Prevention of tuberculosis in household members: estimates of children eligible for treatment

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**Introduction**

The management of latent tuberculosis infection is a critical component of the World Health Organization’s (WHO’s) End TB Strategy. Given that between a quarter and a third of the global population is estimated to be infected with *Mycobacterium tuberculosis*, the Strategy’s ambitious targets and the United Nations’ Sustainable Development Goals cannot be achieved without tackling the reservoir of latent infection.

The risk of progression from tuberculosis infection to active disease is particularly high in young children, who are also at the greatest risk of severe and disseminated disease. As a result, treatment of tuberculosis infection (i.e. tuberculosis preventive treatment) is strongly recommended for children younger than 5 years who are household contacts of people with bacteriologically confirmed pulmonary tuberculosis. Accordingly, coverage of tuberculosis preventive treatment is one of the key indicators used to monitor the implementation of the End TB Strategy.

In 2018, world leaders committed to providing 4 million child household contacts younger than 5 years with tuberculosis preventive treatment by 2022.

A recent survey of policy and practice on latent tuberculosis infection in countries with a low tuberculosis burden and in African countries found that many lacked recording and reporting systems for infection. In 2016, WHO started collecting data on the number of children younger than 5 years globally who were household contacts of people with pulmonary tuberculosis and who had started tuberculosis preventive treatment. Although 118 countries, including 16 of the 30 countries with a high tuberculosis burden, reported data in 2017, there was a lack of clearly defined denominators for assessing coverage of preventive treatment, which makes planning and monitoring difficult.

Consequently, the aim of this study was to use tuberculosis notification data from 2017 to estimate of the number of children younger than 5 years in individual countries who were household contacts of people with pulmonary tuberculosis and who were eligible for tuberculosis preventive treatment. This information should help countries implement and monitor preventive treatment.

**Methods**

Countries with a low tuberculosis burden comprised the 113 high-income or upper-middle-income countries in which the estimated annual incidence of tuberculosis disease in 2015 was fewer than 100 cases per 100,000 population. WHO’s 2015 guidelines on the management of latent tuberculosis infection are intended primarily for these countries. Countries with 100 or more cases per 100,000 population were regarded as having a high tuberculosis burden.

In countries with a high tuberculosis burden, the number of children eligible for tuberculosis preventive treatment was defined as the number younger than 5 years who are household contacts (hereafter referred to as child household contacts) of people with bacteriologically confirmed pulmonary tuberculosis and who do not themselves have active tuberculosis, regardless of whether they have a confirmed tuberculosis infection (in accordance with WHO guidelines on the management of tuberculosis in children).

In countries with a low tuberculosis burden, the number of children eligible for tuberculosis preventive treatment was defined as the number of children younger than 5 years who are household contacts of people with bacteriologically confirmed pulmonary tuberculosis, who do not themselves have active tuberculosis and who have a confirmed tuberculosis infection, as indicated by...
a positive result on a standard tuberculin skin test or an interferon-gamma release assay. Consequently, the number of child household contacts eligible for tuberculosis preventive treatment, \( N \), was calculated using:

\[
N = \frac{n}{c} \cdot h \cdot (1 - T)
\] (1)

in countries with a high tuberculosis burden; and

\[
N = \frac{n}{c} \cdot h \cdot (1 - T) \cdot L
\] (2)

in countries with a low tuberculosis burden; where \( n \) was the number of notified cases of bacteriologically confirmed, pulmonary tuberculosis in the country, \( c \) was the average number of active tuberculosis cases per household with an index case, \( h \) was the average household size, \( p \) was the proportion of the national population that was younger than 5 years, \( T \) was the proportion of child household contacts who had active tuberculosis, and \( L \) was the prevalence of a confirmed latent tuberculosis infection among child household contacts. For countries with a high tuberculosis burden, \( L \) was not included in the calculation because eligibility for tuberculosis preventive treatment did not depend on confirmation of infection. We did not estimate numbers for countries or territories with a population under 300 000.

Table 1 details how we derived values for the parameters in these two equations. From the literature, we obtained country-specific values of \( n \) and \( p \) for 2017, country-specific values of \( h \) for different years and a global estimate of \( T \). To obtain a global value for \( L \), we updated a recent systematic review and meta-analysis, and to obtain a global value for \( c \), we carried out a new systematic review of the literature from 1 January 2005 to 11 November 2017.18 For both the updated and new systematic reviews, we used the reference list of Fox et al.'s systematic review,18 which included publications up until 1 October 2011, and supplemented it with papers subsequently published up until 11 November 2017. The new systematic review did not consider publications before 2005 because we judged that earlier publications would not reflect the current situation. The following search string was used in PubMed for both reviews: (tuberculosis[Title] OR "tuberculosis"[MeSH Terms] OR "mycobacterium tuberculosis"[MeSH Terms] OR "tuberculosis, pulmonary"[MeSH Terms]) AND (("contact$"[All Fields]) OR "contact tracing"[MeSH Terms]) OR "disease transmission"[All Fields] OR "case find$"[Title] OR (cluster[Title] AND analysis[Title]) OR "household$"[All Fields] OR "household contact$"[All Fields] OR ("case finding"[All Fields]) OR ("casefinding"[All Fields]) OR "case detection"[All Fields]).

For the updated and new systematic reviews: (i) household contacts were defined as people living in the same household or people who satisfied the definition of a household contact in the original publication; (ii) an index case was defined as the first identified case of new or recurrent tuberculosis disease in a person of any age in a specific household or as defined in the original publication; (iii) a person was defined as having a tuberculosis infection if the induration 48 to 72 hours after a tuberculin skin test was 10 mm or greater or, if this information was not available, the person satisfied the definition of a tuberculosis infection in the original publication; and (iv) a prevalent tuberculosis case was defined as a case of active disease that was diagnosed at the baseline visit during the study or within 3 months of diagnosis of the index case.

To obtain a global value for \( L \), we included studies in the updated systematic review that reported the prevalence of tuberculosis infection among child contacts in countries with an annual incidence of tuberculosis under 100 cases per 100 000 population at the time of the study, according to WHO estimates.19 If an appropriate WHO estimate was not available, we used estimates from the published literature. We also included studies that reported data on children up to 4 or 6 years of age. The reasons for excluding studies are listed in Fig. 1.

| Parameter | Value, mean (95% CI) | Source |
|-----------|----------------------|--------|
| Number of notified cases of bacteriologically confirmed pulmonary tuberculosis in 2017 (n) | Country-specific values (Table 4) | WHO tuberculosis burden estimates<sup>c</sup> |
| Number of active tuberculosis cases per household with an index case (C) | 1.06 (1.04–1.07) | New systematic review of the literature from January 2005 to November 2017 |
| Average household size (h) | Country-specific values<sup>b</sup> | National censuses, national surveys (e.g. DHSs), statistical yearbooks and official websites of national statistical authorities |
| Proportion of the population aged < 5 years in 2017 (p) | Country-specific values<sup>b</sup> | United Nations 2017 revision of world population prospects<sup>16</sup> |
| Proportion of child household contacts (age < 5 years) of a tuberculosis case who had active tuberculosis themselves (T) | 6.1% (1.0–16.3) | Dodd et al., 2014<sup>17</sup> |
| Prevalence of a confirmed latent tuberculosis infection among children aged < 3 years who were household contacts of a tuberculosis case in countries with fewer than 100 cases per 100 000 population (L) | 27.9% (18.8–39.4) | Updated systematic review of the literature from inception to November 2017 |

CI: confidence interval; DHS: demographic and health survey; WHO: World Health Organization.
<sup>a</sup> The characters in parentheses represent the parameters in equations in the text.
<sup>b</sup> Details available from the corresponding author on request.
<sup>c</sup> Provided by the World Health Organization.
Fig. 1. Flowchart for the selection of studies on the prevalence of latent tuberculosis infection among child household contacts, countries with a low tuberculosis burden, worldwide, 1964–2017

- 2508 publications between October 2011 and November 2017 identified in PubMed
- 240 publications up to October 2011 from the reference list of a systematic review by Fox et al.
- 2501 publications excluded on screening of titles and abstracts
- 230 publications excluded on full text review:
  - 32 articles had no data on tuberculosis infection
  - 28 articles had no data on household contacts
  - 137 articles had no data on children aged <5 years
  - 3 articles had insufficient data for calculating prevalence
  - 2 articles had same data as reported in another publication
  - 10 articles were reporting from a country with a high tuberculosis burden
  - 16 articles not in English
  - 2 articles full text not available

Fig. 2. Flowchart for the selection of studies on active tuberculosis cases in households with an index case, worldwide, 2005–2017

- 2508 publications between October 2011 and November 2017 identified in PubMed
- 247 publications full text review
- 17 studies included in updated systematic review

Notes: We defined a child household contact as a child younger than 5 years living in the same household as a person with active tuberculosis disease. A low tuberculosis burden was defined as fewer than 100 cases per 100,000 population.

To obtain a global value for \( C \), we included studies in the new systematic review that reported the number of index tuberculosis cases, the number of household contacts and the number of prevalent active tuberculosis cases among household contacts. We excluded studies if: (i) data on contacts other than household contacts were included; (ii) the number of cases or household contacts was less than 10; (iii) only child contacts were included (this would have led to an underestimate of the number of active tuberculosis cases in the household); or (iv) the study was not published in English (Fig. 2).

One author screened all titles and abstracts for relevance and then reviewed the full text of all potentially eligible articles. For both reviews, we extracted information on the country’s name, the year of the study, the definitions of index cases and household contacts, and the number of household contacts. For the updated systematic review, we obtained information about the number of child household contacts with a confirmed latent tuberculosis infection, the tuberculin skin test cut-off criterion for infection in a child contact, the child’s bacillus Calmette–Guérin (BCG) vaccination status and the age of index cases. For the new systematic review, we extracted information on the age and number of index cases and the number of active tuberculosis cases among household contacts. In evaluating the quality of individual studies, we used a checklist modified from an existing tool to assess issues related to contact investigations and tuberculosis infection.19

Data analysis

The meta-analysis of the prevalence of a confirmed latent tuberculosis infection among child household contacts (L) was conducted using a logistic-normal random-effects model.20 In the primary analysis, we did not consider the different definitions of tuberculosis infection used in the studies. The heterogeneity of study findings was assessed by visual inspection of forest plots and from the results of likelihood-ratio tests. Potential sources of heterogeneity were investigated in subgroup analyses that considered the following factors: (i) whether the index case tested positive or negative on smear microscopy; (ii) the tuberculin skin test cut-off value (i.e. 10 mm or more versus other values); (iii) the year of study publication (i.e. before 2000 or later); (iv) the country’s income status (i.e. whether high- or upper-middle-income);21 and (v) BCG vaccination coverage.

The average number of active tuberculosis cases per household with an index case (C) was estimated as follows. For each study, the average number of active tuberculosis cases among contacts in each household was calculated by dividing the number of prevalent active tuberculosis cases among household contacts by the number of index cases, which was assumed to be equal to the number of households. Data were pooled using mixed-effects, Poisson regression models. Subsequently, the
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### Table 2. Systematic review of the prevalence of latent tuberculosis infection among child household contacts, \(^a\) countries with a low tuberculosis burden, \(^b\) worldwide, 1964–2017

| Study reference | Country | Year of study enrolment | Definition of index tuberculosis case | Prevalence of latent tuberculosis infection among child household contacts aged < 5 years, no. infected children/no. all children (%) | Criterion for tuberculosis infection | BCG vaccination status |
|-----------------|---------|-------------------------|--------------------------------------|----------------------------------------------------------------------------------|-------------------------------------|------------------------|
| Chapman et al., 1964 | United States | NA | Pulmonary tuberculosis (no information on bacteriological status) | 200/414 (48.3) | Not defined | Unknown |
| Grzybowski et al., 1975 | Canada | 1966–1971 | Pulmonary or extrapulmonary tuberculosis | 209/1012 (20.7) | Tuberculin skin test induration ≥ 6 mm or ≥ 10 mm, depending on study site | Unknown |
| Zaki et al., 1976 | United States | 1965–1972 | Pulmonary tuberculosis (no information on bacteriological status) | 254/1122 (22.8) | Tuberculin skin test induration ≥ 10 mm | Unknown |
| Payne, 1978 | United Kingdom | 1968–1974 | Pulmonary or extrapulmonary tuberculosis | 9/85 (10.6) | Heaf grade 2, 3 or 4 | No children vaccinated |
| Almeida et al., 2001 | Brazil | 1998 | Smear-positive pulmonary tuberculosis | 18/40 (45.0) | Tuberculin skin test induration ≥ 10 mm | No specific data for children aged < 5 years; 81% of the study population vaccinated |
| Canvalho et al., 2001 | Brazil | 1995–1997 | Smear-positive pulmonary tuberculosis | 7/33 (21.2) | Tuberculin skin test induration ≥ 10 mm | No specific data for children aged < 5 years; 75% of the study population vaccinated |
| Lobo et al., 2003 | United States | 1994 | Pulmonary tuberculosis (smear-positive or -negative) | 45/93 (48.4) | Tuberculin skin test induration ≥ 5 mm | Unknown |
| Militão de Albuquerque et al., 2004 | Brazil | 1997–1999 | Pulmonary tuberculosis (including clinically diagnosed disease) | 21/74 (28.4) | Tuberculin skin test induration ≥ 10 mm | No specific data for children aged < 5 years; 8% of the study population vaccinated |
| Soysal et al., 2005 | Turkey | 2002–2003 | Smear-positive pulmonary tuberculosis | 171/405 (42.2) | Tuberculin skin test induration ≥ 10 mm | No specific data for children aged < 5 years; 75% of the study population vaccinated |
| Aissa et al., 2008 | France | 2004–2005 | Culture-positive pulmonary tuberculosis | 18/164 (11.0) | Tuberculin skin test induration ≥ 10 mm for BCG-vaccinated people; ≥ 15 mm or conversion from negative (i.e. < 5 mm) to positive (i.e. ≥ 10 mm) for non-vaccinated people | No specific data for children aged < 5 years; 98% of the study population vaccinated |
| Alavi, 2008 | Iran (Islamic Republic of) | 2003–2005 | Pulmonary tuberculosis (smear-positive or -negative) | 36/43 (83.7) | Tuberculin skin test induration ≥ 10 mm | No specific data for children aged < 5 years; 51% of the study population vaccinated |
| Diel et al., 2008 | Germany | 2005–2006 | Smear-positive pulmonary tuberculosis | 1/18 (5.6) | Tuberculin skin test induration ≥ 10 mm | No specific data for children aged < 5 years; 86% of the study population vaccinated |

(continues . . )
### Results

Our systematic review of the prevalence of a latent tuberculosis infection among child household contacts younger than 5 years (L) in countries with a low tuberculosis burden included 17 studies (Fig. 1 and Table 2).23–41 Nine of the 17 (52.9%) were conducted in high-income countries. The presence of a tuberculosis infection was defined as an induration of 10 mm or more on the tuberculin skin test in 11 studies, whereas the other six used different criteria: (i) one used an induration cut-off of 5 mm; (ii) three used multiple induration cut-offs, ranging from 5 to 15 mm depending on BCG vaccination status, the infectiousness of the index case or the study site; (iii) one used a Heaf grade of 2, 3 or 4; and (iv) one did not specify the criterion. The median prevalence of latent tuberculosis infection among child contacts was 26.4% (interquar-
tile range: 11.1–42.2). Twelve studies included children who had received a BCG vaccination, one included only unvaccinated children and BCG vaccination status was not specified in four studies. There was substantial heterogeneity across the studies. The pooled prevalence of latent tuberculosis infection among child contacts younger than 5 years was 27.9% (95% confidence interval, CI: 18.8–39.4; Fig. 3). None of the subgroup analyses found significant differences between subgroups.

Our systematic review of the number of active tuberculosis cases per household with an index case (C) included 58 studies (Fig. 2 and Table 3). Of the 58, 16 (27.6%) were conducted in countries with a low tuberculosis burden. The number of active tuberculosis cases among contacts in each household ranged from 0 to 0.33, except for one study that reported a value of 0.93. The pooled number of active tuberculosis cases among contacts in each household was 0.06 (95% CI: 0.04–0.07). Consequently, the average number of active tuberculosis cases per household was 1.06 once the index case had been included. There was no significant difference between countries with a low or high tuberculosis burden (P = 0.33). Furthermore, excluding the one outlier reduced the average number of cases per household by only 0.002.

Using the values we obtained for L and C with the values of other parameters from the literature (Table 1), we estimated that the number of child household contacts younger than 5 years who were eligible for tuberculosis preventive treatment in 2017 ranged from less than one in four countries (i.e. Bahamas, Iceland, Luxembourg and Malta) to 350 000 (95% uncertainty interval, UI: 320 000–380 000) in India (Table 4; available at: http://www.who.int/bulletin/volumes/96/8/18-218651). Globally, the estimated number of child contacts eligible for preventive treatment was 1.27 million (95% UI: 1.24 to 1.31). Viewed regionally, the highest estimate was for the WHO South-East Asia Region: 510 000 (95% UI: 450 000–580 000; Table 5).

Discussion

We estimated that 1.27 million children younger than 5 years who were household contacts of people with bacteriologically confirmed pulmonary tuberculosis were eligible for preventive treatment globally in 2017. According to the WHO Global tuberculosis report 2018, countries reported that 292 182 child contacts received preventive treatment in 2017, which makes the best estimate of the global coverage of preventive treatment in children only 23%.

Our study has several limitations. First, our estimate of the number of child household contacts was based on the number of notified bacteriologically confirmed tuberculosis cases. However, 3.6 million of the estimated 10.0 million people with incident tuberculosis globally in 2017 were neither reported nor enrolled in tuberculosis care. Consequently, our estimates are conservative, there would be substantially more eligible child contacts if all incident tuberculosis cases were considered. Second, we used national values for the average household size and for the proportion of the population younger than 5 years to estimate the number of child contacts. It is possible that the composition of households with a tuberculosis case may have differed from the national average and thus people with tuberculosis may have lived with a different number of children younger than 5 years from the national average. Furthermore, we did not consider people with tuberculosis who lived in a prison or nursing home. Doing so would have reduced the estimated number of child contacts, especially in countries where where number of tuberculosis cases among the prison and nursing home populations was high. The prison and nursing home populations were high. Third, we used the value for the average number of tuberculosis cases per household from our new systematic review for all countries, even though it may have varied between countries.

Fourth, in our updated systematic review, we observed substantial heterogeneity across studies in the prevalence of a latent tuberculosis infection among child household contacts in countries with a low tuberculosis burden.

### Table 3: Forest plot of the prevalence of latent tuberculosis infection among child household contacts, countries with a low tuberculosis burden, worldwide, 1964–2017

| Study                                      | Prevalence, % (95% CI) | Prevalence, % (95% CI) |
|--------------------------------------------|------------------------|------------------------|
| Chapman et al., 1964                      | 48.3 (43.4–53.2)        | 48.3 (43.4–53.2)        |
| Gryboswolski et al., 1975                  | 20.7 (18.2–22.3)        | 20.7 (18.2–22.3)        |
| Zale et al., 1976                         | 22.6 (20.2–25.2)        | 22.6 (20.2–25.2)        |
| Payne 1978                                 | 10.6 (8.5–12.7)         | 10.6 (8.5–12.7)         |
| Almeida et al., 2001                      | 45.0 (32.3–61.5)        | 45.0 (32.3–61.5)        |
| Canahano et al., 2001                     | 21.2 (9.9–38.9)         | 21.2 (9.9–38.9)         |
| Lobato et al., 2003                       | 48.4 (37.3–59.8)        | 48.4 (37.3–59.8)        |
| Militão de Albuquerque et al., 2004       | 28.4 (18.5–40.1)        | 28.4 (18.5–40.1)        |
| Soykal et al., 2005                       | 42.2 (37.4–47.2)        | 42.2 (37.4–47.2)        |
| Assa et al., 2008                         | 11.0 (6.6–16.8)         | 11.0 (6.6–16.8)         |
| Ali et al., 2008                           | 8.37 (6.9–9.2)          | 8.37 (6.9–9.2)          |
| Del et al., 2008                           | 5.68 (0.01–37.3)        | 5.68 (0.01–37.3)        |
| Lin et al., 2008                           | 0.86 (0.35–1.78)        | 0.86 (0.35–1.78)        |
| Pax et al., 2011                           | 26.4 (17.4–37.8)        | 26.4 (17.4–37.8)        |
| Verhagen et al., 2014                      | 11.1 (4.2–22.6)         | 11.1 (4.2–22.6)         |
| Rose et al., 2015                          | 28.6 (14.6–46.3)        | 28.6 (14.6–46.3)        |
| Perez-Perez et al., 2016                   | 45.0 (31.3–75.3)        | 45.0 (31.3–75.3)        |
| Pooled value                               | 27.9 (18.8–39.4)        | 27.9 (18.8–39.4)        |

**CI:** confidence interval.

Notes: We defined a child household contact as a child younger than 5 years living in the same household as a person with active tuberculosis disease. A low tuberculosis burden was defined as fewer than 100 cases per 100 000 population.
Table 3. Systematic review of active tuberculosis cases in households with an index case, worldwide, 2005–2017

| Study reference | Country | Year of study enrolment | Definition of index tuberculosis case | Eligible age group | No. of index cases | No. of tuberculosis cases among household contacts | No. of tuberculosis cases among contacts per household | Total no. of tuberculosis cases per household, including the index case |
|-----------------|---------|-------------------------|--------------------------------------|-------------------|-------------------|-----------------------------------------------|------------------------------------------------------|---------------------------------------------------------------------|
| Becerra et al., 2005 | Peru | 1996–1998 | Culture-positive pulmonary tuberculosis | All ages | 192 | 10 | 0.05 | 1.05 |
| Chee et al., 2005 | Singapore | 2000 | Culture-positive pulmonary tuberculosis | All ages | 679 | 20 | 0.03 | 1.03 |
| Khalidzadeh et al., 2006 | Iran (Islamic Republic of) | 2002–2004 | Smear-positive pulmonary tuberculosis | All ages | 68 | 17 | 0.25 | 1.25 |
| Yeo et al., 2006 | Canada | 1996–2000 | Pulmonary or extrapulmonary tuberculosis | All ages | 39 | 4 | 0.10 | 1.10 |
| Hussain et al., 2007 | Pakistan | 2001–2003 | Smear-positive pulmonary tuberculosis | All ages | 20 | 0 | 0.00 | 1.00 |
| Alavi, 2008 | Iran (Islamic Republic of) | 2007 | Pulmonary tuberculosis (smear-positive or -negative) | All ages | 69 | 64 | 0.93 | 1.93 |
| Hill et al., 2008 | Gambia | 2002–2004 | Smear-positive pulmonary tuberculosis | ≥ 6 months | 317 | 33 | 0.10 | 1.10 |
| Lee et al., 2008 | China, Hong Kong SAR | 2000 | Pulmonary or extrapulmonary tuberculosis | All ages | 1 635 | 29 | 0.02 | 1.02 |
| Lin et al., 2008 | China | 2006–2007 | Pulmonary or extrapulmonary tuberculosis | All ages | 393 | 5 | 0.01 | 1.01 |
| Borrell et al., 2009 | Spain | 2003–2004 | Pulmonary or extrapulmonary tuberculosis | All ages | 717 | 46 | 0.06 | 1.06 |
| del Corral et al., 2009 | Colombia | 2005–2006 | Smear-positive pulmonary tuberculosis | All ages | 366 | 8 | 0.02 | 1.02 |
| Klicislan et al., 2009 | Turkey | 1997–2000 | Smear-positive pulmonary tuberculosis | All ages | 1 570 | 92 | 0.06 | 1.06 |
| Machado et al., 2009 | Brazil | 2006–2007 | Pulmonary tuberculosis (including clinically diagnosed disease) | All ages | 76 | 2 | 0.03 | 1.03 |
| Nguyen et al., 2009 | Lao People’s Democratic Republic | 2006 | Smear-positive pulmonary tuberculosis | All ages | 72 | 4 | 0.06 | 1.06 |
| Ottmani et al., 2009 | Morocco | 1993–2004 | Smear-positive pulmonary tuberculosis or clinically diagnosed disease | All ages | 20 902 | 44 110 | 0.22 | 1.22 |
| Pai et al., 2009 | India | 2006 | Smear-positive pulmonary tuberculosis | All ages | 54 | 1 | 0.02 | 1.02 |
| Gavalcante et al., 2010 | Brazil | 1999–2004 | Pulmonary or extrapulmonary tuberculosis | All ages | 311 | 26 | 0.08 | 1.08 |
| Lienhardt et al., 2010 | Senegal | 2004–2006 | Smear-positive or culture-positive pulmonary tuberculosis | All ages | 206 | 14 | 0.07 | 1.07 |
| Rakotosamimanana et al., 2010 | Madagascar | 2004–2005 | Smear-positive pulmonary tuberculosis | ≥ 1 year | 85 | 12 | 0.14 | 1.14 |
| Sia et al., 2010 | Philippines | 2001–2008 | Smear-positive pulmonary tuberculosis | All ages | 218 | 20 | 0.09 | 1.09 |
| Becerra et al., 2011 | Peru | 1996–2003 | Multidrug- or extensively drug-resistant tuberculosis | All ages | 693 | 117 | 0.17 | 1.17 |
| Grandjean et al., 2011 | Peru | 2005–2008 | Multidrug-resistant tuberculosis | All ages | 358 | 0 | 0.00 | 1.00 |
(continues . . .)
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| Study reference | Country | Year of study enrolment | Definition of index tuberculosis case | Eligible age group | No. of index cases<sup>a</sup> | No. of tuberculosis cases among household contacts<sup>b</sup> | No. of tuberculosis cases among contacts per household<sup>b</sup> | Total no. of tuberculosis cases per household, including the index case |
|-----------------|---------|-------------------------|---------------------------------------|------------------|------------------|----------------------|----------------------|-----------------------------|
| Hussain et al., 2011<sup>62</sup> | Pakistan | unknown | Smear-positive pulmonary tuberculosis | All ages | 18 | 0 | 0.00 | 1.00 |
| Singla et al., 2011<sup>63</sup> | India | 2005–2008 | Multidrug-resistant tuberculosis | All ages | 58 | 16 | 0.28 | 1.28 |
| Vella et al., 2011<sup>64</sup> | South Africa | 2005–2008 | Multidrug- or extensively drug-resistant tuberculosis | ≥ 13 years | 508 | 64 | 0.13 | 1.13 |
| Whalen et al., 2011<sup>65</sup> | Uganda | 1995–2004 | Smear-positive pulmonary tuberculosis | All ages | 497 | 49 | 0.10 | 1.10 |
| Zhang et al., 2011<sup>66</sup> | China | 2007 | Smear-positive pulmonary tuberculosis | All ages | 4 695 | 40 | 0.01 | 1.01 |
| Fox et al., 2011<sup>67</sup> | Viet Nam | 2009–2011 | Smear-positive pulmonary tuberculosis | All ages | 167 | 8 | 0.05 | 1.05 |
| Gyawali et al., 2012<sup>68</sup> | Nepal | 2009–2010 | Smear-positive pulmonary tuberculosis | ≥ 5 years | 184 | 13 | 0.07 | 1.07 |
| Ntinginya et al., 2012<sup>69</sup> | United Republic of Tanzania | 2010–2011 | Smear-positive pulmonary tuberculosis | ≥ 5 years | 80 | 5 | 0.06 | 1.06 |
| Shaprio et al., 2012<sup>70</sup> | South Africa | 2009–2009 | Tuberculosis based on clinical evaluation (with or without sputum smear test or sputum culture) | All ages | 749 | 169 | 0.23 | 1.23 |
| Third et al., 2012<sup>71</sup> | South Africa | 2009–2010 | Smear-positive pulmonary tuberculosis | All ages | 732 | 127 | 0.17 | 1.17 |
| Chamie et al., 2013<sup>72</sup> | Uganda | Unknown | Pulmonary tuberculosis (with or without sputum smear test) | All ages | 61 | 13 | 0.21 | 1.21 |
| Jones-López et al., 2013<sup>73</sup> | Uganda | 2009–2011 | Smear-positive pulmonary tuberculosis | All ages | 96 | 1 | 0.01 | 1.01 |
| Leung et al., 2013<sup>74</sup> | China, Hong Kong SAR | 1997–2006 | Multidrug-resistant tuberculosis | All ages | 256 | 12 | 0.05 | 1.05 |
| Puryear et al., 2013<sup>75</sup> | Botswana | 2009–2011 | Paediatrician-diagnosed tuberculosis | All ages | 163 | 12 | 0.07 | 1.07 |
| Shah et al., 2013<sup>76</sup> | Pakistan | 2010–2011 | Smear-positive pulmonary tuberculosis | All ages | 3 037 | 490 | 0.16 | 1.16 |
| Singh et al., 2013<sup>77</sup> | India | 2007–2011 | Smear-positive pulmonary tuberculosis | All ages | 450 | 52 | 0.12 | 1.12 |
| Tao et al., 2013<sup>78</sup> | Uganda | 2002–2006 | Culture-positive pulmonary tuberculosis | All ages | 277 | 19 | 0.07 | 1.07 |
| Yassin et al., 2013<sup>79</sup> | Ethiopia | 2010–2011 | Multidrug-resistant pulmonary tuberculosis | All ages | 2 906 | 69 | 0.02 | 1.02 |
| Ja et al., 2014<sup>80</sup> | China | 2008–2008 | Smear-positive pulmonary tuberculosis | All ages | 1 575 | 92 | 0.06 | 1.06 |
| Jones-López et al., 2014<sup>81</sup> | Brazil | 2008–2012 | Smear-positive pulmonary tuberculosis | All ages | 124 | 2 | 0.02 | 1.02 |
| Loredo et al., 2014<sup>82</sup> | Brazil | 2001–2008 | Pulmonary tuberculosis (smear-positive or -negative) | ≥ 15 years | 626 | 51 | 0.08 | 1.08 |
| Thanh et al., 2014<sup>83</sup> | Viet Nam | 2008–2008 | Smear-positive pulmonary tuberculosis | All ages | 1 091 | 27 | 0.02 | 1.02 |
| Zelner et al., 2014<sup>84</sup> | Peru | 2009–2012 | Pulmonary tuberculosis (including clinically diagnosed disease) | All ages | 3 466 | 229 | 0.07 | 1.07 |
| Chamie et al., 2015<sup>85</sup> | Uganda | 2012–2013 | Pulmonary or extrapulmonary tuberculosis | ≥ 18 years | 54 | 1 | 0.02 | 1.02 |
| Grandjean et al., 2015<sup>86</sup> | Peru | 2010–2013 | Multidrug-resistant tuberculosis | All ages | 213 | 5 | 0.02 | 1.02 |

(continues...)

<sup>a</sup>Number of index cases

<sup>b</sup>Number of tuberculosis cases among household contacts

<sup>c</sup>Number of tuberculosis cases among contacts per household

<sup>d</sup>Total no. of tuberculosis cases per household, including the index case

Notes:

- **Smear-positive pulmonary tuberculosis**: Positive result on a sputum smear microscopy test for Mycobacterium tuberculosis
- **Multidrug-resistant tuberculosis**: Resistance to at least two first-line anti-tuberculosis drugs
- **Multidrug- or extensively drug-resistant tuberculosis**: Resistance to any number of first-line anti-tuberculosis drugs
- **Pulmonary tuberculosis**: Involvement of the lungs
- **Culture-positive pulmonary tuberculosis**: Positive result on a culture test for Mycobacterium tuberculosis
- **Paediatrician-diagnosed tuberculosis**: Diagnosis made by a paediatrician
- **Clinically diagnosed disease**: Disease diagnosed based on clinical symptoms
- **≥ 15 years**: Age of at least 15 years
- **≥ 5 years**: Age of at least 5 years
- **≥ 18 years**: Age of at least 18 years

Sources:

- Hussain, S. A., \(\ldots\) (2011)
- Singla, R., \(\ldots\) (2011)
- Vella, J. \(\ldots\) (2011)
- Whalen, M. \(\ldots\) (2011)
- Zhang, W., \(\ldots\) (2011)
- Fox, P., \(\ldots\) (2011)
- Gyawali, R., \(\ldots\) (2012)
- Ntinginya, A., \(\ldots\) (2012)
- Shapiro, A., \(\ldots\) (2012)
- Third, J., \(\ldots\) (2012)
- Chamie, Y., \(\ldots\) (2013)
- Jones-López, M., \(\ldots\) (2013)
- Leung, M., \(\ldots\) (2013)
- Puryear, S., \(\ldots\) (2013)
- Shah, Z., \(\ldots\) (2013)
- Singh, S., \(\ldots\) (2013)
- Tao, P., \(\ldots\) (2013)
- Yassin, A., \(\ldots\) (2013)
- Ja, Y., \(\ldots\) (2014)
- Jones-López, M., \(\ldots\) (2014)
- Loredo, A., \(\ldots\) (2014)
- Thanh, L., \(\ldots\) (2014)
- Zelner, A., \(\ldots\) (2014)
- Chamie, Y., \(\ldots\) (2015)
- Grandjean, P., \(\ldots\) (2015)

For a complete list of references, please consult the original publication.
probably reflects differences between studies in characteristic, such as the study population, setting, incidence of tuberculosis, the tuberculin skin test cut-off used and BCG status. We were unable to identify the source of the heterogeneity because the number of studies included in our subgroup analyses was small. Moreover, our estimates of the number of child household contacts eligible for preventive treatment in these countries were derived using an average value for the prevalence of a confirmed tuberculosis infection among child contacts, whereas the prevalence may have varied between countries. Using country-specific values would have given more accurate estimates. Nevertheless, as countries with a low tuberculosis burden accounted for only 14% of notified tuberculosis cases globally in 2017, their impact on our global estimate was small.

Fifth, we assumed that children were judged eligible for tuberculosis preventive treatment according to WHO guidelines. However, eligibility criteria may have varied between countries according to national policy. Sixth, we used a value for the proportion of child household contacts of a tuberculosis case who had active tuberculosis themselves (T) that was derived from a modelling study in 22 countries with a high tuberculosis burden, which together accounted for 80% of the global burden. However, the prevalence of active disease among household contacts in these countries was likely to have been higher than in others. Consequently, by using this proportion, we may have underestimated the number of child household contacts without active tuberculosis disease who were, therefore, eligible for preventive treatment. Our estimates of the number of children eligible for preventive treatment need to be validated using national data on the number of child contacts from well-functioning surveillance systems or surveys. These data could also be used to assess the coverage of preventive treatment directly, which should give more accurate figures than our modelling estimates with their inherent limitations. Nevertheless, in the absence of such data, our estimates should help galvanize efforts to implement, and monitor the progress.

| Study reference | Country / Year of study enrolment | Eligible age group | Definition of index tuberculosis case | No. of index casesa | No. of tuberculosis cases among household contactsb | No. of tuberculosis cases among contacts per householdc | Total no. of tuberculosis cases per householdd | No. of tuberculosis cases among contacts per household, including the index case |
|----------------|----------------------------------|--------------------|--------------------------------------|-------------------|--------------------------|--------------------------|--------------------------|-------------------------------------------------|
| Jerene et al., 2015 | Ethiopia 2013–2014 | All ages | Smear-positive pulmonary tuberculosis | 6 | 0.06 | 1.06 |
| Zellweger et al., 2015 | Ten European countries 2009–2013 | All ages | Not defined | 1 | 0.01 | 1.01 |
| Gupata et al., 2016 | India 2013–2014 | All ages | Smear-positive pulmonary tuberculosis | 133 | 0.05 | 1.05 |
| Javaid et al., 2016 | Pakistan 2012–2015 | All ages | Multidrug-resistant tuberculosis | 154 | 0.33 | 1.33 |
| Nair et al., 2016 | India 2007–2014 | All ages | Smear-positive pulmonary tuberculosis | 280 | 0.10 | 1.10 |
| Wysocki et al., 2016 | Brazil 2012–2013 | All ages | Pulmonary tuberculosis (microbiological confirmation was required for patients aged ≥ 25 years) | 213 | 0.04 | 1.04 |
| Armstrong-Hough et al., 2017 | Uganda 2011–2013 | All ages | Pulmonary tuberculosis (microbiological confirmation was required for patients aged ≥ 25 years) | 293 | 0.02 | 1.02 |
| Datiko et al., 2017 | Ethiopia 2011–2013 | All ages | Smear-positive pulmonary tuberculosis | 169 | 0.03 | 1.03 |
| Fox et al., 2017 | Viet Nam 2014 | All ages | Initiation of antituberculosis treatment | 354 | 0.10 | 1.10 |
| Mandalakas et al., 2017 | Eswatini 2013–2015 | All ages | Initiation of antituberculosis treatment | 258 | 0.02 | 1.02 |
| Muyoyeta et al., 2017 | Zambia 2013–2014 | All ages | Bacteriologically confirmed tuberculosis | 196 | 0.06 | 1.06 |
| Mandalakas et al., 2017 | Eswatini 2013–2015 | All ages | Initiation of antituberculosis treatment | 354 | 0.10 | 1.10 |
| Mandalakas et al., 2017 | Eswatini 2013–2015 | All ages | Bacteriologically confirmed tuberculosis | 258 | 0.02 | 1.02 |
| Mandalakas et al., 2017 | Eswatini 2013–2015 | All ages | Initiation of antituberculosis treatment | 196 | 0.06 | 1.06 |
of tuberculosis preventive treatment among child contacts.

In conclusion, using our estimate of the number of children younger than 5 years eligible for tuberculosis preventive treatment, we calculated that the coverage of preventive treatment in children in 2017 was only 23%. Despite its proven efficacy, tuberculosis preventive treatment is still being underutilized. As the End TB Strategy targets can only be achieved by addressing the pool of tuberculosis infection, urgent action is needed to scale up the implementation of preventive treatment.

Table 5. Child household contacts\(^a\) eligible for tuberculosis preventive treatment, by region, 2017

| WHO Region     | No. of notified, bacteriologically confirmed, pulmonary tuberculosis cases\(^b\) | Estimated number of child household contacts\(^a\) eligible for tuberculosis preventive treatment, no. (95% UI) |
|----------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| African        | 713,693                                                                          | 470,000 (440,000–490,000)                                                                               |
| Of the Americas | 152,730                                                                          | 25,000 (22,000–28,000)                                                                                  |
| South-East Asia| 1,414,408                                                                         | 510,000 (450,000–580,000)                                                                               |
| European       | 129,110                                                                          | 16,000 (14,000–18,000)                                                                                  |
| Eastern        | 210,073                                                                          | 150,000 (130,000–170,000)                                                                               |
| Mediterranean  |                                                                                 |                                                                                                              |
| Western Pacific | 487,089                                                                          | 95,000 (83,000–110,000)                                                                                  |
| Global         | 3,107,103                                                                        | 1,270,000 (1,240,000–1,310,000)                                                                          |

UI: uncertainty interval; WHO: World Health Organization.

\(\text{a}\) We defined a child household contact as a child younger than 5 years living in the same household as a person with active tuberculosis disease.

In conclusion, using our estimate of the number of children younger than 5 years eligible for tuberculosis preventive treatment, we calculated that the coverage of preventive treatment in children in 2017 was only 23%. Despite its proven efficacy, tuberculosis preventive treatment is still being underutilized. As the End TB Strategy targets can only be achieved by addressing the pool of tuberculosis infection, urgent action is needed to scale up the implementation of preventive treatment.

MLC

The number of children under 5 years of age is 31,310,751 (95% UI 29,010,000–34,010,000), which is lower than the estimated number of children under 5 years of age in the world. However, the proportion of children under 5 years of age who are eligible for tuberculosis preventive treatment is 23% (95% UI 22%–24%).

Competing interests: None declared.
Профилактика туберкулеза у членов семей: оценка количества детей, нуждающихся в лечении

Цель Оценка по состоянию на 2017 год количества детей младше пяти лет, проживающих в одной семье с больным туберкулезом и нуждающихся в профилактическом лечении.

Методы Для оценки количества детей, нуждающихся в лечении, авторы получили из опубликованных источников национальные показатели по состоянию на 2017 год о количестве поставленных на диспансерный учет случаев бактериологически подтвержденного туберкулеза легких, сведения о количестве детей младше 5 лет в 2017 году и средние оценки размера семьи. По результатам систематических обзоров, метаанализа и регрессионных моделей популяционных данных были получены глобальные сведения о количестве случаев активной формы туберкулеза у детей, проживающих в одной семье с больным туберкулезом.

Результаты По предварительным оценкам, во всем мире количество детей младше 5 лет, нуждающихся в профилактическом лечении от туберкулеза, составило в 2017 году 1,27 миллиона человек (95%-й интервал неопределенности, ИН: 1,24–1,31), что в лучшем случае соответствует условной потребности в профилактическом лечении приблизительно на 23%.

Вывод По состоянию на 2017 год во всемире профилактическое лечение от туберкулеза у детей применяется в недостаточной мере. Необходимо наращивать масштабы лечения, чтобы содействовать исключению резервуаров туберкулезной инфекции и достижению целей стратегии по прекращению эпидемии туберкулеза.

Resumen

Prevención de la tuberculosis en los miembros de la familia: estimaciones de niños elegibles para el tratamiento

Objetivo Estimar el número de niños menores de cinco años que tuvieron contacto con personas infectadas en sus hogares y que eran elegibles para el tratamiento preventivo de la tuberculosis en 2017.

Métodos Para estimar el número de niños elegibles, se obtuvieron valores nacionales para el número de casos notificados de tuberculosis pulmonar bacteriológicamente confirmado en 2017, la proporción de la población menor de 5 años en 2017 y el tamaño promedio del hogar de fuentes publicadas. Se obtuvieron valores globales para el número de casos de tuberculosis activa por hogar con un caso índice y para la prevalencia de infección de tuberculosis latente entre los niños menores de 5 años que estaban en contacto con un caso de tuberculosis en el hogar mediante las revisiones sistemáticas, el metanálisis y los modelos de regresión de Poisson.

Resultados El número estimado de niños menores de 5 años elegibles para el tratamiento preventivo de la tuberculosis en 2017 a nivel mundial fue de 1,27 millones (intervalo de incertidumbre del 95 %, IU: 1,24–1,31), lo que corresponde a una cobertura mundial estimada de tratamiento preventivo en niños del 23 % en el mejor de los casos. Por país, el número estimado oscila entre menos de uno en las Bahamas, Islandia, Luxemburgo y Malta y 350 000 (95 % UI: 320 000–380 000) en la India. A nivel regional, las estimaciones más elevadas correspondieron a la Región de Asia Sudoriental de la Organización Mundial de la Salud (OMS) (510 000; IC del 95 %: 450 000–580 000) y a la Región Africana de la OMS (470 000; IC del 95 %: 440 000–490 000).

Conclusión El tratamiento preventivo de la tuberculosis en los niños fue utilizado muy poco a nivel mundial en 2017. El tratamiento debe ampliarse para ayudar a eliminar el conjunto de infecciones de tuberculosis y alcanzar los objetivos de la Estrategia de Fin a la Tuberculosis.
38. Pavl I, Topci RZ, Raos M, Abele N, Dodg S. Interferon-gamma release assay for the diagnosis of latent tuberculosis in children younger than 5 years of age. Pediatr Infect Dis J. 2011 Oct;30(10):866–70. doi: http://dx.doi.org/10.1097/INF.0b013e318220c5a2 PMID: 21527371

39. Verhagen LM, Maes M, Villalba JA, d’Alessandro A, Rodriguez MF, et al. Agreement between Quantiferon®-TB Gold In-Tube and the tuberculin skin test and predictors of positive test results in Warao Amerindian pediatric tuberculosis contacts. BMC Infect Dis. 2014 Oct 7;14:1383. doi: http://dx.doi.org/10.1186/1471-2334-14-1383 PMID: 25012075

40. Rose W, Read SE, Bittrum A, Rea E, Stephens D, Pongsamart W, et al. Relating tuberculosis (TB) contact characteristics to Quantiferon-TB Gold and tuberculin skin test results in the Toronto pediatric TB clinic. J Pediatric Infect Dis Soc. 2015 Jun;6(2):96–103. doi: http://dx.doi.org/10.1093/jpids/pu524 PMID: 26407408

41. Perez-Porcuna TM, Pereira-da-Silva HD, Ascasso C, Malheiro A, Ruiser S, Martinez-Espinoza F, et al. Prevalence and diagnosis of latent tuberculosis infection in young children in the absence of a gold standard. PLoS One. 2016 10 26;11(10):e0161481. doi: http://dx.doi.org/10.1371/journal.pone.0161481 PMID: 27783642

42. Becerra MC, Pachao-Toresblanca IF, Bayona J, Celis R, Shih SS, KimJY, et al. Expanding tuberculosis case detection by screening household contacts. Public Health Rep. 2005 May-Jun;120(3):271–7. doi: http://dx.doi.org/10.1177/003335490512000309 PMID: 16134567

43. Chee CB, Teleman MD, Boudville IC, Wang YT. Contact screening and latent TB infection testing in Singapore correctional facilities. Int J Tuberc Lung Dis. 2008 Mar;12(3):281–7. PMID: 18284833

44. Khalilzadeh S, Masjedi H, Hosseini M, Safavi A, Masjedi MR. Transmission of Mycobacterium tuberculosis to households of tuberculosis patients: a comprehensive continuous contact tracing study. Arch Iran Med. 2006 Jul;9(3):208–12. PMID: 16859052

45. Yeo IK, Tannenbaum T, Scott AN, Kozak R, Behr MA, Thibert LT, et al. Contact investigation and genotyping to identify tuberculosis transmission to children. Pediatr Infect Dis J. 2006 Nov;25(11):1307–43. doi: http://dx.doi.org/10.1097/INF.00002401.101.125.10.3c PMID: 17072127

46. Hussain R, Talat N, Shaffi F, Dawood G. Longitudinal tracking of cytokines after acute exposure to tuberculosis: association of distinct cytokine patterns with protection and disease development. Clin Vaccine Immunol. 2007 Dec;14(12):1578–86. doi: http://dx.doi.org/10.1128/CVI.00289-07 PMID: 17928427

47. Hill PC, Jackson-Sillah DJ, Fox A, Brookes RH, de Jong BC, Lugos MD, et al. Risk of active tuberculosis in adult household contacts of smear-positive tuberculosis patients in rural India. Int J Tuberc Lung Dis. 2009 Dec;14(12):1579–86. doi: http://dx.doi.org/10.1128/CVI.00289-07 PMID: 17928427

48. Lee MS, Leung CC, Kam KM, Wong MY, Leung MC, Tam CM, et al. Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay. Int J Tuberc Lung Dis. 2009 Apr;13(4):446–52. PMID: 19333993

49. del Corral H, Paris SC, Marin ND, Marin OM, Lopez L, Henoa HM, et al. IFN-gamma response to Mycobacterium tuberculosis, risk of infection and disease in household contacts of tuberculosis patients in Colombia. PLoS One. 2009 12 14;4(12):e8257. doi: http://dx.doi.org/10.1371/journal.pone.0008257 PMID: 20015892

50. Kilicarslan Z, Kiyon E, Kucuk C, Kumbeliti S, Sarmanur N, Ozurtk F, et al. Risk of active tuberculosis in adult household contacts of smear-positive pulmonary tuberculosis cases. Int J Tuberc Lung Dis. 2009 Jan;13(1):93–8. PMID: 19105885

51. Machado A Jr, Emoik K, Takenami I, Finkmore BC, Barbosa T, Carvalho J, et al. Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay. Int J Tuberc Lung Dis. 2009 Apr;13(4):446–53. PMID: 19333994

52. Nguyen TH, Dordet F, Slrak S, Barennes H. Risk of latent tuberculosis infection in children living in households with tuberculosis patients: a cross sectional survey in remote northern Lao Peoples Democratic Republic. BMC Infect Dis. 2009 06 17;9(1):1. doi: http://dx.doi.org/10.1186/1471-2334-9-1 PMID: 19346769

53. Ottamia S, Zignol M, Bencheikh N, Laski L, Blanc L, Mahjour J. TB contact investigations: 12 years of experience in the National TB Programme, Morocco 1993–2004. East Mediterr Health J. 2009 May-Jun;15(3):494–503. doi: http://dx.doi.org/10.26719/2009.15.3.494 PMID: 19731765

54. Pai M, Jordi R, Doega S, Zwerver AA, Gajalakshmi D, Goswami K, et al. T-cell assay conversions and reversions among household contacts of tuberculosis patients in rural India. Int J Tuberc Lung Dis. 2009 Jan;13(1):84–92. PMID: 19105884

55. Cavalcante SC, Duobon B, Barnes GL, Souza FB, Silva RF, Barroso FP, et al. Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. Int J Tuberc Lung Dis. 2010 Feb;14(2):203–9. PMID: 20074412

56. Lienhardt C, Fielding K, Hane AA, Niao A, Niao CT, Karam F, et al. Evaluation of the prognostic value of IFN-gamma release assay and tuberculin skin test in household contacts of infectious tuberculosis cases in Senegal. PLoS One. 2010 05 05;e10508. doi: http://dx.doi.org/10.1371/journal.pone.0010508 PMID: 20463900

57. Rakotosamimanana N, Raharimanga V, Andramandidy SF, Soares J, Doherty TM, Ristorahorina M, et al. VACSILVACS Study Group. Variation in gamma interferon responses to different infecting strains of Mycobacterium tuberculosis in acid-fast bacillus smear-positive patients and household contacts in Antananarivo, Madagascar. Clin Vaccine Immunol. 2010 Jul;17(7):1094–103. doi: http://dx.doi.org/10.1128/CVI.00049-10 PMID: 20463103

58. Sia IG, Orrilla RB, ST Sauver JL, Quelapio ID, Lahr BD, Alcañeses RS, et al. Tuberculosis attributed to household contacts in the Philippines. Int J Tuberc Lung Dis. 2010 Jan;14(1):122–5. PMID: 20033706

59. Verhagen LM, Maes M, Villalba JA, d’Alessandro A, Rodriguez LP, España MJ, et al. Prevalence and diagnosis of latent tuberculosis infection in children younger than 5 years of age. PLoS One. 2019;97:534–547D

60. Cavalcante SC, Duobon B, Barnes GL, Souza FB, Silva RF, Barroso FP, et al. Contact screening and latent tuberculosis infection in young children in the absence of a gold standard. PLoS One. 2016 10 26;11(10):e0161481. doi: http://dx.doi.org/10.1371/journal.pone.0161481 PMID: 27783642
A comprehensive review of tuberculosis burden in different regions and populations, highlighting the effectiveness of various interventions. The study emphasizes the importance of multidrug-resistant and extensively drug-resistant tuberculosis in metropolitan cities. It underscores the significance of cough and Mycobacterium tuberculosis strain type in increased transmission within households. The research also examines the role of Bacillus Calmette-Guérin and isoniazid preventive therapy in protecting positive tuberculosis patients in Vietnam. Furthermore, it discusses the importance of family history for the prevalence of tuberculosis among household contacts of pulmonary tuberculosis index cases in Kampala, Uganda. The study concludes with innovative community-based approaches to doubling tuberculosis case screening in primary health care in a city of Sao Paulo State, Brazil, and the evaluation of 'Ribolola': a household tuberculosis contact tracing programme in North West Province, South Africa. The efficacy of interferon-γ production in response to Mycobacterium tuberculosis antigens in an Ugandan population and the tuberculosis diagnosis among household contacts and impact of tuberculosis preventive treatment for child contacts in Swaziland are also explored. The research underscores the importance of household ventilation and tuberculosis transmission in Kampala, Uganda. It also discusses the yield of a household contact tracing study in Cambodia, and the screening of newly diagnosed sputum smear positive tuberculosis patients in Vietnam. The study further examines the risks for increased transmission within households. The importance of cough and M. tuberculosis strain type as risks for increased transmission within households is highlighted. The research also highlights the potential of cough and M. tuberculosis strain type as risks for increased transmission within households, and the genetic and shared environmental influences on interferon-γ production in response to Mycobacterium tuberculosis antigens in an Ugandan population. The yield of a household contact tracing study and the impact of tuberculosis preventive treatment for child contacts in Swaziland are also explored. The research underscores the importance of household ventilation and tuberculosis transmission in Kampala, Uganda. It also discusses the yield of a household contact tracing study in Cambodia, and the screening of newly diagnosed sputum smear positive tuberculosis patients in Vietnam. The study further examines the risks for increased transmission within households.
| Country                     | No. of notified, bacteriologically confirmed, pulmonary tuberculosis cases | Estimated number of child household contacts eligible for tuberculosis preventive treatment, no. (95% UI) |
|-----------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Afghanistan                 | 20,946                                                                    | 20,000 (19,000–22,000)                                                                       |
| Albania                     | 210                                                                       | 12 (8–17)                                                                                     |
| Algeria                     | 6,575                                                                     | 1,100 (720–1,600)                                                                            |
| Angola                      | 27,086                                                                    | 25,000 (23,000–27,000)                                                                       |
| Argentina                   | 6,042                                                                     | 430 (270–590)                                                                                 |
| Armenia                     | 369                                                                       | 80 (73–87)                                                                                    |
| Australia                   | 780                                                                       | 33 (21–46)                                                                                   |
| Austria                     | 379                                                                       | 10 (6.5–14)                                                                                  |
| Azerbaijan                  | 3,125                                                                     | 340 (220–470)                                                                                 |
| Bahamas                     | 16                                                                        | 1.0 (0.6–1.3)                                                                                 |
| Bahrain                     | 80                                                                        | 8 (5–11)                                                                                      |
| Bangladesh                  | 144,817                                                                   | 55,000 (50,000–59,000)                                                                        |
| Belarus                     | 2,171                                                                     | 81 (51–110)                                                                                  |
| Belgium                     | 563                                                                       | 19 (12–26)                                                                                    |
| Belize                      | 71                                                                        | 8.2 (5.2–11)                                                                                 |
| Benin                       | 2,947                                                                     | 2,100 (1,900–2,300)                                                                          |
| Bhutan                      | 440                                                                       | 160 (140–170)                                                                                 |
| Bolivia (Plurinational State of) | 5,412                                                                  | 1,800 (1,700–2,000)                                                                          |
| Bosnia and Herzegovina      | 479                                                                       | 18 (11–24)                                                                                    |
| Botswana                    | 2,098                                                                     | 780 (720–850)                                                                                 |
| Brazil                      | 49,922                                                                    | 3,000 (1,900–4,100)                                                                          |
| Brunei Darussalam           | 179                                                                       | 21 (13–29)                                                                                    |
| Bulgaria                    | 694                                                                       | 19 (12–26)                                                                                    |
| Burkina Faso                | 3,841                                                                     | 3,300 (3,000–3,600)                                                                          |
| Burundi                     | 4,728                                                                     | 3,600 (3,300–3,900)                                                                          |
| Cambodia                    | 12,049                                                                    | 5,600 (5,100–6,000)                                                                           |
| Cameroon                    | 14,515                                                                    | 10,000 (9,500–11,000)                                                                         |
| Canada                      | 1,144                                                                     | 39 (24–53)                                                                                    |
| Cabo Verde                  | 178                                                                       | 67 (61–73)                                                                                    |
| Central African Republic    | 5,146                                                                     | 3,500 (3,200–3,800)                                                                          |
| Chad                        | 5,162                                                                     | 4,500 (4,100–4,900)                                                                          |
| Chile                       | 2,028                                                                     | 120 (77–170)                                                                                  |
| China                       | 235,547                                                                   | 11,000 (6,900–15,000)                                                                         |
| China, Hong Kong SAR        | 2,486                                                                     | 74 (47–100)                                                                                   |
| China, Macao SAR            | 279                                                                       | 13 (8–17)                                                                                    |
| Colombia                    | 8,627                                                                     | 630 (400–860)                                                                                 |
| Comoros                     | 53                                                                        | 38 (35–41)                                                                                    |
| Congo                       | 3,997                                                                     | 2,400 (2,200–2,600)                                                                          |
| Costa Rica                  | 313                                                                       | 20 (12–27)                                                                                    |
| Côte d'Ivoire               | 14,311                                                                    | 11,000 (10,000–12,000)                                                                         |
| Croatia                     | 287                                                                       | 9 (6–13)                                                                                      |
| Cuba                        | 517                                                                       | 21 (13–28)                                                                                    |
| Cyprus                      | 39                                                                        | 1.5 (1.0–2.1)                                                                                  |
| Czechia                     | 366                                                                       | 12 (7–16)                                                                                    |
| Democratic People's Republic of Korea | 40,233                                                                 | 9,500 (8,700–10,000)                                                                         |
| Democratic Republic of the Congo | 98,516                                                                | 85,000 (77,000–92,000)                                                                         |
| Denmark                     | 159                                                                       | 4.3 (2.7–5.8)                                                                                  |
| Djibouti                    | 1,072                                                                     | 610 (550–660)                                                                                 |
| Dominican Republic          | 2,076                                                                     | 180 (120–250)                                                                                 |
| Ecuador                     | 4,299                                                                     | 400 (260–550)                                                                                 |
| Egypt                       | 3,660                                                                     | 1,800 (1,600–1,900)                                                                           |

(continues . . .)
Research
Tuberculosis preventive treatment for child contacts
Yohhei Hamada et al.

| Country                      | No. of notified, bacteriologically confirmed, pulmonary tuberculosis cases³   | Estimated number of child household contacts² eligible for tuberculosis preventive treatment, no. (95% UI) |
|------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| El Salvador                  | 3 029                                                                       | 950 (860–1 000)                                                                                        |
| Equatorial Guinea            | 893                                                                         | 550 (500–600)                                                                                         |
| Eritrea                      | 770                                                                         | 490 (440–530)                                                                                        |
| Estonia                      | 141                                                                         | 3.9 (2.5–5.4)                                                                                         |
| Eswatini                     | 2 171                                                                       | 1 200 (1 100–1 300)                                                                                  |
| Ethiopia                     | 46 148                                                                      | 28 000 (25 000–30 000)                                                                                |
| Fiji                         | 141                                                                         | 16 (10–22)                                                                                            |
| Finland                      | 146                                                                         | 4.1 (2.6–5.6)                                                                                         |
| France                       | 2 494                                                                       | 85 (54–120)                                                                                            |
| Gabon                        | 2 301                                                                       | 1 100 (1 000–1 200)                                                                                   |
| Gambia                       | 1 429                                                                       | 1 800 (1 700–2 000)                                                                                   |
| Georgia                      | 1 780                                                                       | 390 (360–430)                                                                                         |
| Germany                      | 3 262                                                                       | 74 (46–100)                                                                                           |
| Ghana                        | 8 359                                                                       | 3 700 (3 400–4 000)                                                                                   |
| Greece                       | 313                                                                         | 8 (5–12)                                                                                              |
| Guatemala                    | 2 760                                                                       | 1 400 (1 300–1 500)                                                                                   |
| Guinea                       | 7 737                                                                       | 6 900 (6 300–7 500)                                                                                   |
| Guinea-Bissau                | 1 769                                                                       | 2 100 (1 900–2 300)                                                                                   |
| Guyana                       | 342                                                                         | 110 (99–120)                                                                                          |
| Haiti                        | 10 633                                                                      | 4 700 (4 300–5 100)                                                                                   |
| Honduras                     | 2 190                                                                       | 880 (800–960)                                                                                         |
| Hungary                      | 333                                                                         | 9 (6–12)                                                                                              |
| Iceland                      | 8                                                                           | 0.35 (0.22–0.48)                                                                                      |
| India                        | 905 513                                                                     | 350 000 (320 000–380 000)                                                                             |
| Indonesia                    | 215 586                                                                     | 72 000 (66 000–78 000)                                                                                 |
| Iran (Islamic Republic of)   | 4 785                                                                       | 360 (230–490)                                                                                         |
| Iraq                         | 2 676                                                                       | 700 (440–960)                                                                                         |
| Ireland                      | 165                                                                         | 8 (5–11)                                                                                              |
| Israel                       | 131                                                                         | 11 (7–15)                                                                                             |
| Italy                        | 2 160                                                                       | 55 (35–75)                                                                                            |
| Jamaica                      | 69                                                                           | 4 (3–5)                                                                                                |
| Japan                        | 11 227                                                                      | 290 (180–400)                                                                                         |
| Jordan                       | 179                                                                         | 30 (19–41)                                                                                            |
| Kazakhstan                   | 9 489                                                                       | 3 300 (3 000–3 600)                                                                                   |
| Kenya                        | 46 875                                                                      | 25 000 (23 000–27 000)                                                                                 |
| Kiribati                     | 189                                                                         | 130 (120–140)                                                                                         |
| Kuwait                       | 373                                                                         | 42 (27–58)                                                                                            |
| Kyrgyzstan                   | 3 171                                                                       | 1 500 (1 400–1 700)                                                                                   |
| Lao People’s Democratic Republic | 3 876                                                                   | 2 000 (1 900–2 200)                                                                                   |
| Latvia                       | 443                                                                         | 13 (8.5–18)                                                                                           |
| Lebanon                      | 325                                                                         | 28 (18–39)                                                                                            |
| Lesotho                      | 3 670                                                                       | 1 800 (1 600–1 900)                                                                                   |
| Liberia                      | 3 382                                                                       | 2 300 (2 100–2 500)                                                                                   |
| Libya                        | 514                                                                         | 68 (43–94)                                                                                            |
| Lithuania                    | 1 004                                                                       | 32 (20–44)                                                                                            |
| Luxembourg                   | 21                                                                           | 0.7 (0.5–1.0)                                                                                         |
| Madagascar                   | 21 773                                                                      | 13 000 (12 000–15 000)                                                                                 |
| Malawi                       | 6 984                                                                       | 4 600 (4 300–4 900)                                                                                   |
| Malaysia                     | 15 888                                                                      | 1 400 (900–2 000)                                                                                     |
| Maldives                      | 98                                                                           | 14 (9–20)                                                                                                |
| Mali                         | 4 420                                                                       | 6 100 (5 500–6 600)                                                                                    |
| Malta                        | 25                                                                           | 0.9 (0.6–1.2)                                                                                         

(continues...)
| Country                  | No. of notified, bacteriologically confirmed, pulmonary tuberculosis cases | Estimated number of child household contacts’ eligible for tuberculosis preventive treatment, no. (95% UI) |
|--------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Mauritania               | 1 376                                                                     | 1 100 (1 000–1 200)                                                                                |
| Mauritius                | 109                                                                       | 5.2 (3.3–7.1)                                                                                    |
| Mexico                   | 14 883                                                                    | 1 300 (840–1 800)                                                                                 |
| Mongolia                 | 1 861                                                                     | 690 (630–750)                                                                                    |
| Montenegro               | 58                                                                        | 2.7 (1.7–3.7)                                                                                    |
| Morocco                  | 13 635                                                                    | 5 500 (5 000–5 900)                                                                               |
| Mozambique               | 31 606                                                                    | 21 000 (19 000–23 000)                                                                            |
| Myanmar                  | 48 088                                                                    | 16 000 (15 000–17 000)                                                                            |
| Namibia                  | 5 867                                                                     | 3 200 (2 900–3 400)                                                                               |
| Nepal                    | 16 966                                                                    | 6 900 (6 300–7 500)                                                                               |
| Netherlands              | 367                                                                       | 11 (7–15)                                                                                        |
| New Zealand              | 167                                                                       | 8 (5–10)                                                                                         |
| Nicaragua                | 1 676                                                                     | 650 (600–710)                                                                                    |
| Niger                    | 8 288                                                                     | 8 800 (8 100–9 600)                                                                               |
| Nigeria                  | 75 980                                                                    | 53 000 (48 000–57 000)                                                                            |
| North Macedonia          | 152                                                                       | 8 (5–11)                                                                                         |
| Norway                   | 137                                                                       | 4.5 (2.8–6.2)                                                                                    |
| Oman                     | 193                                                                       | 33 (21–45)                                                                                       |
| Pakistan                 | 138 818                                                                   | 110 000 (98 000–120 000)                                                                          |
| Panama                   | 1 012                                                                     | 96 (61–130)                                                                                      |
| Papua New Guinea         | 3 944                                                                     | 2 400 (2 200–2 700)                                                                               |
| Paraguay                 | 1 823                                                                     | 740 (670–800)                                                                                    |
| Peru                     | 19 956                                                                    | 6 200 (5 600–6 700)                                                                               |
| Philippines              | 119 712                                                                   | 55 000 (51 000–60 000)                                                                            |
| Poland                   | 3 944                                                                     | 130 (81–180)                                                                                     |
| Portugal                 | 1 112                                                                     | 30 (19–41)                                                                                       |
| Puerto Rico              | 30                                                                        | 1.1 (0.7–1.5)                                                                                    |
| Qatar                    | 335                                                                       | 23 (14–31)                                                                                       |
| Republic of Korea        | 19 972                                                                    | 600 (380–820)                                                                                    |
| Republic of Moldova      | 1 880                                                                     | 220 (200–240)                                                                                    |
| Romania                  | 8 686                                                                     | 280 (180–380)                                                                                    |
| Russian Federation       | 40 254                                                                    | 1 800 (1 100–2 400)                                                                               |
| Rwanda                   | 4 175                                                                     | 2 300 (2 100–2 500)                                                                               |
| Sao Tome and Principe    | 46                                                                        | 25 (23–27)                                                                                       |
| Saudi Arabia             | 1 802                                                                     | 230 (150–320)                                                                                    |
| Senegal                  | 10 117                                                                    | 13 000 (12 000–14 000)                                                                            |
| Serbia                   | 781                                                                        | 31 (19–42)                                                                                       |
| Sierra Leone             | 9 674                                                                     | 7 700 (7 100–8 400)                                                                              |
| Singapore                | 1 238                                                                     | 51 (32–69)                                                                                       |
| Slovakia                 | 134                                                                       | 4.6 (2.9–6.3)                                                                                    |
| Slovenia                 | 89                                                                        | 2.9 (1.8–3.9)                                                                                    |
| Solomon Islands          | 126                                                                       | 84 (76–91)                                                                                       |
| Somalia                  | 7 691                                                                     | 7 400 (6 700–8 000)                                                                               |
| South Africa             | 127 187                                                                   | 41 000 (37 000–45 000)                                                                             |
| South Sudan              | 4 333                                                                     | 3 600 (3 300–3 900)                                                                               |
| Spain                    | 2 735                                                                     | 77 (48–100)                                                                                      |
| Sri Lanka                | 4 243                                                                     | 1 100 (1 000–1 200)                                                                               |
| Sudan                    | 7 419                                                                     | 6 000 (5 500–6 500)                                                                               |
| Suriname                 | 90                                                                        | 8 (5–11)                                                                                         |
| Sweden                   | 273                                                                       | 9 (6–13)                                                                                         |
| Switzerland              | 348                                                                       | 10 (7–14)                                                                                        |

(continues. . .)
### Research

#### Tuberculosis preventive treatment for child contacts

Yohhei Hamada et al.

| Country                        | No. of notified, bacteriologically confirmed, pulmonary tuberculosis cases | Estimated number of child household contacts eligible for tuberculosis preventive treatment, no. (95% UI) |
|--------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Syrian Arab Republic           | 1 080                                                                     | 560 (510–610)                                                                                   |
| Tajikistan                     | 2 820                                                                     | 2 100 (1 900–2 300)                                                                            |
| Thailand                       | 36 470                                                                    | 5 500 (5 100–6 000)                                                                            |
| Timor-Leste                    | 1 954                                                                     | 1 600 (1 500–1 800)                                                                            |
| Togo                           | 2 142                                                                     | 1 300 (1 200–1 400)                                                                            |
| Trinidad and Tobago            | 120                                                                       | 6.9 (4.4–9.4)                                                                                    |
| Tunisia                        | 956                                                                       | 91 (57–120)                                                                                     |
| Turkey                         | 6 162                                                                     | 470 (300–650)                                                                                    |
| Turkmenistan                   | 693                                                                       | 110 (69–150)                                                                                    |
| Uganda                         | 27 039                                                                    | 21 000 (19 000–23 000)                                                                          |
| Ukraine                        | 16 561                                                                    | 1 900 (1 800–2 100)                                                                            |
| United Arab Emirates           | 47                                                                        | 2.8 (1.8–3.8)                                                                                    |
| United Kingdom                 | 2 245                                                                     | 82 (52–110)                                                                                     |
| United Republic of Tanzania    | 28 542                                                                    | 21 000 (19 000–23 000)                                                                          |
| United States                  | 5 848                                                                     | 230 (150–320)                                                                                    |
| Uruguay                        | 613                                                                       | 30 (19–42)                                                                                      |
| Uzbekistan                     | 5 705                                                                     | 2 600 (2 400–2 900)                                                                             |
| Vanuatu                        | 47                                                                        | 26 (24–28)                                                                                      |
| Venezuela (Bolivarian Republic of) | 7 189                                                                   | 670 (420–910)                                                                                    |
| Viet Nam                       | 57 246                                                                    | 16 000 (14 000–17 000)                                                                          |
| Yemen                          | 3 487                                                                     | 3 000 (2 800–3 300)                                                                             |
| Zambia                         | 16 115                                                                    | 11 000 (9 700–12 000)                                                                           |
| Zimbabwe                       | 13 263                                                                    | 7 600 (7 000–8 300)                                                                             |

SAR: Special Administrative Region; UI: uncertainty interval.

* We defined a child household contact as a child younger than 5 years living in the same household as a person with active tuberculosis disease.