as evidence to support early hospital discharge of patients on TB treatment; the premise is that new infections of previously uninfected household contacts are very rare, implying that patients on TB treatment are quickly rendered non-infectious. Another plausible explanation may be that contacts who are tuberculin-negative at the time of index case diagnosis may have escaped infection due to less intense exposure, or they may be individuals in whom acquisition of infection is not reflected by cutaneous delayed hypersensitivity responses.

Review of data from experiments in which experimental animals (all guinea pig studies) were used as indicators of infectiousness of air exhausted from TB patient isolation rooms confirmed that patients receiving effective TB treatment were less infectious than those not receiving such treatment. However, the temporal dynamics of the change in infectiousness could not be elucidated from any of the studies, individually or when combined.

8. References

1 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;6(7):e1000097.

2 Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis*. 1979;119(4):579–85.

3 Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. *Lancet*. 1981;1(8213):171–4.

4 Controlled clinical trial of 4 short-couse regimens of chemotherapy (three 6-month and one 8-month) for pulmonary tuberculosis. *Tubercle*. 1983;64(3):153–66.

5 Study of chemotherapy regimens of 5 and 7 months' duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India. *Tubercle*. 1983;64(2):73–91.

6 Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability. The report of final results. *Ann Intern Med*. 1990;112(6):397–406.

7 Chaulet P, Boulahbal F. [Clinical trial of a combination of three drugs in fixed proportions in the treatment of tuberculosis. Groupe de Travail sur la Chimiotherapie de la Tuberculose]. *Tuber Lung Dis*. 1995;76(5):407–12.

8 Kennedy N, Berger L, Curram J, et al. Randomized controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. *Clin Infect Dis*. 1996;22(5):827–33.

9 Anonymous. A controlled trial of a 4-weekly supplement of rifampicin, pyrazinamide and streptomycin in the continuation phase of a 7-month daily chemotherapy regimen for pulmonary tuberculosis. Tanzania/British Medical Research Council Collaborative Investigation. *South African Med Journal Suid-Afrikaanse Tydskr Vir Geneeskd*. 1996;86(8):960–5.

10 Telzak EE, Fazal BA, Pollard CL, Turett GS, Justman JE, Blum S. Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis. *Clin Infect Dis*. 1997;25(3):666–70.

11 Desjardin LE, Perkins MD, Wolski K, et al. Measurement of sputum Mycobacterium tuberculosis messenger RNA as a surrogate for response to chemotherapy. *Am J Respir Crit Care Med*. 1999;160(1):203–10.

12 Anonymous. Immunotherapy with Mycobacterium vaccae in patients with newly diagnosed pulmonary tuberculosis: a randomised controlled trial. Durban Immunotherapy Trial Group. *Lancet*. 1999;354(9173):116–9.

13 Johnson JL, Kamya RM, Okwera A, et al. Randomized controlled trial of Mycobacterium vaccae immunotherapy in non-human immunodeficiency virus-infected Ugandan adults with newly diagnosed pulmonary tuberculosis. *J Infect Dis*. 2000;181(4):1304–12.

14 Joloba ML, Johnson JL, Namale A, et al. Quantitative sputum bacillary load during rifampin-containing short course chemotherapy in human immunodeficiency virus-infected and non-infected adults with pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2000;4(6):528–36.

15 Hasegawa N, Miura T, Ishizaka A, Yamaguchi K, Ishii K. Detection of mycobacteria in patients with pulmonary tuberculosis undergoing chemotherapy using MGIT and egg-based solid medium culture systems. *Int J Tuberc Lung Dis*. 2002;6(5):447–53.

16 Johnson JL, Ssekasanvu E, Okwera A, et al. Randomized trial of adjunctive interleukin-2 in adults with pulmonary tuberculosis. *Am J Respir Crit Care Med*. 2003;168(2):185–91.

17 Domínguez-Castellano A, Muniain MA, Rodriguez-Baño J, et al. Factors associated with time to sputum smear conversion in active pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2003;7(5):432–8.

18 Singla R, Osman MM, Khan N, Al-Sharif N, Al-Sayegh MO, Shaikh MA. Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment. *Int J Tuberc Lung Dis*. 2003;7(1):58–64.

19 Long R, Bochar K, Chomyc S, et al. Relative versus absolute noncontagiousness of respiratory tuberculosis on treatment. *Infect Control Hosp Epidemiol*. 2003;24(11):831–8.

20 Abal AT, Jayakrishnan B, Parwer S, El Shamy A, Abahussain E, Sharma PN. Effect of cigarette smoking on sputum

smear conversion in adults with active pulmonary tuberculosis. *Respir Med*. 2005;99(4):415–20.

21 Dlugovitzky D, Fiorenza G, Farroni M, Bogue C, Stanford C, Stanford J. Immunological consequences of three doses of heat-killed Mycobacterium vaccae in the immunotherapy of tuberculosis. *Respir Med*. 2006;100(6):1079–87.

22 Babb C, van der Merwe L, Beyers N, et al. Vitamin D receptor gene polymorphisms and sputum conversion time in pulmonary tuberculosis patients. *Tuberculosis (Edinb)*. 2007;87(4):295–302.

23 Pheiffer C, Carroll NM, Beyers N, et al. Time to detection of Mycobacterium tuberculosis in BACTEC systems as a viable alternative to colony counting. *Int J Tuberc Lung Dis*. 2008;12(7):792–8.

24 Dawson R, Condos R, Tse D, et al. Immunomodulation with recombinant interferon-gamma1b in pulmonary tuberculosis. *PLoS ONE [Electronic Resour*. 2009;4(9):e6984.

25 Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet*. 2009;373(9670):1183–9.

26 Dorman SE, Johnson JL, Goldberg S, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. *Am J Respir Crit Care Med*. 2009;180(3):273–80.

27 Siddiqui UA, O'Toole M, Kabir Z, et al. Smoking prolongs the infectivity of patients with tuberculosis. *Ir Med J*. 2010;103(9):278–80.

28 Wang J-Y, Wang J-T, Tsai T-H, et al. Adding moxifloxacin is associated with a shorter time to culture conversion in pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2010;14(1):65–71.

29 Sajid MUD, Imran M, Siddiqique M. Addition of amikacin and levofloxacin is associated with higher culture conversion rate in pulmonary tuberculosis. *Pakistan J Med Heal Sci*. 2011;5(3):450–4.

30 Lienhardt C, Cook S V, Burgos M, et al. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial.[Erratum appears in JAMA. 2011 Sep 28;306(12):1327]. *JAMA*. 2011;305(14):1415–23.

31 Rathored J, Sharma SK, Singh B, et al. Risk and outcome of multidrug-resistant tuberculosis: Vitamin D receptor polymorphisms and serum 25(OH)D. *Int J Tuberc Lung Dis*. 2012;16(11):1522–8.

32 Dorman SE, Goldberg S, Stout JE, et al. Substitution of rifapentine for rifampin during intensive phase treatment of pulmonary tuberculosis: study 29 of the tuberculosis trials consortium. *J Infect Dis*. 2012;206(7):1030–40.

33 Ugarte-Gil CA, Elkington P, Gilman RH, et al. Induced Sputum MMP-1, -3 & -8 Concentrations during Treatment of Tuberculosis. *PLoS One*. 2013;8(4).

34 Click ES, Winston CA, Oeltmann JE, Moonan PK, Mac Kenzie WR. Association between Mycobacterium tuberculosis lineage and time to sputum culture conversion. *Int J Tuberc Lung Dis*. 2013;17(7):878–84.

35 Lee HY, Chae KO, Lee CH, et al. Culture conversion rate at 2 months of treatment according to diagnostic methods among patients with culture-positive pulmonary tuberculosis. *PLoS One*. 2014;9(8):ee103768-ee103768.

36 Stoffel C, Lorenz R, Arce M, Rico M, Fernandez L, Imaz MS. [Treatment of pulmonary tuberculosis in a low-prevalence urban area. Compliance and sputum conversion]. *Medicina (B Aires)*. 2014;74(1):9–18.

37 Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014;371(17):1599–608.

38 Dorman SE, Savic RM, Goldberg S, et al. Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial.[Erratum appears in Am J Respir Crit Care Med. 2015 May 15;191(10):1210; PMID: 25978581]. *Am J Respir Crit Care Med*. 2015;191(3):333–43.

39 Dawson R, Diacon AH, Everitt D, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pul. *Lancet*. 2015;385(9979):1738–47.

40 Dawson R, Narunsky K, Carman D, et al. Two-stage activity-safety study of daily rifapentine during intensive phase treatment of pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2015;19(7):780–6.

41 Kanda R, Nagao T, Tho N V, et al. Factors Affecting Time to Sputum Culture Conversion in Adults with Pulmonary Tuberculosis: A Historical Cohort Study without Censored Cases. *PLoS ONE [Electronic Resour*. 2015;10(11):e0142607.

42 Ruan Q, Liu Q, Sun F, et al. Moxifloxacin and gatifloxacin for initial therapy of tuberculosis: a meta-analysis of randomized clinical trials. *Emerg Microbes Infect*. 2016;5:e12.

43 Conde MB, Mello FC, Duarte RS, et al. A Phase 2 Randomized Trial of a Rifapentine plus Moxifloxacin-Based Regimen for Treatment of Pulmonary Tuberculosis. *PLoS ONE [Electronic Resour*. 2016;11(5):e0154778.

44 Jindani A, Borgulya G, de Patino IW, et al. A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2016;20(6):832–8.

45 Méchaï F, Figoni J, Leblanc C, Gousseff M, Vignier N, Bouchaud O. Active pulmonary tuberculosis: Role for amikacin in early treatment. *Med Mal Infect*. 2016;46(6):318–21.

46 Scott C, Cavanaugh JS, Silk BJ, et al. Comparison of Sputum-Culture Conversion for Mycobacterium bovis and M. tuberculosis. *Emerg Infect Dis*. 2017;23(3):456–62.

47 Leung CC, Yew WW, Mok TYW, et al. Effects of diabetes mellitus on the clinical presentation and treatment response in tuberculosis. *Respirology*. 2017;22(6):1225–32.

48 Ko Y, Shin JH, Lee HK, et al. Duration of Pulmonary Tuberculosis Infectiousness under Adequate Therapy, as Assessed Using Induced Sputum Samples. *Tuberc Respir Dis*. 2017;80(1):27–34.

49 Dharmadhikari AS, Mphahlele M, Venter K, et al. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2014;18(9):1019–25.

50 Escombe AR, Moore DAJ, Gilman RH, et al. The infectiousness of tuberculosis patients coinfected with HIV. *PLoS Med*. 2008;5(9):e188.

51 Escombe AR, Oeser C, Gilman RH, et al. The detection of airborne transmission of tuberculosis from HIV-infected patients, using an in vivo air sampling model. *Clin Infect Dis*. 2007;44(10):1349–57.

52 RILEY RL, MILLS CC, O'GRADY F, SULTAN LU, WITTSTADT F, SHIVPURI DN. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. *Am Rev Respir Dis*. 1962;85:511–25.

9. Annexes

9.1. Additional tables

Annex table 9.1. Details of databases searched and terms used for original search (01 December 2017)

OvidSP Embase Classic+Embase Date: 1947 to 2017 November 30 Search run on 01 December 2017		**OvidSP Global Health** Date: 1910 to 2017 Week 47 Search run on 01 December 2017		**EBSCO CINAHL Plus** Date: full database searched Search run on 01 December 2017.	
1	infectiousness.ti,ab. (1589)	1	infectivity/ (9630)	S1	(TI infectiousness) OR (AB infectiousness) [161]
2	infectivity.ti,ab. (29264)	2	infectiousness.ti,ab. (883)	S2	(TI infectivity) OR (AB infectivity) [506]
3	((transmis* or transmit*) adj2 (dynamic* or risk* or event? or reservoir? or less or more or remain or persist* or sustain* or probabilit*)).ti,ab. (18979)	3	infectivity.ti,ab. (12854)	S3	(TI ((transmis* OR transmit*) N2 (dynamic* OR risk* OR event OR events OR 4reservoir* OR less OR more OR remain OR persist* OR sustain* OR probabilit*))) OR (AB ((transmis* OR transmit*) N2 (dynamic* OR risk* OR event OR events OR reservoir* OR less OR more OR remain OR persist* OR sustain* OR probabilit*))) [4,458]
4	(infection? adj2 (reservoir? or less or more or remain or persist* or sustain*)).ti,ab. (38274)	4	((transmis* or transmit*) adj2 (dynamic* or risk* or event? or reservoir? or less or more or remain or persist* or sustain* or probabilit*)).ti,ab. (8784)	S4	(TI (infection* N2 (reservoir* OR less OR more OR remain OR persist* OR sustain*))) OR (AB (infection* N2 (reservoir* OR less OR more OR remain OR persist* OR sustain*))) [4,651]
5	((viable or live or infectious) adj2 (pathogen? or bacteria or bacterium)).ti,ab. (8420)	5	(infection? adj2 (reservoir? or less or more or remain or persist* or sustain*)).ti,ab. (14299)	S5	(TI ((viable OR live OR infectious) N2 (pathogen* OR bacteria OR bacterium))) OR (AB ((viable OR live OR infectious) N2 (pathogen* OR bacteria OR bacterium))) [575]
6	or/1-5 (94736)	6	((viable or live or infectious) adj2 (pathogen? or bacteria or bacterium)).ti,ab. (2522)	S6	S1 OR S2 OR S3 OR S4 OR S5 [10,087]
7	exp tuberculosis/ (242865)	7	or/1-6 (39977)	S7	(MH "Tuberculosis+") [17,381]
8	exp mycobacterium tuberculosis complex/ (77788)	8	exp mycobacterium tuberculosis/ (73017)	S8	(MH "Mycobacterium Tuberculosis") [2,797]
9	tuberculosis control/ (6263)	9	tuberculosis.ti,ab. (71344)	S9	(TI tuberculosis) OR (AB tuberculosis) [15,336]
10	tuberculosis.ti,ab. (206771)	10	tb.ti,ab. (21195)	S10	(TI tuberculin) OR (AB tuberculin) [1,080]

OvidSP Embase Classic+Embase Date: 1947 to 2017 November 30 Search run on 01 December 2017		**OvidSP Global Health** Date: 1910 to 2017 Week 47 Search run on 01 December 2017		**EBSCO CINAHL Plus** Date: full database searched Search run on 01 December 2017.	
11	tb.ti,ab. (79301)	11	or/8-10 (80137)	S11	(TI tb) OR (AB tb) [6,747]
12	or/7-11 (327882)	12	7 and 11 (1477)	S12	S7 OR S8 OR S9 OR S10 OR S11 [22,540]
13	6 and 12 (3063)	13	(chinese or english or french or japanese or portuguese or russian or spanish).lg. (2988743)	S13	S6 AND S12 [368]
14	(chinese or english or french or japanese or portuguese or russian or spanish).lg. (31240565)	14	12 and 13 (1106)	S14	S13 Limiters – Language: Chinese, English, French, Japanese, Portuguese, Spanish [367]
15	13 and 14 (2913)	15	remove duplicates from 14 (1105)		
16	remove duplicates from 15 (2761)				

Annex table 9.2. Details of databases searched and terms used for secondary search (20 February 2018)

OvidSP Embase Date: 1974 to 2018 February 16 Search run on 20 February 2018		**OvidSP Global Health** Date: 1910 to 2018 Week 06 Search run on 20 February 2018		**EBSCO CINAHL Plus** Date: full database searched Search run on 20 February 2018	
1	lung tuberculosis/ (61525)	1	exp tuberculosis/ (69715)	S1	(MH "Tuberculosis, Pulmonary") [4,148]
2	tuberculosis/ (115121)	2	tuberculosis.ti,ab. (71916)	S2	(MH "Tuberculosis") [12,326]
3	exp drug resistant tuberculosis/ (7333)	3	tb.ti,ab. (21579)	S3	(MH "Tuberculosis, Multidrug-Resistant") [1,703]
4	tuberculosis.ti,ab. (177224)	4	mdr-tb.ti,ab. (2220)	S4	(TI tuberculosis) OR (AB tuberculosis) [15,677]
5	tb.ti,ab. (53718)	5	xdr-tb.ti,ab. (570)	S5	(TI tb) OR (AB tb) [6,927]
6	mdr-tb.ti,ab. (4118)	6	or/1-5 (80272)	S6	(TI "mdr-tb") OR (AB "mdr-tb") [479]
7	xdr-tb.ti,ab. (1257)	7	randomized controlled trials/ (29327)	S7	(TI "xdr-tb") OR (AB "xdr-tb") [127]
8	or/1-7 (243269)	8	randomized.ab. (63103)	S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 [22,456]
9	randomized controlled trial/ (487494)	9	placebo.ab. (31442)	S9	(MH "Randomized Controlled Trials") [66,801]
10	exp "controlled clinical trial (topic)"/ (145459)	10	randomly.ab. (75022)	S10	(AB randomized) [110,522]
11	randomized.ab. (569353)	11	trial.ti. (27552)	S11	(AB placebo) [39,335]
12	placebo.ab. (258930)	12	or/7-11 (155921)	S12	(AB randomly) [60,865]
13	randomly.ab. (369989)	13	ethambutol/ (2321)	S13	(TI trial) [77,531]
14	trial.ti. (242339)	14	isoniazid/ (7542)	S14	S9 OR S10 OR S11 OR S12 OR S13 [236,660]
15	or/9-14 (1324245)	15	pyrazinamide/ (1516)	S15	(MH "Isoniazid") [829]
16	ethambutol/ (27323)	16	rifampicin/ (8560)	S16	(MH "Rifampin") [1,264]
17	isoniazid/ (53149)	17	isoniazid.ti,ab. (8197)	S17	(MH "Ethambutol") [9]
18	pyrazinamide/ (21643)	18	isonicotinic acid hydrazide.ti,ab. (263)	S18	(MH "Pyrazinamide") [215]
19	rifampicin/ (81004)	19	phthivazid.ti,ab. (4)	S19	(TI isoniazid) OR (AB isoniazid) [949]
20	aminosalicylic acid plus isoniazid/ (5)	20	phthivazide.ti,ab. (5)	S20	(TI "isonicotinic acid hydrazide") OR (AB "isonicotinic acid hydrazide") [5]

OvidSP Embase Date: 1974 to 2018 February 16 Search run on 20 February 2018		**OvidSP Global Health** Date: 1910 to 2018 Week 06 Search run on 20 February 2018		**EBSCO CINAHL Plus** Date: full database searched Search run on 20 February 2018	
21	cycloserine plus isoniazid/ (0)	21	tubazide.ti,ab. (4)	S21	(TI phthivazid) OR (AB phthivazid) [0]
22	ethambutol plus isoniazid/ (84)	22	rifampin.ti,ab. (3016)	S22	(TI phthivazide) OR (AB phthivazide) [0]
23	isoniazid plus rifampicin/ (1009)	23	benemycin.ti,ab. (3)	S23	(TI tubazide) OR (AB tubazide) [0]
24	rifampicin plus trimethoprim/ (14)	24	rifadin.ti,ab. (9)	S24	(TI rifampin) OR (AB rifampin) [692]
25	isoniazid plus pyrazinamide plus rifampicin/ (306)	25	rifampicin.ti,ab. (7340)	S25	(TI benemycin) OR (AB benemycin) [0]
26	ethambutol plus isoniazid plus pyrazinamide plus rifampicin/ (479)	26	rimactan.ti,ab. (5)	S26	(TI rifadin) OR (AB rifadin) [1]
27	isoniazid.ti,ab. (17268)	27	rimactane.ti,ab. (7)	S27	(TI rifampicin) OR (AB rifampicin) [849]
28	isonicotinic acid hydrazide.ti,ab. (1720)	28	ethambutol.ti,ab. (2418)	S28	(TI rimactan) OR (AB rimactan) [0]
29	phthivazid.ti,ab. (38)	29	myambutol.ti,ab. (8)	S29	(TI rimactane) OR (AB rimactane) [1]
30	phthivazide.ti,ab. (47)	30	pyrazinamide.ti,ab. (1970)	S30	(TI ethambutol) OR (AB ethambutol) [307]
31	tubazide.ti,ab. (15)	31	or/13-30 (16293)	S31	(TI myambutol) OR (AB myambutol) [2]
32	rifampin.ti,ab. (9266)	32	6 and 12 and 31 (627)	S32	(TI pyrazinamide) OR (AB pyrazinamide) [280]
33	benemycin.ti,ab. (19)	33	limit 32 to yr="1990 -Current" (452)	S33	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 [2,859]
34	rifadin.ti,ab. (77)	34	remove duplicates from 33 (452)	S34	S34 S8 AND S14 AND S33 [147]
35	rifampicin.ti,ab. (18669)				
36	rimactan.ti,ab. (46)				
37	rimactane.ti,ab. (19)				
38	ethambutol.ti,ab. (6693)				
39	myambutol.ti,ab. (62)				
40	pyrazinamide.ti,ab. (4562)				

	OvidSP Embase Date: 1974 to 2018 February 16 Search run on 20 February 2018	**OvidSP Global Health** Date: 1910 to 2018 Week 06 Search run on 20 February 2018	**EBSCO CINAHL Plus** Date: full database searched Search run on 20 February 2018
41	or/16-40 (114515)		
42	8 and 15 and 41 (1845)		
43	limit 42 to yr="1990 -Current" (1510)		
44	remove duplicates from 43 (1463)		

Annex table 9.3. Summary of quality scores for primary research studies included in background question 3 analysis, assessed using an adapted NIH tool for case series (n = 46 studies[1])

First author, year published	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive or randomly allocated in an RCT?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently?	Was the length of follow-up adequate (at least 2 months, 90% retention)?	Were the statistical methods well-described?	Were the results well-described?	Total (/9)
Abal, 2005	1	0	1	0	1	1	1	1	1	**7**
Babb, 2007	1	0	0	0	0	0	0	1	1	**3**
Chaulet, 1995	1	1	1	1	1	1	1	1	1	**9**
Click, 2013	1	0	1	1	0	0	0	1	1	**5**
Combs, 1990	1	1	1	1	1	1	1	1	0	**8**
Conde, 2009	1	1	1	1	1	1	1	1	1	**9**
Conde, 2016	1	1	1	1	1	1	1	1	1	**9**
Dawson, 2009	1	1	1	1	0	1	1	1	1	**8**
Dawson, 2015	1	1	1	1	0	1	1	1	1	**8**
Dawson, 2015b	1	1	1	1	1	1	1	1	0	**8**
DesJardin, 1999	1	1	0	0	0	1	0	1	1	**5**
Dlugovitzky, 2006	0	0	0	0	1	1	1	0	1	**4**
Dominguez-Castellano, 2003	1	1	1	1	0	1	1	1	1	**8**
Dorman, 2009	1	1	0	1	1	1	1	1	1	**8**
Dorman, 2012	1	1	1	1	1	1	0	1	1	**8**
Dorman, 2015	1	1	1	1	1	1	1	1	1	**9**
Durban Immunotherapy Trial Group, 1999	1	1	1	1	1	1	0	1	0	**7**

First author, year published	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive or randomly allocated in an RCT?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently?	Was the length of follow-up adequate (at least 2 months, 90% retention)?	Were the statistical methods well-described?	Were the results well-described?	Total (/9)
East and Central African/ British MRC, 1983	1	1	1	1	1	1	1	0	1	**8**
Hasegawa, 2002	1	0	0	1	1	1	1	1	1	**7**
Hong Kong Chest Service/ British MRC, 1981	1	0	1	1	1	1	1	0	1	**7**
Jindani, 2014	1	1	1	1	1	1	1	1	1	**9**
Jindani, 2016	1	1	1	1	1	1	1	1	1	**9**
Johnson, 2000	1	1	1	1	1	1	1	1	1	**9**
Johnson, 2003	1	1	1	1	1	1	1	1	1	**9**
Joloba, 2000	1	1	0	1	1	1	1	1	1	**8**
Kanda, 2015	1	1	1	0	1	1	1	1	1	**8**
Kennedy, 1996	1	1	1	1	1	1	1	1	1	**9**
Ko, 2017	1	1	1	1	0	1	0	1	1	**7**
Lee, 2014	1	1	1	1	0	1	0	1	1	**7**
Leung, 2017	1	1	1	1	0	1	1	1	1	**8**
Lienhardt, 2011	1	1	1	1	1	1	1	1	1	**9**
Long, 2003	1	1	1	1	0	1	0	1	0	**6**
Mechai, 2016	1	1	0	1	1	1	1	1	1	**8**
Pheiffer, 2008	1	0	0	0	0	1	0	1	1	**4**
Rathored, 2012	1	0	1	0	0	0	0	1	1	**4**
Sajid, 2011	1	1	1	0	1	1	1	1	1	**8**

First author, year published	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive or randomly allocated in an RCT?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently?	Was the length of follow-up adequate (at least 2 months, 90% retention)?	Were the statistical methods well-described?	Were the results well-described?	Total (/9)
Scott, 2017	1	1	1	1	1	1	1	1	1	**9**
Siddiqui, 2010	1	0	1	0	0	0	0	1	1	**4**
Singapore TB service/ British MRC, 1979	1	0	1	1	1	1	1	0	1	**7**
Singla, 2003	1	1	1	0	1	1	1	1	1	**8**
Stoffel, 2014	1	0	1	1	1	1	1	1	0	**7**
Tanzania/ British MRC Collaborative Investigation, 1996	1	1	1	1	1	1	0	0	0	**6**
TB Research Centre, 1983	0	1	1	1	1	1	1	0	1	**7**
Telzak, 1997	1	0	1	1	0	1	1	1	1	**7**
Ugarte-Gil, 2013	1	1	0	1	0	1	1	1	1	**7**
Wang, 2010	1	1	0	1	1	1	0	1	0	**6**

[1] Ruan 2016 (a meta-analysis) was not assessed using this tool designed for case series

Systematic review for evidence of administrative infection control interventions to reduce TB transmission and three related background questions

PICO 1

Final report (revised)

04 October 2018

Authors: Katherine Fielding, Aaron Karat, Rebecca Harris, Dave Moore

Contributors: Hannah Barton, Maria Calderon, Jayne Ellis, Jane Falconer, Indira Govender, Meghann Gregg, Mpho Tlali

Enquiries: katherine.fielding@lshtm.ac.uk

Contents

List of tables

List of figures

1. Executive summary

1.1. Question

A systematic review of the literature was conducted aiming to answer the following question: do 1) triage of people with tuberculosis (TB) signs, symptoms or with confirmed TB disease; and/or 2) respiratory isolation (spatial separation) of presumed or demonstrated infectious TB cases; and/or 3) effective treatment of TB disease reduce the transmission of *M. tuberculosis* to healthcare workers (HCW) (including community health workers [CHWs]) or other populations in healthcare settings, when compared with transmission to the same populations in settings without, or with different, infection control interventions?

1.2. Methods

Search strategies were constructed and run by a professional librarian. The search strategy was compiled and tested on the OvidSP Medline database before it was edited and run across other relevant information sources. The search strategies used subject headings, where available, and search terms were run in the title and abstract, where possible. Literature was limited to papers written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese. Animal studies were excluded. No date limits or publication type limits were added to the search.

Sifting and data extraction were conducted in duplicate by two reviewers. A check of all inclusions after title and abstract sifting was conducted by a third reviewer; if any additional articles were identified for exclusion, a majority decision was reached through discussion with the original reviewers or independent reviewers. Articles identified from the reference lists and citations of all included articles which had not been previously identified by the literature search were also sifted in the same way and included for data extraction if eligible. Citation tracking was conducted in Web of Science and/or SCOPUS. Any unresolved disagreements in sifting were resolved by a third, independent reviewer.

Assessment of bias was conducted at the study and outcome level. An assessment of quality of evidence across studies for each key outcome was conducted using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

1.3. Results

After de-duplication of records identified by the literature search strategy, 14,765 records were listed for title and abstract sifting. After full text review, 43 articles were listed for inclusion, of which 25 were reports of primary research. Nineteen (76%) of these were conducted in low-TB burden and six (24%) in high-TB burden settings; 24 (96%) were conducted in hospitals and only one (4%) in primary care facilities. Two

studies (8%) reported data on HIV-positive individuals; 23 (92%) studies described outcomes in HCW only; and two (8%) studies described outcomes in non-HCW. The incidence of latent TB infection (LTBI) was reported by 19 (76%) studies and the incidence of active TB disease was reported by seven (28%) studies.

Of the 25 primary research articles, 16 (64%) implemented interventions of interest in combination: 11 assessed triage and isolation; two assessed isolation and effective treatment; and three assessed triage, isolation and effective treatment. Of the remainder, eight (32%) studies assessed isolation alone and one (4%) study assessed triage alone. A major obstacle to the evaluation of the three-armed intervention (triage/isolation/treatment) was the lack of studies in which this intervention alone was introduced. All studies except two implemented any or all of the three interventions of interest as part of a wider suite of measures. Thus, attribution of the entire reported effect upon outcome, or estimation of the proportion of a demonstrated effect that could be attributed to the intervention (whether one, two, or all three elements), was not feasible or correct; meta-analysis was not conducted.

1.3.1. Triage

Studies varied greatly in their definitions of triage. Among the studies that implemented triage and reported a change in LTBI incidence, estimates of effect ranged from an absolute reduction of 2.3% to 20.5%. Among the studies that implemented triage and estimated the incidence of TB disease, three (in high TB burden settings) showed slight or no reduction in TB incidence among healthcare workers and one (in low TB burden settings) showed a moderate reduction in TB incidence.

1.3.2. Isolation

Among the 12 studies that reported differences in LTBI incidence, effects ranged from an increase of 1% to a reduction of 21%. The two largest studies (more than 300 outcomes) both showed reductions in incidence (of 1% [low TB burden] and 2% [high TB burden]; crude estimates). Six studies reported the incidence of TB disease; estimates of effect ranged from almost no difference between intervention and control groups in three studies (all in high TB burden settings) to a reduction of 29% in one study (low TB burden setting).

1.3.3. Effective treatment

Four studies showed an absolute reduction in TST conversion after implementation of (composite) infection control measures, ranging from 0.1% to 21%, though all studies had small numbers of outcomes and all except one had small sample sizes. Only one study (conducted in a low TB burden setting) estimated the incidence of TB disease and found a change in incidence among HIV-positive individuals, from 8.8% before implementation of the (composite) intervention, to 2.6% after implementation.

2. Background and question

Tuberculosis (TB) transmission is known to occur in healthcare settings; this has been shown mostly through studies measuring the prevalence and incidence of TB infection and active TB disease in healthcare workers in a variety of settings.[1–4] A number of administrative, environmental, and personal protective measures are thought to reduce the risk of TB transmission in healthcare facilities.[5,6]

A systematic review of the literature was conducted aiming to answer the following question: do 1) triage of people with TB signs, symptoms or with confirmed TB disease; and/or 2) respiratory isolation (spatial separation) of presumed or demonstrated infectious TB cases; and/or 3) effective treatment of TB disease reduce the transmission of *M. tuberculosis* to HCW (including CHWs) or other populations in healthcare settings, when compared with transmission to the same populations in settings without, or with different, infection control interventions?

3. Methods

3.1. Population, interventions, comparators, and outcomes

3.1.1. Population

(i) HCWs (including CHWs) working in healthcare settings with applied intervention

(ii) Non-HCWs (other staff working in a healthcare setting, patients, and visitors) attending healthcare settings with applied intervention

3.1.2. Interventions

Healthcare setting with any of the following administrative infection control interventions, either individually or in any combination:

(i) Triage of people with TB signs, symptoms or confirmed TB

(ii) Respiratory isolation (spatial separation) of presumed infectious TB cases

(iii) Effective treatment of TB based on bacteriologic susceptibility

Note: (ii) basis for isolation can include microbiological, radiological, or clinical criteria and where possible and meaningful this is presented separately

3.1.3. Comparators

(i) HCWs (including CHWs) working in healthcare settings with no intervention or different intervention

(ii) Non-HCWs (other staff working in a healthcare setting, patients, and visitors) attending healthcare settings with no intervention or different intervention

3.1.4. Outcomes

(i) Difference in LTBI incidence/prevalence or

(ii) Difference in TB disease incidence/ prevalence or

(iii) Incidence/prevalence (of TB or LTBI) ratio (or other measures of relative difference)

3.2. Search strategy

Search strategies for the PICO question were constructed and run by a professional librarian with experience of systematic review literature searching. Lists of search terms were circulated to all authors for discussion before the construction of the search strategy. The search strategy was compiled and tested on the OvidSP Medline database before it was edited and run across other relevant information sources. Search strategies were checked by a professional librarian not connected with the research team for typographical or syntax errors.

The search strategies used subject headings, where available, and search terms were run in the title and abstract, where possible. Due to language skills available in the research team, literature was limited to papers written in English, Japanese, Chinese, Russian, French, Spanish, or Portuguese. Animal studies were excluded. No date limits or publication type limits were added to the search.

3.3. Search terms

The following search was constructed in OvidSP Medline. This was adapted, as appropriate, for the other search sources.

1. exp tuberculosis/
2. Mycobacterium tuberculosis/
3. tuberculosis.ti,ab.
4. tuberculin.ti,ab.
5. tb.ti,ab.
6. or/1-5 [TUBERCULOSIS]
7. administrat* control.ti,ab.
8. (administrat* adj3 (transmis* control or infect* control)).ti,ab.
9. or/7-8 [ADMINISTRATIVE INFECTION CONTROL]
10. bacteri* suscept*.ti,ab.
11. suscept* test*.ti,ab.
12. sensitiv* test*.ti,ab.
13. ADST.ti,ab.
14. molecul* screen*.ti,ab.
15. GeneXpert.ti,ab.
16. xpert.ti,ab.
17. line probe assay.ti,ab.
18. molecular assay.ti,ab.
19. nucleic acid amplification test*.ti,ab.
20. (NAAT or NAATs).ti,ab.
21. MTBDRplus.ti,ab.
22. rifampicin resistan*.ti,ab.
23. isoniazid resistan*.ti,ab.
24. or/10-23
25. infect*.ti,ab.
26. transmis*.ti,ab.
27. transmit*.ti,ab.
28. expos*.ti,ab.
29. (acquisition* or acquire*).ti,ab.

30. risk*.ti,ab.
31. or/25-30
32. 24 and 31 [BACTERIOLOGIC SUSCEPTIBILITY TESTS]
33. Triage/
34. triage.ti,ab.
35. ((transfer or distribution or referral or referred or assessment or assess) adj2 (severity or priority or prioriti#e)).ti,ab.
36. assign priority.ti,ab.
37. (systematic adj2 admission).ti,ab.
38. (patient adj3 (evaluat* or sorting or sort)).ti,ab.
39. or/33-38 [TRIAGE]
40. Patient Isolation/
41. respirat* isolat*.ti,ab.
42. ((patient* or inpatient* or in-patient* or outpatient* or out-patient*) adj2 isolat*).ti,ab.
43. air* infect* isolat*.ti,ab.
44. AII.ti,ab.
45. air* isolat*.ti,ab.
46. negative-pressure isolat*.ti,ab.
47. negative-pressure room*.ti,ab.
48. spatial separat*.ti,ab.
49. distancing.ti,ab.
50. or/40-49 [RESPIRATORY ISOLATION]
51. 9 or 32 or 39 or 50 [ALL INTERVENTIONS]
52. 6 and 51
53. infectious disease transmission, patient-to-professional/
54. infectious disease transmission, professional-to-patient/
55. or/53-54 [DISEASE TRANSMISSION BETWEEN HCW AND PATIENT]
56. 6 and 55
57. 52 or 56
58. Humans/
59. Animals/
60. 58 and 59
61. 59 not 60 [ANIMAL STUDIES ONLY]
62. 57 not 61
63. (chinese or english or french or japanese or portuguese or russian or spanish).lg.
64. 62 and 63
65. remove duplicates from 64

Terms ending in "/" are MeSH terms. Terms ending in "ti,ab" limit the search to the title and abstract only. Terms ending in "lg" limit the search to language only. Words enclosed in square brackets are ignored by the search. "ADJn" searches for terms within n words of each other. "*" is the truncation symbol. "#" is the wildcard symbol.

3.4. Search sources

3.4.1. Bibliographic databases

The following databases were searched, using the terms described above:

1. OvidSP MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to present;
2. OvidSP EMBASE Classic + Embase 1947 to present;
3. EBSCO CINAHL Plus;
4. OvidSP Global Health 1910 to present;
5. Elsevier SCOPUS;
6. Web of Science Core Collection (Citation Index Expanded (SCI-EXPANDED) --1970-present; Social Sciences Citation Index (SSCI) --1970-present; Arts & Humanities Citation Index (A&HCI) --1975-present; Emerging Sources Citation Index (ESCI) --2015-present);
7. EBSCO Africa-Wide Information;
8. Web of Science Korean Journals Database 1980 to present;
9. Web of Science Russian Science Citation Index 2005 to present;
10. Web of Science SciELO Citation Index 1997 to present; and
11. Wiley Cochrane Library (Cochrane Database of Systematic Reviews; DARE; Cochrane Central Register of Controlled Trials; Health Technology Assessments; Economics Evaluations)

3.4.2. Grey literature

1. Open Grey
2. OvidSP Northern Light Life Sciences Conference Abstracts 2010 to present
3. Conference Proceedings Citation Index- Science (CPCI-S) --1990-present; Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present (searched as part of the Web of Science Core Collection).
4. New York Academy of Medicine Grey Literature Report
5. WHO ICTRP
6. ClinicalTrials.gov
7. International Union against Tuberculosis and Lung Disease Conference Electronic Abstract Database from 2017 only

3.5. Selection of studies - inclusion and exclusion criteria

Sifting and data extraction were conducted in duplicate by two reviewers. A two-stage sifting process was employed to screen publications at: (1) title and abstract; and (2) full text level for eligibility for inclusion using the criteria below (sections 3.5.1 and 3.5.2). A check of all inclusions after title and abstract sifting was conducted by a third reviewer; if any additional articles were identified for exclusion, a majority decision was reached through discussion with the original reviewers or independent reviewers. Articles identified from the reference lists and citations of all included articles which had not been previously identified by the literature search were also sifted in the same way and included for data extraction if eligible. Citation tracking was conducted in Web of Science and/or SCOPUS. Any unresolved disagreements in sifting were resolved by a third, independent reviewer.

3.5.1. Inclusion criteria

Types of participants

Studies of HCWs (including CHWs) working in healthcare settings, or other staff working in a healthcare setting, or persons of all ages (patients and visitors) attending healthcare settings, anywhere in the world.

Types of intervention

At least one of: 1) triage of people with TB signs or TB symptoms or confirmed TB; 2) respiratory isolation (spatial separation) of presumed infectious TB cases; or 3) effective treatment of TB based on bacteriologic susceptibility.

Types of comparator

Studies reporting data (for outcomes of interest) from a control or comparator group of HCWs (including CHWs) working in healthcare settings, or other staff or persons of all ages (patients and visitors) attending healthcare settings, with no or different administrative infection control interventions.

Types of outcome measures

Studies reporting data on at least one of the outcome measures of interest (incidence / prevalence of LTBI or TB disease).

Types of study

Any consecutive case series, case control study, cohort study, randomised controlled study, systematic review, or meta-analysis.

3.5.2. Exclusion criteria

1. Any study not in humans
2. Any study that did not report any of the above-stated outcomes of interest

3. Any study reporting solely on primary outcomes of interest without a control or comparator group.
4. Any systematic review superseded by an updated systematic review
5. Narrative reviews not adding new data or new analysis of data to existing knowledge
6. Commentaries and mathematical modelling studies
7. Studies with fewer than 10 participants per comparator arm
8. Any study not written in English, Japanese, Chinese, Russian, French, Spanish or Portuguese
9. Any study published before 1946

3.6. Data management

Lists of articles, including reasons for inclusion and exclusion were maintained in Microsoft® Excel spreadsheets; articles were organised using Mendeley and/or Endnote®. Data were extracted by two independent reviewers into Microsoft® Excel spreadsheets and a single consensus dataset produced after discussion, as necessary. In cases where consensus could not be reached, the article and data were reviewed by a third, independent reviewer and a decision reached after discussion between reviewers. Data extracted included HIV status and age of individuals in the population, population role (e.g., HCW, patient, visitor), healthcare setting (e.g., TB clinic, TB ward, MDR-TB ward), and high or low TB burden setting (based on WHO definitions).[7]

3.7. Assessment of risk of bias in the included studies

Assessment of bias was conducted at the study and outcome level. At the study level, bias was assessed using the Cochrane collaboration tool for experimental studies and prospective cohort studies (http://www.cochrane-handbook.org), Downs and Black for observational studies (excluding prospective cohort studies),[8] and the AHRQ tool for systematic reviews (http://www.thecre.com/pdf/ahrq-system-strength.pdf). An assessment of quality of evidence across studies for each key outcome was conducted using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (http://www.gradeworkinggroup.org).[9,10]

3.8. Data analysis

Due to the heterogeneity of the data, meta-analysis could not be conducted. Findings were synthesised using a narrative approach, with studies grouped according to the criteria described above and organised in line with the key outcomes of interest that were pre-specified by WHO.[11]

4. Results: Articles identified

The initial literature search yielded 31,015 records; after de-duplication, 14,765 records were listed for title and abstract sifting. Figure 1 provides an overview of the sifting and review process: 43 articles were finally listed for inclusion, 25 reports of primary research and 18 systematic reviews (Table 1 and Table 2). In addition, six guidelines on TB infection control were reviewed for possible primary research articles (Table 2). Of the 25 primary research articles identified (Table 1), 19 (76%) were conducted in low-TB burden and six (24%) in high-TB burden settings; 24 (96%) were conducted in hospitals and only one (4%) in primary care facilities. Two (8%) studies reported outcomes in HIV-positive individuals. Twenty-three (92%) studies described outcomes in HCW only and two (8%) studies described outcomes in both HCW and non-HCW. Nineteen (76%) studies described the incidence of LTBI and seven (28%) described the incidence of active TB disease (one study described both LTBI and active TB incidence).

5. Results: Key findings

5.1. Findings from individual studies

Of the 25 primary research articles, 16 (64%) implemented interventions of interest in combination: 11 assessed triage and isolation; two assessed isolation and effective treatment; and three assessed triage, isolation and effective treatment (Table 3). Of the remainder, eight (36%) studies assessed isolation alone and one (5%) study assessed triage alone (Figure 2)

A major obstacle to the evaluation of the three-armed intervention (triage/isolation/treatment) was the lack of studies in which this intervention alone was introduced. All studies except two[12,13] implemented any or all of the three interventions of interest as part of a wider suite of measures, including the use of personal protective equipment (PPE) for HCW; changes to ventilation and other environmental controls; and broader administrative interventions, such as changes to policy around cough etiquette and employment of staff specifically to improve adherence to infection control policies (Table 3; Figure 2). Disaggregation of the effects of individual interventions was not possible. Thus, attribution of the entire reported effect upon outcome, or estimation of the proportion of a demonstrated effect that could be attributed to the intervention (whether one, two, or all three elements), was neither feasible or correct. All data reported below must be considered with this in mind.

5.1.1. Triage of people with TB signs and/or symptoms

Fifteen studies implemented triage on and measured the incidence of LTBI or TB disease in HCW (Table 7; 13 studies) and non-HCW (Table 10; two studies). Eleven were conducted in low TB burden settings (the four in high-burden settings were conducted in Malawi,[14] Thailand,[15] Brazil,[16] and South Africa)[17] and all 15 were conducted in secondary or tertiary health facilities.

Triage definitions

Definitions of “triage” varied widely between studies: Bangsberg et al.[18] reported that “all patients known HIV-positive, with HIV risk factors, or homelessness presenting with pneumonia/evidence of TB were isolated on presentation at ER”; Baussano et al.[19] described a “screening programme for the diagnosis of active TB & LTBI”; Blumberg et al, in the two papers included (published in 1995[20] & 1998[21]), described an “expanded respiratory isolation policy”; Harries et al.[14] described a process of giving "priority to patients with chronic cough; rapid collection of sputum specimens"; Jacobson et al.,[12] a "routine chest x-ray screening for all new admissions"; Louther et al.[22] isolated people with HIV, respiratory symptoms, or unexplained fever; Roth et al.[16] simply called it “rapid diagnosis and treatment”; Welbel et al.[23] reported that they implemented

a “revised policy (based on CDC guidelines) for isolation”*; Wenger et al.[24] operated a "higher index of suspicion for TB and stricter application of isolation criteria"; and Yanai et al.[15] described "triage/isolation and expedited diagnosis training for health care workers".

Incidence of LTBI

All studies implemented multiple other infection control interventions in addition to triage. Sample sizes also varied widely between studies, from 65 (Wenger, 1995, USA)[24] to 21,197 (Blumberg, 1995, USA;[20] Table 3). Among the studies that reported a change in LTBI incidence, estimates of effect ranged from an absolute reduction of 2.3% (118/3,579 [3.3%] ‘control’ to 171/17,618 [1.0%] ‘intervention; Blumberg 1995) to 20.5% (7/25 [28.0%] ‘control’ vs. 3/40 [7.5%] ‘intervention’; Wenger;[24] Table 3, Table 6, and Table 9). Several studies reported changes in incidence rates and did not provide estimates of risk, for example, Baussano et al. (2007, Italy)[19] described an incidence rate of 2.19 per 100 person-years (PY; 106 conversions/4,034 person-years) before TBIC interventions were implemented, versus 0.84 per 100 PY (42 conversions/4,463 person-years) after implementation (crude rate ratio 0.36); Blumberg et al (1998, USA)[21] reported TST conversion rates of 5.98 per 100 PY (before) and 1.09 per 100 PY (after; crude rate ratio 0.18); and Louther et al. (1997, USA)[22] reported a change in incidence rate from 7.2 per 100 PY (before) to 3.3 per 100 PY (after; crude rate ratio 0.46).

Incidence of TB disease

Six studies implemented triage and measured the incidence of TB disease: three were conducted in high TB burden settings (one each in Malawi [Harries, 2002],[14]Thailand [Yanai, 2003],[15] and South Africa [O’Hara, 2017][17]) and all were conducted in secondary or tertiary health facilities. Five studies implemented multiple other infection control measures together with triage, including isolation, respiratory protection, and environmental controls. The study by Jacobson et al. (1957, USA)[12] was the only one to implement triage without any other interventions: they reported an incidence rate of 78 episodes of TB disease among healthcare workers in 38,331 person-years in the control group (before the intervention was implemented) and 12 episodes in 18,229 person-years after the implementation of triage (crude incidence rate ratio 0.32, after vs. before). Studies by Harries, Yanai, and O’Hara showed very slight or no reduction in TB incidence among healthcare workers after the implementation of infection control measures, from 100/2,697 (3.7%) in the ‘control’ group to 96/2,979 (3.2%) in the ‘intervention’ group (Harries); 29/4,464 (0.6%) in the ‘control’ group to 14/3,237 (0.4%) in the ‘intervention’ group (Yanai); and an unadjusted odds ratio (OR) of 0.94 (95%

* CDC 1994 guidelines state that "in hospitals and other inpatient facilities, any patient suspected of having or known to have infectious TB should be placed in a TB isolation room"

confidence interval [CI] 0.87–1.02) TB disease in HCW at facilities with higher administrative scores vs. lower (adjusted OR 0.97 [95% CI 0.90–1.04]; O'Hara; Table 3, Table 6, and Table 9).

Both studies in low TB burden settings showed a reduction in TB incidence in the period after implementation of the composite interventions, from incidence in 19/216 (8.8%) individuals before implementation to 5/193 (2.6%) after implementation (Stroud, 1995, USA)[25] and an incidence rate of 10.6 per 1,000 person-days before implementation (90 individuals at risk) to 0 per 1,000 person-days after implementation (44 individuals at risk; Moro, 2000, Italy).[26]

5.1.2. Isolation or spatial separation

Twenty-four studies examined the impact of respiratory isolation or spatial separation on TB transmission and measured incidence of LTBI or active TB disease; 22 among HCWs and two among non-HCWs (Table 7 and Table 10). All studies, except one, were conducted in secondary or tertiary health facilities and 18/24 (75%) were conducted in low TB burden countries. Among the 16 studies that reported denominators, total sample sizes ranged from 65 (Wenger, 1995, USA)[24] to 81,147 (Fridkin, 1995, USA)[27]. All studies, except one,[13] implemented isolation along with a number of other administrative, environmental, and protective infection control measures, including triage and effective treatment based on drug susceptibility; the Harries (2002, Malawi)[14] study implemented spatial separation, not respiratory isolation, described by the authors as the placement of potentially infectious individuals "in one part of [the] ward near good ventilation".

Incidence of LTBI

All studies reporting changes in LTBI incidence or prevalence measured this in HCW. Studies reported outcomes in different ways, either as incidence (i.e., the proportion of participants with LTBI or TB disease) or as incidence rates (i.e., numbers of events during a specific time period). Among the 12 studies that reported differences in LTBI incidence, effects ranged from an increase of 1% (92/4000 [2.3%] 'control', to 2/60 [3.3%] 'intervention'; Jones [2002, USA])[28] to a reduction of 21% (7/25 [28.0%] 'control', to 3/40 [7.5%] 'intervention'; Wenger)[24]. The two largest studies (more than 300 outcomes) both showed reductions in incidence (380/20,776 [1.8%] 'control', to 376/60,371 [0.6%] 'intervention'; 1% reduction; Fridkin [1995, USA][27]; and 1,028/1,602 [64.2%] 'control' to 1,760/2,817 [62.5%] 'intervention'; 2% reduction; Roth [2005, Brazil][16]). Among the six studies reporting incidence rates, rate ratios (intervention vs. control) ranged from 0.01 (95% CI 0–0.04; p <0.001; Yanai [2003, Thailand],[15] adjusted) to 0.24 (95% CI 0.10–0.54; da Costa [2009, Brazil],[29] adjusted for exposure and occupation), 0.36 (Baussano [2000, Italy],[19] crude ratio derived from data presented), and 0.46 (Louther [1997, USA],[22] crude ratio derived from data presented; Table 3, Table 7, and Table 10).

Incidence of TB disease

Six studies implementing isolation reported the incidence of TB disease: four reported this in HCW and two in non-HCW. All six studies implemented isolation along with a range of other infection control measures, including triage (n = 5) and effective treatment (n = 1). Estimates of effect ranged from almost no difference between intervention and control groups (Harries [2002, Malawi],[14] Yanai [2003, Thailand][15], and O'Hara [2017, South Africa]; all in HCW)[17] to reductions of 6% (Stroud [1995, USA],[25] crude estimate, non-HCW) and 29% (Moro [2000, Italy], crude estimate, non-HCW;[26] Table 3, Table 7, and Table 10) after the implementation of infection control measures.

5.1.3. Effective treatment based on drug susceptibility

Five studies examined the impact of effective treatment (based on drug susceptibility); all were conducted in low TB burden settings and in secondary or tertiary facilities and four measured outcomes among HCWs (Table 3, Table 8, and Table 11). All studies implemented a range of infection control measures, making it difficult to isolate the effect of treatment alone; these included additional administrative controls, such as education of health care workers, respiratory isolation, and triage; environmental controls, such as improved ventilation and the use of ultraviolet light; and personal protective controls, such as the use of masks for health care workers and patients. Implementation of 'effective treatment' was also variable; for example, in the study by Wenger et al. (1995, USA),[24] the treatment regimen was changed only slightly, from three to four drugs; it has also been assumed that the implementation of "radiometric susceptibility testing" in the study by Welbel et al. (2009, USA)[23] would have led to appropriate treatment based on drug susceptibility, though this is not stated explicitly by the authors.

Incidence of LTBI

Some outcomes were not reported completely in the articles by Jarvis et al. (1995, USA)[30] and Welbel et al.[23] All studies showed an absolute reduction in TST conversion after implementation of infection control measures, ranging from 0.1% (26/840 [3.1%] before to 22/727 [3.0%] after; Maloney [1995, USA])[31] to 21% (7/25 [0.28] before to 3/40 [0.08] after; Wenger;[24] Table 8 and Table 11), though all studies had small numbers of outcomes (range 10–104) and two had small sample sizes (n ≤650, except Maloney [n = 1,567][31] and Welbel[23] [n = 4,329]).

Incidence of TB disease

Only one study estimated the effect of effective treatment on the incidence of TB disease. Stroud et al. (1995, USA)[25] implemented an 'expanded anti-TB regimen' (though in practice this was a change from only ~1.5 [range 0–4] drugs to 2.0 [range 0–4] drugs between pre- and post-implementation) as part of a composite intervention that included triage, an amended isolation policy, and changes to diagnostic processes. They found a change in incidence (described by the authors as an "attack rate") in active TB

disease among HIV-positive individuals admitted to the ward, from 19/216 (8.8%) in the period prior to the intervention, to 5/193 (2.6%) after implementation (p = 0.01).

5.2. Quality assessment

The 18 retrospective studies were assessed using the Downs and Black tool (maximum score 27); scores are summarised in Table 4. All studies scored poorly (median score 10 [IQR 8.3–12.0; range 6–13]). Assessments for prospective studies are summarised in Table 5: one study was marked down for incomplete reporting of outcomes and three for selective reporting of outcomes. The overall low quality of studies was reflected in the GRADE assessment (Section 6.3), where the quality of the evidence was consistently downgraded due to serious risk of bias and very serious indirectness, the latter of which was often due to the implementation of multiple infection control measures in almost all studies.

6. Annexes

6.1. Tables

Table 1. Basic characteristics of primary research articles from which data were extracted (n = 25)

First author	Year pub-lished	Country/ies	TB burden*	Primary or secondary care	Outcomes measured in HIV+ people	Intervention(s) implemented			Outcome(s) measured	
						Triage	Isolation	Effective treatment	LTBI incidence†	Active TB incidence
Bangsberg[18]	1997	USA	Low	S	NS	Yes	Yes		Yes	
Baussano[19]	2007	Italy	Low	S	NS	Yes	Yes		Yes	
Behrman[32]	1998	USA	Low	S	NS		Yes		Yes	
Blumberg[20]	1995	USA	Low	S	NS	Yes	Yes		Yes	
Blumberg[21]	1998	USA	Low	S	NS	Yes	Yes		Yes	
Bryan[33]	1983	USA	Low	S	NS		Yes		Yes	
Claassens[34]	2013	South Africa	High	P	NS		Yes			Yes
da Costa[29]	2009	Brazil	High	S	NS		Yes		Yes	
Fridkin[27]	1995	USA	Low	S	NS		Yes		Yes	
Harries[14]	2002	Malawi	High	S	NS	Yes	Yes			Yes
Holzman[35]	1995	USA	Low	S	NS	Yes	Yes		Yes	
Jacobson[12]	1957	USA	Low	S	NS	Yes				Yes
Jarvis[30]	1995	USA	Low	S	NS		Yes	Yes	Yes	
Jones[28]	2002	USA	Low	S	NS		Yes		Yes	
Louther[22]	1997	USA	Low	S	NS	Yes	Yes		Yes	
Maloney[31]	1995	USA	Low	S	NS		Yes	Yes	Yes	
Moro[26]	2000	Italy	Low	S	Yes	Yes	Yes			Yes
O'Hara[17]	2017	South Africa	High	S	NS	Yes	Yes			Yes
Roth[16]	2005	Brazil	High	S	NS	Yes	Yes		Yes‡	
Sinkowitz[36]	1996	USA	Low	S	NS		Yes		Yes	
Stroud[25]	1995	USA	Low	S	Yes	Yes	Yes	Yes		Yes
Uyamadu[13]	1997	USA	Low	S	NS		Yes		Yes	
Welbel[23]	2009	USA	Low	S	NS	Yes	Yes	Yes	Yes	
Wenger[24]	1995	USA	Low	S	NS	Yes	Yes	Yes	Yes	
Yanai[15]	2003	Thailand	High	S	NS	Yes	Yes		Yes	Yes

*Per WHO list of high burden countries for use in the post-2015 era[37];

†measured by TST conversion

‡also reported TST prevalence (≥10 mm on the first or second step of the two-step TST)

HIV+: HIV-positive; LTBI: latent TB infection; NS: not specified; P: primary; S: secondary; TB: tuberculosis; WHO: World Health Organization; TST: tuberculin skin test

Table 2. List of systematic reviews (n = 18) and guidelines (n = 6) for which reference lists were reviewed

Author(s)	Year published	Title
Canada CDC[38]	1996	Guidelines for preventing the transmission of tuberculosis in Canadian health care facilities and other institutional settings
Cookson[39]	1997	Prevention of nosocomial transmission of *Mycobacterium tuberculosis*
Conde[40]	2009	III Brazilian thoracic association guidelines on tuberculosis
Davis[41]	1997	Hospital infection control practices for tuberculosis
Harries[42]	1997	Practical and affordable measures for the protection of health care workers from tuberculosis in low-income countries
Humphreys[43]	2007	Control and prevention of healthcare-associated tuberculosis: the role of respiratory isolation and personal respiratory protection
Jensen (US CDC)[44]	2005	Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005
Joshi[2]	2006	Tuberculosis among health-care workers in low- and middle-income countries: a systematic review
L'Ecuyer[45]	1996	Further progress in the protection of healthcare workers
McGowan[46]	1995	Nosocomial tuberculosis: new progress in control and prevention
Menzies[1]	1995	Tuberculosis among health care workers
Menzies[3]	2007	Risk of tuberculosis infection and disease associated with work in health care settings
Nasreen[47]	2016	Prevalence of latent tuberculosis among health care workers in high burden countries: a systematic review and meta-analysis
Nathavitharana[48]	2017	Agents of change: The role of healthcare workers in the prevention of nosocomial and occupational tuberculosis
Punjabi[49]	2016	Preventing transmission of *Mycobacterium tuberculosis* in health care settings
Raymond[50]	1998	ACOEM guidelines for protecting health care workers against tuberculosis
Sepkowitz[51]	2001	Tuberculosis control in the 21st century
Seyferth[52]	1994	Guidelines for preventing occupational exposure to TB
Tam[53]	2006	Occupational tuberculosis: a review of the literature and the local situation
Trajman[54]	2010	Occupational respiratory infections
van Cutsem[55]	2016	Infection control for drug-resistant tuberculosis: early diagnosis and treatment is the key
Verkuijl[56]	2016	Protecting our front-liners: occupational tuberculosis prevention through infection control strategies
WHO[5]	2009	WHO policy on TB infection control in health-care facilities, congregate settings and households
Zuckerman[57]	2011	Prevention of health care-acquired pneumonia and transmission of *Mycobacterium tuberculosis* in health care settings

ACOEM: American College of Occupational and Environmental Medicine; CDC: Centers for Disease Control and Prevention; TB: tuberculosis; WHO: World Health Organization

Table 3. Design, setting, interventions implemented, outcomes, and main findings of studies included (n = 25)

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	Other					
High TB burden settings								
Claassens, 2013, South Africa; cross-sectional[34]	121 primary health care facilities	TB infection control audit in May-Sep2009; separate score for administrative controls	Scores also for (i) environmental controls and (ii) personal respiratory protection; as well as overall score	TB disease among HCWs (Jan 2006–Dec 2008). In analyses binary outcome was defined as ≥ 1 TB episode among HCWs in health care facility	Not reported	Not reported	Unadj OR for administrative score (continuous): 1.09 (95% CI 0.99–1.19), *p* = 0.07	Administrative score: range from −4 to 19, mean 8 (SD 4). Administrative score not included in adjusted model. ORs also shown for total, environmental controls and personal respiratory protection scores
da Costa, 2009, Brazil; during/after[29]	One hospital	Isolation of: all patients with sputum sent for AFB +/- mycobacterial culture, patients with productive cough until one smear negative, and HIV+ patients with abnormal CXR; education of HCWs	Specialised TB o/p clinic. Use of N-95 respirator for all person entering room with isolated patient. Patients leaving room for diagnostic tests wore surgical mask and educated on cough etiquette.	TST conversion/ 10^3 months	1998–2001: 5.8 (25/4,307 pmths); 95% CI 4.9–6.7.	2002–2003: 3.7 (15/3,858 pmths); 95% CI 2.8–4.6.	RR = 0.46 (95% CI 0.23–0.89), *p* = 0.006	Adjusted RR 0.24 (95% CI 0.10–0.54), adjusted for exposure to PTB case in hospital & occupation. Fidelity to intervention: ↓ time between microscopy request and result between two time-periods ↑ %PTB diagnosed among suspected cases isolated
Harries, 2002, Malawi; before/after[14]	40 hospitals	Guidelines on control of TB infection (mid-1998), including rapid collection of sputum;	ventilation (windows left open) and masks (worn by PTB patients	TB disease in HCWs (1996, 1999)	**1996**: 3.7% (100/2,697)	**1999**: 3.2% (96/2,979)	Reported as "non-significant"	Fidelity (Jan-Jun1998 vs. Jan-Jun 1999)- similar length of time from admission to diagnosis and treatment

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	**Other**					
		frequency of processing specimens	when undergoing surgery)					
O'Hara, 2017, South Africa; cross-sectional[17]	28 public hospitals	TB infection control audit in 2012; separate score for administrative controls (triage, isolation)	Scores also for (i) environmental controls; (ii) personal respiratory protection; and (iii) miscellaneous measures, as well as overall score	TB disease incidence in HCW	Not reported	Not reported	Unadj OR for administrative score 0.94 (95% CI 0.87–1.02), p = 0.12 Adj OR for administrative score 0.97 (95% CI 0.90–1.04), p = 0.36	Median administrative score 21 (IQR 18–24, range 15–28); max possible score 32. Adj OR adjusted for environmental score, PPE score, miscellaneous score, and number of TB patients
Roth, 2005, Brazil; cross-sectional[16]	Four general hospitals	TB IC measures including rapid diagnosis, treatment, isolation. Compared all four hospitals and two hospitals (A & B) with better IC vs two hospitals (C & D) with worse IC measures.	Some hospitals had engineering measures (negative pressure isolation rooms with HEPA filtration and 20 ACH; N95 respirator for HCWs and surgical mask for patient until isolated.	TST prevalence (%) and TST conversion (1,000 pmths) in HCWs	**TST prevalence:** **Hosp C:** 65.8% (574/872) **Hosp D:** 62.2% (454/730) **TST conversion:** **Hosp C:** 19.8/10^3 pmths (n = 34) **Hosp D:** 12.2/10^3 pmths (n = 21)	**TST prevalence:** **Hosp A:** 46.7% (407/872) **Hosp B:** 69.6% (1,353/1945)) **TST conversion:** **Hosp A:** 7.4/103 pmths (n = 19) **Hosp B**: 8.1/103 pmths (n = 31)	Hospital C & D 16.0/10^3 pmths vs A & B 7.8/10^3 pmths; p <0.001. Hospitals B, C and D vs A: unadjusted OR 1.3, 3.2 and 3.4, respectively; adjusted OR (95% CI; p-value) 1.0 (0.5–1.8; NS),	Reported annual number of new PTB cases: Hosp A 200–250; Hosp B 100–150; Hosp C 450–500; Hosp D 50–60

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	Other					
							2.3 (1.2-4.2; 0.01), 2.8 (1.4-5.6; 0.002), respectively.	
Yanai, 2003, Thailand; before/after[15]	One referral hospital	Interventions (SOPs & IC plan) aimed at: time from admission to initiation of TB treatment; timeliness of suspicion of TB, collection of specimens, reporting results, isolation & initiation of treatment monitored	Prevention interventions for HCWs & patients; engineering control measures (negative & natural ventilation; in lab air exhaust and UVGI) and personal respirators (N-95 masks encouraged when HCWs exposed themselves to infectious TB patients. Lab staff processing Mtb cultures used personal respirators)	TST conversion rate (per 1,000 pyrs) and TB disease rate, per 100 pyrs; HCWs	**TST conversion** **1995–1997:** 9.3 (95% CI 3.3–15.3) /100pyrs	**TST conversion** **1998:** 6.4 (95% CI 1.5–11.4) /100pyrs; **1999**: 2.2 (95% CI 0–5.1) /100pyrs	**TST conversion** **RR (vs. 1995–1997)** **1998**: unadj. 0.9 (0.4–2.2); adj. 0.4 (0.1–1.6), p = 0.2. **1999**: unadj. 0.03 (0.01–0.2); adj. 0.01 (0–0.04), p <0.001	Intervention implemented in 1996. Increase in numbers of smear+ TB pts identified 1990 (102) to 1999 (356). Numerators & denominators unclear. Active TB disease incidence among HCWs also reported for the period 1988-1994.
					Active TB: **1995–1997:** 0.65 (29/4464) /100pyrs	**Active TB**: **1998:** 0.42 (7/1654) /100pyrs. **1999:** 0.44 (7/1583) /100pyrs	**Active TB**: No RR reported	
Low TB burden settings								

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	Other					
Bangsberg, 1999, USA; during/after[18]	One tertiary referral centre	All pts with known HIV infection, HIV risk factors or homelessness presenting with pneumonia/evidence of TB were isolated on presentation at ER; admitted to negative-pressure isolation room; remained in respiratory isolation until 3 –ve AFBs	Implementation of revised policy in 1992 based on CDC guidelines (published in 1993). Modifications to facility & personal protective equipment	TST conversion/100 pyrs; HCWs	**Jun1992:** 5.8/100pyrs (10%, 9/88)	**Dec92**: 5.1/100pyrs (2/77); **Jun93**: 0/100pyrs (0/88); **Dec93**: 2.3/100pyrs (1/93); **Jun94**: 0/100pyrs (0/86)	Not reported overall. Data also reported for interns showing a decline over 1992–1994 (p = 0.029)	Fidelity of the intervention: % properly isolated increased from 38% (Jan–Jun 1992) to 75% (Jul–Dec 1993)
Baussano, 2007, Italy; before/after[19]	Three health units	Implementation of regional guidelines. Administrative: appointment of TB official at each facility; adoption of procedures to assess risk of TB transmission; prompt diagnosis & isolation of potentially infectious TB cases	Organisational, technical & educational interventions; respiratory protection measures, particularly while performing cough-inducing procedures.	TST conversion, rates/100 pyrs, sex & age-adjusted; HCWs	**Jan98–Jun00**: 2.19 (106/4,034*), 95% CI 1.81–2.56	**Jan02–Dec04**: 0.84 (42/4,463), 95% CI 0.55–1.28	Not reported.	*events/pyrs includes data to Dec2001. Data also shown by occupation (work activity) & workplace
Behrman, 1998, USA; before/after[32]	ED in one hospital	New TB control measures in the ED, including four respiratory isolation rooms	100% non-recirculated air in trauma area, improved ventilation, laminar flow of	TST conversion, %; HCWs (not clearly defined)	**Jul94-Dec95** (cycle 2) ED staff : 12% (6/50)	**1996** (cycle 3) ED staff:0% (0/64)	Not reported.	No change in the number of culture-positive admissions from 1993–96. No data reported on frequency of use of respiratory isolation rooms.

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	Other					
			air from registrars to patients, and acrylic plastic droplet shields for registrars		Other hospital employees: 2% (51/2,514)	Other hospital employees: 2% 1.2(36/3,000)		No data on TST conversions from Mar93–Dec94 (cycle 1). Data from other hospital employees also presented
Blumberg, 1995, USA; during/after[20]	One public hospital	Mandatory isolation of all patients with active TB, those with TB from differential diagnosis (or when sputum tests ordered), HIV+ or at high risk of HIV infection. Isolation discontinued after 3 consecutive –ve AFBs/patient discharged	Interim engineering controls (conversion of 90 rooms to negative pressure rooms by addition of window fan); personal respiratory protection equipment (submicron mask used by all HCWs entering respiratory isolation room.	TST conversion rate, expressed as %, in HCWs at the hospital (not those on rotation)	**Jan–Jun1992**: 3.3% (118/3579)	**Jul–Dec92:** 1.7% (51/2975); **Jan–Jun93:** 1.4% (67/4715); **Jul–Dec93:** 0.6% (30/4775); **Jan–Jun94**: 0.4% (23/5153)	Not reported. Reported p-value comparing the five time-periods: <0.001	Fidelity to the intervention: Jul91–Feb1992 (8 mths) 4.4 TB exposure episodes/mth (n = 35/103 not appropriately isolated); versus Mar92–Jun94 (28 mths) 0.6 TB exposure episodes/mth (n = 18/358 not appropriately isolated)
Blumberg, 1998, USA; during/after[21]	One public hospital	Mandatory isolation of all patients with active TB, those with TB from differential diagnosis (or when sputum tests ordered), HIV+ or at high risk of HIV	interim engineering controls (as above), personal respiratory protection	TST conversion rate, per 100 pyrs, among staff in a teaching program (50% of their clinical rotations in the hospital)	**Jul–Dec92:** 5.98/100pyrs (21 conv.)	**Jan93–Jun97:** 1.09/100pyrs (31 conv.)	Not reported. Reported a p-value comparing the two time-	Also showed data by the house staff department; US medical school graduate staff (5.26 vs. 0.72/100 pyrs, *p* <0.001)

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	**Other**					
		infection. Isolation discontinued after 3 consecutive –ve AFBs/patient discharged	equipment (as above)				periods: <0.001	
Bryan, 1983, USA; during/after[33]	One teaching hospital	TB Registry – documents dates/results of AFBs, CXR results, whether patient is put in respiratory isolation & when; register reviewed weekly by TB epidemiologist		TST conversion rates, expressed as %, among HCWs	**1976**: 4.5%	**1977**: 5.1%; **1979**: 1.5%; **1980**: 0.85%; **1981**: 0.59%		?potential problem of faulty performance of test/ presence of booster phenomenon in 1976–77. n/N not reported. Fidelity of intervention (% pts with culture confirmed TB who were isolated): 1976: 3/15; 1977: 9/24; 1978: 8/23; 1979: 18/30; 1980: 14/26
Fridkin, 1995, USA; cross-sectional[27]	210 hospitals	Compliance with 1990 CDC TB guideline AFB isolation room (survey conducted in Mar93, 50% response rate). 1. All 4 criteria no vs yes (includes single/cohorting of patients); 2. ≥ 3criteria (includes single/cohorting of patients).	All 4 criteria; at least 3 criteria (negative-pressure, exhaust directed outside & single/ cohorting of patients); at least negative-pressure criterion; at least the direct outside exhausted air criterion	TST conversion rates, %; among HCWs measured in 1992, among hospitals reporting at least 6 TB patients in 1992	**All 4 criteria - no**: 1.89% (383/20,296; 17 hospitals). **≥ 3 criteria- no:** 1.83% (380/20,776; 16 hospitals).	**All 4 criteria - yes**: 0.60% (348/57,600; 28 hospitals). **≥ 3 criteria- yes:** 0.62% (376/60,371; 30 hospitals).	**All 4 criteria: yes vs no**: p = 0.02; **≥ 3 criteria: yes vs no**: p = 0.03	Similar trend for at least negative-pressure or at least the direct outside exhausted air criterion. Also restricted analysis to high risk HCWs (includes bronchoscopists & respiratory therapists) and found similar results

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	Other					
Holzman, 1995, USA; before/after[35]	One municipal hospital	Implementation of 1990 CDC guidelines. Triage; early isolation & treatment (drug-susceptibility testing not specified); written criteria for starting/stopping precautions	Negative pressure rooms with ventilation, filtration, and UV radiation equivalent to 28 air changes/hour; PPE: dust-mist & HEPA respirators	TST conversion; HCWs	**Nov 1992–Oct 1993** **Overall: 90/2,132 (4.2%)** Nursing:54/608 (8.9) Housekeeping: 9/105 (8.6) Radiology: 2/50 (4.0) Misc./Unk.: 14/474 (3.0)	**Nov 1993–Oct 1994** **Overall: 23/1,995 (1.2%)** Nursing: 11/519 (2.1) Housekeeping: 3/90 (3.3) Radiology: 1/74 (1.4) Misc./Unk.: 1/573 (0.2)	**Percentage reduction (95% CI), p-value** **Overall: 73% (57–43), <0.001** Nursing: 76% (44–90), <0.001 Housekeeping: 61% (0–89) Radiology: 66% (0–97) Misc./ Unknown: 94% (55–99), <0.001	
Jacobson, 1957, USA; before/after[12]	One general hospital	Routine admission CXR screening programme		TB disease rate, per 1000 pyrs; HCWs	**1942–51 (overall time period)**: 2.0/1,000pys (78/38,331);	**1952-53:** 1.0/1,000pys (9/9,030); **1954–55:** 0.3/1,000pys (3/9,199)	Not reported.	Peak in 1948-50 coincided with community wide case-finding activities. Also showed data by HCW occupation.
Jarvis, 1995, USA; before/after[30]	Three hospitals (A[1989–91], B [1989–91] & D [1990–1])	Implementation of 1990 CDC guidelines. Including education of HCW to increase index of suspicion for TB; prompt collection & processing of	engineering controls (negative pressure isolation rooms & air exhausted outside) and	Annual TST conversion, %; HCWs	**Baseline period (not defined):** **A**: 24% (7/29); **B**: 9% (2/22); **D**: 12% (15/123)	**Intervention period (not defined)** **A**: 0% (0/23); **B**: 18% (6/33); **D**: 3% (5/150)	**A**: p = 0.01; **B**: p = NS; **D**: p = 0.01	Fidelity – proportion of patients on ward with same-ward exposures decreased in intervention (15%) vs baseline period (74%). Decreased in all hospitals.

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	**Other**					
		specimens; prompt identification & isolation of pts with known/suspected TB;	respiratory protective devices (submicron or dust-mist)					In hospital B there was incomplete implementation of CDC guidelines
Jones, 2002, USA; during/after[28]	One teaching medical centre	Rule-out negative pathway: (1) initiation of respiratory isolation protocols; (2) direct pt admission/transfer to Special Immunology/Infectious Disease [SI/ID] unit; (3) immediate pt placement in respiratory isolation	Isolation rooms designed to provide negative pressure, six air exchanges/hour and venting of air outside.	TST conversion, %; HCWs		**Overall**: **95–98**: 2.3% (92/~4000); **In SI/ID unit: Jan94–Jan98** 0% (0/60); **Feb–Jun98** 3.33% (2/60)		Fidelity – 50 pts placed on pathway 1995–98
Louther, 1997, USA; during/after[22]	Urban hospital with a dedicated 'AIDS centre'	Respiratory isolation of all individuals suspected of having active TB; Triage of people attending ED or o/p department and isolation of HIV+ people with particular symptoms (methods described in detail in separate article by Fella et al.)[58]	Negative-pressure ventilation rooms Germicidal UV (n = 125 units) in patient rooms, waiting areas, and nursing stations PPE: Technol shield masks, dust-mist-fume respirators, and	TST conversion rate per 100 person-years; HCWs	**1991–1992 Overall 7.2 conversions/100 pyrs** (Lab workers 6.3; Physicians/nurses 7.2; Social service 8.1; Housekeeping 11.7, Finance 3.0)	**1993–1994 Overall 3.3 conversions/100 pyrs** (Lab workers 2.3 Physicians/nurses 3.0 Social service 2.2; Housekeeping 6.7; Finance 1.9)	**Overall crude rate ratio 0.46*; *p* = 0.001** (Lab workers 0.37, *p* = 0.42 Physicians/nurses 0.42, *p* = 0.01 Social service 0.27, *p* = 0.04; Housekeeping 0.57, *p* = 0.12; Finance 0.63, *p* = 0.48)	

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	Other					
			HEPA respirators					
Maloney, 1995, USA; before/after[31]	One teaching hospital	Implementation of 1990 CDC guidelines, including prompt isolation & treatment of patients with TB; rapid diagnosis	negative-pressure isolation rooms; moulded surgical masks for HCWs	TST conversion, %; HCWs	**Jan90–Jun91 Overall:** 3.1% (26/840) **Wards housing TB** pts: 16.7% (15/90); **Other wards**: 2.8% (7/254)	**Jul91–Aug92 Overall:** 3.0% (22/727) **Wards housing TB** pts: 5% (4/78); **Other wards**: 4% (9/228)	**Overall:** p=0.9 **Wards housing TB** pts: RR = 3.2, *p* = 0.02; **Other wards**: RR = 0.7, *p* = 0.5	TST conversion data also reported subgroup direct/no direct pt contact. Fidelity: AFB isolation before 40% after 90%; receiving adequate treatment before 43% vs after 90%.
Moro, 2000, Italy; before/after [26]	One HIV ward in hospital	Implementation of TB infection control strategies: strict AFB isolation procedures initiated for all pts with respirator disease/fever	Patients wore surgical masks when being transported for diagnostic purposes. Surgical masks mandatory for persons entering pts rooms.	MDR-TB incidence among HIV+ patients per 1000 pdays	**Oct–Jun93**: 10.6/100 pdays (26/2,455, 90 pts)	**Jul93–Feb94**: 0/100 pdays (0/654, 44 pts)	Not reported.	37 pts followed up before/after period: 0/1839 MDR-TB episodes. Over the entire time period there were several infectious MDR TB cases in the ward
Sinkowitz, 1996, USA; cross-sectional[36]	1,494 hospitals	Compliance with 1990 CDC TB guideline AFB isolation room (survey conducted in March 1993, 50% response rate). All 4 criteria no vs yes.	Per Fridkin et al.	TST conversion rates, %; among bronchoscopists & HCWs measured in 1992, stratified by number of TB patients	**All 4 criteria - no: Bronchoscopists** No TB pts: 0% (n = 0); 1–5 TB pts: 8.0%; (n=22); ≥6 TB pts: 5.1% (n = 11)	**All 4 criteria - yes**: **Bronchoscopists** No TB pts: 3.3% (n = 13); 1–5 TB pts: 8.3% (n = 39); ≥6 TB pts: 5.7% (n = 16)	Not reported.	Also results reported for negative-pressure, air exhaust & respiratory protection criterion

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	Other					
				hospitalised in 1992 (none, 1–5, ≥6 TB pts).	**HCWs** No TB pts: 0.49% (n = 127); 1–5 TB pts: 0.64% (n = 116); ≥6 TB pts 0.76% (n = 34).	**HCWs** No TB pts: 0.53% (n = 75); 1–5 TB pts: 0.69% (n = 185); ≥6 TB pts 0.90% (n = 66).		
Stroud, 1995, USA; before/after[25]	One hospital	Aggressive implementation of administrative controls - rapid placement of TB pts or suspected TB pts in single-patient rooms. Expanded TB treatment prescribed.	In period III engineering changes (some isolation rooms fitted with UV lights and fans that exhausted air outside, provided ≥6 air exchanges/hr and created negative pressure in hallway) were made	MDR-TB risk in AIDS patients with same ward exposure to MDR TB pts, %	**Jan89–Mar90** (period I): 8.8% (19/216)	**Apr90–May1991** (period II): 2.6% (5/193)	*p* = 0.01	Period I, n = 16 MDR case pts; period II, n = 22 MDR case pts. MDR-TB risk was 4.8% (4/84) for those with exposures to periods I and II; and 0.5% (4/863) for AIDS pts without same-ward exposure.
Uyamadu, 1997, USA; before/after[13]	One teaching hospital	Mandatory respiratory isolation of all patients with community-acquired pneumonia, until 2 negative AFBs/TB ruled out on clinical grounds		TST conversion, %; HCWs	**1988-90**: overall 0.6% (23/3,842); **Jan–Jul91**: 1.7% (13/768).	**Jul91–Dec94**: average 0.6% **Jul-Dec91**: 1.3% (10/774) **1992**: 0.5% (9/1,637) **1993**: 0.7% (9/1,325)	Not reported.	Fidelity – 100% compliance with respiratory isolation. Number of new TB cases in hospital remained stable 1991–1994

First author, year, country; study design	Setting	Intervention/s		Outcome measured	No intervention	Intervention	Effect estimate	Other data
		Administrative	Other					
						1994: 0.6% (8/1,381)		
Welbel, 2009, USA; during/after[23]	One public hospital	Creation of respiratory isolation service for proper & prompt isolation of patients; dedicated technician for service, collection of sputum daily. All HIV+ patients with respiratory symptoms placed in isolation. Implemented 92-97.	Engineering changes (neg pressure, UV lights); N-95 respirators introduced in 1997	TST conversion rate, per 100pyrs, in HCWs	**1994**: 4.22/100pyrs **1995**: 2.92/100pyrs; **1996**: 1.41/100pyrs; **1997**: 1.48/100pyrs	**1998**: 0.74/100pyrs; **1999**: 0.57/100pyrs; **2000**: 1.04/100pyrs; **2001**: 0.71/100pyrs; **2002**: 0.28/100pyrs	*p* <0.001	Number of inpatients with active TB declining from 1997–
Wenger, 1995, USA; before/after[24]	One HIV ward in hospital	Higher index of suspicion for TB, stricter criteria for discontinuing isolation; restriction of cough procedures to isolation rooms; expansion of initial TB treatment to 4 agents; shorter turnaround time for AFB, DST.	Negative pressure, masks	TST conversion, %; HCWs	**Jan–May90**: 28% (7/25)	**Jun90–Feb91** [early]: 18% (3/17); **Mar91–Jun92** [late]: 0% (0/23)	Chi-square for trend (3 time-periods), *p* <0.01	Stringent isolation criteria were only put into effect in Feb 1991.

↑: increase; ↓: decrease; adj.: adjusted; AFB: acid-fast bacilli; AIDS: acquired immune deficiency syndrome; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CXR: chest x-ray; DST: drug sensitivity testing; ED: emergency department; HCW: health care worker; HIV+: HIV-positive; IC: infection control; MDR: multidrug-resistant; mth: month; o/p: outpatient; OR: odds ratio; pday: person-day; pmth: person-month; pt: patient; pyr: person-year; RR: risk ratio; SD: standard deviation; SOP: standard operating procedure; TB: tuberculosis; TST: tuberculin skin test; unadj.: unadjusted; USA: United States of America; UV: ultraviolet

Table 4. Summary of quality assessments for retrospective studies (Downs & Black tool; n = 18 studies)

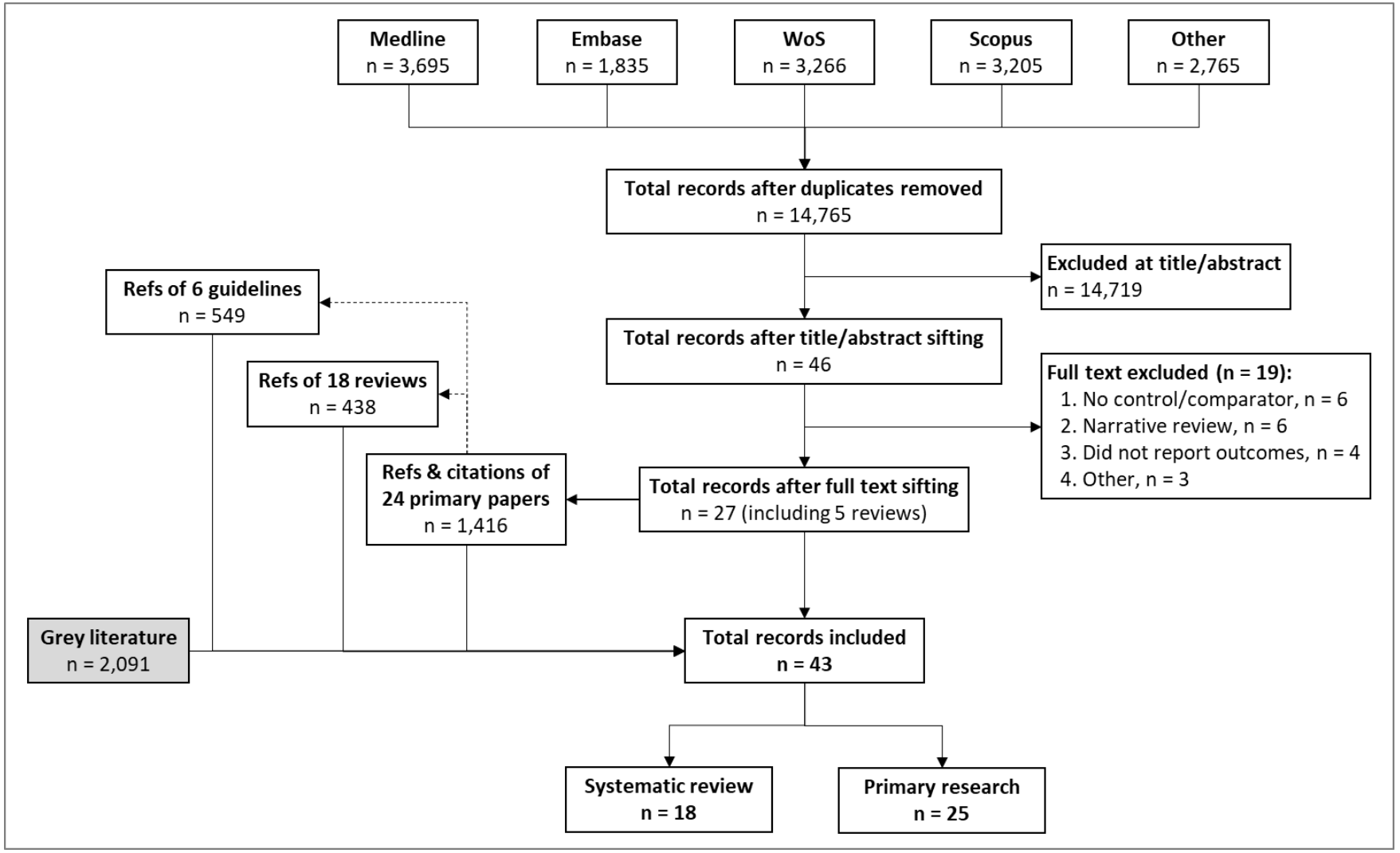
First author	Year	Reporting (max = 11)	External validity (max = 3)	Internal validity: bias (max = 7)	Internal validity: confounding (max = 6)	Total (max = 27)
Bangsberg	1999	5	2	4	1	12
Blumberg	1995	6	2	4	1	13
Blumberg	1997	6	2	4	1	13
Bryan	1983	3	1	1	1	6
Claassens	2013	6	1	2	2	11
Fridkin	1995	4	0	2	1	7
Harries	2002	7	1	4	1	13
Holzman	1995	4	2	2	2	10
Jacobson	1957	4	0	3	2	9
Jarvis	1995	6	1	4	2	13
Jones	2002	3	1	2	2	8
Louther	1997	3	2	2	2	9
Maloney	1995	5	2	2	1	10
O'Hara	2017	7	1	1	3	12
Sinkowitz	1996	6	0	4	2	12
Stroud	1995	4	0	2	1	7
Uyamadu	1997	3	0	2	1	6
Welbel	2009	5	0	3	1	9

Table 5. Summary of quality assessment for prospective studies (n = 7 studies)

First author	Year	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Baussano	2007	No	No	No	Yes	No	No
Behrman	1998	No	No	No	No	No	No
da Costa	2009	No	No	No	No	No	No
Moro	2000	No	No	No	No	Yes	No
Roth	2005	No	No	No	No	Yes	No
Wenger	1995	No	No	No	No	No	No
Yanai	2003	No	No	No	No	Yes	No

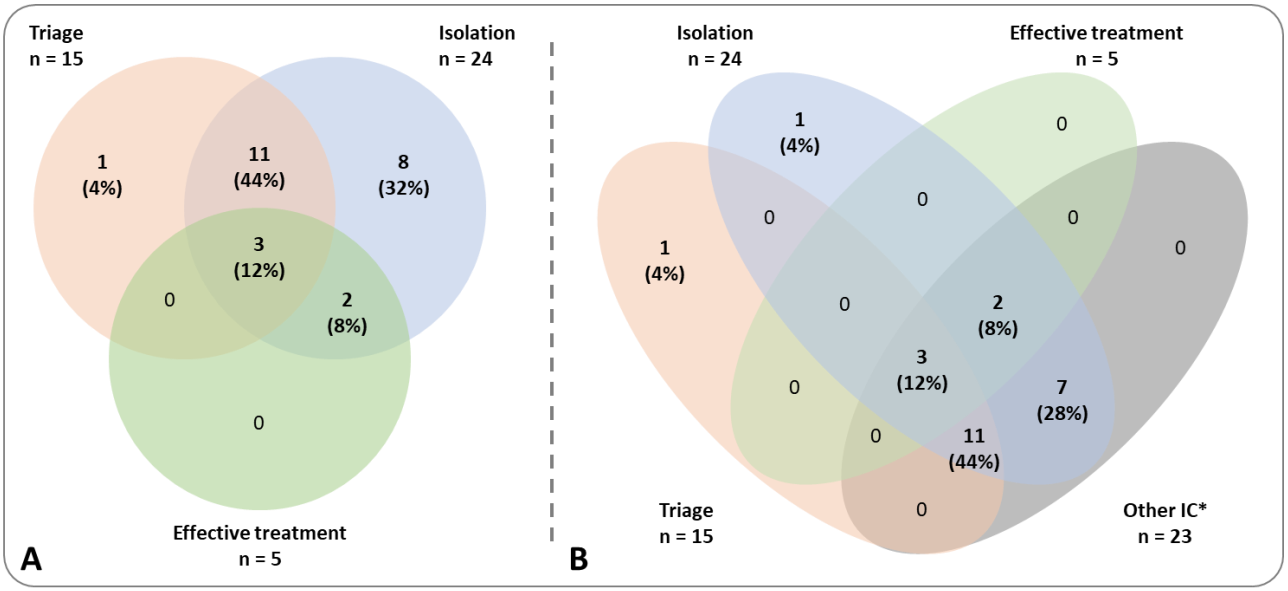
6.2. Figures

Figure 1. Flow diagram showing databases searched; numbers of records identified, sifted, reviewed, and included; and reasons for exclusion



Refs: references; WoS: Web of Science

Figure 2. Venn diagram showing overlap between interventions of interest implemented in the 25 studies included



Panel A: overlap between the three interventions of interest; Panel B: overlap between the three interventions of interest and other infection control measures implemented

*Includes administrative, personal protective, and environmental infection control measures

IC: infection control

Figure developed with Venny v2.1.[59]

6.3. GRADE assessment (exported from GRADEpro on 03 October 2018)

6.3.1. PICO 1:1, can triage of people with TB signs and/or symptoms be used in health care settings to reduce TB transmission to HCWs (including CHWs) when compared to transmission to HCW (including) CHWs in settings with no or different interventions?

Table 6. PICO 1:1, evidence summary

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Triage**	**No triage**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in LTBI incidence/prevalence in all settings [a]												
6 [1,2,3,4,5,6,b,c,d,e,f]	observational studies [g]	serious [h]	not serious	very serious [i]	serious [j]	none	1966/24852 (7.9%)	1350/9647 (14.0%)	**RR 0.57** (-- to --)	**60 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in low TB burden settings [k]												
5 [2,3,4,5,6,b,c,f,l]	observational studies [g]	serious [h]	not serious	very serious [i]	serious [m]	none	206/22035 (0.9%)	322/8045 (4.0%)	**RR 0.23** (-- to --)	**31 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in high TB burden settings [n]												
1 [1,d]	observational studies	serious [o]	not serious [p]	serious [q]	not serious	none	1760/2817 (62.5%)	1028/1602 (64.2%)	**RR 0.97** (-- to --)	**19 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in LTBI incidence/prevalence in secondary/tertiary care [r]												
6 [1,2,3,4,5,6,b,c,d,e,f]	observational studies [g]	serious [h]	not serious	very serious [i]	serious [j]	none	1966/24852 (7.9%)	1350/9647 (14.0%)	**RR 0.57** (-- to --)	**60 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in all settings [s]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Triage**	**No triage**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [7,8,t,u,v]	observational studies	serious [w]	not serious	very serious [x]	serious [y]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in low TB burden settings												
1 [9]	observational studies	not serious	not serious [p]	not serious	serious [z]	none			**RR 0.32** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in high TB burden settings [aa]												
2 [7,8,u,v]	observational studies	serious [w]	not serious	very serious [x]	serious [y]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in secondary/tertiary care [ab]												
2 [7,8,t,u,v]	observational studies	serious [w]	not serious	very serious [x]	serious [y]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

PICO 1:1, explanations

a. PLEASE NOTE: The total number of studies measuring the effect of triage on the incidence of LTBI in all settings was 10. Four studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Louther, 1997; and 4) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.

b. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Baussano, 2007: incidence rate of TST conversions of 106/4034 person-years before TBIC interventions were implemented, vs. 42 TST conversions per 4463 person-years after implementation (crude rate ratio 0.36 after vs. before).

c. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Blumberg, 1998 (some overlap with 1995 paper): TST conversion rate of 5.98/100 person-years in 1992 (pre-intervention) to 1.09/100 person-years from 1993–1997 (after the intervention was implemented; crude incidence rate ratio 0.18, after vs. before [derived from data presented]; authors report a p-value comparing the two time periods: <0.001).

d. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Yanai, 2003: TST conversions from 9.3 per 100 person-years (95% CI 3.3–15.3) before the implementation of TBIC measures (in 1995–1997) to 6.4 per 100 person-years (95% CI 1.5–11.4) and 2.2 per 100 person-years (95% CI 0–5.1), after implementation, in 1998 and 1999, respectively. Unadjusted rate ratio 0.9 (95% CI 0.4–2.2) for 1998 vs. 1995–1997 and 0.03 (95% CI 0.01–0.2) for 1999 vs. 1995–1997; adjusted rate ratio 0.4 (95% CI 0.1–1.6) and 0.01 (95% CI 0–0.04) for 1998 and 1999 vs. 1995–1997, respectively).

e. Definitions of triage varied widely between the six studies: Bangsberg - "all patients known HIV+, with HIV risk factors, or homelessness presenting with pneumonia/evidence of TB were isolated on presentation at the emergency room"; Blumberg 1995 - "expanded respiratory isolation policy"; Holzman - not defined; Roth - "rapid diagnosis and treatment"; Welbel - "revised policy (based on CDC guidelines) for isolation [CDC 1994: "in hospitals and other inpatient facilities, any patient suspected of having or known to have infectious TB should be placed in a TB isolation room"]; and Wenger - "higher index of suspicion for TB and stricter application of isolation criteria"

f. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Louther, 1997: 7.2 TST conversions per 100 person-years before the implementation of infection control measures, compared with 3.3 per 100 person-years after the implementation (crude rate ratio 0.46 [derived from data presented]; authors report p-value comparing the two groups: 0.001).

g. A mix of before/after, during/after, and prospective and retrospective cohort studies.

h. All studies are observational. Several studies have high risk of bias, with loss to follow-up, or incomplete ascertainment and/or reporting of outcomes of interest

i. Indirectness exists in the wide variation in types of triage and the descriptions of their implementation, as well as the implementation of a large number of infection control measures at one time. Please see assessment of directness for details.

j. Low number of events (<300) in almost all studies and two studies (Bangsberg and Wenger) have fewer than 20 events. The exception is the study by Roth et al., which has a total 2,878 events.

k. PLEASE NOTE: The total number of studies estimating the effect of triage on the incidence of LTBI in low TB burden settings was eight. Three studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; and 3) Louther, 1997. Please see separate footnotes that summarise the results of these studies.

l. Definitions of triage varied widely between the five studies: Bangsberg - "all patients known HIV+, with HIV risk factors, or homelessness presenting with pneumonia/evidence of TB were isolated on presentation at the emergency room"; Blumberg 1995 - "expanded respiratory isolation policy"; Holzman - not defined; Welbel - "revised policy (based on CDC guidelines) for isolation [CDC 1994: "in hospitals and other inpatient facilities, any patient suspected of having or known to have infectious TB should be placed in a TB isolation room"]; and Wenger - "higher index of suspicion for TB and stricter application of isolation criteria"

m. All studies have small numbers of events (<300; two had <20 events) and moderate overall sample sizes (except for Blumberg et al.)

n. PLEASE NOTE: The total number of studies estimating the effect of triage on the incidence of LTBI in high TB burden settings was two. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) Yanai, 2003. Please see the separate footnote that summarises the results of this study.

o. High loss to follow-up.

p. Cannot comment on inconsistency as data from only one study included.

q. Very different definitions of triage used, population not well described, differences in background risk, and triage implemented along with other infection control measures. Please see assessment of directness for details.

r. PLEASE NOTE: The total number of studies measuring the effect of triage on the incidence of LTBI in secondary/tertiary care settings was 10. Four studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Louther, 1997; and 4) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.

s. PLEASE NOTE: The total number of studies measuring the effect of triage on the incidence of TB disease in all settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Jacobson, 1957; and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.

t. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Jacobson, 1957: incidence rate of 78 episodes of TB disease among healthcare workers in 38,331 person-years in the control group (1942–51, before the intervention was implemented) to 12 episodes in 18,229 person-years after the implementation of triage (1952–55; crude incidence rate ratio 0.32, after vs. before).

u. Definitions of triage differed between the two studies: Harries - "priority to patients with chronic cough; rapid collection of sputum specimens" and Yanai - "triage/isolation and expedited diagnosis training for health care workers"

v. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. O'Hara, 2017: Unadjusted odds ratio (OR) for TB disease in HCW at facilities with a higher administrative score was 0.94 (95% CI 0.87–1.02; p = 0.12). Adjusted OR (adjusted for environmental score, PPE score, miscellaneous score, and number of TB patients) 0.97 (95% CI 0.90–1.04; p = 0.36).

w. Under-ascertainment of outcomes in at least one study; poor reporting of loss to follow-up.

x. Very serious indirectness exists in terms of the population studied and the nature and implementation of the intervention. Please see assessment of directness for details.

y. Small numbers of events in both studies.

z. Small number of outcomes in before (n = 78) and after (n = 12) periods.

aa. PLEASE NOTE: The total number of studies measuring the effect of triage on the incidence of TB disease in high TB burden settings was three. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) O'Hara, 2017. Please see the separate footnote that summarises the results of this study.

ab. PLEASE NOTE: The total number of studies measuring the effect of triage on the incidence of TB disease in secondary/tertiary care settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Jacobson, 1957; and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.

PICO 1:1, references

1. Roth VR, Garrett DO,Laserson KF,Starling CE,Kritski AL,Medeiros EAS,Binkin N,Jarvis WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals.. Int J Tuberc Lung Dis; 2005.
2. Wenger PN, Otten J,Breeden A,Orfas D,Beck-Sague CM,Jarvis WR. Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. Lancet; 1995.
3. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.
4. Blumberg HM, Watkins DL,Berschling JD,Antle A,Moore P,White N,Hunter M,Green B,Ray SM,McGowan Jr. J E. Preventing the nosocomial transmission of tuberculosis. Ann Intern Med; 1995.
5. Bangsberg DR, Crowley K,Moss A,Dobkin JF,McGregor C,Neu HC. Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. Infect Control Hosp Epidemiol; 1997.
6. Holzman, RS. A comprehensive control program reduces transmission of tuberculosis to hospital staff. Clin Infect Dis; 1995.
7. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
8. Harries AD, Hargreaves NJ,Gausi F,Kwanjana JH,Salaniponi FM. Preventing tuberculosis among health workers in Malawi. Bull WHO; 2002.
9. Jacobson G, Hoyt DD,Bogen E. Tuberculosis in hospital employees as affected by an admission chest X-ray screening program. Dis Chest; 1957.

6.3.2. PICO 1:2, can respiratory isolation (spatial separation) of presumed or demonstrated infectious TB cases reduce TB transmission to HCWs (including CHWs) when compared to transmission to HCWs (including CHWs) in settings with no intervention or different interventions?

Table 7. PICO 1:2, evidence summary

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Respiratory isolation**	**No respiratory isolation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in LTBI incidence/prevalence in all settings [a]												
12 [1,2,3,4,5,6,7,8,9,10,11,12,b,c,d,e,f,g,h]	observational studies	very serious [i]	not serious	very serious [j]	serious [k]	none	2413/91397 (2.6%)	1914/40097 (4.8%)	**RR 0.55** (-- to --)	**21 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in low TB burden settings [l]												
11 [1,2,4,5,6,7,8,9,10,11,12,b,c,d,f,h]	observational studies	very serious [m]	not serious	very serious [j]	serious [k]	none	653/88580 (0.7%)	886/38495 (2.3%)	**RR 0.32** (-- to --)	**16 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in high TB burden settings [n]												
1 [3,e,g]	observational studies	serious [o]	not serious [p]	serious [j]	not serious	none	1760/2817 (62.5%)	1028/1602 (64.2%)	**RR 0.97** (-- to --)	**19 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in LTBI incidence/prevalence in secondary/tertiary care [q]												
12 [1,2,3,4,5,6,7,8,9,10,11,12,b,c,d,e,f,g,h]	observational studies	very serious [i]	not serious	very serious [j]	serious [k]	none	2413/91397 (2.6%)	1914/40097 (4.8%)	**RR 0.55** (-- to --)	**21 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in all settings [r]												
2 [13,14,s,t]	observational studies	serious [u]	not serious	very serious [v]	serious [w]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirect-ness**	**Impre-cision**	**Other con-siderations**	**Respiratory isolation**	**No respiratory isolation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reductions in active TB incidence/prevalence in low TB burden settings - not measured												
-	-	-	-	-	-	-					-	
Reductions in active TB incidence/prevalence in high TB burden settings [x]												
2 [13,14,s,t]	observational studies	serious [u]	not serious	very serious [v]	serious [w]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reductions in active TB incidence/prevalence in primary care												
1 [15,y]	observational studies	very serious [z]	not serious [p]	very serious [aa]	serious [ab]	none			**OR 1.09** (0.99 to 1.19)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Reductions in active TB incidence/prevalence in secondary/tertiary care [ac]												
2 [13,14,t]	observational studies	serious [u]	not serious	very serious [v]	serious [w]	none	110/6216 (1.8%)	129/7161 (1.8%)	**RR 0.98** (-- to --)	**0 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

PICO 1:2, explanations

a. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in all settings was 19. Seven studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) da Costa, 2009; 5) Louther, 1997; 6) Sinkowitz, 1996; and 7) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.

b. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Baussano, 2007: incidence rate of TST conversions of 106/4034 person-years before TBIC interventions were implemented, vs. 42 TST conversions per 4463 person-years after implementation (crude rate ratio 0.36 after vs. before).

c. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Blumberg, 1998; some overlap with 1995 paper): TST conversion rate of 5.98/100 person-years in 1992 (pre-intervention) to 1.09/100 person-years from 1993-1997 (after the intervention was implemented; crude incidence rate ratio 0.18, after vs. before [derived from data presented]; authors report a p-value comparing the two time periods: <0.001).

d. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Bryan, 1983: TST conversion of 4.5% of HCWs in 1976, before the implementation of TBIC measures, vs. 5.1%, 1.5%, 0.85%, and 0.59% in the four years after implementation (crude risk ratio 1.13, 0.33, 0.19, and 0.13 for 1977–1981, respectively).

e. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. da Costa, 2009: TST conversions incidence rate from 5.8 per 1,000 person-months (95% CI 4.9–6.7), to 3.7 per 1,000 person-months (95% CI 2.8–4.6); rate ratio 0.46 (95% CI 0.23–0.89) after vs. before, p = 0.006; adjusted rate ratio (adjusted for exposure and occupation) 0.24 (95% CI 0.10–0.54).

f. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Sinkowitz, 1996: TST conversion in 0%, 8.0%, and 5.1% of bronchoscopists in hospitals without IC measures and zero TB patients, 1–5 TB patients, and ≥6 TB patients, vs. 3.3%, 8.3%, and 5.7% in hospitals with the same numbers of TB patients but which had implemented four IC measures (crude risk ratio 1.04 and 1.12 [IC vs. no IC] for hospitals with 1–5 TB patients and ≥6 TB patients, respectively). In other HCW, TST conversion in 0.49%, 0.64%, and 0.76% in hospitals without IC measures and zero TB patients, 1–5 TB patients, and 6 TB patients, vs. 0.53%, 0.69% and 0.90% in hospitals with the same numbers of TB patients but which had implemented four IC measures (crude risk ratio 1.08, 1.08, and 1.18 [IC vs. no IC] for hospitals with zero, 1–5 and ≥6 TB patients, respectively).

g. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Yanai, 2003: TST conversions from 9.3 per 100 person-years (95% CI 3.3–15.3) before the implementation of TBIC measures (in 1995–1997) to 6.4 per 100 person-years (95% CI 1.5–11.4) and 2.2 per 100 person-years (95% CI 0–5.1), after implementation, in 1998 and 1999, respectively. Unadjusted rate ratio 0.9 (95% CI 0.4–2.2) for 1998 vs. 1995–1997 and 0.03 (95% CI 0.01–0.2) for 1999 vs. 1995–1997; adjusted rate ratio 0.4 (95% CI 0.1–1.6) and 0.01 (95% CI 0–0.04) for 1998 and 1999 vs. 1995–1997, respectively).

h. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Louther, 1997: 7.2 TST conversions per 100 person-years before the implementation of infection control measures, compared with 3.3 per 100 person-years after the implementation (crude rate ratio 0.46 [derived from data presented]; authors report p-value comparing the two groups: 0.001).

i. Most studies included here have a high or unclear risk of bias. All are observational studies, some with high rates of loss to follow-up (e.g., Roth), low or unclear levels of participation, or incomplete reporting of outcomes (e.g., Blumberg). Two studies do not report results correctly or have missing results.

j. Indirectness was primarily through the implementation of multiple infection control measures together with isolation. Please see assessment of directness for details.

k. Imprecision exists: all except two studies (Fridkin and Roth) have fewer than 300 outcomes and three studies (Bangsberg, Behrman, and Wenger) have fewer than 20 outcomes.

l. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in low TB burden settings was 16. Five studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) Louther, 1997; and 5) Sinkowitz, 1996. Please see separate footnotes that summarise the results of these studies.

m. Most studies included here have a high or unclear risk of bias. All are observational studies, some have incomplete reporting of outcomes (e.g., Blumberg), and two studies do not report results correctly or have missing results.

n. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in high TB burden settings was three. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) da Costa, 2009 and 2) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.

o. High proportions were lost to follow-up; those lost to follow-up may have been at higher risk of disease (more likely to be physicians).

p. Cannot comment on inconsistency as data from only one study are included.

q. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of LTBI in secondary/tertiary care settings was 19. Seven studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Baussano, 2007; 2) Blumberg, 1998; 3) Bryan, 1983; 4) da Costa, 2009; 5) Louther, 1997; 6) Sinkowitz, 1996; and 7) Yanai, 2003. Please see separate footnotes that summarise the results of these studies.

r. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in all settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Claassens, 2013 and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.

s. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. Claassens, 2013: Unadjusted odds ratio for smear-positive TB among health care workers in facilities where administrative controls were implemented vs. facilities without (or with fewer) administrative controls 1.09 (95% CI 0.99–1.19), p = 0.07.

t. STUDY REPORTING OUTCOME BUT NOT INCLUDED IN SUMMARY ASSESSMENTS. O'Hara, 2017: Unadjusted odds ratio (OR) for TB disease in HCW at facilities with a higher administrative score was 0.94 (95% CI 0.87–1.02; p = 0.12). Adjusted OR (adjusted for environmental score, PPE score, miscellaneous score, and number of TB patients) 0.97 (95% CI 0.90–1.04; p = 0.36).

u. Under-ascertainment of outcome in at least one study. All studies implemented isolation/spatial separation in addition to a number of other TBIC interventions; the effect of isolation/separation on the outcome of interest cannot be determined. Poor reporting of loss to follow-up.

v. Very serious indirectness exists, for populations studied and in the nature of and fidelity to the intervention. Please see assessment of directness for details.

w. Both studies had fewer than 200 events; one had fewer than 100 events.

x. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in high TB burden settings was four. Two studies were excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because they did not report results in a format suitable for aggregation. These were (first author, year published): 1) Claassens, 2013 and 2) O'Hara, 2017. Please see separate footnotes that summarise the results of these studies.

y. Please note that the odds ratio quoted for this study is for the development of smear-positive TB among healthcare workers at facilities classified by their implementation of infection control measures (i.e., the authors reported slightly increased odds of developing smear-positive TB in healthcare workers in facilities where administrative controls were implemented compared with facilities without or with fewer administrative controls).

z. High likelihood of under-ascertainment of outcome (smear-positive disease in HCW), as only routine records used, without verification or any additional efforts to estimate numbers of cases. In addition, high variability in implementation intervention across different facilities, with isolation only implemented in ~50% of facilities. Most importantly, the study used the facilities as the base unit for assessing risk of TB disease (so reduced TB incidence to a binary of 'any' vs. 'no' HCW developing TB at a particular facility) - individual HCW data not analysed.

aa. Indirectness is severe. Please see assessment of directness for details.

ab. Small effect seen, and in the opposite direction to expected. Confidence interval is narrow, but crosses 1.

ac. PLEASE NOTE: The total number of studies measuring the effect of isolation on the incidence of active TB disease in secondary/tertiary care settings was three. One study was excluded from the summary analysis (certainty estimates and crude summaries of findings [meta-analysis was NOT conducted]) because it did not report results in a format suitable for aggregation. This was (first author, year published): 1) O'Hara, 2017. Please see the separate footnote that summarises the results of this study.

PICO 1:2, references

1. Jones, SG. Evaluation of a human immunodeficiency virus rule out tuberculosis critical pathway as an intervention to decrease nosocomial transmission of tuberculosis in the inpatient setting. AIDS Patient Care Stds; 2002.
2. Jarvis, WR. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis. Am J Infect Control; 1995.
3. Roth VR, Garrett DO,Laserson KF,Starling CE,Kritski AL,Medeiros EAS,Binkin N,Jarvis WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals.. Int J Tuberc Lung Dis; 2005.
4. Wenger PN, Otten J,Breeden A,Orfas D,Beck-Sague CM,Jarvis WR. Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. Lancet; 1995.
5. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.
6. Uyamadu N, Ahkee S,Carrico R,Tolentino A,Wojda B,Ramirez J. Reduction in tuberculin skin-test conversion rate after improved adherence to tuberculosis isolation. Infect Control Hosp Epidemiol; 1997.
7. Maloney SA, Pearson ML,Gordon MT,Del Castillo R,Boyle JF,Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med; 1995.
8. Fridkin SK, Manangan L,Bolyard E,Jarvis WR. SHEA-CDC TB survey, Part II: Efficacy of TB infection control programs at member hospitals, 1992. Society for Healthcare Epidemiology of America. Infect Control Hosp Epidemiol; 1995.
9. Blumberg HM, Watkins DL,Berschling JD,Antle A,Moore P,White N,Hunter M,Green B,Ray SM,McGowan Jr. J E. Preventing the nosocomial transmission of tuberculosis. Ann Intern Med; 1995.
10. Behrman AJ, Shofer FS. Tuberculosis exposure and control in an urban emergency department. Ann Emerg Med; 1998.
11. Bangsberg DR, Crowley K,Moss A,Dobkin JF,McGregor C,Neu HC. Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. Infect Control Hosp Epidemiol; 1997.

12. Holzman, RS. A comprehensive control program reduces transmission of tuberculosis to hospital staff. Clin Infect Dis; 1995.
13. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
14. Harries AD, Hargreaves NJ,Gausi F,Kwanjana JH,Salaniponi FM. Preventing tuberculosis among health workers in Malawi. Bull WHO; 2002.
15. Claassens M, van Schalkwyk C,du Toit E,Roest E,Lombard CJ,Enarson DA,Beyers N,Borgdorff MW. Tuberculosis in Healthcare Workers and Infection Control Measures at Primary Healthcare Facilities in South Africa. PLoS One; 2013.

6.3.3. PICO 1:3, can effective treatment of TB disease reduce TB transmission to HCWs (including CHWs) when compared to transmission to the same populations in settings where treatment is not yet administered?

Table 8. PICO 1:3, evidence summary

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other con-siderations**	**Effective treatment**	**No effective treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in LTBI incidence/prevalence in all settings												
4 [1,2,3,4,a,b]	observational studies	very serious [c]	serious [d]	very serious [e]	very serious [f]	none	42/3081 (1.4%)	155/3260 (4.8%)	**RR 0.29** (-- to --)	**34 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in low TB burden settings												
4 [1,2,3,4,a,b]	observational studies	very serious [c]	serious [d]	very serious [e]	very serious [f]	none	42/3081 (1.4%)	155/3260 (4.8%)	**RR 0.29** (-- to --)	**34 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence in high TB burden settings - not measured												
-	-	-	-	-	-	-					-	
Reduction in LTBI incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in LTBI incidence/prevalence in secondary/tertiary care												
4 [1,2,3,4,a,b]	observational studies	very serious [c]	serious [d]	very serious [e]	very serious [f]	none	42/3081 (1.4%)	155/3260 (4.8%)	**RR 0.29** (-- to --)	**34 fewer per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in all settings - not measured												
-	-	-	-	-	-	-					-	CRITICAL

CI: Confidence interval; RR: Risk ratio

PICO 1:3, explanations

a. Please note that the study included by Welbel et al. does not describe, specifically, the implementation of treatment based on drug susceptibility, but only describes the introduction of drug susceptibility testing. We have assumed that the results of testing were then used to inform treatment.

b. Please note that meta-analysis was *not* conducted - pooled estimates and measures of effect are crude estimates.

c. There are design specific issues to these studies. Mainly, it is not possible to ascertain the effect of the intervention in question as the intervention is grouped with other interventions, which presents a serious risk of bias. There is also a serious design issue with the study by Wenger et al., as the intervention only differs slightly between before and after (3 agents vs. 4 agents). Though studies were not designed specifically to answer our question, the way they are designed does not give us confidence in the results of interest.

d. Some inconsistency exists. In the study by Jarvis, in particular, certain results are reported as unavailable, but the site of origin of these results is not specified, so this cannot be accounted for in analysis. In addition, in the study by Welbel et al., overall denominators for at-risk individuals are provided, but not the time period for which these individuals were at risk, reducing confidence in the estimates of risk.

e. Indirectness is severe and from many sources: population, intervention, and comparators (please see assessment of directness for details).

f. Serious imprecision exists. For a dichotomous outcome all studies have fewer than 110 cases (range 10–104). Samples sizes are also low in three studies (range 65–650; the exception is Welbel et al, with a sample size of 4,329).

PICO 1:3, references

1. Jarvis, WR. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*. Am J Infect Control; 1995.
2. Wenger PN, Otten J,Breeden A,Orfas D,Beck-Sague CM,Jarvis WR. Control of nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* among healthcare workers and HIV-infected patients. Lancet; 1995.
3. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.
4. Maloney SA, Pearson ML,Gordon MT,Del Castillo R,Boyle JF,Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med; 1995.

6.3.4. PICO 1:4, can triage of people with TB signs, symptoms reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?

Table 9. PICO 1:4, evidence summary

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consider-ations**	**Triage**	**No triage**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in LTBI incidence/prevalence in all settings - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in all settings												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.14** (-- to --)	**126 fewer per 1,000 (from -- to --)**	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in low TB burden settings												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.14** (-- to --)	**126 fewer per 1,000 (from -- to --)**	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in high TB burden settings - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in secondary/tertiary care												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.14** (-- to --)	**126 fewer per 1,000 (from -- to --)**	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in HIV-negative individuals - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in HIV-positive individuals												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consider-ations**	**Triage**	**No triage**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.14** (-- to --)	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

PICO 1:4, explanations

a. Please note that meta-analysis was *not* conducted - all summary estimates and measures of effect are crude estimates.

b. Serious risk of bias, probable to alter the results: exposure is different for each study between before and after groups; and not a clear differentiation of intervention vs. no intervention.

c. Multiple interventions were introduced at the same time. In addition, 'triage' was poorly defined in both studies, as targeting people with "respiratory disease and fever'" but with no mention of expedited diagnosis, or as an "increased index of suspicion for TB" without description of how this was implemented. Please see also assessment of directness.

d. Both studies had small sample sizes. The total at-risk population was 543; a total 50 events were included.

PICO 1:4, references

1. Stroud LA, Tokars JI Grieco MH Crawford JT Culver DH Edlin BR Sordillo EM Woodley CL Gilligan ME Schnieder N Williams J Jarvis WR. Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* in a New York city hospital. Infect Control Hosp Epidemiol; 1995.

2. Moro ML, Errante I Infuso A Sodano L Gori A Orcese CA Salamina G D'Amico C Besozii G Caggese L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy.. Int J Tuberc Lung Dis; 2000.

6.3.5. PICO 1:5, can respiratory isolation (spatial separation) reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?

Table 10. PICO 1:5, evidence summary

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Respiratory isolation**	**No respiratory isolation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in LTBI incidence/prevalence in all settings - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in all settings												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.14** (-- to --)	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in low TB burden settings												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.14** (-- to --)	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in high TB burden settings - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in secondary/tertiary care												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.14** (-- to --)	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in HIV-negative individuals - not measured												
-	-	-	-	-	-	-					-	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Respiratory isolation**	**No respiratory isolation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in active TB incidence/prevalence in HIV-positive individuals												
2 [1,2,a]	observational studies	serious [b]	not serious	very serious [c]	serious [d]	none	5/237 (2.1%)	45/306 (14.7%)	**RR 0.14** (-- to --)	**126 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

PICO 1:5, explanations

a. Please note that meta-analysis was *not* conducted - all summary estimates and measures of effect are crude estimates.

b. Serious risk of bias, probable to alter the results: exposure is different for each study between before and after groups; also isolation measures were in effect before and then more so after. Not a clear differentiation of intervention vs. no intervention.

c. Multiple interventions were introduced at the same time.

d. Both studies had small sample sizes. The total at-risk population was 543; a total 50 events were included.

PICO 1:5, references

1. Moro ML, Errante I Infuso A Sodano L Gori A Orcese CA Salamina G D'Amico C Besozii G Caggese L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy.. Int J Tuberc Lung Dis; 2000.

2. Stroud LA, Tokars JI Grieco MH Crawford JT Culver DH Edlin BR Sordillo EM Woodley CL Gilligan ME Schnieder N Williams J Jarvis WR. Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* in a New York city hospital. Infect Control Hosp Epidemiol; 1995.

6.3.6. PICO 1:6, can effective treatment of TB disease reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings where treatment administration is delayed?

Table 11. PICO 1:6, evidence summary

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consider-ations**	**Effective treatment**	**No effective treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in LTBI incidence/prevalence in all settings - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in all settings												
1 [1,a]	observational studies	serious [b]	not serious [c]	very serious [d]	serious [e]	none	5/193 (2.6%)	19/216 (8.8%)	**RR 0.29** (-- to --)	**62 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in low TB burden settings												
1 [1,a]	observational studies	serious [b]	not serious [c]	very serious [d]	serious [e]	none	5/193 (2.6%)	19/216 (8.8%)	**RR 0.29** (-- to --)	**62 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in high TB burden settings - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in primary care - not measured												
-	-	-	-	-	-	-					-	
Reduction in active TB incidence/prevalence in secondary/tertiary care												
1 [1,a]	observational studies	serious [b]	not serious [c]	very serious [d]	serious [e]	none	5/193 (2.6%)	19/216 (8.8%)	**RR 0.29** (-- to --)	**62 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in active TB incidence/prevalence in HIV-negative individuals - not measured												
-	-	-	-	-	-	-					-	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other consider-ations**	**Effective treatment**	**No effective treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in active TB incidence/prevalence in HIV-positive individuals												
1 [1,a]	observational studies	serious [b]	not serious [c]	very serious [d]	serious [e]	none	5/193 (2.6%)	19/216 (8.8%)	**RR 0.29** (-- to --)	**62 fewer per 1,000 (from -- to --)**	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

PICO 1:6, explanations

a. Please note that meta-analysis was *not* conducted - all summary estimates and measures of effect are crude estimates.

b. No significant difference in the treatment in the before and after groups (1.5 vs. 2.0 drugs given before vs. after; range 0-4 in both periods; p = 0.2). Exposure is also different for between before and after groups.

c. As there is only one study included we cannot comment on heterogeneity of results between studies.

d. Authors describe "expanded use of antituberculous drugs" in 'after' period, but no description of time to treatment; therefore unable to assess for difference compared with delayed treatment administration.

e. Small numbers of cases in both arms. Overall number of exposed individuals = 409 (n = 216 before; n = 193 after)

PICO 1:6, references

1. Stroud LA, Tokars JI Grieco MH Crawford JT Culver DH Edlin BR Sordillo EM Woodley CL Gilligan ME Schnieder N Williams J Jarvis WR. Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* in a New York city hospital. Infect Control Hosp Epidemiol; 1995.

7. References

1 Menzies D, Fanning A, Yuan L, Fitzgerald M. Tuberculosis among health care workers. *N Engl J Med*. 1995;**332**(2):92–8.

2 Joshi R, Reingold AL, Menzies D, Pai M. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. *PLoS Med / Public Libr Sci*. 2006;**3**(12):e494–e494.

3 Menzies D, Joshi R, Pai M. Risk of tuberculosis infection and disease associated with work in health care settings. *Int J Tuberc Lung Dis*. 2007;**11**(6):593–605.

4 Uden L, Barber E, Ford N, Cooke GS. Risk of Tuberculosis Infection and Disease for Health Care Workers: An Updated Meta-Analysis. *Open forum Infect Dis*. 2017;**4**(3):ofx137.

5 World Health Organization. WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Households. 2009. http://www.who.int/tb/publications/2009/infection_control/en/ (accessed 2018 Mar 22)

6 Jensen PA, Lambert LA, Iademarco MF, Ridzon R, CDC. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. *MMWR Recomm reports Morb Mortal Wkly report Recomm reports*. 2005;**54**(RR-17):1–141.

7 World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. 2016. http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf?ua=1 (accessed 2018 Mar 2)

8 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;**52**(6):377–84.

9 Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Intervention Version 5.1 (updated March 2011). The Cochrane Collaboration. 2011. http://handbook.cochrane.org (accessed 2018 Apr 30)

10 West S, King V, Carey TS, et al. Systems to rate the strength of scientific evidence. *Evid Rep Technol Assess (Summ)*. 2002;(47):1–11.

11 Fielding KL, Harris RC, Karat AS, Falconer J, Moore DAJ. Systematic review for evidence of administrative infection control interventions to reduce tuberculosis transmission and three related background questions: Study protocol. PROSPERO 2018 CRD42018085226. 2018. http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018085226 (accessed 2018 Apr 30)

12 Jacobson G, Hoyt DD, Bogen E. Tuberculosis in hospital employees as affected by an admission chest X-ray screening program. *Dis Chest*. 1957;**32**(1):27–38.

13 Uyamadu N, Ahkee S, Carrico R, Tolentino A, Wojda B, Ramirez J. Reduction in tuberculin skin-test conversion rate after improved adherence to tuberculosis isolation. *Infect Control Hosp Epidemiol*. 1997;**18**(8):575–9.

14 Harries AD, Hargreaves NJ, Gausi F, Kwanjana JH, Salaniponi FM. Preventing tuberculosis among health workers in Malawi. *Bull World Health Org*. 2002;**80**(7):526–31.

15 Yanai H, Limpakarnjanarat K, Uthaivoravit W, Mastro TD, Mori T, Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. *Int J Tuberc Lung Dis*. 2003;**7**(1):36–45.

16 Roth VR, Garrett DO, Laserson KF, et al. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals. *Int J Tuberc Lung Dis*. 2005;**9**(12):1335–42.

17 O'Hara LM, Yassi A, Bryce EA, et al. Infection control and tuberculosis in health care workers: an assessment of 28 hospitals in South Africa. *Int J Tuberc Lung Dis*. 2017;**21**(3):320–6.

18 Bangsberg DR, Crowley K, Moss A, Dobkin JF, McGregor C, Neu HC. Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. *Infect Control Hosp Epidemiol*. 1997;**18**(8):566–70.

19 Baussano I, Bugiani M, Carosso A, et al. Risk of tuberculin conversion among healthcare workers and the adoption of preventive measures. *Occup Environ Med*. 2007;**64**(3):161–6.

20 Blumberg HM, Watkins DL, Berschling JD, et al. Preventing the nosocomial transmission of tuberculosis. *Ann Intern Med*. 1995;**122**(9):658–63.

21 Blumberg HM, Sotir M, Erwin M, Bachman R, Shulman JA. Risk of house staff tuberculin skin test conversion in an area with a high incidence of tuberculosis. *Clin Infect Dis*. 1998;**27**(4):826–33.

22 Louther J, Rivera P, Feldman J, Villa N, DeHovitz J, Sepkowitz KA. Risk of tuberculin conversion according to occupation among health care workers at a New York City hospital. *Am J Respir Crit Care Med*. 1997;**156**(1):201–5.

23 Welbel SF, French AL, Bush P, DeGuzman D, Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. *Am J Infect Control*. 2009;**37**(8):668–73.

24 Wenger PN, Otten J, Breeden A, Orfas D, Beck-Sague CM, Jarvis WR. Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. *Lancet*. 1995;**345**(8944):235–40.

25 Stroud LA, Tokars JI, Grieco MH, et al. Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in a New York City hospital. *Infect Control Hosp Epidemiol*. 1995;**16**(3):141–7.

26 Moro ML, Errante I, Infuso A, et al. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy. *Int J Tuberc Lung Dis*. 2000;**4**(1):61–8.

27 Fridkin SK, Manangan L, Bolyard E, Jarvis WR. SHEA-CDC TB survey, Part II: Efficacy of TB infection control programs at member hospitals, 1992. Society for Healthcare Epidemiology of America. *Infect Control Hosp Epidemiol*. 1995;**16**(3):135–40.

28 Jones SG. Evaluation of a human immunodeficiency virus rule out tuberculosis critical pathway as an intervention to decrease nosocomial transmission of tuberculosis in the inpatient setting. *AIDS Patient Care Stds*. 2002;**16**(8):389–94.

29 da Costa PA, Trajman A, Mello FC, et al. Administrative measures for preventing Mycobacterium tuberculosis infection among healthcare workers in a teaching hospital in Rio de Janeiro, Brazil. *J Hosp Infect*. 2009;**72**(1):57–64.

30 Jarvis WR. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis. *Am J Infect Control*. 1995;**23**(2):146–51.

31 Maloney SA, Pearson ML, Gordon MT, Del Castillo R, Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Ann Intern Med*. 1995;**122**(2):90–5.

32 Behrman AJ, Shofer FS. Tuberculosis exposure and control in an urban emergency department. *Ann Emerg Med*. 1998;**31**(3):370–5.

33 Bryan CS. The hospital tuberculosis registry: an aid to infection control. *Am J Infect Control*. 1983;**11**(2):57–62.

34 Claassens MM, van Schalkwyk C, du Toit E, et al. Tuberculosis in healthcare workers and infection control measures at primary healthcare facilities in South Africa. *PLoS ONE [Electronic Resour*. 2013;**8**(10):e76272–e76272.

35 Holzman RS. A comprehensive control program reduces transmission of tuberculosis to hospital staff (Abstract 80, 33rd Annual Meeting of the Infectious Diseases Society of America, San Francisco, USA). *Clin Infect Dis*. 1995;**21**(733).

36 Sinkowitz RL, Fridkin SK, Manangan L, Wenger PN, Jarvis WR. Status of tuberculosis infection control programs at United States hospitals, 1989 to 1992. *Am J Infect Control*. 1996;**24**(4):226–34.

37 World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. 2015. p. 19. http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020.pdf?ua=1 (accessed 2018 Jan 10)

38 Members of the Ad Hoc Committee for the Guidelines for Preventing the Transmission fo Tuberculosis in Canadian Health Care F, Other Institutional S. Guidelines for preventing the transmission of tuberculosis in Canadian Health Care Facilities and other institutional settings. *Canada Commun Dis Rep*. 1996;**22 Suppl 1**:i–iv,

1-50, i–iv, 1-55.

39 Cookson ST, Jarvis WR. Prevention of nosocomial transmission of Mycobacterium tuberculosis. *Infect Dis Clin North Am*. 1997;**11**(2):385–409.

40 Conde MB, Melo FAF de, Marques AMC, et al. III Brazilian Thoracic Association Guidelines on tuberculosis. *J Bras Pneumol*. 2009;**35**(10):1018–48.

41 Davis YM, McCray E, Simone PM. Hospital infection control practices for tuberculosis. *Clin Chest Med*. 1997;**18**(1):19–33.

42 Harries AD, Maher D, Nunn P. Practical and affordable measures for the protection of health care workers from tuberculosis in low-income countries. *Bull World Health Org*. 1997;**75**(5):477–89.

43 Humphreys H. Control and prevention of healthcare-associated tuberculosis: the role of respiratory isolation and personal respiratory protection. *J Hosp Infect*. 2007;**66**(1):1–5.

44 Jensen PA, Lambert LA, Iademarco MF, Ridzon R, CDC. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. *MMWR Recomm reports Morb Mortal Wkly report Recomm reports*. 2005;**54**(RR-17):1–141.

45 L'Ecuyer PB, Fraser VJ. Further progress in the portection of healthcare workers. *Curr Opin Infect Dis*. 1996;**9**:280–5.

46 McGowan JEJ. Nosocomial tuberculosis: new progress in control and prevention. *Clin Infect Dis*. 1995;**21**(3):489–505.

47 Nasreen S, Shokoohi M, Malvankar-Mehta MS. Prevalence of Latent Tuberculosis among Health Care Workers in High Burden Countries: A Systematic Review and Meta-Analysis. *PLoS One*. 2016;**11**(10):e0164034.

48 Nathavitharana RR, Bond P, Dramowski A, et al. Agents of change: The role of healthcare workers in the prevention of nosocomial and occupational tuberculosis. *Press Medicale*. 2017;**46**(2 Pt 2):e53–62.

49 Punjabi CD, Perloff SR, Zuckerman JM. Preventing Transmission of Mycobacterium tuberculosis in Health Care Settings. *Infect Dis Clin North Am*. 2016;**30**(4):1013–22.

50 Raymond L. ACOEM guidelines for protecting health care workers against tuberculosis. American College of Occupational and Environmental Medicine. *J Occup Environ Med*. 1998;**40**(9):765–7.

51 Sepkowitz KA. Tuberculosis control in the 21st century. *Emerg Infect Dis*. 2001;**7**(2):259–62.

52 Seyferth PD. Guidelines for preventing occupational exposure to TB. *Missouri Dent J*. 1994;**74**(4):10–1.

53 Tam CM, Leung CC. Occupational tuberculosis: a review of the literature and the local situation. *Hong Kong Med J*. 2006;**12**(6):448–55.

54 Trajman A, Menzies D. Occupational respiratory infections. *Curr Opin Pulm Med*. 2010;**16**(3):226–34.

55 Van Cutsem G, Isaakidis P, Farley J, Nardell E, Volchenkov G, Cox H. Infection Control for Drug-Resistant Tuberculosis: Early Diagnosis and Treatment Is the Key. *Clin Infect Dis*. 2016;**62**:S238–43.

56 Verkuijl S, Middelkoop K. Protecting Our Front-liners: Occupational Tuberculosis Prevention Through Infection Control Strategies. *Clin Infect Dis*. 2016;**62**:S231–7.

57 Zuckerman JM. Prevention of health care-acquired pneumonia and transmission of Mycobacterium tuberculosis in health care settings. *Infect Dis Clin North Am*. 2011;**25**(1):117–33.

58 Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City. *Am J Infect Control*. 1995;**23**(6):352–6.

59 Oliveros J. Venny. An interactive tool for comparing lists with Venn's diagrams. 2015. http://bioinfogp.cnb.csic.es/tools/venny/index.html (accessed 2018 Apr 30)

Systematic Review of the Evidence regarding TB Infection Prevention and Control strategies in Clinical and Programmatic Settings

PICO Questions 2, 3 and 4

March 2018

Updated 26th March 2018

Reviewers:

A/Prof Greg Fox PhD MBBS FRACP MIPH
Miss Lisa Redwood BNurs MIPH
Dr Vicky Chang BSc(Med) MBBS FRACP
Dr Jennifer Ho PhD MBBS MPH FRACP

University of Sydney, Australia

Contents

Index of Tables

1. Background

Transmission of *M. tuberculosis* within health care settings is an important driver of the global TB epidemic. The extent to which the infection spreads to others is influenced by the infectiousness of the TB patient, local environmental conditions and the susceptibility of exposed individuals. Institutional strategies to prevent transmission integrate the use of managerial processes, administrative guidelines, environmental protections and personal protective devices. This systematic review will evaluate the published evidence for infection control practices within the health sector. Specifically, it focuses upon techniques for respiratory hygiene, engineering and environmental controls to reduce transmission and the use of personal respiratory protection. This review addresses three Population-Intervention-Comparator-Outcome (PICO) questions developed for the WHO policy on TB infection control in health-care facilities, congregate settings and households. These are:

- PICO 2: In health care workers (HCWs) or other persons attending healthcare or congregate settings, can respiratory hygiene and/or cough etiquette reduce TB transmission when compared to settings where these interventions are not implemented?
- PICO 3: In persons in TB care or other high TB transmission risk settings does use of selected engineering and environmental controls reduce TB transmission when compared to similar populations in settings with no intervention?
- PICO 4: In persons in TB care or other high TB transmission risk settings do the use of particulate filters or implementing a respiratory protection

programme, when compared to no intervention, reduce risk of TB transmission?

2. Methods

We have performed a systematic review for each of the three PICO questions, in accordance with the PRISMA guidelines. The protocol was be reviewed and approved by the secretariat of the World Health Organization prior to commencement.

Search strategy

We searched electronic health care databases, evidence based reviews, and selected grey literature. Search terms developed by the authors for each PICO question are provided Appendix 1.

The information sources searched to identify relevant literature are listed in Table 2.1. No search limits were applied to: language, publication type, date of publication or study design during the database searches.

We have reviewed clinical trials registries to identify any unpublished studies of relevance. Where studies were listed as nearing completion, we attempted to contact study authors to obtain preliminary findings. Similarly, planned to contact the authors of relevant published conference abstracts for study findings.

Table 2.1: Information sources to be searched

Category	**Sources**
Healthcare databases	MEDLINE EMBASE Web of Science PubMed CENTRAL LILACS Clinical trials registries (e.g. clinicaltrials.gov*)
Evidence-based reviews	Cochrane Database of Systematic Reviews Database of Abstracts of Reviews of Effect (DARE) (ended in 2015) HTA database (University of York)
Grey literature	International Union of Tuberculosis and Lung Disease conference electronic abstract database OpenSIGLE

The following clinical trial websites were also reviewed with the search terms ‘tuberculosis OR TB: ANZCTR, Rebec, ChrCTR, RPCEC, CTRI, EU-CTR, DRKS, IRCT, UMIN-CTR, Thailand, NL, ISRCTN, US clinical trials.gov, PACTR and SLCTR.

In conducting the search, intervention terms were combined using Boolean operator “OR”. Outcome terms were be combined using OR. Intervention and outcome term groupings were combined using AND. Population and comparator terms were not

included in the search strategy, as a manageable number of hits were expected to be identified using only the intervention and outcome terms. By avoiding the need to restrict the search according to the population and comparator, the likelihood of missing a potentially relevant paper was reduced.

In the first stage of study selection, two reviewers for suitability for subsequent full text review independently screened the titles and abstracts of papers identified from the above search. For studies that were in a language other than English, we consulted an individual with fluency in that language for interpretation and translation.

Study selection and data extraction

In the second stage of study selection, full-text papers identified from the first stage were reviewed independently by two reviewers. Data were extracted from those papers selected for final inclusion, using a standardized database according to the PICO framework outlined above, by one reviewer and checked by a second reviewer for consistency. Unresolved disagreements in study selection or extraction were resolved by a third, independent reviewer. An additional search of reference lists of all included articles and a search of all articles citing included articles were also conducted to identify any further articles eligible for inclusion.

Data compilation and quality assessment

Assessment of bias was conducted for individual studies and across studies as prescribed in the PRISMA statement for reporting of systematic reviews. Risk of bias was assessed at the study level using the Cochrane Collaboration Tool[1111111111] for

prospective cohort studies and animal studies (if included), and the Down's and Black tool for retrospective cohort studies[2].

Analysis

We intended to perform a meta-analysis if two or more studies addressing the same research question, population, intervention, comparator and outcome were identified. In this situation, pooled aggregate data meta-analysis, using a random effects model according to the method of DerSImonian Laird, was planned. Summary odds ratios and 95% confidence intervals comparing the intervention to the comparator were to be calculated using a generalised linear mixed model with study as a random effect. Where a meta-analysis was performed, forest plots were to summarise the data for individual trials. We intended to calculate the I^2 statistic to evaluate heterogeneity between studies. We intended to assess publication bias by funnel plot, where possible. Where possible, results will be stratified by World Bank county classification as low-middle or high-income countries, and (where possible) HIV status, comorbidities such as diabetes, degree of drug resistance (MDR-TB, drug susceptible TB) and age group.

Where insufficient studies were available to perform a meta-analysis, or where substantial heterogeneity precluded meta-analysis, we presented a table of findings of individual included studies. An assessment of the overall study outcomes will be performed using the GRADE methodology, summarized using GRADEPro software. Where meta-analyses were not possible, on account of heterogeneity in the intervention or outcome measures between studies, we followed the GRADE approach to narrative synthesis of the evidence, as described by Murad et al[3].

Eligibility criteria for studies

The following inclusion and exclusion criteria were applied to the searches:

Inclusion criteria

- The following study types were included: randomized controlled-trials, prospective cohort studies, retrospective cohort studies or consecutive case control studies.
- Outcomes were included when measured in either humans or animals.

Exclusion criteria

- Any study that did not report any of the outcomes of interest.
- Any study reporting solely on primary outcomes of interest without a control or comparator group.
- Commentaries or mathematical modelling studies.
- Number of enrolled subjects in the intervention arm <10.
- No language restrictions will be applied.

For studies that were in a language other than English, we consulted an individual fluent in that language for interpretation and translation. For studies where only an abstract was available, the study authors were contacted to obtain additional study information. Contactable, consenting authors were asked to complete a data collection form, specifically designed for this review, to obtain relevant study data. Studies were included from 1940 to the present.

Study selection and data extraction

In the first stage of study selection, titles and abstracts of papers identified from the above search were screened independently by two reviewers (two of LR, VC and JH), for suitability for subsequent full text review.

In the second stage of study selection, full-text papers identified from the first stage were reviewed independently by two reviewers (two of LR, VC and JH). A standardised extraction form was developed and pilot tested. Two reviewers (two of LR, VC or JH, and GF), independently extracted the data from the papers selected for final inclusion. Data were compared, and unresolved disagreements in study selection or extraction were resolved consensus. An additional search of reference lists of all included articles, a search of all articles citing the included articles, and review articles related to the research question were also conducted, to identify any further articles eligible for inclusion. For studies where interim findings were reported in one paper, and then more completely in a subsequent paper, the latter was selected for review inclusion. Study authors were contacted to clarify or obtain missing data where necessary.

Data extracted

Variables extracted from included studies include the following, where available:

- Country
- Setting (e.g. inpatient ward, outpatient clinic, congregate setting, emergency department)
- Participant demographics
- Participant comorbidities (HIV, diabetes)
- Details of the intervention (administrative measures, respiratory protection, mask types, fitting, engineering)

- Details of the comparator
- Outcomes of interest (e.g. incidence of LTBI, prevalence of TB)

Study quality assessment

Risk of bias was assessed using the Downs and Black checklist for assessing the quality of retrospective cohort study [2]. For prospective cohort studies (including animal studies), risk of bias was assessed using the Cochrane Collaboration risk of bias tool [4].

Analysis

Outcomes were presented as proportions, and effect estimates were presented as absolute risk differences. Findings of animal and human studies presented separately, given that the certainty of evidence is likely to differ between the two groups of studies.

A narrative summary was provided for each study. A summary of evidence is also presented on GradePro according to the GRADE domains (including methodological limitations / risk of bias; indirectness; imprecision; inconsistency and likelihood of publication bias).

Funding

This review was funded by the World Health Organization.

3. PICO 2: Respiratory hygiene and/or cough etiquette

Background

Respiratory hygiene is defined as the practice of covering the mouth and nose during breathing, coughing or sneezing (such as wearing a surgical mask, cloth mask, covering mouth with tissues, a sleeve, flexed elbow or hand, followed by hand hygiene), to reduce the dispersal of respiratory secretions that may contain infectious particles (Glossary of Terms). Respiratory hygiene may be undertaken by individuals with tuberculosis, or presumptive tuberculosis to reduce transmission – either within healthcare settings, congregate settings or the general community.

Research question

The research question for PICO 2 is: “In HCWs or other persons attending healthcare or congregate settings, can respiratory hygiene and/or cough etiquette reduce TB transmission when compared to settings where these interventions are not implemented?” The PICO for this question is summarised in Table 3.1

Table 3.1: Summary of PICO 2 - Respiratory hygiene and/or cough etiquette

Population	• Persons attending healthcare settings or non-healthcare congregate settings (listed in stratifications) • HCWs in healthcare settings or non-healthcare congregate settings (listed in stratifications) <u>Stratification of population:</u> *HIV status* *In-patient healthcare settings* *Out-patient healthcare settings* *Congregate settings* *MDR ward* *TB ward* *in high TB prevalence settings (usually HIC)* *in low TB prevalence settings (usually LMIC)* *(Attempting to stratify by prevalence and not by the country income level if possible)*
Intervention	• Respiratory hygiene (or training on RH)* and/or • Cough etiquette (or training on cough etiquette)
Comparator	• Setting with no intervention
Outcome	• Reduction in LTBI incidence/prevalence; or • Reduction in TB incidence/prevalence; or • Reduction in incidence rate (of TB or LTBI) ratio may also be used for comparison between population of interest and comparator group

*Respiratory hygiene was also defined as use of a surgical mask by patients to reduce transmission to others in their environment.

Results for PICO 2

The Literature review was conducted on the 6th March 2018. Medline, PubMed, Embase, LILACS, Web of Science and the Cochrane library databases were used with the search terms listed in the Appendix. In total there were 3,293 unique papers

for title and abstract screening. At this stage the search was conducted in two parts, one for the human studies and one for the animal studies, which was included later in the review due to the lack of quality and quantity of human studies available. The review of the human studies was conducted by two reviewers (JH reviewed all studies, with a second review by one of LR, VC and GF). Any discrepancies in their included papers were discussed. A total of 13 papers were identified for full text review. These were screened separately with the use of data inclusion/exclusion form by two reviewers (JH and GF). Any discrepancies were reviewed by the third reviewed (GF). In total 8 papers met the inclusion criteria, of which 5 studies met the inclusion criteria (4 where the outcome was measured in humans, and 1 where the outcome was measured in animals). Both primary studies included in the 2009 WHO Policy on Infection Control in Health-care Facilities were also included in the present review [5,6].

Figure 1: Diagram of search results for eligible studies included in review of the ability of respiratory hygiene, cough etiquette and masks (worn by patients) to reduce tuberculosis transmission

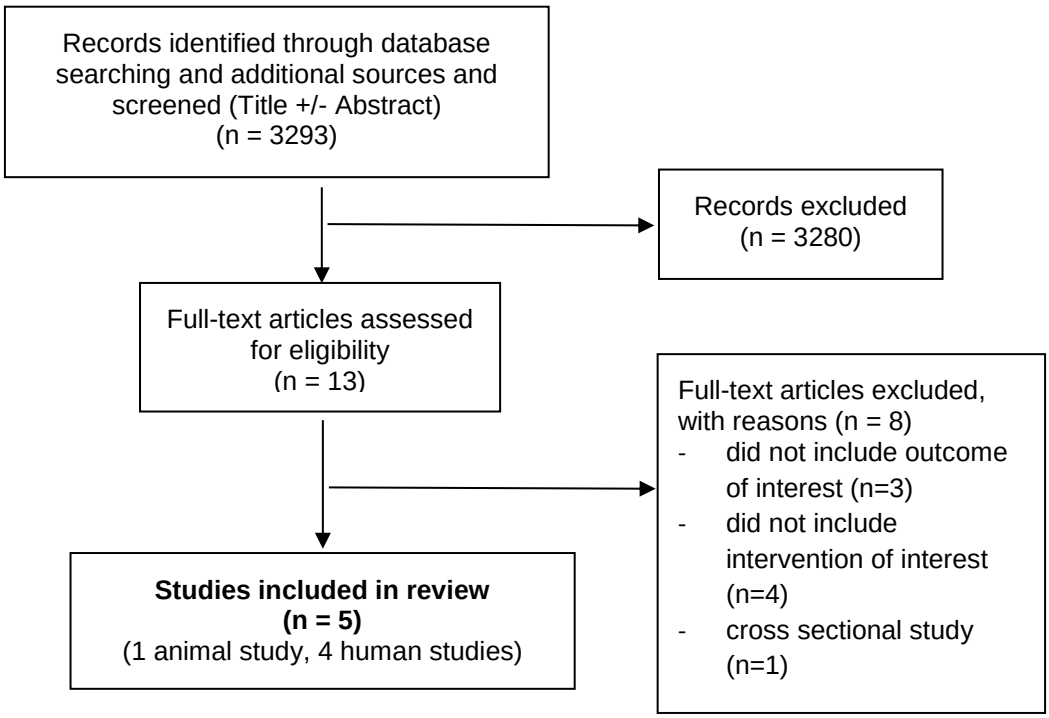


Table 2.1: Summary of included studies for PICO 2, with outcomes measured in humans

Author, Year, Country	**Study Design (years)**	**Setting**	**Study participants (sample size)**	**Type of intervention**	**Description of Control**	**Description of Intervention**	**Outcomes Measures**	**Results in control group**	**Results in intervention group**
Harries et al, 2002, Malawi[6]	Before and after (1996-1999)	40 district and mission hospitals in Malawi	HCWs	Masks worn by patients (part of Introduction of guidelines for TB control in hospitals)	Hospital procedures before implement-ation of TB control guidelines	Composite of 13 different interventions including: masks worn by patients when undergoing surgical procedures and education to TB suspects on cough hygiene	TB	Case notification rate of TB in 100/2697 HCWs: 3.7% (in 1996)	Case notification rate of TB in 96/2979 HCWs: 3.2% (in 1999) (*reduction in TB notifications by 0.5%)*
Moro et al, 2000, Italy [5]	Before and after (1992-1994)	HIV ward in a hospital in Milan, Italy with an outbreak of MDR-TB	HIV patients hospitalised in the ward implicated in this outbreak whose stay overlapped the infectious periods of the MDR-TB patients	Surgical masks (part of implement-ation of infection control measures)	Hospital procedures before implement-ation of TB infection control measures	Composite of interventions including use of surgical masks for TB during transport	MDR-TB (Number of HIV patients hospitalised on this ward diagnosed with MDR-TB)	26/90 (2455 patient days) (28.9%) developed MDR-TB (Oct 92-June 93)	0/44 (654 patient days) developed MDR-TB (after June 93) *(reduction of 28.9% in TB cases)*
Yanai 2003, Thailand [7]	Before/after study (1995-1999)	TB hospital	HCW	Surgical mask use by patients outside of TB isolation room	Pre-intervention. Not described in detail.	**Composite (A,CE,R)** Administrative: HCW training, promoting use of fit test; reduced waiting time for TB	Outcome 1: TST conversions Outcome 2: TB cases among HCWs	1: 13/77 (16.9%) 2: 30/4357 0.7/100 person years	Outcome 1 2/96 TST conversions (2.1%) *(TST conversions reduced by*

Author, Year, Country	Study Design (years)	Setting	Study participants (sample size)	Type of intervention	Description of Control	Description of Intervention	Outcomes Measures	Results in control group	Results in intervention group
						management; **patient surgical mask use and cough etiquette** outside of TB isolation room. Infection control SOP and plan **Etiquette:** education about cough etiquette. Engineering and Respiratory Protection*			*14.8% post intervention)* Outcome 2: 19/4780 (0.4 TB cases /100 person years) *(TB cases decreased by 0.29 cases/100 person yrs)*
Roth et al, 1995, Brazil [8]	Cohort study, (1998-1999)	4 Hospitals	HCWs	Surgical mask for patients	No surgical mask use (Hospitals C and D). Hospital C also had UVGI in laboratory.	Hospitals A and B: Composite intervention (A, E, R) **Cough etiquette**: **patient use of surgical masks** Respiratory: N95 respirators for HCWs. Administrative controls also used in Hospital A, and Engineering controls used in Hospital B.	TST conversions	Hospital C: Conversions 19.8 / 1,000 person months Hospital D: Conversions 12.2 / 1,000 person months	Hospital A: Conversions 7.4 / 1,000 person months Hospital B: Conversions 8.1 / 1,000 person months *(Reduction of between 4.1 and 12.4 conversions per 1,000 person months)*

Studies conducted in humans unless otherwise stated. MDR-TB = multidrug resistant tuberculosis; TST = tuberculin skin test; HCW = health-care workers

*Yanai et al 1995. Composite interventions: covering mouth with surgical masks etc when coughing or sneezing. Engineering: local exhaust ventilation system; control of airflow direction; maximise natural ventilation in other high-risk areas; laboratory (class II safety cabinet, UVGI systems and air exhaust) Respiratory: Use of personal N95 respirators encouraged, including fit test for staff
A = Administrative Controls. CE = Cough etiquette and surgical masks. R = Respiratory Protection. E = Engineering Controls. UVGI = Ultraviolet Germicidal Irradiation

Table 2.2: Summary of included study for PICO 2, with outcomes measured in animals

Author, Year, Country	**Study Design (years)**	**Setting**	**Study participants (sample size)**	**Type of intervention**	**Description of Control**	**Description of Intervention**	**Outcomes Measures**	**Results in control group**	**Results in intervention group**
Dharmadhikari et al, 2012, South Africa [9]	Animal (guinea pig), cohort study (2010)	Airborne Infections Research Facility	Guinea pigs (n=90, control; n=90, intervention)	Masks worn by patients	No masks worn by patients	Ear loop face masks worn by 17 MDR-TB patients (14 smear positive) newly admitted to hospital*.	Guinea pigs were exposed (intervention, n=90) or not exposed (control, n=90) to exhaust air from TB patients. TST, in both groups of guinea pigs, were performed at end of study period	69/90 (76.6%; 95% CI, 68–85%) guinea pigs TST positive	36/90 (40%; 95% CI, 31–51%) guinea pigs TST positive *(36.6% absolute risk reduction in infection with intervention)*

* Masks worn between 7am and 7pm excluding meals for 3 months on alternate days. Exhaust air expelled into intervention animal chamber on mask days and control chamber on non-mask days

Fulltext papers reviewed but excluded and reasons for exclusion

Author	Year	Title	Inclusion	Rationale
Emerson et al	2016	Evaluation of a TB infection control implementation initiative in out-patient HIV clinics in Zambia and Botswana. Int J Tuberc Lung Dis. 2016 Jul;20(7):941-7.	Excluded	- Did not include outcome of interest
Bhuket et al	2013	Hospital tuberculosis control activities and treatment success in Thailand during the implementation year of the admission policy for new smear positive pulmonary tuberculosis patients. J Med Assoc Thai. 2013 Jul;96(7):782-5.	Excluded	Did not include outcome of interest
Zayas et al	2013	Effectiveness of cough etiquette maneuvers in disrupting the chain of transmission of infectious respiratory diseases. BMC Public Health. 2013 Sep 8;13:811		Did not include outcome of interest
He et al	2010	Infection control and the burden of tuberculosis infection and disease in health care workers in china: a cross-sectional study. BMC Infect Dis. 2010 Oct 28;10:313.	Excluded	No intervention or control group
Stroud et al	1995	Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in a New York City hospital. Infect Control Hosp Epidemiol. 1995 Mar;16(3):141-7.	Excluded	Did not include intervention of interest
Ticona et al	2016	Impact of infection control measures to	Excluded	Lacked

Author	Year	Title	Inclusion	Rationale
		control an outbreak of multidrug-resistant tuberculosis in a human immunodeficiency virus ward, Peru. American Journal of Tropical Medicine and Hygiene 2016 95:6 (1247-1256)		intervention of interest
Fella et al	1995	Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Control 1995; 23:352-6	Excluded	Lacked intervention of interest
O'Hara et al	2017	Infection control and tuberculosis in health care workers: an assessment of 28 hospitals in South Africa. Int J Tuberc Lung Dis. 2017 Mar 1;21(3):320-326.	Excluded	Cross sectional study design

Summary of Included Studies

Harries et al, 2002: This was a retrospective study assessing the impact of implementing TB introducing TB control guidelines in 40 district and mission hospitals in Malawi. The guidelines were introduced in mid-1998 and included 13 separate interventions focusing on rapid diagnosis of patients with smear-positive pulmonary TB, administrative attempts to isolate infectious patients, and the education of patients on cough hygiene. In addition the guidelines included masks to be worn by pulmonary TB patients when undergoing surgical procedures. The TB case notification rate for 2,979 health workers in 1999 (after the guidelines were introduced) was 3.2%; this was slightly lower than the case notification of 3.7% for 2697 health workers in 1996, prior to the guideline introduction.

Moro et al, 2000: Retrospective study assessing the effectiveness of introducing infection control (IC) measures on TB transmission during an outbreak of MDR-TB amongst HIV patients in a HIV ward in a large general hospital in Milan, Italy. After recognition of the outbreak, IC measures were initiated in May 1998 (and fully implemented in Jun 1993) consisting of strict isolation of patients with respiratory disease or fever, limited transportation outside of room and surgical masks during transport and surgical masks for persons entering all patient rooms. Cases of MDR-TB in this ward were identified between October 1992 and March 1994. Among the 90 patients exposed from October 1992 to June 1993 (2455 patient-days), 26 (28.9%) developed MDR-TB (10.6/1000 patient-days). None of the 44 (0%) patients exposed exclusively after 30 June 1993 (654 patient-days), when infection control measures were already fully implemented, subsequently developed MDR-TB.

Roth 2005: A retrospective study in four general Brazilian hospitals. The authors compared the TST conversions of the health care workers of the four hospitals and compared their HIV and TB incidence and TB infection control activities. Hospital A has administrative controls, N95 respirators and surgical masks for patients. Hospital B has administrative controls, negative pressure rooms, N95 respirators for HCW and surgical masks for patients. Hospital C and D had not TBIC. The study reported the initial TST results which were Hospital A 407/872 (46.7%), Hospital B 1353/1945 (69.6%), Hospital C 574/872 (65.8%) and Hospital D 454/730 (62.2%). The follow-up results (comparing intervention Hospitals A / B, with control hospitals C / D) found the rate/1000 person-months were Hospital A 7.4, Hospital B 8.1, Hospital C 19.8, Hospital D 12.2. Depending upon which hospitals are compared, overall there was a

reduction of TST conversion of between 4.1 and 12.4 conversions per 1,000 person months with the respiratory hygiene intervention.

Yanai et al, 2002: A retrospective study that described the effectiveness of prevention strategies of nosocomial tuberculosis. The study was conducted in a provincial referral hospital in northern Thailand between 1995-1999. The nosocomial interventions were introduced in 1996 and included cough etiquette training for patients (*), as well as other interventions (N-95 masks for HCW, exhaust ventilation to provide negative pressure in the newly built isolations rooms (one in each medical ward), the lab also received a class 2 safety cabinet, air exhaust and UVGI and administrative controls). TST were conducted yearly using the two step procedure. During 1997 (at baseline), the TST conversion rate was 13/77 (16.1%), decreasing to 2/96 (2.1% in 1999. TB incidence also decreased from 30/4357 (0.7 per 100 person years) in 1994-6 to 14/4780 (0.4 / 100 person years) from 1997-1999.

(b) Studies with outcomes measured in animals

Dharmadhikari et al, 2012: This prospective cohort study was conducted in the Airborne Infections Research Facility, South Africa where over 3 months, 17 MDR-TB patients newly admitted to hospital were instructed to wear surgical face masks between 7am and 7pm (excluding meal times) on alternate days. Ward air was exhausted into two different chambers each housing 90 guinea pigs each. On the mask wearing days the ward air was exhausted into the ‘intervention’ guinea pig chamber, and on the non-mask wearing days into the ‘control’ guinea pig chamber. The outcome measure was TST positivity in guinea pigs at the end of study duration. 69/90 (76.6%) guinea pigs became infected in the control group, compared with

36/90 (40%) in the intervention group, representing a 36.6% absolute decrease in risk of TB transmission when patients used masks.

Stratification of the study population

1. HCWs in healthcare settings or non-healthcare congregate settings

Two studies evaluated the outcome in HCWs in heathcare settings, Yanai 2003 and Roth 2005.

1.1. **HIV status:** Neither study was among HCWs affected by HIV, and therefore stratification was not possible.

1.2. **In-patient versus out-patient status:** Both included studies were undertaken in in-patient settings. No studies were available in outpatient settings. Therefore, stratification was not possible.

1.3. **Congregate settings:** No included studies were undertaken in congregate settings, hence stratification was not possible.

1.4. **High versus low prevalence settings:** Both Yanai 2003 and Roth 2005 were undertaken in high-prevalence settings. Therefore, stratification was not possible.

2. Persons attending healthcare settings or non-healthcare congregate settings

Just one included study, Moro 2000, was undertaken among patients in a healthcare setting. This population was people living with HIV in an in-patient setting in a low-prevalence country (Italy). Stratification according to the pre-specified strata was not possible.

Methodological quality of included studies

The quality of included studies is summarised in Table 2.3. Two out of the four human studies were before and after study, resulting in possible temporal factors unrelated to the intervention of interest affecting the study outcomes, and there was no blinding for all the studies. The overall risk of bias was assessed as high in all studies.

Indirectness is a major concern for all included studies, including the included animal studies. Composite interventions were implemented in the studies in humans, meaning it is not possible to assess the effect of any one intervention. Overall, we judged there to be a serious risk of indirectness. All human studies reported reductions in infection, and/or reductions in TB among health workers. However, the magnitude varied considerably. Nevertheless, we did not identifiy a serious risk of imprecision.

The direction of the effect was consistent across all studies. We cannot exclude publication bias, however we have conducted a comprehensive search.

Table 2.3. Downs and Black quality assessment tool for retrospective cohort studies

Study	**Reporting (/10)**	**External Validity (/3)**	**Bias (/7)**	**Confounding (/6)**	**Power (/5)**	**Total (/32)**
Animal study						
Dharmadhikari et al	8	2	5	4	0	19
Human studies						
Harries et al	8	3	6	3	0	21
Moro et al	9	3	4	0	0	16
Roth et al	8	3	6	3	0	21
Yanai et al	6	3	4	1	0	15

Number in () = highest possible score. A higher score is associated with a lower risk of bias.

Author(s): Fox, Redwood, Chang and Ho
Date: 26th March 2018

PICO 2 - Administrative controls (1) – in healthcare workers (Q7)

Question 7: Can respiratory hygiene (or cough etiquette) in people with presumed or confirmed TB reduce TB transmission to other persons attending healthcare settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	respiratory hygiene (or cough etiquette)	no respiratory hygiene (or cough etiquette)	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n=1) (Animal study, surgical mask use by patient with TB)												
1 [1,a]	observational studies	not serious [b]	not serious	serious [c]	not serious	dose response gradient	36/90 (40.0%)	69/90 (76.7%)	not pooled	see comment	⨁⨁◯◯ LOW	CRITICAL
Reduction in TB incidence/prevalence (n=1)												
1 [2,d]	observational studies	serious [e]	not serious	serious [f]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/44 (0.0%)	26/90 (28.9%)	not pooled	see comment	⨁⨁◯◯ LOW	CRITICAL
Reduction in TB incidence/prevalence in people living with HIV (n=1)												
1 [2,d]	observational studies	serious [e]	not serious	serious [f]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/44 (0.0%)	26/90 (28.9%)	not estimable		⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Dharmadhikari 2012 measured the effect of surgical mask use by MDR-TB patients upon TST conversion in guinea pigs. The mask use was associated with a substantial reduction in infection 69/90 (76.6%) to 36/90 (40.0%), a reduction by 36.6% in guinea pigs. The reviewers assessed that indirectness was an important concern, given differences between humans and guinea pigs. This led to downgrading the quality of evidence by one point. A steady rise in infection risk over the study period, indicating a dose-response relationship with the duration of exposure. This led to upgrading the quality assessment by one. Therefore, this was rated as low quality evidence.
b. The blinding of the individuals reporting the outcomes was not stated.
c. The biology of latent TB infection in guinea pigs is different than that in humans. Therefore there is a serious concern of indirectness (Downgraded by one level).
d. Moro 2000 (n= 134) study evaluated the effect of surgical mask use for prevention of transmission of MDR-TB, with the outcome of MDR-TB. In this study, surgical mask use by patients was a part of a composite intervention. There was a reduction of 29% in the incidence of TB between the intervention group (0/44 (0%)) and the control group (26/90 (29%)).

e. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
f. The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

References

1. Dharmadhikari, . Surgical Face Masks Worn by Patients with Multidrug-Resistant Tuberculosis. Am J Respir Crit Care Med; 2012.
2. Moro ML, Errante I Infuso A Sodano L Gori A Orcese CA Salamina G D'Amico C Besozii G Caggese L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy.. Int J Tuberc Lung Dis; 2000.

PICO 2 - Administrative controls (2) – Other persons attending HC settings or high TB transmission risk (Q8)

Question 8: Can respiratory hygiene (or cough etiquette) in people with presumed or confirmed TB reduce TB transmission to healthcare workers in other healthcare or congregate settings to reduce TB transmission when compared to settings where these interventions are not implemented?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence - all settings (n=2)									
2 [1,2]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies were included. Heterogeneity in the interventions precluded meta-analysis. The two studies both found a reduction in TST conversions in the intervention compared to control group. In Roth (n=7735), a composite intervention including surgical mask use by patients (comparing two hospitals in the intervention arm to two in the control arm) reduced TST conversions by between 4.1 and 12.4 conversions per 1,000 person months. In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. [1,2,c]	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n=2)									
2 [2,3]	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies were included. Heterogeneity in the interventions precluded meta-analysis. In these two studies, surgical mask use by patients was a part of a composite intervention. They both found a reduction in TB in the intervention compared to control group. In Harries 2002, the use of surgical masks by patients as a part of a composite intervention of 13 components reduced the TB notification rate from 100/2697 (3.7%) to 96/2979 (3.2%). In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years. Therefore, both studies were associated with a decrease in TB cases. [2,3,c]	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The one included study had a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The intervention is a composite intervention including engineering, respiratory protection and administrative controls, of which cough hygiene is one component (downgraded by one level).
c. No single effect estimate/meta-analysis was possible due to heterogeneity of outcomes.

References

1. Roth VR, Garrett DO,Laserson KF,Starling CE,Kritski AL,Medeiros EAS,Binkin N,Jarvis WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals.. Int J Tuberc Lung Dis; 2005.
2. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
3. Harries AD, Hargreaves NJ,Gausi F,Kwanjana JH,Salaniponi FM. Preventing tuberculosis among health workers in Malawi. Bull WHO; 2002.

4. PICO 3: Engineering and environmental controls

Background

Engineering and environmental controls aim to reduce transmission of *M. tuberculosis* contained in airborne droplets, through the implementation of ventilation (natural, mechanical or mixed mode or re-circulated air filtration), irradiation of the upper room air (ultraviolet germicidal irradiation, UVGI) or use of room air cleaner appliances. These may be implemented either in a healthcare setting or other setting.

Research question

In persons in TB care or other high TB transmission risk settings does use of the following engineering and environmental controls reduce TB transmission when compared to similar populations in settings with no intervention?

Population	• Persons in TB care or other high TB transmission risk settings • HCWs in TB care or other high TB transmission risk settings *Stratification of population:* *HIV status* *In-patient healthcare settings* *Out-patient healthcare settings* *Congregate settings* *Community settings* *Households in contact with TB patient* *Transportation* *TB ward* *MDR ward* *TB laboratories* *Operating rooms* *Mortuaries*

Intervention	• Natural ventilation • Mechanical ventilation • Mixed mode ventilation (natural and mechanical) • Recirculated air filtration • Upper room GUV (germicidal ultraviolet) • Room air cleaner appliances
Comparator	• Same population in settings with no intervention
Outcome	• Reduction in LTBI incidence/prevalence; or • Reduction in TB incidence/prevalence; or • Reduction in incidence rate ratio (of TB or LTBI) may also be used for comparison between population of interest and comparator group

Results

The Literature review was conducted on the 6th October 2017. Medline, PubMed, Embase, LILACS, Web of Science and the Cochrane library databases were used with the search terms listed in Table 2.1. In total there were 9,255 hits, of which 3,640 were duplicates, which left 5,615 papers for title and abstract screening (See Figure 4.1). At this stage the search was conducted in two parts, one for studies where outcomes were reported for humans, and one where outcomes in animals were reported.

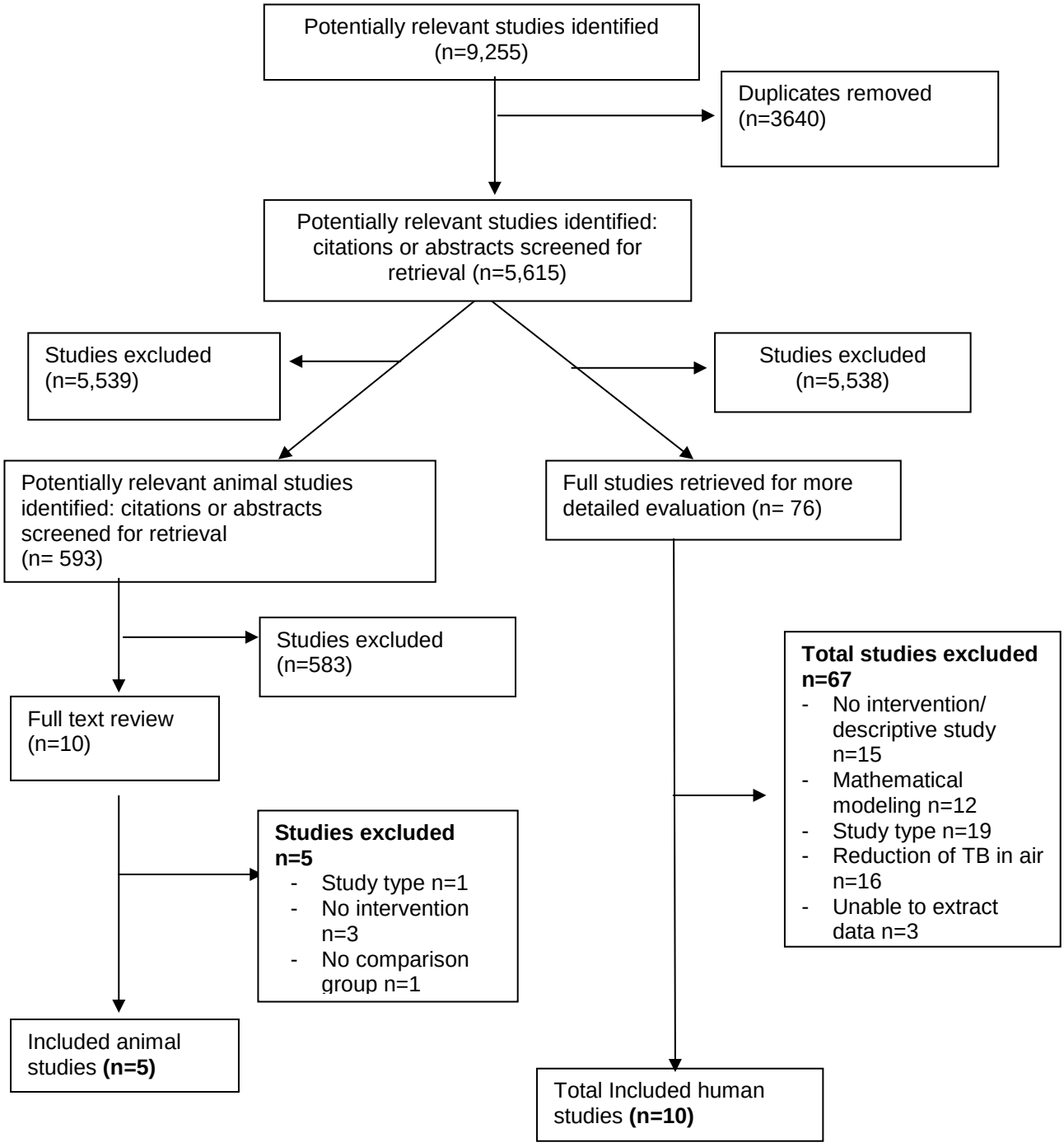
(a) Human studies: The review of the human studies was conducted by two reviewers (LR and VC) separately; any discrepancies in their included papers were discussed and if no consensus was found a third reviewer (GF) was consulted. A total of 76 papers were identified for full text review. These were screened separately with the use of data inclusion/exclusion form by two reviewers (LR and VC). Any discrepancies were reviewed by the third reviewed (GF). In total, 10 papers met the inclusion criteria. There were several other papers that contained similar information

that was required for this systematic literature review, however they were either descriptive studies, or the intervention was not clearly defined for analysis.

(b) Animal studies: To review for animal studies the same Endnote library was used. Previously the intervention and outcome were used as search terms as the population was widely defined. To narrow the search for animal studies, population terms were included. The Endnote library was keyword and abstract searched for the following terms: mice, rats, pig, guinea, animal, nonhuman and rabbit. Papers with no abstract and keywords were also included in this search. This search found 593 papers for title abstract review. These were reviewed by one reviewer, which indicated 10 papers for full text review and 5 were included in the study.

The references of the included papers and review articles found were screened for inclusion, however none met the inclusion criteria.

Figure 4.1: Consort diagram of study selection for PICO 3, engineering and environmental controls, in human and animals



Comparison with previous WHO Infection Control review

The previous guidelines, titled "WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Household" [10], identified 19 papers for environmental TB controls. Of these, just 14 were considered for full text review, and 4 were included in the final review. The main reasons for exclusion included testing reduction of *Mycobacterium tuberculosis* in the air and mathematical modeling of predicted reduction in TB incidence (see Table 4.1).

Table 4.1: Inclusion and exclusion of papers from the 2009 WHO infection control guidelines

Author	**Year**	**Title**	**Inclusion**	**Rationale**
Ultraviolet germicidal irradiate fixtures				
Fella, et al.	**1995**	**Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City**	**Included**	**Human Study**
Menzies et al.	2003	Efficacy of Environmental Measures in Reducing Potentially Infectious Bioaerosols During Sputum Induction	Excluded	Did not measure required outcome(s)
Xu et al.	2003	Efficacy of ultraviolet germicidal irradiation of upper-room air in inactivating airborne bacterial spores and mycobacteria in full-scale studies	Excluded	Did not measure required outcome(s)
Ko et al.	2001	Estimation of Tuberculosis Risk and Incidence under Upper Room Ultraviolet Germicidal Irradiation in a Waiting Room in a Hypothetical Scenario	Excluded	No outcome: risk analysis/modeling
Nardell, et al.	2008	Safety of Upper-Room Ultraviolet Germicidal Air Disinfection for Room	Excluded	Did not measure required

Author	Year	Title	Inclusion	Rationale
		Occupants: Results from the Tuberculosis Ultraviolet Shelter Study		outcome(s)
Kellerman, et al.	1997	The Cost of Selected Tuberculosis Control Measures at Hospitals with a History of Mycobacterium tuberculosis Outbreaks	Excluded	Cost-analysis
Riley, et al.	1996	Ultraviolet Susceptibility of BCG and Virulent Tubercle Bacilli	Excluded	Did not measure required outcome(s)
Escombe, et al.	**2009**	**Upper-Room Ultraviolet Light and Negative Air Ionization to Prevent Tuberculosis Transmission**	**Included**	**Animal study**
Ventilation				
Gammaitoni, et al.	1997	Using a Mathematical Model to Evaluate the Efficacy of TB Control Measures	Excluded	Mathematical Model
Riley, et al.	**1957**	**Air Hygiene in Tuberculosis: Quantitative Studies of Infectivity and Control in a Pilot Ward.**	**Included**	**Animal study**
Nardell, et al.	1991	Airborne Infection: Theoretical Limits of Protection Achievable by Building Ventilation	Excluded	Study Design
Dragan	2000	Comparative analysis of HVAC systems that minimize the risk of airborne infectious disease transmission	Excluded	Cost analysis
Menzies, et al.	**2003**	**Factors Associated with Tuberculin Conversion in Canadian Microbiology and Pathology Workers**	**Included**	**Human study**
Menzies, et al.	2000	Hospital Ventilation and Risk for Tuberculous Infection in Canadian Health Care Workers	Excluded	Study design (cross-sectional)

Author	Year	Title	Inclusion	Rationale
Escombe, et al.	2009	Natural Ventilation for the Prevention of Airborne Contagion	Excluded	No outcome: mathematical model
Cooper-Arnold, et al.	1999	Occupational tuberculosis among deputy sheriffs in Connecticut: a risk model of transmission.	Exclude	Study design (modeling study)
Basu et al.	2007	Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modeling study	Excluded	Study design (modeling study)
Behrman, et al.	**1998**	**Tuberculosis Exposure and Control in an Urban Emergency Department**	**Included**	**Human Study**
Ray, et al.	1951	An Evaluation of Ultraviolet lights in a dental clinic	Excluded	Did not measure required outcome(s)

Table 4.2. Summary of included summaries in PICO 3, Engineering and Environmental controls (outcomes measured in humans)

Author, Year, Country	**Study Design/years**	**Setting**	**Study participants**	**Type of ventilation/ intervention**	**Description of control**	**Intervention**	**Outcomes Measures**	**Results before (control) intervention**	**Results after intervention** *(absolute reduction, %)*
Mechanical ventilation									
Blumberg, 1995, USA[11]	Before/after January 1992- 1994	Tertiary hospital	HCW	Particulate respirator	Pre-intervention standard practice (not clearly defined)	Composite (C + R+E) Administrative: (a) Mandatory respiratory isolation policy for TB, possible TB and HIV infection with abnormal chest Xray, increased surveillance, infection control coordinator, expanded HCW education **Engineering: Converted 90 rooms into neg pressure rooms with fan** Respiratory protection: 3M 1812 submicron mask used for all staff in respiratory isolation room.	TST conversions	118/3579 (3.3%) HCW	23/5153 (0.4%) HCW (July 1993-Dec 1993) *(Reduced TST conversion by 2.9% in intervention***)**

Author, Year, Country	**Study Design/years**	**Setting**	**Study participants**	**Type of ventilation/ intervention**	**Description of control**	**Intervention**	**Outcomes Measures**	**Results before (control) intervention**	**Results after intervention** *(absolute reduction, %)*
Welbel, 2009, USA[12]	Before/after, study 1992-1997	Urban Hospital	All workers at the hospital	Mechanical Ventilation	Before intervention	1992: conversion of 36 isolation rooms to negative pressure rooms. 1993: UVGI in isolation rooms and corridors 1995: Daily checks of isolation rooms for negative pressure, 2 HEPA filters in ED 1996: outside consultants, 1 time evaluation of TB IC.	TST conversions	1994: 98/2221, (4.4%)	2002: 6/2108 (0.28%) *(Reduced TST by 4.1% in the intervention group)*
Wenger, 1995, USA[13]	Before / after study 1990-1992)	HIV wards of an Urban Hospital	HCW	Mechanical Ventilation	Pre-intervention standard practice (no negative pressure rooms)	April 1990-April 1991, implemented negative pressure in all 23 isolation rooms.	TST conversion rate	7/25 (28%)	3/17 (18%) *(Reduction of 10% when compared to pre-intervention period)*
Maloney 1995, USA[14]	Before / after 1990-1992	MDR-TB wards	HCWs	Mechanical ventilation	Pre-intervention standard practice	Composite (A,E,R) Administrative: Improved isolation, routine use of AFB smear to	TST conversions	15/90 (16.7%) converted over 18 months in pre-intervention	4/78 (5.1%) converted over 18 months in intervention period

Author, Year, Country	Study Design/years	Setting	Study participants	Type of ventilation/ intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention *(absolute reduction, %)*
						determine duration of isolation, expanded lab processing of samples. **Engineering: Exhaust fans in isolation rooms; portable Aeroguard chambers for cough-inducing procedures** Respiratory protection: Molded surgical masks		period	*(Reduced TST conversion by 11.5% after intervention)*
Muecke, 2006, Canada[15]	Before/after study 2002	University	Students and teachers	Mechanical Ventilation	Rooms without mechanical ventilation	Rooms with mechanical ventilation	TST conversion by contact tracing	75/297 (25%)	73/189 (39%) *(Increase in TST conversion by 14%)*
Roth et al, 1995, Brazil[8]	Cohort study 1998-1999	4 Hospitals	HCWs	Mechanical ventilation	No mechanical ventilation (Hospital A)	Composite intervention (Hospital B) Respiratory: patient use of surgical masks and N95 respirators for HCWs.	TST conversions	Conversions 7.4 / 1,000 person years	Conversions 8.1 per 1,000 person years *(similar conversion rate - 0.7 / 1,000 person years higher*

Author, Year, Country	**Study Design/years**	**Setting**	**Study participants**	**Type of ventilation/ intervention**	**Description of control**	**Intervention**	**Outcomes Measures**	**Results before (control) intervention**	**Results after intervention** *(absolute reduction, %)*
						Administrative controls also used in Hospital A, and **Engineering: Negative pressure in rooms.**			*with intervention)*
Menzies 2003, Canada[16]	Case-control study	Microbiology and pathology laboratories	HCWs in laboratories	Mechanical	Lower ventiation	Higher ventilation	TST conversion	N/A	Among conversions, mean ventilation was 16.7 (SD 2.4) ACH. Among non-conversions, mean ventilation was 32.5 (SD 22.7) ACH. P<0.001.
Mixed mode ventilation									
Behrman, 1998, USA[17]	Before – after study 1993-1996	ED of Urban Hospital	HCW	Mixed mode ventilation	Pre-intervention standard practice	Composite interventions (respiratory protection -100% non-recirculated air in the trauma area (intubation area) - improved ventilation with at	TST conversion	6/50 (12%)	0/64 (0%) *(Intervention reduced TST conversion by 12%)* No change in TST conversion infection in

Author, Year, Country	Study Design/years	Setting	Study participants	Type of ventilation/ intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention *(absolute reduction, %)*
						least 25% of fresh air - Laminar flow from registrars to patients			control wards over the same period.
Mixed mode ventilation and UVGI									
Yanai, 2003, Thailand [7]	Before/after study 1995-1999	Urban TB Hospital	HCW	Mixed mode ventilation, UVGI	Pre-intervention. Not described in detail.	1 TB isolation room for each medical ward. Local exhaust ventilation system, control of airflow direction to achieve negative ventilation in isolation rooms. Maximise natural ventilation on high risk wards. TB lab got a class 2 safety cabinet, air exhaust and UVGI.	Outcome 1: TST conversions Outcome 2: TB cases among HCWs	1: 13/77 (16.9%) 2: 30/4357 0.7/100 person years	Outcome 1 2/96 TST conversions (2.1%) *(Conversions reduced by 14.8% post intervention)* Outcome 2: 19/4780 (0.4 TB cases /100 person years) *(TB cases decreased by 0.29 cases/100 person yrs)*
Mechanical ventilation and UVGI									
Fella, 1995, USA[18]	Before/after 1991-1993	Urban AIDS centre and prison hospital	HCW	Mechanical ventilation (Negative pressure) and UVGI	Period 1: fewer negative pressure rooms	**Composite** (A,E,R) Administrative: Immediate isolation of suspected TB, or	TST conversion	41/303 (13.5%) (Jan 1991-Dec 1991)	21/446 tests (4.7%) (Jan 1992 – Dec 1992) *(Reduction of*

Author, Year, Country	Study Design/years	Setting	Study participants	Type of ventilation/ intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention *(absolute reduction, %)*
					No UVGI lights and fewer negative pressure rooms.	HIV with dyspnoea or unknown HIV status with dyspnoea, cough, abnormal Xray. **Engineering**: **(1) Gradually installing neg press. rooms - 44 rooms over 2 years, (6 ACH); (2) UVGI 8 feet above floor, serviced (introduced between Jul 1992 and Jan 1993)** Respiratory protection: Particulate respirators (Jan 1992) then Dust mist fume respirators (Jan 1993)			*8.8%)*

A = administrative controls, E = engineering and environmental controls, R = respiratory protection. TST = tuberculin skin test.
ACH = air changes per hour. UVGI = Ultraviolet Germicidal Irradiation. HCW = healthcare workers. UVGI = ultraviolet germicidal irradiation.

Summary of included papers, outcomes measured in humans (PICO 3)

Behrman 1998: A prospective cohort study set in the emergency department (ER) in a 1000 bed urban hospital during 1993 to 1996. The intervention was four respiratory isolation rooms in the ED that meet the CDC standards. 100% non-recycled air in the trauma area (where most intubations occur) and improved ventilation with at least 25% fresh air in the entire ED. There was also a laminar flow from registrars to the patients. Before the intervention the TST conversion was 6/50 (12%) in the ED. After the intervention the TST conversion rate was 0/64 (0%), showing a decrease in TST conversion of 12%, this was also compared to the TST conversion rates of non-intervention, non-TB prevalent wards of 36/3000 (1.2%).

Blumberg 1995: conducted a study at a 1000 bed inner city hospital during 1991 and 1994. There were 3 interventions, (1) Administrative controls which included the expansion of the respiratory protection policy and 6 month mandatory TST screening, which were implemented on 1st March 1992. (2) Environmental controls which included converting 90 rooms with no recirculated air to negative pressure rooms by adding a window fan on the 1st March 1992. (3) Personal respiratory protection (3M 1812 submicron masks were implemented for use by all health care workers that entered a respiratory isolation room - previously they used surgical face masks). The results showed a decrease in TST conversion rates among health care workers over the duration of the study period. It reduced from 118/3,579 (3.3%) in the control period, to 23/5,153 (0.4%) in the intervention period (a reduction of 2.9%).

Fella 1995: a retrospective cohort study in an urban AIDS centre and prison hospital in the USA. They use respiratory and environmental interventions; the environmental

interventions included negative pressure rooms and UVGI lights in patient's rooms and in congregate areas. To assess the outcome the employee TST conversions were reviewed every 6 months between 1991 as 1993. After the implementation of the negative pressure rooms there was a reduction of 13.7% in TST conversions among HCW, from 20.7% to 7%. After the implementation of the UVGI light the TST conversion rate dropped by 8.8%, from 13.5% to 4.7% - a reduction of 8.8%.

Maloney 1995: This study was performed in the major referral hospital at New York in USA between 1991- 1993. It evaluated a composite intervention including administrative and engineering controls and respiratory protection. Moulded surgical masks were used (3M 1800+ Aseptex).

The administrative components included improved isolation, routine use of AFB smear to determine duration of isolation and expanded lab processing of samples. Engineering controls included use of exhaust fans in isolation rooms and portable Aeroguard chambers for cough-inducing procedures. Prior to the intervention, HCWs used non-molded surgical masks, and there were no negative pressure rooms. The outcome of the study was TST conversion for HCWs working with MDR-TB patients.

TST conversions occurred in 15/90 (16.7%) HCWs over 18 months in the pre-intervention period, and 4/78 (5.1%) over 18 months during the intervention period. The intervention period was associated with a decline in conversions by 11.5%. However, the patient numbers of MDR-TB also declined over the period from 30 in the period Jan 1990-Jun 1991, to 10 from July 1991-Aug 1992. And for HCWs TST

conversion rate in other wards of the hospital also declined from 9/40 (4.0%) to 7/254 (2.8%).

Menzies 2002: This study conducted among HCWs in microbiology and pathology laboratories in 17 Canadian hospitals. The study measured mechanical ventilation within the laboratory facilities, and assesed the number of health workers with TST conversions during the study period. The study found that among 14 HCWs with TST conversions, the mean mechanical ventilation was 16.7 (SD 2.4) air changes per hour (ACH) . Among 97 staff without TST conversions, the mean mechanical ventilation was 32.5 (SD 22.7) ACH. Therefore, ventilation was lower among those with TST conversion than among those without TST conversion ($p<0.001$). The adjusted odds ratio for those with half of the recommended ventilation versus the recommended ventilation was 1.3 (95% CI 0.9-1.9).

Muecke 2006: This Canadian study evaluated case finding for contacts of a student with TB. The university contacts were divided into cohort by those that shared classed with the case patients in a room with or without mechanical ventilation. The results showed that 75/297 (25%) of students in non-mechanically ventilated rooms at the university had TST positive results compared to 73/189 (39%) in those contacts from mechanically ventilated rooms. This shows an increase of 14% in TST conversion in contacts in rooms with mechanical ventilation.

Roth et al, 1995: A cohort study of four hospitals in Brazil compared the TST conversion rate over a 19 month period (1998-1999). Health workers who were TST

negative had repeat screening for conversion at the end of follow-up. Four hospitals had different combinations of interventions:

- Hospital A: Administrative controls and Respiratory protection (N95 respirators for all HCWs entering a TB isolation room; surgical mask until patients isolated)
- Hospital B: **Engineering controls (negative pressure room introduction),** Respiratory protection (N95 respirators for HCWs, surgical mask until patient isolated)
- Hospital C: **Engineering (UVGI in laboratory when lab not in use),** no masks
- Hospital D: No interventions

Outcomes were reported for each hospital in conversions per 1,000 person-years (the number of patients tested at the end of follow-up was not stated).

(a) Effect of engineering controls: Comparing Hospital B (with negative pressure room introduction) to Hospital A (without Engineering controls), TST conversions were similar (8.1 vs 7.4 / 1,000 person years).

(b) Effect of UVGI in laboratory: Comparing Hospital C (UVGI in lab) vs Hospital D (no UVGI in lab), TST conversions were higher (19.8 vs 12.2 / 1,000 person years). However, given that only laboratory staff would have been affected by this intervention, it appears unlikely to have been related to the overall outcomes in health workers throughout the institutions.

This analysis was confounded by the use of N95 masks for health workers, as well as surgical masks for patients until isolation. Furthermore, the population served by Hospitals C and D were substantially smaller than for Hospitals A and B, and HIV rates were lower in Hospitals C and D. Engineering controls also differed by site.

Welbel 2009: A retrospective study of TB infection control methods and TST results of HCW at a large inner city hospital in Chicago. The study time is from 1992-1997. The infection control interventions included administrative controls implemented from 1992-1995, environmental controls implemented from 1992-1996 and respiratory protection programs from 1995-1997. The environmental controls consisted of the conversion on isolation rooms to negative pressure rooms in 1992, installing UVGI lights in corridors and isolation rooms in 1993, daily checks of negative pressure and 2 HEPA filters in the ED in 1995 and an outside consultant to evaluate the ventilation systems in 1996. The TST conversion rate declined over the follow up period - from 4.22% in 1994 to 1.48% in 1997 and 0.28% in 2002.

Wenger 1995: This prospective study was conducted between 1990 and 1992 at Jackson Memorial Hospital in Miami, USA. It used 4 monthly TST conversion among HCW in the HIV (intervention ward) and annual TST conversion in other wards (control) to assess the effectiveness of multiple interventions. The interventions included negative pressure in all 23 TB isolation rooms, surgical submicron masks which were later updated to dust-mist particulate respirator for HCW. It also included multiple administrative controls. These interventions were staggered with clear dates so some of the interventions were able to be evaluated independently. In May 1990, before the intervention the TST conversion in HCW working on the HIV ward and the control ward was 7/25 (28%) and 0/16 (0%) respectively. After the intervention the TST conversion rates in the HIV ward in 02/1991 and 6/1992 were 3/17 (18%) and 0/23 (0%) respectively. This is a decrease of 10% after 15 months and 28% after 25 months.

Yanai et al, 2002: A retrospective study that described the effectiveness of prevention strategies of nosocomial tuberculosis. The study was conducted in a provincial referral hospital in northern Thailand between 1995-1999. The nosocomial interventions were introduced in 1996 and included N-95 masks for HCW, exhaust ventilation to provide negative pressure in the newly built isolations rooms (one in each medical ward), the lab also received a class 2 safety cabinet, air exhaust and UVGI. They also included administrative controls. TST were conducted yearly using the two-step procedure. During 1997 (at the start of the intervention), the TST conversion rate was 13/77 (16.1%), decreasing to 2/96 (2.1%) in 1999. TB incidence also decreased from 30/4357 (0.7 per 100 person years) in 1994-6 to 14/4780 (0.4 / 100 person years) from 1997-1999. Overall, TST conversions reduced by 14.8% post intervention and TB cases decreased by 0.29 cases/100 person yrs.

Stratification according to population and setting

1. For HCWs in TB care or other high TB transmission risk settings

Nine included human studies evaluated the effect of mechanical ventilation among HCW in high TB transmission-risk environments (Blumberg 1995, Fella 1995, Maloney 1995, Welbel 2009, Wegner 1995, Roth 1995, Behrman 1998, Yanai 1995, Menzies 2002). The following lists the results for stratification, according to the strata identified for PICO 3.

1.1. **HIV status:** This could not be performed, as no included studies reported outcomes according to HIV status.

1.2. **Inpatient versus outpatient healthcare setting:** This could not be performed, as no studies were available that presented findings in outpatient settings.

1.3. **TB vs MDR-TB ward:** This could not be performed, as no studies presented findings for HCWs exposed in MDR-TB wards.

1.4. **TB laboratories**: One study, Menzies 2003, showed that the mean ventilation among HCWs in laboratories with TST conversion was lower than among HCWs with no TST conversion[16].

1.5. **Household contacts**: No relevant studies were identified.

1.6. **Operating rooms**: No relevant included studies were identified.

1.7. **Mortuaries**: No relevant included studies were identified.

2. For persons exposed in TB care or other high TB transmission risk settings

One study was available that evaluated the association between mechanical ventilation and TST conversion in a community setting (Muecke, 2006). Therefore, stratification according to congregate setting, community setting, household contact or transportation was not able to be performed.

Table 4.3. Summary of included summaries in PICO 3, Engineering and Environmental controls (outcomes measured in animals)

Author, Year, Country	Study Design	Setting	Study participants (outcomes)	Type of intervention	Description of control	Intervention	Outcomes Measures	Results control	Results intervention + summary
Ultraviolet Germicidal Irradiation									
Mphaphlele, 2015, Peru[19]	Cohort study	MDR-TB ward	Guinea Pigs	UVGI	Ward air with no intervention on alternate days filtered through control cages	UVGI turned on alternate days and filtered through the intervention cages	TST conversion	Period 1: 9/90 (10%) Period 2: 49/90 (54.4%) Overall 58/90 (64.4%)	Period 1: 0/90 (0%) (*Reduction of 10%)* Period 2: 16/90 (17.7%) *(Reduction of 36.8%)* Overall 16/90 *(There was an overall reduction of 46.7% over both periods.)*
Riley, 1962, Peru[20]	Cohort study	TB ward	Guinea Pigs	UVGI	Ward air with no intervention on alternate days filtered through control cages	UVGI turned on alternate days and filtered through the intervention cages	a) TST conversion b) Autopsy	a) 63/120 (52.5%) b) 51/120 (42.5%)	a) 0/120 (0%) TST conversions *(Reduction of 52.5%)* b) 0/120 (0%) TB on autopsy *(Reduction in TB of 42.5%)*
Lurie, 1944, USA[21]	Cohort study	1: Animal cages+ peanut shells	Rabbits	UVGI	No UVGI lamps	UVGI laps	Autopsy	Period 1: 2/18 (11.1%)	Period 1: 1/16 (6.3%) *(Reduction of*

Author, Year, Country	Study Design	Setting	Study participants (outcomes)	Type of intervention	Description of control	Intervention	Outcomes Measures	Results control	Results intervention + summary
		2: Animal cages + peat moss						Period 2: 11/15 (73%)	*6.2%)* Period 2: 0/15 (0%) *(Reduction of 73%)*
Riley, 1957, Peru[22]	Cohort study	TB ward	Guinea pigs	UVGI	No UVGI lamps	UVGI lamps	Autopsy	6/6 (100%)	0/6 (0%) Reduction of 100%
UVGI and air ioniser									
Escombe, 2009, Peru[23]	Cohort Study	HIV-TB ward	Guinea Pigs	Intervention 1: UVGI Intervention 2: Negative air ionisation	Neither intervention 1 or 2.	1: UVGI and mixing fans (2 day cycle, one on one off for 2: Negative air ionisation on "UV off" days	Two outcome measures: a) TST conversion b) Autopsy	Outcome for intervention 1 (UVGI) 106/304 (35%) Outcome for Intervention 2 (ionisation) 26/304 (8.6%)	Intervention 1: UVGI a) 29/307 (9.5%) *TST conv reduced by 25.5%* b) 11/307 (3.6%), *TB on autopsy reduced by 5%* *Intervention 2: air ionization* a) 43/303 (14%), *TST conv reduced by 20.7%* b) 13/303 (4.3%), TB reduced by 4.3% - Comparison of 1 & 2 a) UV TST conv reduced by 4.5% b) UV reduced by 0.7%

Summary of included papers for PICO 3, outcomes measured in animals

Mphaphlele 2015: A prospective cohort study was conducted in an airborne infectious research (AIR) facility in South Africa. The air from a 6 bed MDR-TB ward was exhausted into 2 animal chambers containing 90 guinea pigs each. There was an initial exposure period of 4 months. The intervention consisted of UVGI light located in each patient room and the corridor turned on every other day. On UVGI days, the air from the MDR-TB ward were directed to the intervention animal chamber. On non-UVGI days, the ward air was directed to the control animal chamber. The initial experiment resulted in too few guinea pigs becoming infected in the control chamber to meet the power calculation so the study was extended for a further 3 months. This gave a total exposure period of 7 months. The control animal chamber had 58/90 (64.4%) TST conversions and the intervention chamber had 16/90 (17.7%) TST conversions, this is a reduction of 46.7% in the intervention group.

Riley 1961: This animal study was conducted over two years, from April 1958 to April 1961. The study exhausted the ward air from a 6 bed TB ward, which sometimes housed patients with drug resistant disease, to two animal chambers. Each chamber contained 120 male guinea pigs among 36 cages. The control animals received ward air and the intervention animals received ward air that had been irradiated with ultraviolet lights. The animals had TSTs performed every month. If the TST result was positive (>10mm in size), the animal was sacrificed within a few days and they were tested for culture and microscopy. The results showed 65/120 (52.5%) of the control animals contracted TB, of which 51 had cultures positive for TB – an absolute risk reduction of infection of 52.5%. In comparison, for TB disease (at autopsy), 0/120 of the intervention group contracted TB – a risk reduction of 42.5% compared to control.

Lurie 1944: This paper consisted of two consecutive studies. The first study lasted 15 months and consisted of four rabbits which were artificially infected intravenously with bovine tuberculosis. The rabbits shed tuberculosis in their urine onto the peanut shell beds of the cage. The contacts were divided into two sections, one section was irradiated with UVGI and the other section was not. The results showed that 2/18 (11.1%) of the contact rabbits became developed evidence of TB, compared with 1/16 (6.3%) in the UVGI group. The risk reduction for TB with UVGI was 6.2%.

The author also conducted a second experiment which more closely matched the previous study. In the second study, the bedding was changed from peanut shells to peat moss. The whole room was divided into two with a large wooden partition to prevent the UVGI from affecting the control group nearby. The second study also consisted of bovine TB being injected directly into the kidneys of the rabbits. The results showed that 11/15 (73%) control rabbits contracted TB and 0/15 intervention rabbits contracted TB – a reduction in TB on biopsy of 73%.

Riley 1957: This study was conducted in March 1955. 12 rabbits were places in a pilot ward with atomized bovine tubercule bacilli for two hours with UV lights turned on. After two hours, 6 of the rabbits were removed and the UV lights were turned off, the remaining 6 rabbits were exposed for 3 hours. All of the rabbits in the cohort with the UV lights turned off cohort were autopsied. 5 of 6 rabbits in the UV lights on cohort were autopsied. The remaining rabbit was alive and well 18 months after the experiment. The results showed that all (6/6) of the rabbits in the UV light off cohort

had tubercules on the lungs. None of the rabbits in the UV “light on” cohort (0/5) had developed tubercules. The risk reduction was 100% (although the outcome was not reported for one rabbit).

Escombe 2009: A prospective cohort study conducted in a specially built airborne transmission study (ATSF) facility in Lima Peru. This study was conducted over 535 days with three cohorts, ultraviolet (UV) lights, air ionization and a control chamber. The air from four HIV-TB isolation room were exhausted to the roof, which housed 3 animal exposure chambers of 150 guinea pigs each. On UV “on” days, the intervention animal chambers were exposed. On UV “off” days, half of the air from the isolation rooms was exhausted half into an air ionizer animal chamber, and half into the control chamber. These days were alternated throughout the study. There was a 45-minute purge period between study days to allow the replacement of partially UV treated wars air with fresh air after UV on days. The outcomes tested were TB infection, measured by TST conversion and TB disease, measured by positive organ culture on autopsy. In the control ward, 106/305 (35%) of animals developed infection and 26/304 (8.6%) developed TB disease. In the air ionization cohort, 43/303 (14%) developed TB infection and 13/303 (4.3%) developed TB disease – a reduction of 4.3%. Lastly, the cohort with air treated with UV lights demonstrated 29/307 (9.5%) of the guinea pigs having TB infection and 11/307 (3.6%) having TB disease.

The effect of UVGI (intervention 1): There was an overall risk reduction of 25.5% for infection and 5% for TB disease in the UV cohort, when compared to the control cohort.

The effect of ionization (Intervention 2): A risk reduction 20.7% in infection and 4.3% in TB disease for the air ionization cohort, when compared to the control cohort.

Methodological quality of included studies

The quality of included studies is summarised in Tables 4.4 and 4.5. Eight out of the ten human studies were before and after study and there was no blinding for all the studies. Selection bias were significant for all the studies. The overall risk of bias was assessed as high in all studies.

Indirectness is an important concern for all included studies, including the included animal studies. Composite interventions were implemented in the studies in humans, meaning it is not possible to assess the effect of any one intervention. Overall, we judged there to be a serious risk of indirectness.

All human studies reported reductions in infection, and/or reductions in TB among health workers. The direction and magnitude of the effect was similar across the studies. Overall, we did not identifiy a serious risk of imprecision. While publication bias cannot be excluded, we have conducted a comprehensive literature search.

Animal studies were included, and have the advantage of overcoming the potential confounders identified above. However, there were serious concerns about indirectness due to differences in the intensity of exposure, and differences in the way in which animals and humans acquire infection and are diagnosed. Nevertheless the direction of the effect was consistent with that seen in the human studies.

Table 4.4. Downs and Black risk of Bias assessments for retrospective cohort studies, PICO 3

Study	**Reporting (/11)**	**External Validity (/3)**	**Bias (/7)**	**Confounding (/9)**	**Power (/5)**	**Total (/32)**
Behrman, 1998	6	3	4	1	0	14
Blumberg, 1995	7	3	4	1	0	15
Fella, 1995	6	3	5	1	0	15
Maloney, 1995	6	3	4	1	0	14
Menzies, 2003	7	3	6	3	0	19
Muecke, 2006	6	3	5	3	0	17
Welbel, 2009	7	3	4	1	0	15
Wenger, 1995	5	3	4	1	0	13
Yanai, 2002	6	3	4	2	0	15

*Scored out of 32. A higher score is associate with a lower risk of bias in the Downs and Black tool [2].

Table 4.5. Cochrane risk of bias tool for prospective cohort studies (animal studies)

Study	**Confounding Bias**	**Selection Bias**	**Measurement of intervention Bias**	**Intervention departure Bias**	**Missing Data Bias**	**Measurement of outcome Bias**	**Selection of Reporting Bias**	**Overall ROB judgment**
Lurie, 1944	Low	Low	Moderate	Moderate	Low	Low	Low	Moderate
Mphaphlele, 2015	Low	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
Riley, 1961	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Riley, 1957	Low	Low	Moderate	Serious	Serious	Serious	Serious	Serious
Escombe, 2009	Low	Low	Low	Low	Low	Low	Low	Low

PICO 3 - Engineering and environmental controls (1) – in Healthcare workers (Q9-14)

Question 9: Can natural ventilation reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n= 0)									
0								-	CRITICAL
Reduction in TB incidence/prevalence (n= 0)									
0								-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Question 10: Can mechanical ventilation reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mechanical ventilation	no mechanical ventilation	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n= 6)												
6 [1,2,3,4,5,6]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Six studies evaluated the effect of mechanical ventilation upon TST conversion, each as a part of a composite intervention. Heterogeneity in the interventions precludes meta-analysis. Blumberg 1995 showed that the composite intervention, including 90 negative pressure rooms with fans, was associated with a reduction in TST conversions from 118/3579 (3.3%) to 23/5,153 (0.4%) – a reduction of 2.9%. Welbel 1995 showed that mechanical ventilation, in combination with other engineering measures, was associated with a reduction in TST conversions from 98/2,221 (4.4%) to 6/2108 (0.28%), a reduction of 4.1%. Wenger 1995 found that mechanical ventilation, including installation of 23 isolation rooms, was associated with a reduction in TST conversion from 7/25 (28%) to 3/17 (18%), a reduction of 10%. Maloney 1995 found that mechanical ventilation, in combination with other measures, was associated with a reduction in TST conversions from 15/90 (16.7%) to 4/78 (5.1%), a reduction by 11.5%. Muecke 2006 found rooms with mechanical ventilation were associated with a reduction in TST conversions from 75/297 (25%) to 73/189 (39%). Finally, Roth 1995 showed that mechanical ventilation was associated with a similar TST conversion rate (7.4 / 1,000 person years without the measures, and 8.1 per 1,000 person years with the measures). In summary, five of the six studies showed a reduction in the incidence of TST over the study period. Heterogeneity in the interventions precluded meta-analysis.				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n=0)												
0											-	CRITICAL
Reduction in LTBI incidence/prevalence in TB laboratory workers (n=1)												
1 [7,c]	observational studies	serious [a]	not serious	serious [d]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	14	97	-	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included studies have a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions are largely comprised of multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. This study conducted among HCWs in microbiology and pathology laboratories in 17 Canadian hospitals. The study measured mechanical ventilation within the laboratory facilities, and assesed the number of health workers with TST conversions during the study period. The study found that among 14 HCWs with TST conversions, the mean mechanical ventilation was 16.7 (SD 2.4) air changes per hour (ACH) . Among 97 staff without TST conversions, the mean mechanical ventilation was 32.5 (SD 22.7) ACH. Therefore, ventilation was lower among those with TST conversion than among those without TST conversion (p<0.001). The adjusted odds ratio for those with half of the recommended ventilation versus the recommended ventilation was 1.3 (95% CI 0.9-1.9).

d. Differences in the intervention (applicability). Mechanical ventilation varied considerably between settings, and was not described in detail. Average ventilation rates (expressed in air changes per hour) were reported and compared for individuals with TST conversion, and those without TST conversion. Mechanical ventilation was measured with windows and doors closed, which may exclude the component of natural ventilation present in some of the laboratories (downgraded by one level).

References

1. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic increase in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Control; 1995.
2. Wenger PN, Otten J,Breeden A,Orfas D,Beck-Sague CM,Jarvis WR. Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. Lancet; 1995.
3. Welbel SF, French AL,Bush P,DeGuzman D,Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. Am J Infect Control; 2009.
4. Maloney SA, Pearson ML,Gordon MT,Del Castillo R,Boyle JF,Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med; 1995.
5. Blumberg HM, Watkins DL,Berschling JD,Antle A,Moore P,White N,Hunter M,Green B,Ray SM,McGowan Jr. J E. Preventing the nosocomial transmission of tuberculosis. Ann Intern Med; 1995.
6. Roth VR, Garrett DO,Laserson KF,Starling CE,Kritski AL,Medeiros EAS,Binkin N,Jarvis WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals.. Int J Tuberc Lung Dis; 2005.
7. Menzies D, Fanning A,Yuan L,FitzGerald JM. Factors associated with tuberculin conversion in Canadian microbiology and pathology workers. Am J Respir Crit Care Med; 2003.

Question 11: Can mixed mode ventilation reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed mode ventilation	no mixed mode ventilation	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n= 2)												
2 [1,2]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies addressed this question. Heterogeneity in the interventions precludes meta-analysis. In Yanai 2003, a composite intervention including mixed mode ventilation was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Behrman 1998 evaluated mixed mode ventilation, and other interventions including respirtory protection. TST conversions decreased from 6/50 (12%) to 0/64 (0%) over the study period. Therefore, both studies showed a reduction in TST conversions. Heterogeneity in the interventions precluded meta-analysis.				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n= 1)												
1 [1,c]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and intervention is poorly described. The intervention comprises multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. The one included study, Yanai 2003, demonstrated that the composite intervention, including mixed mode ventilation, was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction of 0.29 cases/100 person years.

References

1. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
2. Behrman AJ, Shofer FS. Tuberculosis exposure and control in an urban emergency department. Ann Emerg Med; 1998.

Question 12: Can recirculated air filtration reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n=0)									
0								-	CRITICAL
Reduction in TB incidence/prevalence (n=0)									
0								-	CRITICAL

CI: Confidence interval

Question 13: Can upper room GUV reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	upper room GUV	no upper room GUV	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n=2) (human studies)												
2 [1,2]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies in humans evaluated this outcome. In Fella, a composite outcome including UVGI was associated with a reduction in TST conversion from 41/303 (13.5%) in the intervention group to 21/446 (4.7%) in the control group – a reduction of 8.8%. In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Therefore, both studies demonstrated a reduction in TST conversions. Heterogeneity in the interventions precluded meta-analysis.				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n=2)												
1 [2,c]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in LTBI incidence/prevalence (n=5) (animal studies)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	upper room GUV	no upper room GUV	Relative (95% CI)	Absolute (95% CI)		
5 [3,4,5,6,7]	observational studies	not serious	not serious	serious [d]	not serious	strong association	Five animal studies have been performed evaluating the effectiveness of ultraviolet germicidal irradiation (UVGI). In summary, all five animal studies show a significant reduction in infection with UVGI. The studies also show a reduction in TB disease, diagnosed on autopsy. The direction of the effect (reduction in infection) is consistent across studies. Meta-analysis was not performed due to differences in exposure and outcomes. The first three studies were performed in the mid twentieth century. Riley 1962 exposed guinea pigs to either ward air or ward air which had been treated with UVGI. TST conversion reduced from 63/120 (52.5%) to 0/12 (0%) with the intervention. Autopsy-confirmed TB occurred in 51/120 (42.5%) animals, and 0/120 animals (reduction in confirmed disease of 42.5%). Lurie 1944 tested rabbits who had been exposed to M. tuberculosis in urine. One group was exposed to UVGI, and the other was not. The incidence of autopsy-confirmed TB decreased from 2/18 (11.1%) and 11/15 (73%) in the control group to 1/16 (6.3%) and 0/15 (0%) in the UVGI group. This represents a decrease of 6.2% and 73% in periods 1 and 2. Thirdly, Riley 1957 compared the effect of TB ward air exposure of guinea pigs to UVGI. In the control group, 6/6 (100%) guinea pigs developed TB on autopsy, versus 0/6 (0%) in the UVGI group. Two contemporary animal studies have also been performed. Mphaphlele exposed a cohort of guinea pigs in Peru to ward air with either UVGI or no UVGI. In total, in the control group there were 58/90 (64.4%) TST conversion (9 in first time period, 49 infections second period). In the UVGI group there were 16/90 (17.8%) TST conversion (0 in first time period, 16 infections second period). There was a 46.7% reduction in infection overall, among the guinea pigs. Secondly, Escombe 2009 exposed guinea pigs in Peru to UVGI, negative air ionisation or neither. Outcomes were TST conversion or TB on autopsy. In the control group, 106/304 (35%) of animals were infected, in comparison to 29/307 (9.5%) in the UVGI group, and 43/303 (14%) in the ionization group. TB disease occurred in 26/304 (8.6%) in the control group, versus 11/307 (3.6%) in the UVGI group and 13/303 (4.3%) in the ionization group.				⨁⨁◯◯ LOW	

CI: Confidence interval

Explanations

a. The included studies have a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. Only one study evaluated this outcome In Yanai 2003, a composite intervention including patient masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.
d. The interventions were performed in animals. The biology of M. tuberculosis infection in guinea pigs and rabbits differs from LTBI in humans. Concerns regarding indirectness in animal models justify downgrading the certainty of the evidence by one point.

References

1. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic increase in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Control; 1995.
2. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
3. Mphaphlele M, Dharmadhikari AS,Jensen PA et al. Institutional Tuberculosis Transmission. Controlled Trial of Upper Room Ultraviolet Air Disinfection: A Basis for New Dosing Guidelines. Am J Respir Crit Care Med; 2015.
4. Riley RL, Mills CC,O'Grady F et al. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. Am Rev Respir Dis; 1962.
5. MB, Lurie. Experimental Epidemiology of Tuberculosis : The Prevention of Natural Air-Borne Contagion of Tuberculosis in Rabbits by Ultraviolet Irradiation. J Exp Med; 1944.
6. Riley RL, Wells WF,Mills CC et al. Air hygiene in tuberculosis: quantitative studies of infectivity and control in a pilot ward. Am Rev Tuberc; 1957.
7. Escombe AR, Moore DA,Gilman RH et al.. Upper-room ultraviolet light and negative air ionization to prevent tuberculosis transmission. PLoS Med; 2009.

Question 14: Can the use of room air cleaner appliances reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n=0)									
								-	CRITICAL
Reduction in TB incidence/prevalence (n=0)									
								-	CRITICAL

CI: Confidence interval

PICO 3 - Engineering and environmental controls (2) – Other persons attending healthcare settings or high TB transmission risk (Q15-20)

Question 15: Can natural ventilation reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n=0)									
0								-	CRITICAL
Reduction in TB incidence/prevalence (n=0)									
0								-	CRITICAL

CI: Confidence interval

Question 16: Can mechanical ventilation reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n= 1)									
1 [1]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed		⨁◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n=0)									
0								-	CRITICAL

CI: Confidence interval

Explanations

a. Temporal factors may have explained difference, shown by the increased infectivity in the second semester. The opening of windows in ventilated and non-ventilated rooms was not reported.
b. Transmission in rooms with mechanical ventilation was compared to transmission in rooms without mechanical ventilation. The duration of exposure varied between rooms, and seasonal variation means that other forms of ventilation (e.g. open windows) cannot be excluded.

References

1. Muecke C, Isler M,Menzies D,Allard R,Tannenbaum TN,Brassard R. The use of environmental factors as adjuncts to traditional tuberculosis contact investigation. Int J Tuberc Lung Dis; 2006.

Question 17: Can mixed mode ventilation reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n=0)									
0								-	CRITICAL
Reduction in TB incidence/prevalence (n=0)									
0								-	CRITICAL

CI: Confidence interval

Question 18: Can recirculated air filtration reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n=0)									
0								-	CRITICAL
Reduction in TB incidence/prevalence (n=0)									
								-	CRITICAL

CI: Confidence interval

Question 19: Can upper room GUV reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n=0)									
0								-	CRITICAL
Reduction in TB incidence/prevalence (n=0)									
0								-	CRITICAL
Reduction in LTBI incidence/prevalence (animal studies) (n=3)									
3 [1,2,3]	observational studies	not serious	not serious [1,a]	serious [b]	not serious	none		⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in TB incidence/prevalence (animal studies) (n=4)									
4 [2,3,4,5]	observational studies	not serious	not serious [c]	serious [d]	not serious	none		⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

a. The direction and magnitude of the effect was consistent across the studies. One study (Mphaphlele) involved two study periods, where the rate of infectiousness differed based upon the location of the exhaust outlet in the room. The data were pooled in the final analysis. The direction of the effect was the same in both time periods.
b. These three studies evaluated tuberculin skin test conversion among guinea pigs exposed to air removed from tuberculosis wards. Differences in the nature of transmission to guinea pigs, compared to humans, are likely to be significant (Downgraded one level).
c. The direction and magnitude of the effect was consistent across the studies.
d. These studies were conducted among guinea pigs (3 studies) and rabbits (1 study). Tuberculosis was diagnosed by autopy. Differences in the nature of transmission to animals and the measurement of the outcome (autopsy diagnosed disease) compared to humans are likely to be significant (Downgraded one level).

References

1. Mphaphlele M, Dharmadhikari AS,Jensen PA,Rudnick SN,van Reenen TH,Pagano MA,Leuschner W,Sears TA,Milonova SP,van der Walt M,Stoltz AC,Weyer K,Nardell EA. Institutional Tuberculosis Transmission Controlled Trial of Upper Room Ultraviolet Air Disinfection: A Basis for New Dosing Guidelines. Am J Respir Crit Care Med; 2015.
2. Riley RL, Shivpuri DN,Wittstadt F,Ogrady F,Sultan LU,Mills CC. Infectiousness of Air from a Tuberculosis Ward - Ultraviolet Irradiation of Infected Air - Comparative Infectiousness of Different Patients. Am Rev Respir Dis; 1962.
3. Escombe AR, Moore DAJ,Gilman RH,Navicopa M,Ticona E,Mitchell B,Noakes C,Martinez C,Sheen P,Ramirez R,Quino W,Gonzalez A,Friedland JS,Evans CA. Upper-Room Ultraviolet Light and Negative Air Ionization to Prevent Tuberculosis Transmission. Plos Medicine; 2009.
4. Riley RL, Wells WF,Mills CC,Nyka W,McLean RL. Air hygiene in tuberculosis: quantitative studies of infectivity and control in a pilot ward.. Am Rev Tuberc; 1957.
5. MB, Lurie. Experimental Epidemiology of Tuberculosis the Prevention of Natural Air-Borne Contagion of Tuberculosis in Rabbits by Ultraviolet Irradiation. Journal of Experimental Medicine; 1944.

Question 20: Can room air cleaner appliances reduce TB transmission in persons in TB care or others in high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Reduction in LTBI incidence/prevalence (n=0)									
0								-	CRITICAL
Reduction in TB incidence/prevalence (n=0)									
0								-	CRITICAL

CI: Confidence interval

5. PICO 4: Personal respiratory protection

Background

Personal respiratory protection strategies aim to reduce the risk that the wearer inhales infectious particles for contaminated air. Particulate respirators aim to reduce inhalation of droplet nuclei from1 to 5 □m in diameter, the size of airborne droplets containing M*. tuberculosis.* These typically meet the N95 standards set by the US guidelines (e.g. N95, N99, N100, R95, R99, P95, P99 filters or PAPRs) or meet the European FFP2 standards.

Introduction of personal respiratory protection in a health institution may be implemented as a part of a personal respiratory protection program. This is defined as a plan of action aimed in accomplishing an effective and sustainable use of particulate respirators by HCWs in high-risk for TB transmission settings, with activity details, responsibilities, and timelines, and what means or resources will be used. This includes but is not limited to policy development, education and training of HCWs, respirator fit testing, selecting respirator models and sizes, budgeting, procurement of respirators, installing signage in high risk areas of a facility for mandatory respirator use, supervision, and, respirator disposal.

Research question

In persons in TB care or other high TB transmission risk settings do the following interventions, when compared to no intervention, reduce risk of TB transmission?

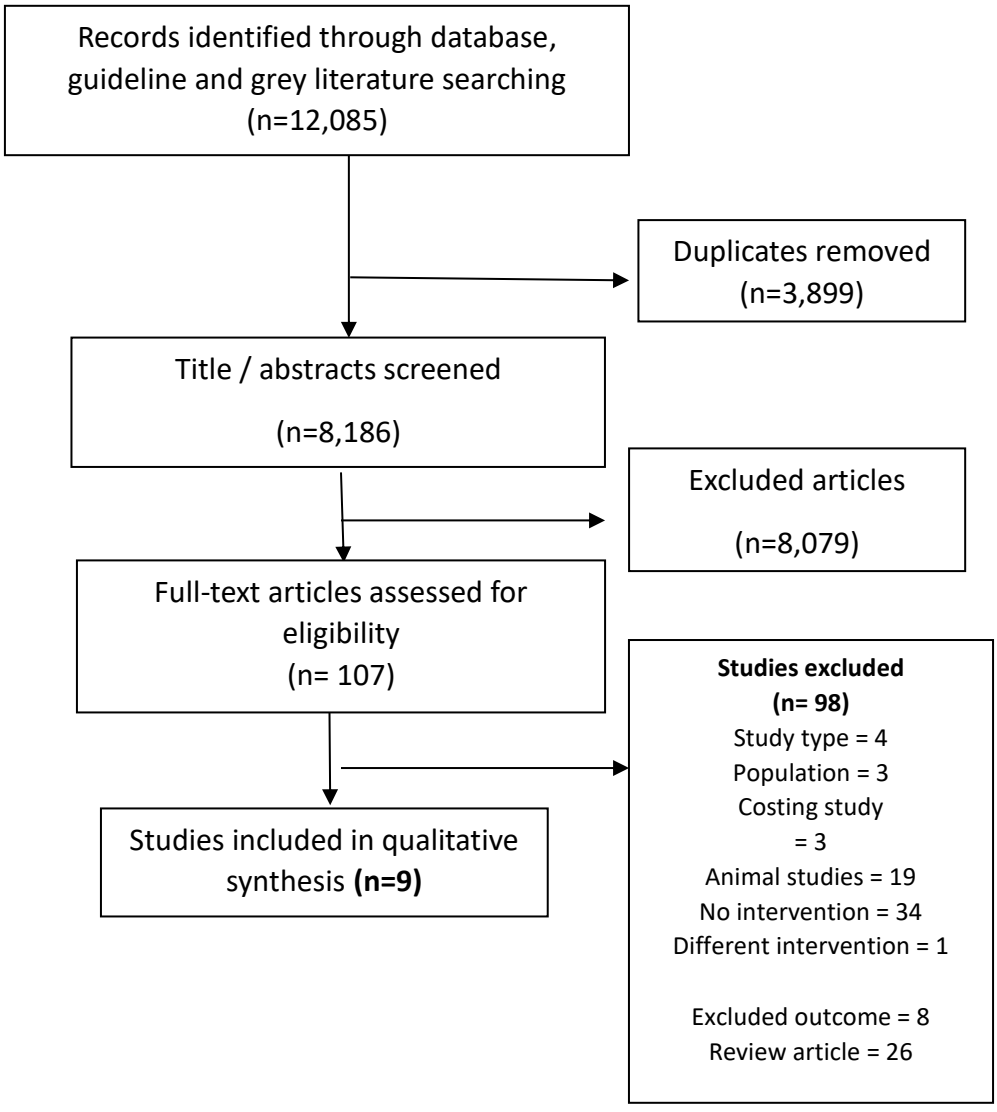
Population	• Persons in TB care or other high TB transmission risk settings • HCWs in TB care or other high TB transmission risk settings *Stratification of population:* *HIV status* *In-patient healthcare settings* *Out-patient healthcare settings* *Congregate settings* *TB ward or MDR ward*
Intervention	• Use of particulate respirators (N95 or equivalent; with or without fit test); or • Implementing a respiratory protection program (defined in the glossary of the Terms of Reference).
Comparator	• No intervention in the same type of setting
Outcome	• Reduction in LTBI incidence/prevalence (defined by tuberculin skin test or interferon gamma release assay); or • Reduction in TB incidence/prevalence (defined according to clinical or microbiological criteria); or • Reduction in Incidence rate (of TB or LTBI) ratio may also be used for comparison between population of interest and comparator group.

Results

Search results

We identified 8,186 non-duplicate records. The title and abstract these records were reviewed identifying 107 articles for full-text review. Of these, 98 did not meet the inclusion criteria, leaving nine eligible studies for review inclusion for human studies. Figure 5.1 shows the flow of search results and selection of eligible studies.

Figure 5.1. Consort diagram for study inclusion for PICO 4



Key characteristics of the nine included studies are presented in Table 5.1. Of these studies, only one is a prospective cohort study[5]. The rest of the studies are before and after studies. The majority were performed in United States, with others performed in Italy, Thailand and Brazil[7,8,24]. Most of the studies are performed in the urban tertiary hospitals with one of the studies is performed at the MDR-TB wards [5]. One study was performed at the TB hospital in Thailand[7].

All included studies evaluated composite infection control measures including administrative policies, use of respiratory protection and engineering controls as the intervention. Two studies examine an intervention to train staff to use personal respiratory protection[7,25].

In all except for one study[5], authors all reported on TST conversion as the outcome measurement. The prospective cohort study conducted by Moro *et al,* was conducted in HIV wards [5]. This study used surgical masks to protect staff and visitors, rather than personal respirators. The outcome measure was the incidence rate of MDR-TB in those exposed in hospital. We identifed no randomised controlled trials evaluating personal respiratory protection and incidence of LTBI/ TB.

On account of considerable variation between the included studies, in relation to the intervention and study populations, a meta-analysis was not performed. A summary of the included studies is included in Table 5.1. A narrative summary is provided for each study, below.

Table 5.1. Summary of characteristics of included studies for PICO 4

Author, Year, Country	Study Design/years	Setting	Study participants	Type of intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention
Particulate respirators for health workers									
Bangsberg 1997 (USA)	Before/after (1992-1993)	Urban hospital	HCW	Particulate respirator	Patients given surgical masks. Patients placed in non-ventilated bed prior to bed assignment.	Composite (A,R,E) (Administrative: Isolation of high-risk patients in 28 negative pressure isolation rooms (1992); dedicated clinical team + education for treating TB patients (6/1993) **Respiratory protection: Respirator masks (3M) and <u>fit testing</u> for medical house staff (Jul 1993)**	TST conversion	Period 1: 9/109 (10%) conversion in June 1992 Period 2: 2/101 (2%) conversion in December 1992 Period 3: 0/100 (0%) conversion in Jun 1993	(intervention Jul 1993): Period 4: 1/107 (1%) in Dec 1993 Period 5: 0/106 (0%) in Jun 1994 *(no difference identified; conversion rate had already decreased prior to intervention)*

Author, Year, Country	Study Design/years	Setting	Study participants	Type of intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention
Baussano 2007 (Italy)	Before/after	Urban health facilities	HCW	Particulate respirator	Prior to implementing guidelines	Composite (A,R,E) (Administrative: Appointment of local TB official, and risk evaluation and prompt isolation policy; education of HCWs about prevention and control of TB; Engineering: laboratory containment (Bio Hazard type III) **Personal protection: Respiratory protection measures during cough-inducing procedures**	TST conversion	106 infections in 4034 person-years (26.3/1000 person years)	42 infections in 4,463 person years (9.4/1000 person years) *(Reduction by 16.9 conversions / 1000 person years)*

Author, Year, Country	Study Design/years	Setting	Study participants	Type of intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention
Blumberg 1995 (USA)*	Before/after 1/1/1992-30/6/1994	Tertiary hospital	HCW	Particulate respirator	Pre-intervention standard practice (not clearly defined)	Composite (C,R+E) Administrative: (a) Mandatory respiratory isolation policy for TB, possible TB and HIV infection with abnormal CXR, increased surveillance, infection control coordinator, HCW education; Engineering: Converted 90 rooms into neg pressure rooms with fan (Mar 1992) **Respiratory protection: 3M 1812 submicron mask used for all staff in respiratory isolation room**	TST conversions	118/3579 (3.3%) HCW (Jan 1992-June 1992)	23/5153 (0.4%) HCW (July 1993-Dec 1993) **Reduced TST conversion by 2.9% in intervention**

Author, Year, Country	Study Design/years	Setting	Study participants	Type of intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention
Fella 1995 (USA)	Before/after (1991-1993)	Urban AIDS centre and prison hospital	HCW	Particulate respirator	Period 1 (1991): Staff use of technol shields Period 2: (Jan 1992-Jan 1993) Particulate respirators	**Composite** (A,E,R) Administrative: Immediate isolation of suspected TB, or HIV with dyspnoea or unknown HIV status with dyspnoea, cough, abnormal Xray. Engineering: (1) Gradually installing neg press. rooms - over 2y; (2) UVGI **Respiratory protection: Particulate respirators (Jan 1992) then Dust mist fume respirators (Jan 1993)**	TST conversions	Period 1: 41/303 (13.5%) (Jan 1991-Dec 1991) Period 2: 21/446 tests (4.7%) (Jan 1992 – Dec 1992)	Period 2: 21/446 tests (4.7%) (Jan 1992 – Dec 1992) *(Particular respirators reduced TST conversion by 8.8%)* Period 3: 19/403 (4.7%) (Jan 1993-Dec 1993) (*Dust mist fume respirators had no effect (0%))*
Maloney 1995 (USA)	Before / after (1990-1992)	MDR-TB wards	HCWs	Particulate respirator	Pre-intervention standard practice	Composite (A,E,R) Administrative: Improved isolation, routine use of AFB smear to determine duration of isolation, expanded lab processing of samples.	TST conversions	15/90 (16.7%) converted over 18 months in pre-intervention period	4/78 (5.1%) converted over 18 months in intervention period ***Reduced TST***

Author, Year, Country	Study Design/years	Setting	Study participants	Type of intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention
						Engineering: Exhaust fans in isolation rooms; portable Aeroguard chambers for cough-inducing procedures **Respiratory protection: Molded surgical masks (3M 1800+ Aseptex)**				***conversion by 11.5% after intervention***
Yanai 2003 (Thailand)	Before/after study (1995-1999)	TB hospital	HCW	Respiratory protection and fit testing	Pre-intervention. Not described in detail.	**Composite (A,Et,R)** Administrative: HCW training, promoting use of fit test; reduced waiting time for TB management; surgical mask use outside of TB isolation room. Infection control SOP and plan Personal etiquette: education about cough etiquette (covering mouth with surgical masks etc when coughing or sneezing). Engineering: local exhaust ventilation	1: TST conversion 2: TB cases among HCWs	1: 13/77 (13.1%) 2: 30/4357 0.7/100 person years	1: 2/96 (2.1%) *(TST conversions reduced by 14.8% post intervention)* 2: 19/4780 0.4/100 person years *(TB cases decreased by 0.29 cases/100 person yrs)*

Author, Year, Country	Study Design/years	Setting	Study participants	Type of intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention
						system; control of airflow direction; maximise natural ventilation in other high-risk areas; laboratory (class II safety cabinet, UVGI systems and air exhaust) **Respiratory: Use of personal N95 respirators encouraged, including <u>fit test</u> for staff**			
Roth et al, 2005, Brazil	1998-1999	4 Hospitals	HCWs	Particulate respirators	No particulate respirators	Composite intervention (Hospitals A and B: **Respiratory: N95 respirators for HCWs.** Administrative controls also used in Hospital A. Engineering controls in Hospital B (mechanical ventilation)	TST conversions	19.8 / 1,000 person years (Hospital C) and 12.2 / 1,000 person years (Hospital D)	7.4 / 1,000 person years (Hospital A) and 8.1 / 1,000 person years (Hospital B) *(reduction of 4.1 to 12.4 conversions / 1,000 person years, depending upon the comparison)*

Author, Year, Country	Study Design/years	Setting	Study participants	Type of intervention	Description of control	Intervention	Outcomes Measures	Results before (control) intervention	Results after intervention
Other populations									
Moro 2000 (Italy)*	Prospective cohort study	HIV wards	Other populations (People living with HIV, exposed to MDR-TB patients)	Particulate respirators	Pre-intervention standard practice	Composite (A,R) Administrative: isolation in single rooms if AFB positive; no pentamidine administration **Respiratory protection: Use of surgical masks mandatory for people entering patient rooms**	Incident MDR-TB	26/90 (29%) developed MDR-TB during 2455 patient days (10.6 / 1000 patient days)	0/44 (0%) patients developed MDR-TB during 654 patient days (0 / 1000 patient days) *(Reduced MDR-TB inc. rate by 10.6 /1000 patient days)*
Personal respiratory protection program									
da Costa, 2009	Before-after	Large urban general hospital	HCWs	Personal respiratory protection program	Prior to implementation of reparatory protection program	Composite (administrative: rapid separation and diagnosis; respiratory protection program training to implement N95 masks)	TST conversions	406 employees tested in first period; 25 cases / 4307 months (5.8 / 1000 person-months) in period 1999-2001	193 employees tested second period; 15 cases / 3858 months (3.9 / 1000 person-months) (*Reduction in TST conversion of 1.9 / 1,000 person months)*

A = administrative controls, E = engineering and environmental controls, R = respiratory protection. TST = tuberculin skin test.
*Does not use particulate respirators, but surgical masks. HCWs = healthcare workers.

Narrative summary of included studies for PICO 4

Bangsberg 1997: This was performed in urban hospital at New York in USA between 1992- 1994. It was a before and after study looking at a composite infection control (IC) program which included administrative, respiratory protection measures at implemented in hospital from 1992 to July 1993. Administrative measures included: Isolation of high-risk populations in 28 negative pressure isolation rooms (1992); dedicated clinical team + education for treating TB patients (Jun 1993) Respiratory protection included Respiratory masks (3M) and fit testing for medical house staff (Jul 1993).

Prior to the implementation of the IC program, patients placed in non-ventilated room or corridor prior to bed assignment and patients are only given surgical mask. The study reported the TST conversion rate in HCWs.
TST conversions were low in the period before and after the introduction of the respirator masks. Comparing six months before the introduction of the masks (0% in Jun 1993) to six months after (1% in Dec 1993) there was a 1% *increase* in conversion after intervention. Comparing the same control period (0% in Jun 1993) to the period 6-12 months after (0% in Jun 1993) there was no difference. The decrease in conversion rate seen in this study occurred before the respiratory protection intervention was introduced.

Baussano 2007: This study was performed at local health facilities in Italy between 1997- 2004. It looked at the composite intervention of preventive measures according to regional guidelines. Administrative controls were the appointment of local TB official, and risk evaluation and prompt isolation policy;

education of HCWs about prevention and control of TB. Engineering controls comprised laboratory containment of specimen handling (Bio Hazard type III). Personal protection comprised the use of respiratory protection measures during cough-inducing procedures.

This before and after study compared HCW TST conversion prior to implementation of guidelines and after the implementation of the new guidelines. It showed 106 infections in 4034 person-years in the prior to the implementation of guidelines compared to 42 infections in 4463 person years after the implementation of guidelines (excluding the period of implementation). The difference in conversion was 16.9 fewer conversions per 1000 person years in intervention compared to control.

Blumberg 1995 was carried out at the large urban hospital in Georgia, USA between 1992- 1994. This composite intervention compared the TST conversion in all HCWs (all employees, including medical and allied health) before and after the intervention. Administrative controls were mandatory respiratory isolation policy for TB, possible TB and HIV infection with abnormal chest Xray, increased surveillance, infection control coordinator, expanded HCW education. Engineering controls comprised conversion of 90 rooms into neg pressure rooms with fan. Respiratory protection comprised the provision of 3M 1812-submicron masks for all staff in the respiratory isolation room.

The TST conversion rate was 118/3579 (3.3%) in HCWs (Jan 1992-June 1992) before the intervention and 23/5153 (0.4%) in HCW (July 1993-Dec

1993) after the intervention. The intervention was associated with a reduction in TST conversion of 2.9% after intervention.

In this study, 354/752 patients (44.4%) with TB were HIV positive. TB exposure episodes by staff decreased markedly after intervention (4.4/month before, 0.6/month after) while the admissions with TB was similar.

Da Costa, 2009. This was a before-after study from a single urban hospital in Brazil evaluating the effect of a composite administrative, engineering and respiratory protection intervention upon TST conversion among health workers. The respiratory protection component comprised education of health workers to use particulate respirators (N95 masks), including instructions for their use, maintenance and re-use. TST conversion was assessed at the start of the implementation of the intervention, and after it was implemented. The study found TST conversion decreased from 25/4307 person months (5.8 per 1,000 person months) in 1999-2001 to 15/3858 person months (3.9 per 1,000 person months) – a reduction of 1.9 conversions / person-months. The contribution of the respiratory protection program was not distinguishable from the effect of other components of the intervention (rapid isolation and diagnosis, a ‘one stop shop’ for management of TB, the construction of isolation rooms).

Fella 1995: a retrospective cohort study in an urban AIDS centre and prison hospital. This was a composite intervention. Environmental interventions included negative pressure rooms and UVGI in patient’s rooms and in

congregate areas. To assess the outcome the employee TST conversions were reviewed every 6 months between 1991 as 1993. Two masks (a particulate respirator and a dust-mist-fume respirator) were evaluated. With the introduction of particulate respirators, the proportion of TST conversions fell from 41/303 (13.5%) to 21/446 (4.7%). There was no difference seen when a dust-mist-fume respirator was then introduced.

Maloney 1995: This study was performed in the major referral hospital at New York City, USA, between 1991- 1993. It evaluated a composite intervention including administrative and engineering controls and respiratory protection. Moulded surgical masks were used (3M 1800+ Aseptex).

The administrative components included improved isolation, routine use of AFB smear to determine duration of isolation and expanded lab processing of samples. Engineering controls included use of exhaust fans in isolation rooms and portable Aeroguard chambers for cough-inducing procedures.

Prior to the intervention, HCWs used non-molded surgical masks, and there were no negative pressure rooms. The outcome of the study was TST conversion for HCWs working with MDR-TB patients.

TST conversions occurred in 15/90 (16.7%) HCWs over 18 months in the pre-intervention period, and 4/78 (5.1%) over 18 months during the intervention period. The intervention period was associated with a decline in conversions by 11.5%.

However, secular trends are likely to have contributed to this outcome. The patient numbers of MDR-TB also declined over the period from 30 in the period Jan 1990-Jun 1991, to 10 from July 1991-Aug 1992. And for HCWs TST conversion rate in other wards of the hospital also declined from 9/40 (4.0%) to 7/254 (2.8%).

Moro 2000. This prospective cohort study was performed in an HIV ward in Italy between 1992 and 1994. The composite intervention included administrative components (isolation in single rooms for patients who were AFB positive, and cessation of pentamidine administration) and respiratory protection (use of simple surgical masks mandatory for people entering patient rooms).

The control group was the population prior to the intervention, when respiratory protection was not documented. The outcome was the incidence of MDR-TB for people with HIV exposed to patient with MDR-TB on ward.

In the control group, 26/90 (29%) developed MDR-TB (10.6 / 1000 patient days) compared to 0/44 (0%) patients developed MDR-TB during 654 patient days (0 / 1000 patient days) in the intervention group. The intervention was associated with a decrease of 10.6 cases of MDR-TB / 1000 patient days. If the patients in the overlapping period of intervention are included (before Jun 1993), the incidence-rate before the intervention was 6.1/1000 patient days,

and after the intervention 0 / 1000 patient days. This is a decline of 10.6 cases of TB within the hospital per 1000 patient days.

Roth et al, 2005: A cohort study of four hospitals in Brazil compared the TST conversion rate over a 19 month period (1998-1999). Health workers who were TST negative had repeat screening for conversion at the end of follow-up. Four hospitals had different combinations of interventions:

- Hospital A: Administrative controls and **Respiratory protection (N95 respirators for all HCWs entering a TB isolation room;** surgical mask until patients isolated)
- Hospital B: Engineering controls (negative pressure room introduction), **Respiratory protection (N95 respirators for HCWs,** surgical mask until patient isolated)
- Hospital C: Engineering (UVGI in laboratory when lab not in use), no mask use
- Hospital D: No interventions

Outcomes were reported for each hospital in conversions per 1,000 person-years (the number of patients tested at the end of follow-up was not stated). Respiratory protection was present in both Hospitals A and B, but not in Hospitals C and D. The TST conversion rate was lower in intervention sites (7.4 and 8.1 / 1,000 person years for Hospitals A and B respectively) than control sites (19.8 and 12.2 / 1,000 person years for Hospitals C and D respectively). This represented a reduction of between 4.1 and 12.4 conversions / 1,000 person years, depending upon the comparison.

This analysis was confounded by the use of masks for patients in both Hospitals A and B, but not C and D. Engineering controls also differed between sites.

Yanai et al, 2002: A retrospective study that described the effectiveness of prevention strategies of nosocomial tuberculosis. The study was conducted in a provincial referral hospital in northern Thailand between 1995-1999. The nosocomial interventions were introduced in 1996 and included N95 masks for HCW, exhaust ventilation to provide negative pressure in the newly built isolations rooms (one in each medical ward), the lab also received a class 2 safety cabinet, air exhaust and UVGI. They also included administrative controls. TST were conducted yearly using the two-step procedure. During 1997 (at the start of the intervention), the TST conversion rate was 13/77 (16.1%), decreasing to 2/96 (2.1%) in 1999 – a decline of 14.8%. TB incidence also decreased from 30/4357 (0.7 per 100 person years) in 1994-6 to 14/4780 (0.4 / 100 person years) from 1997-1999 – a decline of 0.29 cases / 100 person years.

In summary, this review had 19,776 participants in 9 included studies, TST conversions were reported in 8 studies and the incidence of TB in HCWs was reported in 2 studies[5,7]. All but one study showed a reduction in TST conversions in this population.

Stratification of the population

1. HCWs in TB care or other high TB transmission risk settings

Seven included human studies evaluated the effect of particulate respirators in HCWs in high TB transmission risk settings (Bangsberg 1997, Baussano 2007, Blumberg 1995, Fella 1995, Maloney 1995, Yanai 2003, Roth 1995). The following lists the results for stratification, according to the strata identified for PICO 4.

1.1. **HIV status:** This could not be performed, as no included studies reported outcomes according to HIV status.

1.2. **Inpatient versus outpatient healthcare settings**: Only one study (Baussano, 2007) reported the outcomes for inpatients versus outpatients. However, insufficient details of the two groups were included in the paper to allow stratified analysis. No other studies reported the effect of interventions according to outpatient or inpatient setting.

1.3. **Congregate settings**: This could not be performed, as no included studies involved congregate settings.

1.4. **TB vs MDR-TB ward:** This could not be performed, as no studies presented findings for HCWs exposed in MDR-TB wards.

2. Persons in TB care or other high TB transmission risk settings

One study reported the effect of particulate respirators, and a respiratory protection program, in high TB transmission risk settings (Moro et al). Therefore, stratification of this population according to setting was not able to be performed.

Methodological quality of included studies

Tables 5.3 shows the risk of bias assessment for the included studies. Eight out of the nine studies were before and after study and there was no blinding for all the studies. Selection bias were significant for all the studies. The overall risk of bias was assessed as ‘high’ in all studies.

This review incorporated a comprehensive search of databases and other relevant information sources. All nine included studies were found to have serious limitations in their bias assessment. Eight studies were before/after studies, meaning that temporal factors may have affected outcomes. Studies were unblinded and non-randomised. We judged these studies to have serious methodological limitations.

We judged that indirectness was a major concern for all included studies. Composite interventions were implemented in all included human studies, meaning it is not possible to assess the effect of any one intervention. Overall, a serious risk of indirectness was identified. All studies reported reductions in infection, and/or reductions in TB among health workers. Given the direction of the effect was consistent between studies, and despite some variation in the magnitude of that effect, we did not find a serious risk of imprecision. While we cannot exclude publication bias, we have conducted a comprehensive search of the literature.

Table 5.2. Downs and Black risk of bias tool for retrospective cohort studies in PICO 4

Study, year	Study design	Intervention(s)	Reporting (/11)	External validity (/3)	Bias (/7)	Confounding (/9)	Power (/5)	TOTAL (/32)
Bangsberg 1997	Before/after	Respirator mask, administrative interventions	6	3	5	1	0	15
Baussano 2007	Before/after	Administrative, Respiratory protection, Engineering	6	3	3	2	0	14
Behrman 1998	Before / after	Administrative, Respiratory protection	6	3	4	1	0	14
Blumberg 1995*	Before / after	Administrative, Engineering, Respiratory	7	3	4	1	0	15
Fella 1995	Before/after	Particulate respirators / Dust-mist fume respirator	6	3	5	1	0	15
Maloney 1995	Before / after	Composite (Administrative, engineering, Resp. protection)	7	3	4	1	0	15
Yanai 2003	Before/after study	Composite (Administrative, cough etiquette, engineering, respiratory)	6	3	4	2	0	15
da Costa 2009	Before/after	Composite (Administrative, personal respiratory protection program)	8	3	4	2	0	17

Table 5.3. Cochrane risk of bias tool for one prospective cohort study in PICO 4

Bias	Confounding	Selection of participants	Measurement of interventions	Departure form intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall Judgment
Moro 2000 (Italy)*	high	high	low	high	high	low	low	high

Table 5.4. Summary of excluded studies from the 2009 WHO review for PICO 4

Author/ Journal	**Title**	**Reason for rejection**
Adal KA New England Journal of Medicine, 1994, 331(3):169–173.	The use of high-efficiency particulate air-filter respirators to protect hospital workers from tuberculosis – a cost-effectiveness analysis	Study design (Cost analysis study)
Biscotto CR International Journal of Tuberculosis and Lung Disease, 2005, 9(5):545–549.	Evaluation of N95 respirator use as a tuberculosis control measure in a resource-limited setting.	No intervention
Derrick JL Journal of Hospital Infection, 2005, 59(2):152–155.	Predictive value of the user seal check in determining half-face respirator fit.	No outcome
Fennelly KP Infection Control and Hospital Epidemiology, 1998, 19(10):754–759.	The relative efficacy of respirators and room ventilation in preventing occupational tuberculosis.	Mathematical model study No outcome
Fridkin SK Society for Healthcare Epidemiology of America.	SHEA-CDC TB survey, Part II: Efficacy of TB infection control programs at member	Study design (cross-sectional survey)

Author/ Journal	Title	Reason for rejection
Infection Control and Hospital Epidemiology, 1995, 16(3):135–140	hospitals, 1992.	
Nettleman MD Annals of Internal Medicine, 1994, 121(1):37–40.	Tuberculosis control strategies: The cost of particulate respirators.	Cost analysis study No outcome
Barnhart S Journal of Occupational and Environmental Medicine, 1997, 39(9):849–854.	Tuberculosis in health care settings and the estimated benefits of engineering controls and respiratory protection.	No intervention
Basu S Lancet, 2007, 370(9597):1500–1507.	Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modeling study.	Mathematical model No outcome
Maciel EL Revista da Sociedade Brasileira de Medicina Tropical, 2005, 38(6):469–472	Prevalence and incidence of Mycobacterium tuberculosis infection in nursing students in Vitoria, Espirito Santo.	No intervention
Nicas M.	Respiratory protection and	No outcome

Author/ Journal	Title	Reason for rejection
American Journal of Industrial Medicine, 1995, 27(3):317–333.	the risk of Mycobacterium tuberculosis infection.	
Rivera P Infection Control and Hospital Epidemiology, 1997, 18(1):24–27.	Does a cheaper mask save money? The cost of implementing a respiratory personal protective equipment program	Cost analysis study No outcome

PICO 4 - Personal respiratory protection (1) – In healthcare workers (Q21-22)

Question 21: Can the use of particulate respirators reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	use of particulate respirators	no use of particulate respirators	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n=7)												
7 [1,2,3,4,5,6,7]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Seven studies examined the effect of particulate respirators upon TST conversion. These studies produced effects in the same direction (reducing infection), however the magnitude of the effect varied considerably between settings. Concerns around confounding due to multiple interventions, and heterogeneity of the interventions, means that the findings were not meta-analyzed. Bangsberg 1997 compared the effect of respiratory masks and fit testing for staff against usual care, prior to the introduction of a new infection control policy. Comparing six months before (0/100, 0% in Jun 1993) to six months after (1/107 1% in Dec 1993) there was a 1% increase in conversion. Comparing the same control period (0% in Jun 1993) to the period 6-12 months after (0% in Jun 1993) there was no difference. Given the low event numbers, these findings were not of significance. Second, Baussano found that staff respiratory protection was associated in a reduction in TST conversion from 26.3/1000 person years to 9.4 / 1000 person years – a reduction of 16.9 / 1000 person years. Third, Blumberg 1995 showed a composite intervention with a particulate respiratory was associated in a reduction of TST conversions from 18/3579 (3.3%) to 25/5153 (0.4%), a 2.9% reduction. Fella 1995 showed that particulate respirators were associated with a reduction in TST conversion from 41/303 (13.5%) to 21/446 (4.7%), a reduction of 8.8%. Dust fume respirators had no effect. Maloney 1995 showed a composite intervention including molded surgical masks was associated with a reduction in TST conversion from 15/90 (16.7%) to 4/78 (5.1%), a reduction by 11.5%. In Yanai 2003, a composite intervention including mixed mode ventilation was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Finally, Roth 1995 showed a composite intervention including respirators for health workers was associated with a reduction of infection of between 4.1 and 12.4 conversions per 1,000 persons.				⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	use of particulate respirators	no use of particulate respirators	Relative (95% CI)	Absolute (95% CI)		
Reduction in TB incidence/prevalence (n=1)												
1 [4,c]	observational studies	serious [a]	not serious	very serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included studies have a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).

b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

c. Only one study evaluated this outcome. In Yanai 2003, a composite intervention including use of staff particulate respirators was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.

References

1. Maloney SA, Pearson ML,Gordon MT,Del Castillo R,Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med; 1995.
2. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic increase in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Control; 1995.
3. Baussano I, Bugiani M,Carosso A,Mairano D,Barocelli AP,Tagna M,Cascio V,Piccioni P,Arossa W. Risk of tuberculin conversion among healthcare workers and the adoption of preventive measures. Occup Environ Med; 2007.
4. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
5. Roth VR, Garrett DO,Laserson KF,Starling CE,Kritski AL,Medeiros EAS,Binkin N,Jarvis WR. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals.. Int J Tuberc Lung Dis; 2005.
6. Blumberg HM, Sotir M,Erwin M,Bachman R,Shulman JA. Risk of house staff tuberculin skin test conversion in an area with a high incidence of tuberculosis. Clin Infect Dis; 1998.
7. Bangsberg DR, Crowley K,Moss A,Dobkin JF,McGregor C,Neu HC. Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. Infect Control Hosp Epidemiol; 1997.

Question 22: Can the implementation of respiratory protection programs reduce TB transmission in healthcare workers in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	the implementation of respiratory protection programs	no implementation	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n= 2)												
2 [1,2]	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies reported on the evaluation of fit testing of particulate respirators, as a part of complex composite interventions. In Yanai 2003, a composite intervention including fit testing of HCWs was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Bangsberg 1997 compared the effect of particulate respirators and fit testing for staff against usual care, prior to the introduction of a new infection control policy. Comparing six months before (0/100, 0% in Jun 1993) to six months after (1/107, 1% in Dec 1993) there was a 1% increase in conversion. Comparing the same control period (0% in Jun 1993) to the period 6-12 months after (0% in Jun 1993) there was no difference. Given the low event numbers, these findings were not of significance. Therefore, the two studies show a stable or reduced proportion of HCWs developing LTBI. Heterogeneity in the interventions precludes meta-analysis.				⊕◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence (n= 1)												
1 [1,c]	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations
a. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).
b. Differences in intervention (applicability). The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).
c. One study evaluated this outcome. In Yanai 2003, a composite intervention including fit testing for HCW masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.

References

1. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.
2. Bangsberg DR, Crowley K,Moss A,Dobkin JF,McGregor C,Neu HC. Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. Infect Control Hosp Epidemiol; 1997.

PICO 4 - Personal respiratory protection (2) – Other persons attending healthcare settings or high TB transmission risk (Q22-24)

Question 23: Can the use of particulate respirators reduce TB transmission in persons in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**use of particulate respirators**	**no use of particulate respirators**	**Relative (95% CI)**	**Absolute (95% CI)**		
Reduction in LTBI incidence/prevalence (n=0)												
0											-	CRITICAL
Reduction in TB incidence/prevalence (n=1)												
1 [1,a]	observational studies	serious [b]	not serious	very serious [c]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/44 (0.0%)	26/90 (28.9%)	not pooled	see comment	⊕◯◯◯ VERY LOW	CRITICAL
Reduction in TB incidence/prevalence in people living with HIV (n=1)												
1 [1,a]	observational studies	serious [b]	not serious	very serious [c]	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/44 (0.0%)	26/90 (28.9%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. Moro 2000 evaluated the effect of mask use by people entering isolation rooms (including visitors). Surgical masks were used. At the same time, high-risk pentamidine use (a risk for increased cough and transmission) was also ceased. The effect of this intervention reflects a combination of multiple components. Incident MDR-TB reduced from 26/90 (29%) to 0/44 (0%) during the period after the intervention began. The reduction in MDR-TB incidence was 10.6 / 1,000 patient days. Confounding factors are likely, and the effect cannot only be attributed to the respiratory protection program.

b. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).

c. The intervention comprises multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

References

1. Moro ML, Errante I Infuso A Sodano L Gori A Orcese CA Salamina G D'Amico C Besozii G Caggese L. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy.. Int J Tuberc Lung Dis; 2000.

Question 24: Can the implementation of respiratory protection programs reduce TB transmission in persons in TB care or other high TB transmission risk settings when compared to transmission to the same populations in settings with no intervention or different interventions?
Setting: International

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	the implementation of respiratory protection programs	no implementation	Relative (95% CI)	Absolute (95% CI)		
Reduction in LTBI incidence/prevalence (n=1)												
2 [1,2]	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Two studies were included. Heterogeneity in the interventions precludes meta-analysis. Da Costa 2009 was a before-after study evaluating the effect of a composite administrative, engineering and respiratory protection intervention upon TST conversion among health workers. The respiratory protection component comprised education of health workers to use particulate respirators (N95 masks), including instructions for their use, maintenance and re-use. TST conversion was assessed at the start of the implementation of the intervention, and after it was implemented. The study found TST conversion decreased from 25/4307 person months (5.8 per 1,000 person months) in 1999-2001 to 15/3858 person months (3.9 per 1,000 person months) – a reduction of 1.9 conversions / person-months. In Yanai 2003, a composite intervention including fit testing of HCWs was associated with a decrease in TST conversions from 13/77 (16.9%) to 2/96 (2.1%) – a decrease of 14.8%. Both studies were associated with a decrease in conversion, however temporal factors and the effect of other components of the composite interventions preclude attribution of the cause of the decline.				⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	the implementation of respiratory protection programs	no implementation	Relative (95% CI)	Absolute (95% CI)		
Reduction in TB incidence/prevalence (n=1)												
1 [2,c]	observational studies	serious [a]	not serious	serious [b]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	19/4780 (0.4%)	30/4357 (0.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. The included study has a high risk of bias (confounding relating to secular trends, non-randomised group allocation, lack of allocation concealment, no adjustment for confounding).

b. The comparator and interventions are poorly described. The interventions comprise multiple simultaneous components, including engineering, respiratory protection and administrative controls (downgraded by one level).

c. One study evaluated this outcome. In Yanai 2003, a composite intervention including fit testing for HCW masks was associated with a decrease in TB cases from 30/4357 (0.7%) to 19/4780 (0.4%), a reduction in 0.29 cases/100 person years.

References

1. da Costa P, Trajman A ,Mello FC,Goudinho S,Silva MA,Garret D,Ruffino-Netto A,Kritski AL. Administrative measures for preventing Mycobacterium tuberculosis infection among healthcare workers in a teaching hospital in Rio de Janeiro, Brazil. J Hosp Infect; 2009.

2. Yanai H, Limpakarnjanarat K,Uthaivoravit W,Mastro TD,Mori T,Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis; 2003.

6. Appendix: Search strategies

Table 6.1. Summary of strategy for PICO Question 2

Database	Intervention	Outcomes
PubMed	respiratory hygiene[Text Word] OR cough etiquette[Text Word] OR face mask[Title/Abstract] OR surgical mask[Title/Abstract] OR facial mask[Title/Abstract] OR cloth mask[Title/Abstract] OR mask[Title/Abstract] OR mask[MeSH Terms] OR Infectious Disease Transmission, Patient-to-Professional[MeSH Terms] OR infection control[MeSH Terms]	Tuberculosis[MeSH Terms] OR Latent tuberculosis[MeSH Terms] OR mycobacterium tuberculosis[MeSH Terms] OR mycobacterium tuberculosis[Title/Abstract] OR latent tuberculosis infection[Title/Abstract] OR tuberculin test[MeSH Terms] OR tuberculosis[Title/Abstract] OR LTBI[Title/Abstract] OR tuberculin skin test[Text Word] OR TB[Title/Abstract]
Embase	respiratory hygiene OR cough etiquette OR face mask OR surgical mask OR facial mask OR cloth mask OR mask OR Patient-to-Professional OR infection control (all Title/Abstract/Author Keyword)	tuberculosis OR mycobacterium tuberculosis OR TB OR latent tuberculosis OR LTBI (all Title/Abstract/Author Keyword)
Central	respiratory hygiene OR cough etiquette OR mask	tuberculosis
WHO global index medicus		
WHO portal of clinical trials		
LILACS		
Clinicaltrials.gov		
Cochrane database of systematic reviews		
Union journal		
OpenSIGLE		

Table 6.2. Summary of strategy for PICO Question 3

Search set	MEDLINE	EMBASE	Web of Science	LILACS, PubMed & Cochrane Library
Intervention				
1.	ventilation[MeSH Terms]	ventilation[MeSH Terms]		ventilation[MeSH Terms]
2.	air filter[MeSH Terms]	air filter[MeSH Terms]		air filter[MeSH Terms]
3.	Ultraviolet rays (MeSH terms)	Ultraviolet rays (MeSH terms)		Ultraviolet rays (MeSH terms)
4.	environmental medicine[MeSH Terms]	environmental medicine[MeSH Terms]	environmental medicine[Text Word]	environmental medicine[MeSH Terms]
5.	(facility design and construction[MeSH Terms]	(facility design and construction[MeSH Terms]	(facility design and construction[Text Word]	(facility design and construction[MeSH Terms]
6.	Infectious Disease Transmission, prevention[MeSH Terms])	Disease Transmission, prevention (MeSH Terms)	infectious disease transmission, patient-to-professional (Text Word)	infectious disease transmission, patient-to-professional
7.	cross infection[MeSH Terms]	cross infection[MeSH Terms]	cross infection[Text Word]	cross infection[MeSH Terms]
8.	ventilation[Text Word]	ventilation[Text Word]	ventilation[Text Word]	ventilation[Text Word]
9.	"air filt*"[Text Word]	"air filt*"[Text Word]	"air filt*"[Text Word]	"air filt*"[Text Word]
10.	ultraviolet[Text Word]	ultraviolet[Text Word]	ultraviolet[Text Word]	ultraviolet[Text Word]
11.	UVGI[Text Word]	UVGI[Text Word]	UVGI[Text Word]	UVGI[Text Word]
12.	"environmental control*"[Text Word]	"environmental control*"[Text Word]	"environmental control*"[Text Word]	"environmental control*"[Text Word]
13.	HEPA[Text Word]	HEPA[Text Word]	HEPA[Text Word]	HEPA[Text Word]
14.	"high efficiency particulate air"[Text Word]	"high efficiency particulate air"[Text Word]	"high efficiency particulate air"[Text Word]	"high efficiency particulate air"[Text Word]
15.	"engineering control*"[Text Word]	"engineering control*"[Text Word]	"engineering control*"[Text Word]	"engineering control*"[Text Word]

Outcomes				
16.	Tuberculosis[MeSH Terms]	Tuberculosis[MeSH Terms]		Tuberculosis[MeSH Terms]
17.	Latent tuberculosis[MeSH Terms]	Latent tuberculosis[MeSH Terms]		Latent tuberculosis[MeSH Terms]
18.	tuberculin test[MeSH Terms]	tuberculin test[MeSH Terms]		tuberculin test[MeSH Terms]
19.	tuberculosis[Text Word]	tuberculosis[Text Word]	tuberculosis[Text Word]	tuberculosis[Text Word]
20.	LTBI[Text Word]	LTBI[Text Word]	LTBI[Text Word]	LTBI[Text Word]
21.	"tuberculin skin test"[Text Word]	"tuberculin skin test"[Text Word]	"tuberculin skin test"[Text Word]	"tuberculin skin test"[Text Word]
22.	TB[Text Word]	TB[Text Word]	TB[Text Word]	TB[Text Word]
Combined				
23	1 or 2 or ….or 15	1 or 2 or ….or 15	4 or 5 or ….or 15	1 or 2 or ….or 15
24	16 or 17 … or 22	16 or 17 … or 22	19 or 20 or … or 22	16 or 17 … or 22
25	23 AND 24	23 AND 24	23 AND 24	23 AND 24

Table 6.3. Summary of strategy for PICO Question 4

Search set	MEDLINE/ PUBMED	EMBASE	Web of Science	LILACS
Intervention				
1	Respiratory protective device[MeSH]	Face mask[MeSH]	Respirator [TW]	Respirator [TW]
2	Disease transmission, infectious [MeSH]	Protective equipment [MeSH]	Respirators [TW]	Respirators [TW]
3	Infection control [MeSH]	Infection control [MeSH]	N95[TW]	N95[TW]
4	Cross infection [MeSH]	Cross infection [MeSH]	“seal test”[TW]	“seal test”[TW]
5	Respirator[Title/ abstract]	Disease transmission [prevention] [MeSH]	“fit test”[TW]	“fit test”[TW]
6	Respirators[Title /abstract]	Respirator[Title /abstract	Mask[TW]	Mask[TW]
7	N95[Title/ abstract]	Respirators[Title /abstract	Respiratory protective device [TW]	Respiratory protective device[mh]
8	“seal test”[Title/ abstract]	N95[Title /abstract	Infection control[TW]	Infection control[mh]
9	“fit test” [Title/abstract]	“seal test” [Title /abstract	Cross infection[TW]	Cross infection[mh]
10	Mask[Title/ abstract]	“fit test” [Title /abstract	Disease transmission[TW]	Disease transmission[mh]
11		mask[Title /abstract		
12		FFP2[Title /abstract		
Outcomes				
13	Tuberculosis[MeSH Terms]	Tuberculosis[MeSH Terms]	TB[TW]	TB[TW]
14	Latent tuberculosis[MeSH Terms]	Latent tuberculosis[MeSH Terms]	Tuberculosis [TW]	Tuberculosis [TW]
15	tuberculin test[MeSH Terms]	tuberculin test[MeSH Terms]	LTBI[TW]	LTBI[TW]
16	tuberculosis[Title/ abstract]	tuberculosis[Title/ abstract]	“tuberculin skin test” [TW]	“tuberculin skin test” [TW]
17	LTBI[Title/Abstract]	LTBI[Title/Abstract]		Tuberculosis[mh]
18	"tuberculin skin test"[Text Word]	"tuberculin skin test"[Text Word]		Latent tuberculosis[mh]
19	TB[Title/Abstract]	TB[Title/Abstract]		tuberculin test[mh]
Combined				
20	1 or 2 or ….or 10	1 or 2 or…or 12	1 or 2 or…or 10	1 or 2 or ….or 10
21	13 or 14 …or 19	13 or 14 …or 19	13 or 14 or …16	13 or 14…or19
22	20 AND 21	20 AND 21	20 AND 21	20 AND 21

References

1. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration; 2011.
2. Downs SH, N B. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;1998:377-84.
3. Murad MH, Mustafa RA, Schunemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med 2017;22:85-7.
4. A Cochrane risk of bias assessment tool: for non-randomized studies of interventions. 2014. at Available: http://www. riskofbias.info.)
5. Moro ML, Errante I, Infuso A, et al. Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug-resistant tuberculosis among HIV patients in Italy. Int J Tuberc Lung Dis 2000;4:61-8.
6. Harries AD HN, Gausi F, Kwanjana JH, Salaniponi FM. . Preventing tuberculosis among health workers in Malawi. Bull World Health Organ 2002;80:526-31.
7. Yanai H, Limpakarnjanarat K, Uthaivoravit W, Mastro TD, Mori T, Tappero JW. Risk of Mycobacterium tuberculosis infection and disease among health care workers, Chiang Rai, Thailand. Int J Tuberc Lung Dis 2003;7:36-45.
8. Roth VR, Garrett DO, Laserson KF, et al. A multicenter evaluation of tuberculin skin test positivity and conversion among health care workers in Brazilian hospitals. Int J Tuberc Lung Dis 2005;9:1335-42.

9. Dharmadhikari AS, Mphahlele M, Stoltz A, et al. Surgical face masks worn by patients with multidrug-resistant tuberculosis: impact on infectivity of air on a hospital ward. Am J Respir Crit Care Med 2012;185:1104-9.
10. World Health Organization. WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Households. Geneva: WHO; 2009.
11. Blumberg HM, Watkins DL, Berschling JD, et al. Preventing the nosocomial transmission of tuberculosis. Annals of internal medicine 1995;122:658-63.
12. Welbel SF, French AL, Bush P, DeGuzman D, Weinstein RA. Protecting health care workers from tuberculosis: a 10-year experience. American journal of infection control 2009;37:668-73.
13. Wenger PN, Otten J, Breeden A, Orfas D, Beck-Sague CM, Jarvis WR. Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. Lancet 1995;345:235-40.
14. Maloney SA, Pearson ML, Gordon MT, Del Castillo R, Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Annals of internal medicine 1995;122:90-5.
15. Muecke C, Isler M, Menzies D, Allard R, Tannenbaum TN, Brassard P. The use of environmental factors as adjuncts to traditional tuberculosis contact investigation. Int J Tuberc Lung Dis 2006;10:530-5.
16. Menzies D, Fanning A, Yuan L, FitzGerald JM, Canadian Collaborative Group in Nosocomial Transmission of T. Factors associated with tuberculin conversion in Canadian microbiology and pathology workers. Am J Respir Crit Care Med 2003;167:599-602.

17. Behrman AJ, Shofer FS. Tuberculosis exposure and control in an urban emergency department. Ann Emerg Med 1998;31:370-5.
18. Fella P, Rivera P, Hale M, Squires K, Sepkowitz K. Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City. American journal of infection control 1995;23:352-6.
19. Mphaphlele M, Dharmadhikari AS, Jensen PA, et al. Institutional Tuberculosis Transmission. Controlled Trial of Upper Room Ultraviolet Air Disinfection: A Basis for New Dosing Guidelines. Am J Respir Crit Care Med 2015;192:477-84.
20. Riley RL, Mills CC, O'Grady F, Sultan LU, Wittstadt F, Shivpuri DN. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. Am Rev Respir Dis 1962;85:511-25.
21. Lurie MB, Collaboration of Helen T, Samuel A. Experimental Epidemiology of Tuberculosis : The Prevention of Natural Air-Borne Contagion of Tuberculosis in Rabbits by Ultraviolet Irradiation. J Exp Med 1944;79:559-72.
22. Riley RL, Wells WF, Mills CC, Nyka W, McLean RL. Air hygiene in tuberculosis: quantitative studies of infectivity and control in a pilot ward. Am Rev Tuberc 1957;75:420-31.
23. Escombe AR, Moore DA, Gilman RH, et al. Upper-room ultraviolet light and negative air ionization to prevent tuberculosis transmission. PLoS medicine 2009;6:e43.
24. Baussano I, Bugiani M, Carosso A, et al. Risk of Tuberculin Conversion among Healthcare Workers and the Adoption of Preventive Measures. Occupational and Environmental Health 2007;64:161-6.

25. da Costa PA, Trajman A, Mello FC, et al. Administrative measures for preventing Mycobacterium tuberculosis infection among healthcare workers in a teaching hospital in Rio de Janeiro, Brazil. J Hosp Infect 2009;72:57-64.