**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, 2016Nair, 2016Jones-Lopez, 2016Kifai, 2009Tornee, 2004Rathi, 2002Cayla, 1996Xu, 2008  | [1][2][3][4][5][6][7][8] |
| * Confirmed PTB patients
 | Mendes, 2012Golub, 2006Lienhardt, 2003Mohammad, 2002Madhi, 2002Carvalho, 2001Espinal, 2000Gessner, 1998Nunn, 1994Elliott, 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, 2015Teixeira, 2001Snider, 1985 | [21][22][23] |
| * Newly diagnosed TB patients
 | Faksri, 2015Godoy, 2013Ling, 2011 | [24][25][26] |
| * All TB patients
 | Loredo, 2014Lohmann, 2012Lee, 2008Guwatudde, 2003Castillo 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, 2016Nair, 2016Jones-Lopez, 2016Grandjean, 2015Faksri, 2015Huang, 2014Huang, 2014Elmi, 2014Grandjean, 2011Kifai, 2009Martinez, 2016 Guwatudde, 2003Rathi, 2002Mohammad, 2002Teixeira, 2001Carvalho, 2001Espinal, 2000Nunn, 1994Elliott, 1993Xu, 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, 2016Cayla, 1996 | [20][7] |
| * Close contacts who shared an enclosed space
 | Loredo, 2014Lee, 2008Golub, 2006 | [27][29][10] |
| * Contacts at different level of concentric circle
 | Godoy, 2013Lohmann, 2012 | [25][28] |
| * Close (household) and casual contacts
 | Mendes, 2012Castillo Otero, 1999 | [9][31] |
| * Children and adolescents (aged 15 or younger) household contacts
 | Maciel, 2009Tornee, 2004Madhi, 2002Gessner, 1998Snider, 1985Ling, 2011 | [34][5][13][16][23][26] |
| * Children under the age of 5 years in household contact
 | Singh, 2005Lienhardt, 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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