**Title: Risk factors for infectiousness of patients with tuberculosis: a systematic review and meta-analysis**

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**Running title: Tuberculosis patients’ infectiousness**

**Supplementary materials**

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# Table 1: Complete search strategy

MEDLINE with Ovid software

(“tuberculosis”[Title] OR "tuberculosis"[MeSH Terms] OR "mycobacterium tuberculosis"[MeSH Terms] OR "tuberculosis, pulmonary"[MeSH Terms] OR “TB” [Title] )

AND

(("contact$"[All Fields]) OR ("contact tracing"[MeSH Terms]) OR "disease outbreaks"[MeSH Terms] OR "contact\*"[Title] OR "spread\*"[Title] OR "contact follow\*"[All Fields] OR "contact tracing"[Title] OR "disease transmission"[All Fields] OR "case find\*"[Title] OR (cluster\*[Title] OR “Genotypic cluster\*”[All fields] OR “Phylogenetic cluster\*”[All Feilds]

AND

(Transmiss\*[Title]) OR "index case\*"[All Fields] OR ("secondary case"[All Fields]) OR (“case finding”[All Fields]) OR (“infectiousness”[All Fields]) OR (“Molecular epidemiology”[Title]))

EMBASE search with Ovid software

(“tuberculosis”[Title] OR "tuberculosis"[MeSH Terms] OR "mycobacterium tuberculosis"[MeSH Terms] OR "lung tuberculosis"[MeSH Terms] OR “latent tuberculosis”OR “TB” [Title] )

AND

(("contact$"[All Fields]) OR ("contact examination"[MeSH Terms]) OR "epidemic"[MeSH Terms] OR "contact tracing"[Title] OR "disease transmission"[All Fields] OR "case find\*"[Title] OR (cluster\*[Title] OR “Genotypic cluster\*”[All fields] OR “Phylogenetic cluster\*”[All Feilds]

AND

(Transmission\*[Title]) OR "index case\*"[All Fields] OR ("secondary case"[All Fields]) OR (“case finding”[All Fields]) OR (“infectiousness”[All Fields]) OR (“Molecular epidemiology”[Title]))

Global Health and Global Archieve with CAB-Direct software

Tuberculosis AND Transmission AND Contact tracing [all feilds]

Mycobacterium tuberculosis AND Transmission AND Genotypic Clustering

Web of Science

Tuberculosis [title] OR Mycobacterium tuberculosis (title) OR TB [title]

AND

Contact tracing [title]

Contact\*

Genotypic Clustering [title]

AND

Transmission [title]

# Table 2- Quality assessment of 37 included studies with Newcastle-Ottawa Scale (Point scored)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Studies & reference** | **Selection (4 stars)** | | | | **Comparability (2 star)** | | **Outcome (3 Star)** | | | **Total (9 stars)** |
|  |  | Representativeness of the sample | Sample size | Ascertainment of exposure | Non-respondents | controls for the most important factor (Age) | control for any additional factor | Assessment of outcome | Follow-up long enough for outcomes to occur | Adequacy of follow up of participants |
|  | Baliashvili, 2016 | \* |  | \* |  |  |  | \* |  |  | 3\* |
|  | Elliott, 1993 |  |  | \* |  | \* | \* | \* |  |  | 4\* |
|  | Maciel, 2009 |  |  | \* |  |  |  | \* | \* | \* | 4\* |
|  | Madhi, 2002 |  |  | \* |  | \* | \* | \* |  |  | 4\* |
|  | Singh, 2005 |  |  | \* |  | \* | \* | \* |  |  | 4\* |
|  | Teixeira, 2001 |  |  | \* |  | \* | \* | \* |  |  | 4\* |
|  | Elmi, 2014 | \* |  | \* | \* |  | \* | \* |  |  | 5\* |
|  | Faksri, 2015 |  |  | \* | \* | \* | \* | \* |  |  | 5\* |
|  | Jones-Lopez, 2016 |  |  | \* | \* | \* | \* | \* |  |  | 5\* |
|  | Mendes, 2012 | \* |  | \* |  | \* | \* | \* |  |  | 5\* |
|  | Nair, 2016 | \* |  | \* |  | \* | \* | \* |  |  | 5\* |
|  | Nunn, 1994 | \* |  | \* |  | \* | \* | \* |  |  | 5\* |
|  | Carvalho, 2001 | \* |  | \* |  | \* | \* | \* | \* |  | 6\* |
|  | Castillo Otero, 1999 | \* | \* | \* | \* |  |  | \* |  | \* | 6\* |
|  | Cayla, 1996 | \* |  | \* | \* | \* | \* | \* |  |  | 6\* |
|  | Kifai, 2009 | \* | \* | \* |  | \* | \* | \* |  |  | 6\* |
|  | Mohammad, 2002 | \* |  | \* | \* | \* | \* | \* |  |  | 6\* |
|  | Tornee, 2004 |  | \* | \* | \* | \* | \* | \* |  |  | 6\* |
|  | Espinal, 2000 | \* |  | \* | \* | \* | \* | \* |  | \* | 7\* |
|  | Gessner, 1998 | \* | \* | \* | \* | \* | \* | \* |  |  | 7\* |
|  | Godoy, 2013 | \* | \* | \* | \* | \* | \* | \* |  |  | 7\* |
|  | Golub, 2006 | \* |  | \* | \* | \* | \* | \* |  | \* | 7\* |
|  | Grandjean, 2011 | \* | \* | \* | \* | \* | \* | \* |  |  | 7\* |
|  | Lienhardt, 2003 | \* |  | \* |  | \* | \* | \* | \* | \* | 7\* |
|  | Ling, 2011 | \* | \* | \* | \* | \* | \* | \* |  |  | 7\* |
|  | Rathi, 2002 | \* | \* | \* | \* | \* | \* | \* |  |  | 7\* |
|  | Xu, 2008 | \* | \* | \* | \* | \* | \* | \* |  |  | 7\* |
|  | Lohmann, 2012 | \* | \* | \* | \* |  | \* | \* | \* | \* | 8\* |
|  | Loredo, 2014 | \* | \* | \* | \* |  | \* | \* | \* | \* | 8\* |
|  | Grandjean, 2015 | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9\* |
|  | Guwatudde, 2003 | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9\* |
|  | Huang, 2014 (Cigar) | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9\* |
|  | Huang, 2014 | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9\* |
|  | Lee, 2008 | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9\* |
|  | Martinez, 2016 | \* |  | \* | \* | \* | \* | \* | \* | \* | 9\* |
|  | Otero, 2016 | \* | \* | \* | \* | \* | \* | \* | \* | \* | 9\* |

# Table 3- Definitions of index cases and contacts in the 37 included studies.

|  |  |  |
| --- | --- | --- |
| **Definition of index patients** | **First Author & year** | **Reference** |
| * Newly diagnosed sputum smear-positive PTB | Otero, 2016  Nair, 2016  Jones-Lopez, 2016  Kifai, 2009  Tornee, 2004  Rathi, 2002  Cayla, 1996  Xu, 2008 | [1]  [2]  [3]  [4]  [5]  [6]  [7]  [8] |
| * Confirmed PTB patients | Mendes, 2012  Golub, 2006  Lienhardt, 2003  Mohammad, 2002  Madhi, 2002  Carvalho, 2001  Espinal, 2000  Gessner, 1998  Nunn, 1994  Elliott, 1993  Singh, 2005 | [9]  [10]  [11]  [12]  [13]  [14]  [15]  [16]  [17]  [18]  [19] |
| * Re-treatment AFB positive patients | Baliashvili, 2016 | [20] |
| * MDR-TB patients and drug-susceptible TB patients | Grandjean, 2015  Teixeira, 2001  Snider, 1985 | [21]  [22]  [23] |
| * Newly diagnosed TB patients | Faksri, 2015  Godoy, 2013  Ling, 2011 | [24]  [25]  [26] |
| * All TB patients | Loredo, 2014  Lohmann, 2012  Lee, 2008  Guwatudde, 2003  Castillo Otero, 1999 | [27]  [28]  [29]  [30]  [31] |
| * New culture-positive TB patients | Huang, 2014  Martinez, 2016 Maciel, 2009 | [32]  [33]  [34] |
| * Adults (15 years and above) with drug-susceptible TB | Huang, 2014 | [35] |
| * Patients with MDR-TB and XDR-TB | Elmi, 2014 | [36] |
| * Adults (14 years and above) with MDR-TB | Grandjean, 2011 | [37] |
| **Definition of contacts** |  |  |
| * Household contacts | Otero, 2016  Nair, 2016  Jones-Lopez, 2016  Grandjean, 2015  Faksri, 2015  Huang, 2014  Huang, 2014  Elmi, 2014  Grandjean, 2011  Kifai, 2009  Martinez, 2016 Guwatudde, 2003  Rathi, 2002  Mohammad, 2002  Teixeira, 2001  Carvalho, 2001  Espinal, 2000  Nunn, 1994  Elliott, 1993  Xu, 2008 | [1]  [2]  [3]  [21]  [24]  [32]  [35]  [36]  [37]  [4]  [33]  [30]  [6]  [12]  [22]  [14]  [15]  [17]  [18]  [8] |
| * Daily contacts (both household and non-household) | Baliashvili, 2016  Cayla, 1996 | [20]  [7] |
| * Close contacts who shared an enclosed space | Loredo, 2014  Lee, 2008  Golub, 2006 | [27]  [29]  [10] |
| * Contacts at different level of concentric circle | Godoy, 2013  Lohmann, 2012 | [25]  [28] |
| * Close (household) and casual contacts | Mendes, 2012  Castillo Otero, 1999 | [9]  [31] |
| * Children and adolescents (aged 15 or younger) household contacts | Maciel, 2009  Tornee, 2004  Madhi, 2002  Gessner, 1998  Snider, 1985  Ling, 2011 | [34]  [5]  [13]  [16]  [23]  [26] |
| * Children under the age of 5 years in household contact | Singh, 2005  Lienhardt, 2003 | [19]  [11] |

# **Table 4 - Methods used to detect TB transmission from index patients to their contacts by 37 included studies**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Method of screening (cut-off)** | **First Author** | **Reference** |
| LTBI | TST (≥10mm) | Baliashvili, 2016 | [20] |
| LTBI | TST (≥10mm) | Huang, 2014 | [32] |
| LTBI | TST (≥10mm, ≥5mm HIV+) | Huang, 2014 | [35] |
| LTBI | TST (≥5mm) | Godoy, 2013 | [25] |
| LTBI | TST (≥10mm) | Lohmann, 2012 | [28] |
| LTBI | TST (≥10mm, ≥5mm HIV+) | Kifai, 2009 | [4] |
| LTBI | TST (≥10mm) | Martinez, 2016 | [33] |
| LTBI | TST (≥5mm) | Golub, 2006 | [10] |
| LTBI | TST (≥10mm) | Singh, 2005 | [19] |
| LTBI | TST (≥15mm) | Tornee, 2004 | [5] |
| LTBI | TST (≥5mm) | Lienhardt, 2003 | [11] |
| LTBI | TST (≥10mm) | Rathi, 2002 | [6] |
| LTBI | TST (≥10mm) | Mohammad, 2002 | [12] |
| LTBI | TST (≥10mm) | Teixeira, 2001 | [22] |
| LTBI | TST (≥10mm, ≥5mm HIV+) | Carvalho, 2001 | [14] |
| LTBI | TST (≥5mm) | Espinal, 2000 | [15] |
| LTBI | TST (≥5mm) | Nunn, 1994 | [17] |
| LTBI | TST (≥5mm) | Elliott, 1993 | [18] |
| LTBI | TST (≥10mm) | Snider, 1985 | [23] |
| LTBI | TST (≥15mm) | Xu, 2008 | [8] |
| LTBI | TST (≥10mm) & IGRA | Jones-Lopez, 2016 | [3] |
| LTBI | TST (≥10mm) & IGRA | Faksri, 2015 | [24] |
| LTBI | TST & IGRA | Mendes, 2012 | [9] |
| LTBI | IGRA | Elmi, 2014 | [36] |
| TB disease | symptoms and CXR | Otero, 2016 | [1] |
| TB disease | CXR | Nair, 2016 | [2] |
| TB disease | Bacteriological, CXR or clinical | Grandjean, 2015 | [21] |
| TB disease | Bacteriological, CXR or clinical | Grandjean, 2011 | [37] |
| TB disease | Bacteriological, CXR or clinical | Lee, 2008 | [29] |
| TB disease | Bacteriological, CXR or clinical | Guwatudde, 2003 | [30] |
| TB disease | Bacteriological, CXR or clinical | Ling, 2011 | [26] |
| LTBI & TB | TST& bacteriological, CXR or clinical | Loredo, 2014 | [27] |
| LTBI & TB | TST (≥5mm)& bacteriological, CXR or clinical | Gessner, 1998 | [16] |
| LTBI & TB | TST (≥10mm), CXR or clinical | Maciel, 2009 | [34] |
| LTBI & TB | TST (≥10mm)& CXR | Madhi, 2002 | [13] |
| LTBI & TB | TST (≥5mm) & CXR | Castillo Otero, 1999 | [31] |
| LTBI & TB | TST & CXR | Cayla, 1996 | [7] |

# Table 5: Characteristics of Studies included in Meta-analyses

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Author, year** | **Country** | **Study period** | **Design** | **Index no.** | **Contact no.** | **Method of contact screening** |
|  | Carvalho, 2001 [14] | Brazil | 1995-1997 | Population based | 86 | 360 | TST |
|  | Castillo Otero, 1999 [31] | Spain | 1992-1996 | Population based | 302 | 1029 | TST |
|  | Cayla, 1996 [7] | Spain | 1990-1993 | Population based | 248 | 1080 | TST & CXR |
|  | Elliott, 1993 [18] | Zambia | 1989 | Population based | 71 | 304 | TST |
|  | Elmi, 2014 [36] | Malaysia | 2010-2012 | Population based | 69 | 70 | IGRA |
|  | Espinal, 2000 [15] | Russia | 14months | Population based | 755 | 803 | TST |
|  | Faksri, 2015 [24] | Thailand | 2012-2013 | Population based | 40 | 70 | TST& IGRA |
|  | Gessner, 1998 [16] | USA, | 1987-1994 | Population based |  | 282 | TST |
|  | Godoy, 2013 [25] | Spain | 2005-2006 | Population based | 1329 | 6548 | TST |
|  | Golub, 2006 [10] | USA | 2000-2001 | Population based | 124 | 703 | TST |
|  | Grandjean, 2015 [21] | Peru | 2010-2013 | Population based | 700 | 3417 | Bacteriological,x-ray or clinica |
|  | Guwatudde, 2003 [30] | Uganda | 1995-1999 | Population based | 302 | 1206 | Bacteriological, CXR or clinical |
|  | Jones-Lopez, 2016 [3] | Uganda | 2009–2011 | Population based | 85 | 369 | TST& IGRA |
|  | Lee, 2008 [29] | Hong Kong | 2000 | Population based | 1537 | 4661 | Bacteriological, CXR or clinical |
|  | Ling, 2011 [26] | Taiwan | 2005-2007 | Contacts age <20 | 2952 | 5879 | Sputum, CXR, Clinical TB |
|  | Loredo, 2014 [27] | Brazil | 2005-2008 | Population based | 369 | 1310 | TST |
|  | Maciel, 2009 [34] | Brazil | 2003-2006 | Population based |  | 146 | TST |
|  | Madhi, 2002 [13] | Paris | 1997-2000 | Children contacts 3months-17yrs |  | 408 | TST |
|  | Martinez, 2016 [33] | Uganda | 1995-2006 | Population based | 503 | 1933 | TST |
|  | Mendes, 2012 [9] | Portugal | 2011 | Population based | 69 | 397 | TST& IGRA |
|  | Mohammad, 2002 [12] | Malaysia | 1999-2000 | Population based | 56 | 138 | TST |
|  | Nair, 2016 [2] | India, | 2007-2011 | Population based | 280 | 544 | CXR & Symptoms |
|  | Nunn, 1994 [17] | Kenya | 1989-1990 | Population based | 82 | 357 | TST |
|  | Singh, 2005 [19] | India | 18months | Population based | 200 | 281 | TST |
|  | Teixeira, 2001 [22] | Brazil | 1994-1998 | Population based | 78 | 408 | TST |
|  | Tornee, 2004 [5] | Thailand | 2002-2003 | contacts aged less than 15 years | 342 | 500 | TST |

# Table 6: Sensitivity analysis result for studies included in meta-analyses of sputum smear positivity Crude odds ratios

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Excluded study | Pooled OR | LCI 95% | HCI 95% | Cochran Q | p | I2 | I2 LCI 95% | I2 HCI 95% |
| Castillo Otero, 1999 | 2.44 | 1.96 | 3.04 | 19.33 | 0.04 | 48.26 | 0 | 74.18 |
| Elmi, 2014 | 2.24 | 1.81 | 2.77 | 22.31 | 0.01 | 55.19 | 11.76 | 77.24 |
| Gessner, 1998 | 2.28 | 1.82 | 2.87 | 23.06 | 0.01 | 56.64 | 14.10 | 77.88 |
| Godoy, 2013 | 2.45 | 1.92 | 3.14 | 21.05 | 0.02 | 52.48 | 5.73 | 76.05 |
| Golub, 2006 | 2.20 | 1.79 | 2.71 | 20.76 | 0.02 | 51.82 | 4.26 | 75.76 |
| Lee, 2008 | 2.19 | 1.78 | 2.71 | 20.67 | 0.02 | 51.62 | 3.82 | 75.67 |
| Ling, 2011 | 2.23 | 1.79 | 2.78 | 21.77 | 0.02 | 54.07 | 9.27 | 76.75 |
| Loredo, 2014 | 2.44 | 1.91 | 3.11 | 22.89 | 0.01 | 56.31 | 14.27 | 77.74 |
| Maciel, 2009 | 2.27 | 1.82 | 2.83 | 23.33 | 0.01 | 57.13 | 16.08 | 78.10 |
| Mohammad, 2002 | 2.34 | 1.87 | 2.93 | 24.03 | 0.01 | 58.39 | 18.87 | 78.66 |
| Nunn, 1994 | 2.24 | 1.80 | 2.78 | 22.20 | 0.01 | 54.96 | 11.26 | 77.14 |
| Singh, 2005 | 2.24 | 1.78 | 2.74 | 20.98 | 0.02 | 52.35 | 5.43 | 75.99 |

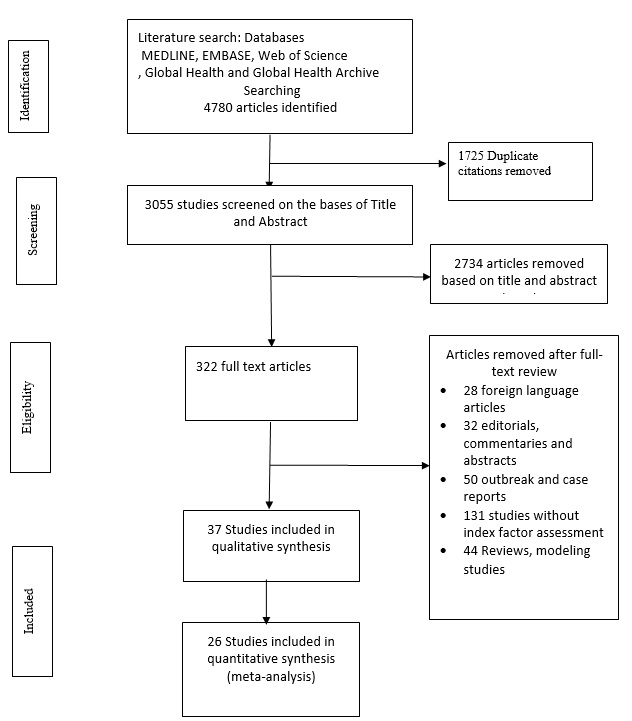
# Table 7: Sensitivity analysis result for studies included in meta-analyses of lung Cavitation Crude odds ratios

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Excluded study** | **Pooled OR** | **LCI 95%** | **HCI 95%** | **Cochran Q** | **p** | **I2** | **I2 LCI 95%** | **I2 HCI 95%** |
| Elliott, 1993 | 1.89 | 1.29 | 2.78 | 84.85 | 4.86E-13 | 85.86 | 77.47 | 91.12 |
| Faksri, 2015 | 2.06 | 1.44 | 2.93 | 82.86 | 1.17E-12 | 85.52 | 76.85 | 90.94 |
| Gessner, 1998 | 1.91 | 1.29 | 2.83 | 85.62 | 3.45E-13 | 85.98 | 77.70 | 91.19 |
| Godoy, 2013 | 1.96 | 1.28 | 3.00 | 66.98 | 1.17E-09 | 82.08 | 70.54 | 89.10 |
| Golub, 2006 | 1.85 | 1.29 | 2.66 | 84.01 | 7.06E-13 | 85.71 | 77.21 | 91.04 |
| Guwatudde, 2003 | 1.93 | 1.32 | 2.81 | 86.66 | 2.18E-13 | 86.15 | 77.10 | 91.28 |
| Jones-Lopez, 2016 | 2.06 | 1.44 | 2.93 | 83.30 | 9.63E-13 | 85.59 | 76.10 | 90.98 |
| Lee, 2008 | 1.92 | 1.32 | 2.80 | 86.61 | 2.23E-13 | 86.14 | 77.10 | 91.28 |
| Madhi, 2002 | 1.82 | 1.28 | 2.60 | 81.65 | 2.00E-12 | 85.30 | 76.47 | 90.82 |
| Mendes, 2012 | 2.03 | 1.39 | 2.96 | 84.52 | 5.63E-13 | 85.80 | 77.37 | 91.09 |
| Mohammad, 2002 | 1.97 | 1.36 | 2.86 | 86.82 | 2.03E-13 | 86.18 | 78.04 | 91.30 |
| Nair, 2016 | 2.04 | 1.41 | 2.95 | 84.60069 | 5.43E-13 | 85.81 | 77.39 | 91.10 |
| Nunn, 1994 | 1.92 | 1.30 | 2.82 | 86.37788 | 2.47E-13 | 86.11 | 77.92 | 91.26 |
| Tornee, 2004 | 1.70 | 1.35 | 2.16 | 27.27098 | 0.01 | 56.00 | 18.09 | 76.36 |

# Table 8: Sensitivity analysis result for studies included in meta-analyses of HIV sero-status Crude odds ratios

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Excluded study** | **Pooled OR** | **LCI 95%** | **HCI 95%** | **Cochran Q** | **p** | **I2** | **I2 LCI 95%** | **I2 HCI 95%** |
| Carvalho, 2001 | 0.82 | 0.57 | 1.16 | 34.97 | 1.13E-05 | 79.98 | 61.16 | 89.68 |
| Cayla, 1996 | 0.68 | 0.49 | 0.93 | 29.89 | 9.94E-05 | 76.58 | 53.33 | 88.25 |
| Godoy, 2013 | 0.71 | 0.48 | 1.05 | 30.31 | 8.34E-05 | 76.90 | 54.08 | 88.38 |
| Grandjean, 2015 | 0.73 | 0.51 | 1.06 | 40.56 | 9.83E-07 | 82.74 | 67.35 | 90.88 |
| Loredo, 2014 | 0.79 | 0.56 | 1.12 | 39.46 | 1.60E-06 | 82.26 | 66.28 | 90.67 |
| Martinez, 2016 | 0.76 | 0.49 | 1.17 | 36.01 | 7.22E-06 | 80.56 | 62.47 | 89.93 |
| Mohammad, 2002 | 0.81 | 0.57 | 1.15 | 37.60 | 3.61E-06 | 81.38 | 64.33 | 90.28 |
| Nunn, 1994 | 0.72 | 0.50 | 1.04 | 39.64 | 1.47E-06 | 82.34 | 66.46 | 90.70 |
| Teixeira, 2001 | 0.84 | 0.61 | 1.17 | 32.05 | 3.98E-05 | 78.16 | 56.99 | 88.91 |

# Figure 1-Flowchart of the identification, screening, and inclusion/exclusion of studies



# Figure 2- Forest plot of crude odds ratios for the association between index patient sputum smear-positivity and infectiousness. \* indicates that these studies take contact active disease as an outcome



# Figure 3-Forest plot of the association between index patient lung cavitation and infectiousness from crude odds ratio analysis. \* indicates that these studies take contact active disease as an outcome



Figure 4-Forest plot of the association between index patient HIV sero-positivity and infectiousness from crude odds ratio analysis. \* indicates that these studies take contact active disease as an outcome



# Figure 5-Funnel plot of results for the crude odds ratio of the association between sputum smear-positivity and infectiousness



# Figure 6-Funnel plot of results for the crude odds ratio of the association between cavitation and infectiousness



# Figure 7-Funnel plot of results for the crude odds ratio of the association between HIV sero-positivity and infectiousness



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