

# Challenging Paradigms in Pediatric Tuberculosis: Where Does Transmission Occur



Leonardo Martinez  
Stanford University, School of Medicine

# Enthusiasm & Energy

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## EDITORIAL

### Children with TB: neglected no more . . .

NOVEMBER 20<sup>TH</sup> is the United Nations' Universal Children's Day, an opportunity to shine a light on the plight of children who have been forgotten or overlooked by the international community, including those affected by tuberculosis (TB). The pediatric TB epidemic has been neglected by national TB control programs, policy makers and the research

Between 2011 and 2015, the world spent US\$80 million on pediatric TB research – just 40% of the US\$200 million target outlined in the Roadmap for Childhood Tuberculosis.<sup>6</sup> Global elimination of TB will only occur as we develop better treatments and improved diagnostics for children. To achieve that, greater investment in pediatric TB research is

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<http://dx.doi.org/10.5588/ijtld.15.0471>

## Counting children with tuberculosis: why numbers matter

J. A. Seddon,\* H. E. Jenkins,<sup>†</sup> L. Liu,<sup>‡§</sup> T. Cohen,<sup>¶</sup> R. E. Black,<sup>‡</sup> T. Vos,<sup>#</sup> M. C. Becerra,\*\*  
S. M. Graham,<sup>††‡§§</sup> C. Sismanidis,<sup>¶¶</sup> P. J. Dodd<sup>##</sup>

## Importance of tuberculosis control to address child survival



Stephen M Graham, Charalambos Sismanidis, Heather J Menzies, Ben J Marais, Anne K Detjen, Robert E Black

Tuberculosis commonly affects young children (<5 years) death and not contributory causes to WHO, vital *Lancet* 2014; 383: 1605–07  
in countries that have high rates of child mortality<sup>1</sup> The registration data cannot be used to estimate the number Published Online

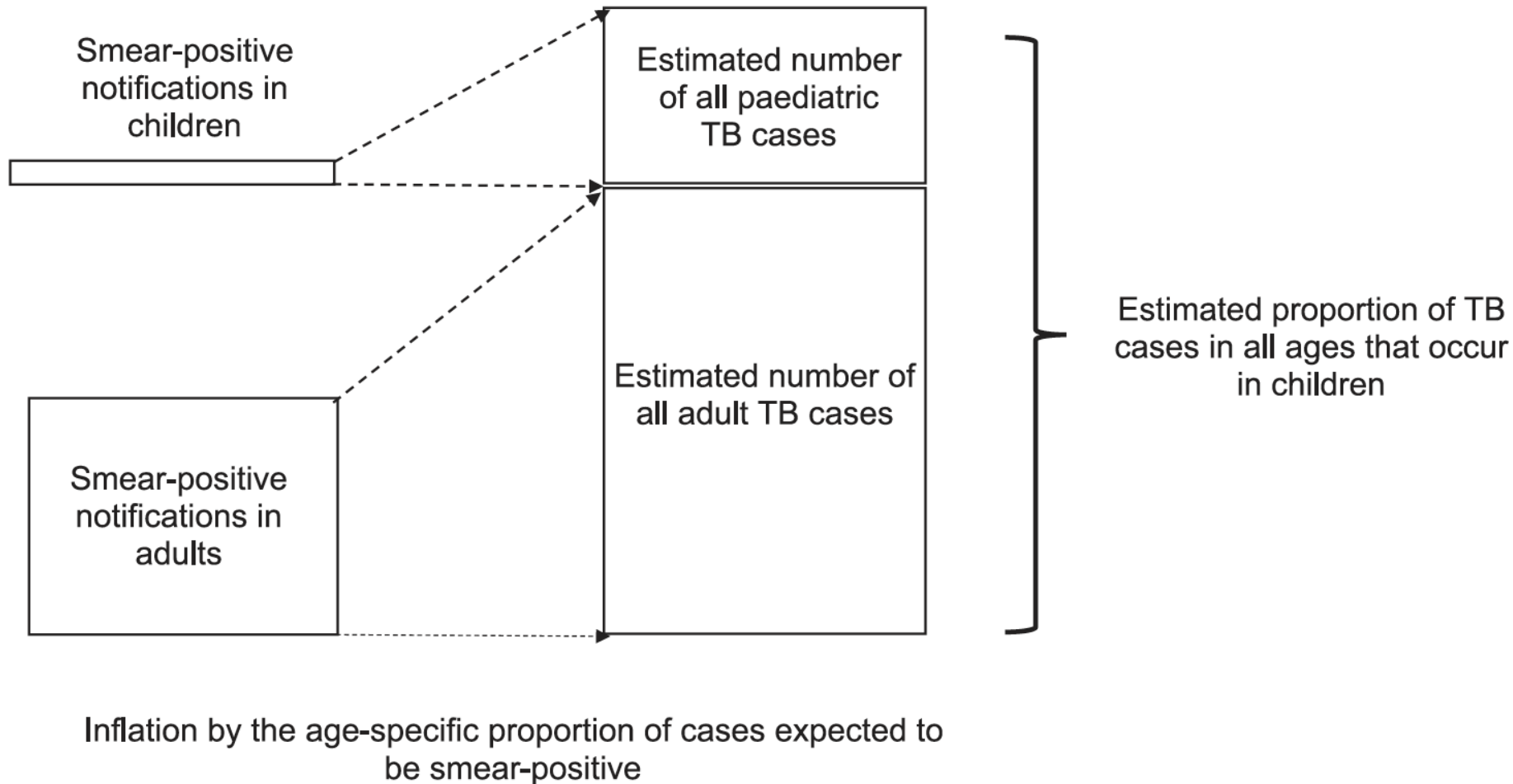
# Global and Regional Pediatric Tuberculosis and MDR-Tuberculosis Incidence

	Estimated number of child tuberculosis cases (95% CI)	Estimated number of child multidrug-resistant tuberculosis cases (95% CI)
African region	279 825 (250 187–308 717)	4736 (2829–6848)
Eastern Mediterranean region	71 162 (60 320–83 193)	2417 (339–5087)
European region	43 224 (39 572–47 242)	5645 (4206–7463)
Region of the Americas	27 199 (24 935–29 635)	606 (374–854)
South-East Asia region	397 040 (350 615–447 474)	10 000 (4993–15 568)
Western Pacific region	179 515 (159 246–202 626)	8349 (5639–11 610)
Total	999 792 (937 877–1 055 414)	31 948 (25 594–38 663)

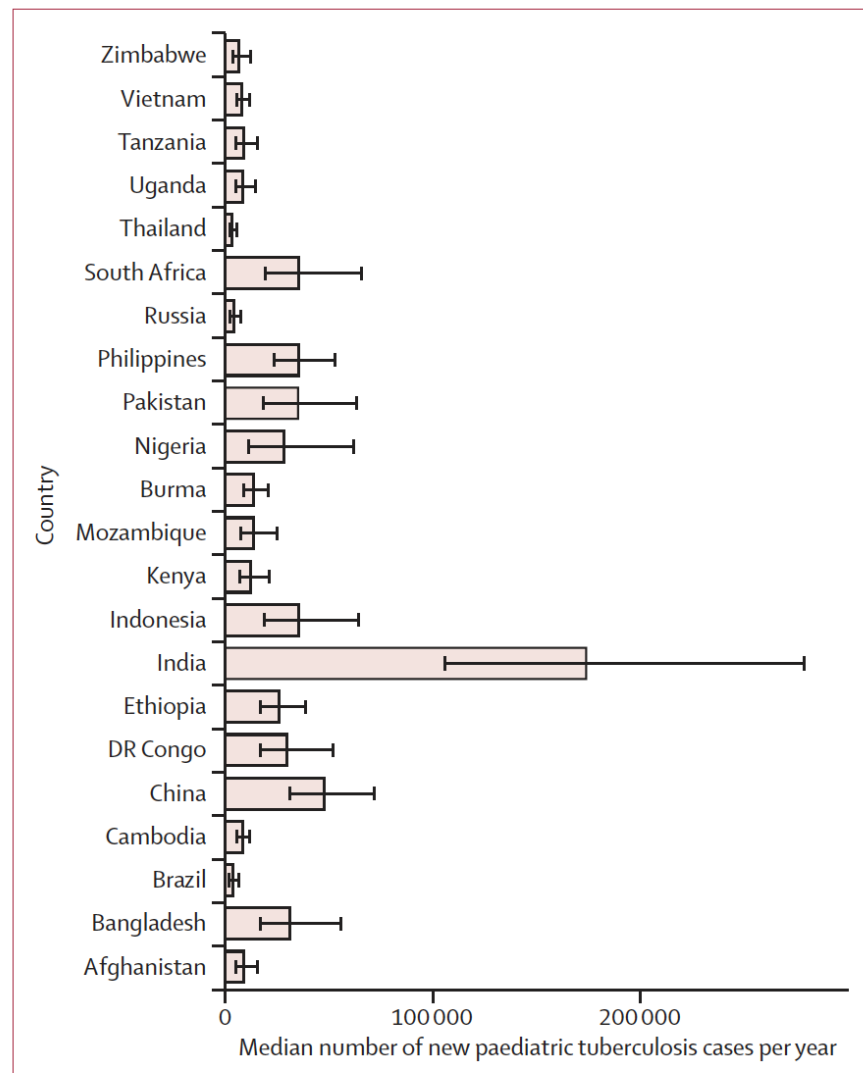
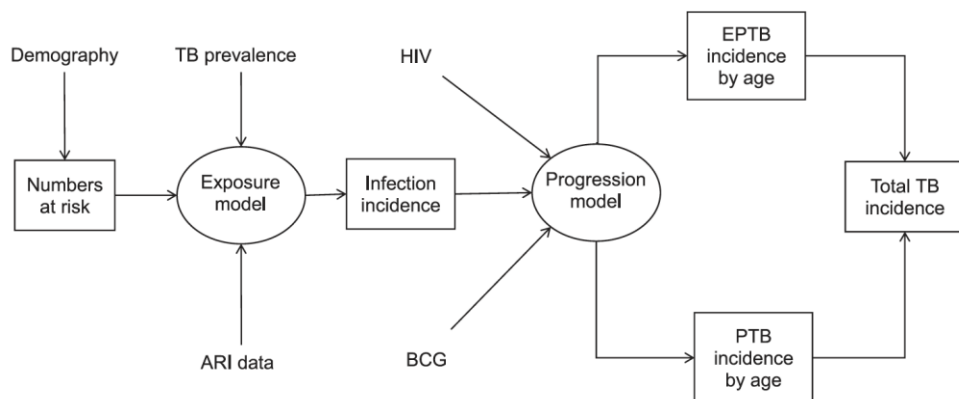
These regions correspond to those defined by WHO.

**Table 2: Estimated number of incident cases of tuberculosis disease and multidrug-resistant tuberculosis disease in children by WHO region, 2010**

# Global and Regional Pediatric Tuberculosis and MDR-Tuberculosis Incidence

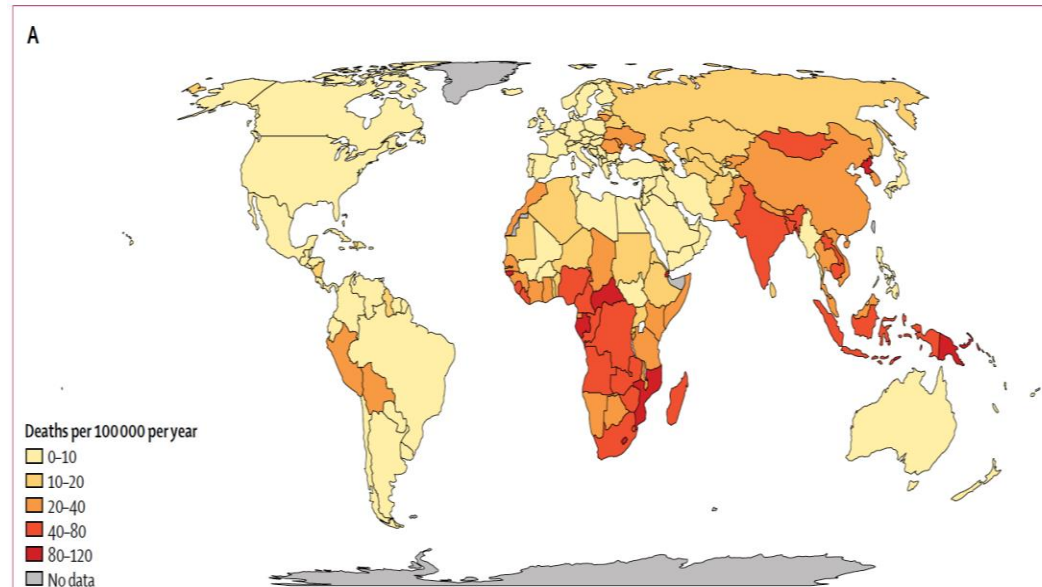
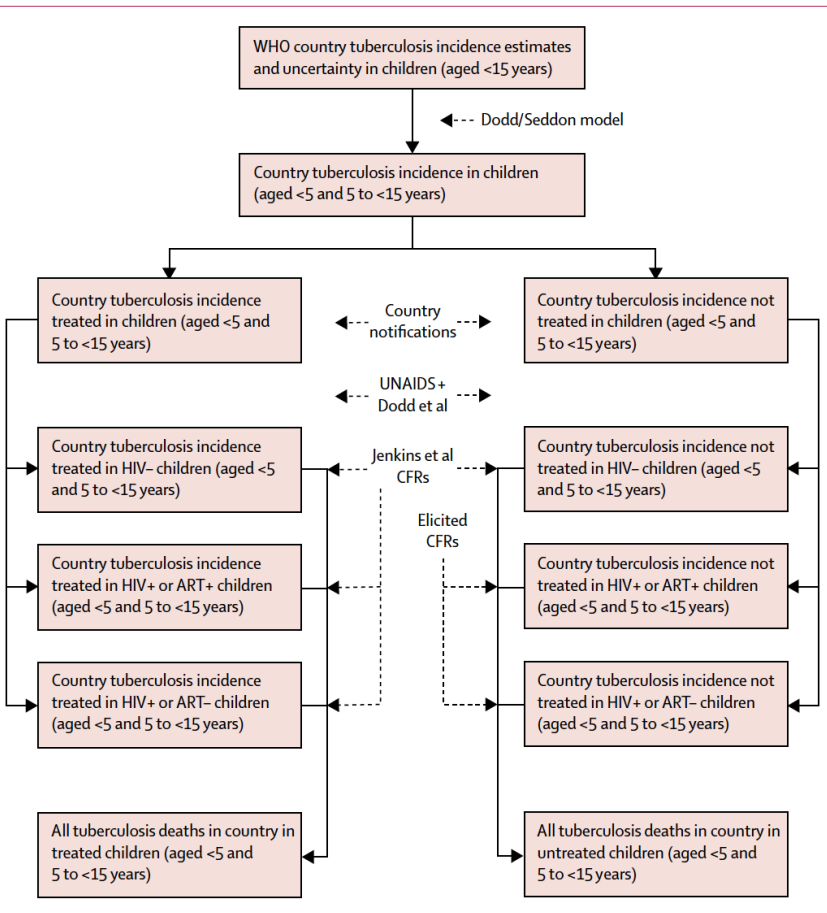


# Pediatric Tuberculosis in 22 High-Burden Countries



**Figure 4: Numbers of new paediatric tuberculosis cases in 2010, by country**  
 Estimates were calculated with the community model. Error bars show IQRs.  
 DR=Democratic Republic.

# Global Pediatric Mortality Due to Tuberculosis





# Pediatric Tuberculosis is a Global Problem



Pediatric Tuberculosis is a  
Global Problem

Historically Neglected





Pediatric Tuberculosis is a  
Global Problem

Historically Neglected

Long Held Beliefs Remain  
Unchallenged



**Widely Held Belief:** Vast majority of tuberculosis transmission to children occurs from a source inside the child's household in high-burden settings

“Most transmission in young children occurs in the household”

“....young children more likely to have been infected by a household member”

“A household contact is often found to be the source of infection in children under 5 years of age with TB; infants and young children are especially likely to have contracted TB at home”

## Tuberculosis transmission in HIV-endemic settings 2



### Transmission of drug-resistant tuberculosis in HIV-endemic settings

Palwasha Y Khan, Tom A Yates, Muhammad Osman, Robin M Warren, Yuri van der Heijden, Nesri Padayatchi, Edward A Nardell, David Moore, Barun Mathema, Neel Gandhi, Vegard Eldholm, Keertan Dheda, Anneke C Hesselting, Valerie Mizrahi, Roxana Rustumjee, Alexander Pym

The emergence and expansion of the multidrug-resistant tuberculosis epidemic is a threat to the global control of *Mycobacterium tuberculosis* complex. *Lancet Infect Dis* 2019;

### The transmission of *Mycobacterium tuberculosis* in high burden settings



Tom A Yates\*, Palwasha Y Khan\*, Gwenan M Knight, Jonathon G Taylor, Timothy D McHugh, Marc Lipman, Richard G White, Ted Cohen, Frank G Cobelens, Robin Wood, David A J Moore, Ibrahim Abubakar

Unacceptable levels of *Mycobacterium tuberculosis* transmission are noted in high burden settings and a renewed focus on reducing person-to-person transmission in these communities is needed. We review recent developments in *Lancet Infect Dis* 2016; 16: 227–38

# Guidance for national tuberculosis programmes on the management of tuberculosis in children

**What proportion of tuberculosis transmission to children is attributable to household tuberculosis exposure?**

# Beginning to Question



American Journal of Epidemiology

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## Systematic Reviews and Meta- and Pooled Analyses

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### Transmission of *Mycobacterium Tuberculosis* in Households and the Community: A Systematic Review and Meta-Analysis

Leonardo Martinez\*, Ye Shen, Ezekiel Mupere, Allan Kizza, Philip C. Hill, and Christopher C. Whalen

\* Correspondence to Dr. Leonardo Martinez, Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia Health Sciences Campus, B.S. Miller Hall Room 108, 101 Buck Road, Athens, Georgia 30602 (e-mail: LeoMarti@uga.edu).

Initially submitted December 3, 2015; accepted for publication June 2, 2016.

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The individual- and population-level impact of household tuberculosis exposure on transmission is unclear but may have implications for the effectiveness and implementation of control interventions. We systematically searched for and included studies in which latent tuberculosis infection was assessed in 2 groups: children exposed and unexposed to a household member with tuberculosis. We also extracted data on the smear and culture status of index cases, the age and bacillus Calmette-Guérin vaccination status of contacts, and study design characteristics. Of 6,176 citations identified from our search strategy, 26 studies (13,999 children with household exposure to tuberculosis and 174,097 children without) from 1929–2015 met inclusion criteria. Exposed children were 3.79 (95% confidence interval (CI): 3.01, 4.78) times more likely to be infected than were their community counterparts. Metaregression demonstrated higher infection among children aged 0–4 years of age compared with children aged 10–14 years (ratio of odds ratios = 2.24, 95% CI: 1.43, 3.51) and among smear-positive versus smear-negative index cases (ratio of odds ratios = 5.45, 95% CI: 3.43, 8.64). At the population level, we estimated that a small proportion (<20%) of transmission was attributable to household exposure. Our results suggest that targeting tuberculosis prevention efforts to household contacts is highly effective. However, a large proportion of transmission at the population level may occur outside the household.

contact tracing; *Mycobacterium tuberculosis*; recent transmission; systematic review; tuberculosis

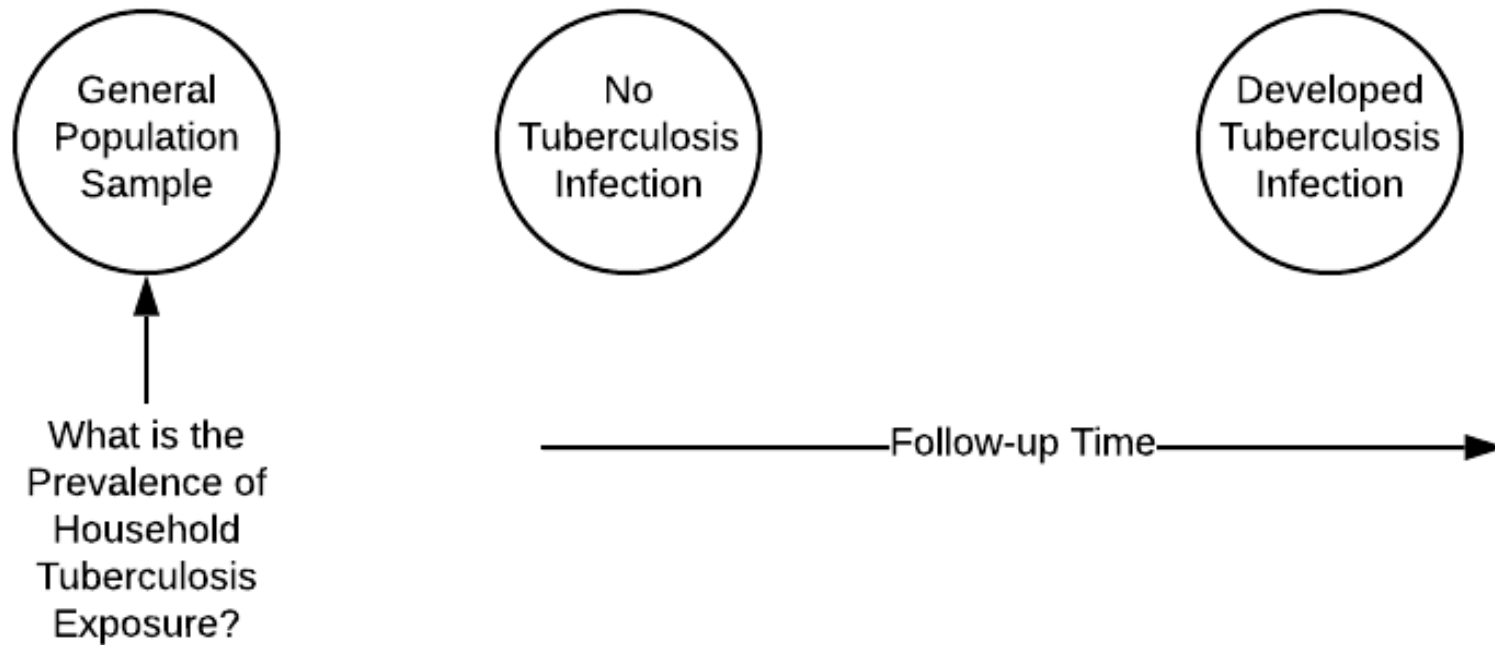
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Abbreviations: CI, confidence interval; OR, odds ratio.

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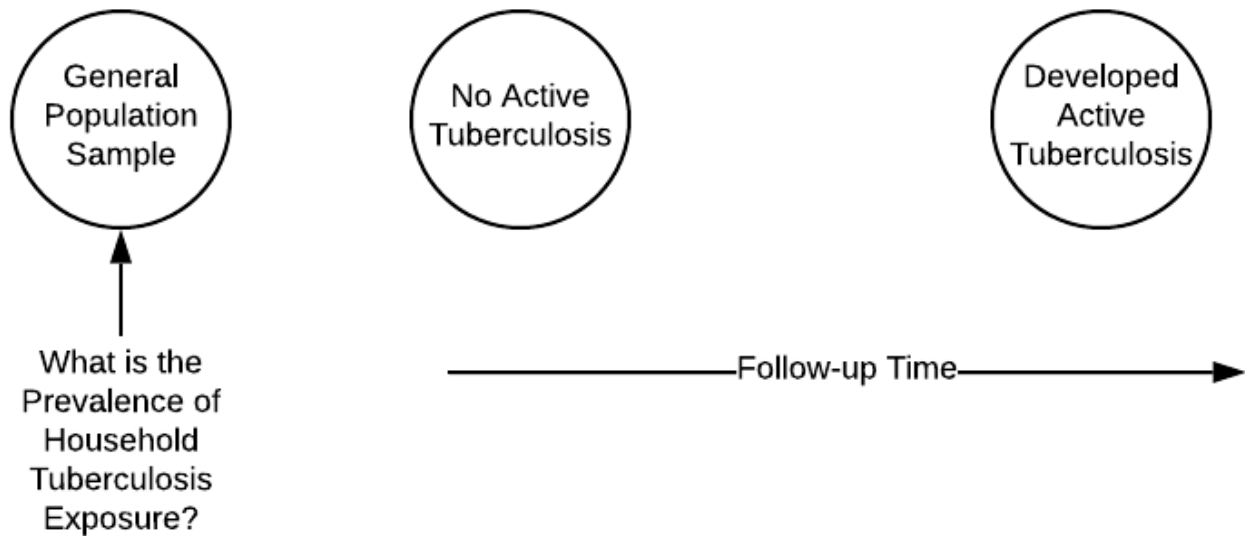


## Cohort Studies



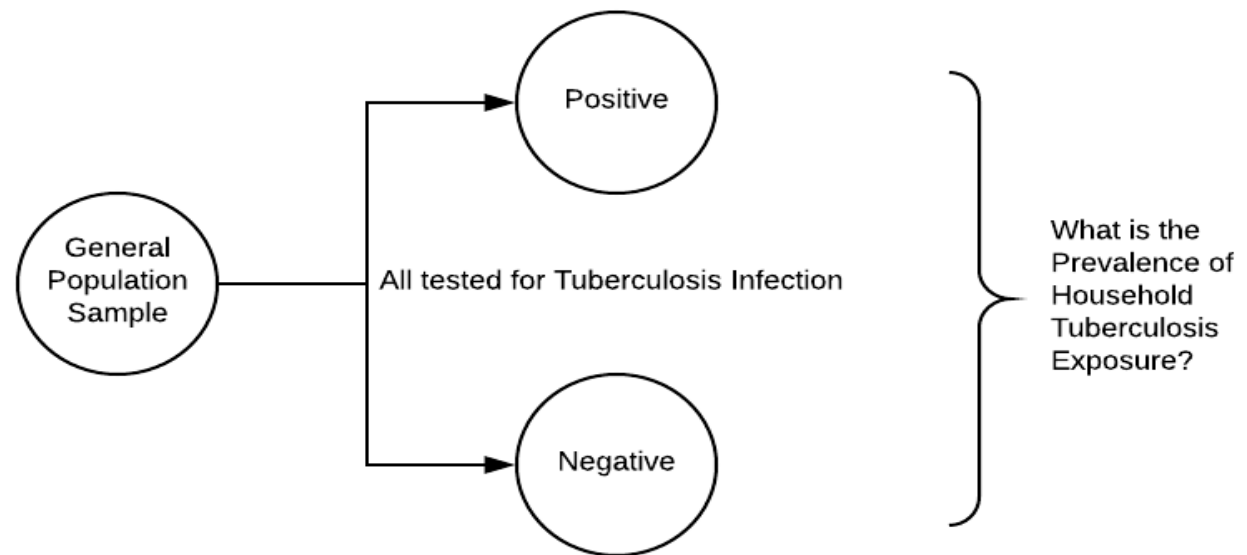
First Author, Year	Years	Age, yrs	Setting	Study Design (Sample Size)‡	Conclusions
<i>Conversion Studies</i>					
Martinez, 2018	2012–2017	0-5	South Africa	Prospective cohort (N=915), tuberculin conversion	11% of conversions occurred in households with a tuberculosis case in the last year
Andrews, 2017	2009–2012	0-2	South Africa	Prospective cohort (N=2512), QuantiFERON conversion	19% of conversions occurred in households with a tuberculosis case
Khan, 2018	2012–2015	<6	Malawi	Prospective cohort (N=3066), tuberculin conversion	11% of conversions lived a distance <200 meters from a known tuberculosis case

# Cohort Studies



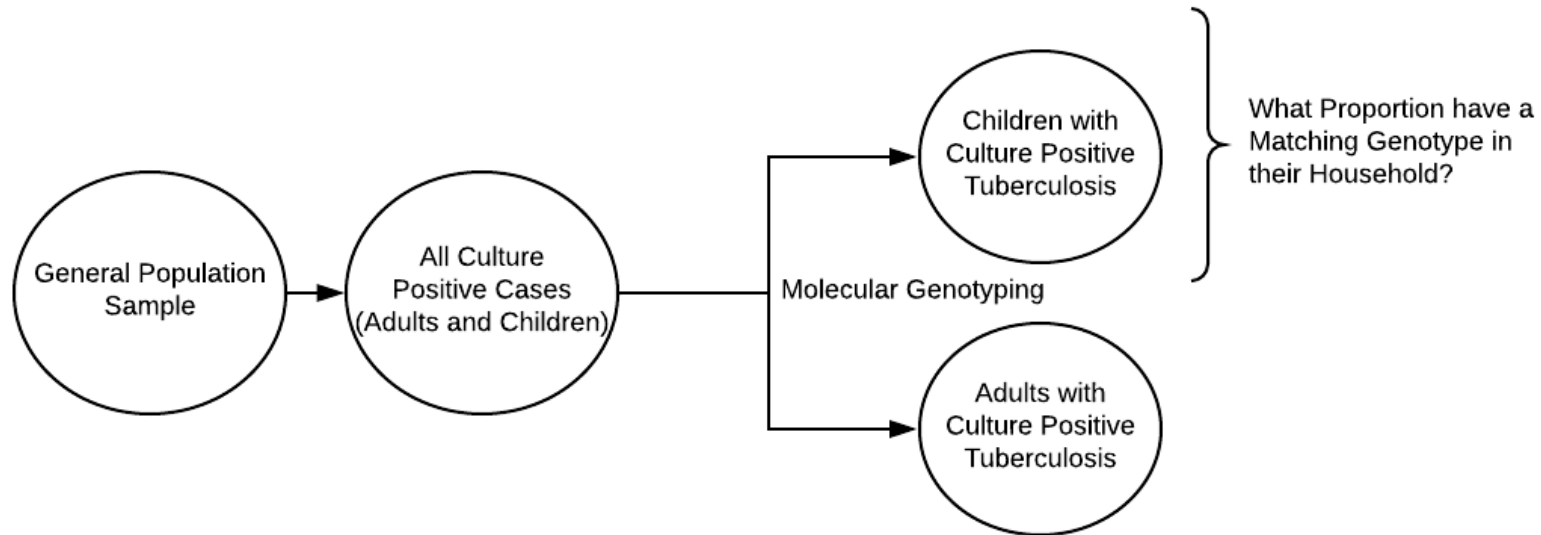
First Author, Year	Years	Age, yrs	Setting	Study Design (Sample Size)‡	Conclusions
<i>Disease Progression Studies</i>					
Martinez, 2018	2012–2017	0-5	South Africa	Prospective cohort (N=915)	19% of children developing tuberculosis were exposed to tuberculosis in the home
Nachman, 2011	2004–2008	0-3	South Africa	Prospective trial data of HIV-exposed infants (N=1329)	45 children developed tuberculosis; 28% were exposed to tuberculosis in the home*

# Tuberculosis Infection Surveys



First Author, Year	Years	Age, yrs	Setting	Study Design (Sample Size)‡	Conclusions
<i>Cross-Sectional Surveys</i>					
Martinez, 2017	1931–2015	<15	14 countries	Systematic review of tuberculin surveys (N=170615)	Household exposure at the population-level was low; <25% of transmission occurred in households
Khan, 2016	2012	2–4	Malawi	Tuberculin survey (N=3170)	<10% transmission occurred in households with a tuberculosis case
Dorjee, 2018	2017–2018	13†	Tibet	Tuberculin survey (N=5234)	<10% of childhood infections were attributable to recent household exposure
Cranmer, 2014	1999–2002	0.5	Kenya	T-SPOT.TB survey (N=128)	14% of infants with a positive T-SPOT.TB were exposed to a parent with active tuberculosis
Lule, 2015	2002–2005	5	Uganda	T-SPOT.TB survey (N=886)	20% of T-SPOT.TB positive children were exposed to a tuberculosis case
Ganmaa, 2018	2015–2017	6–13	Mongolia	QuantiFERON-TB survey (N=9810)	13.1% of tuberculosis infections were attributable to household tuberculosis exposure

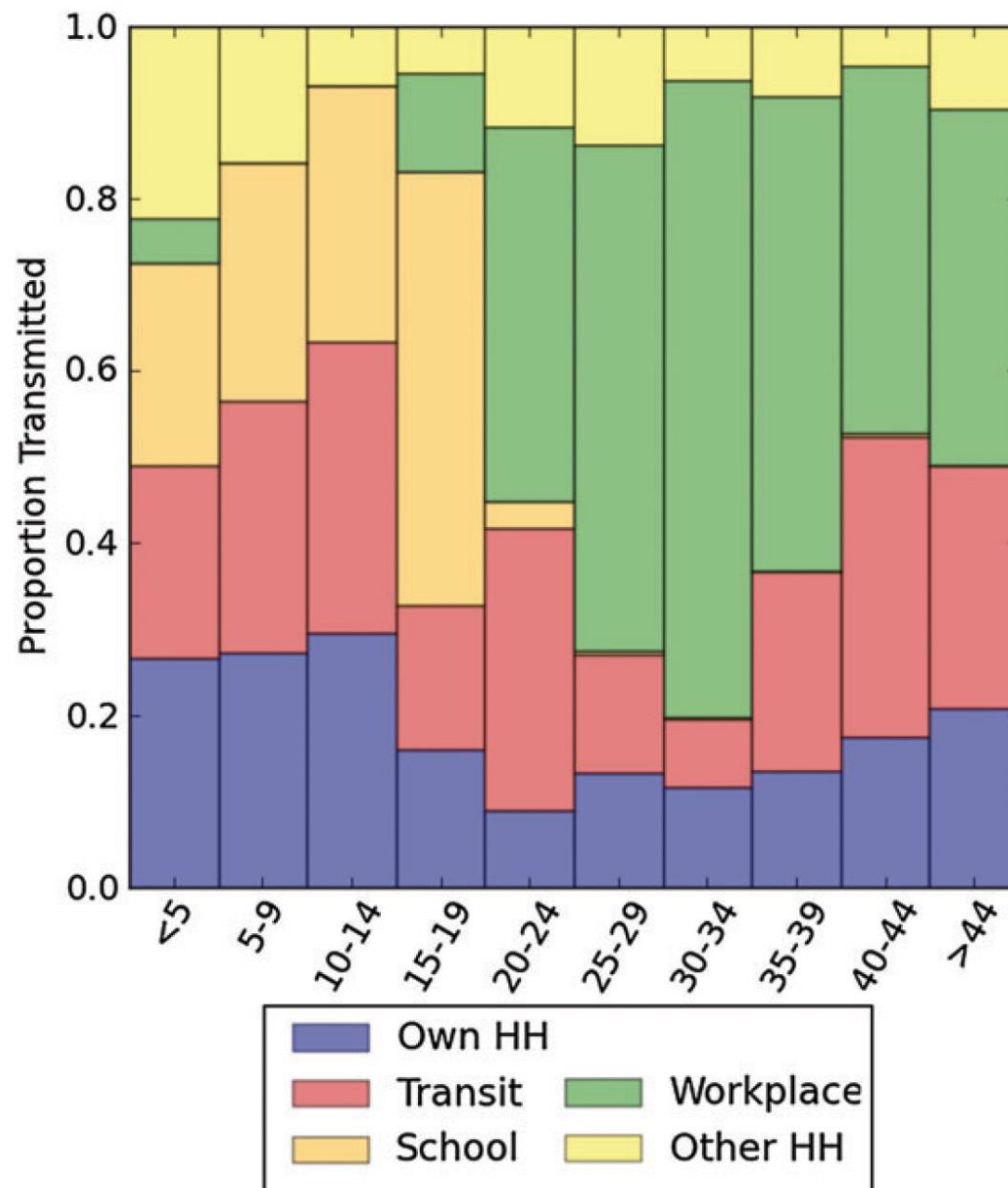
## Molecular Studies



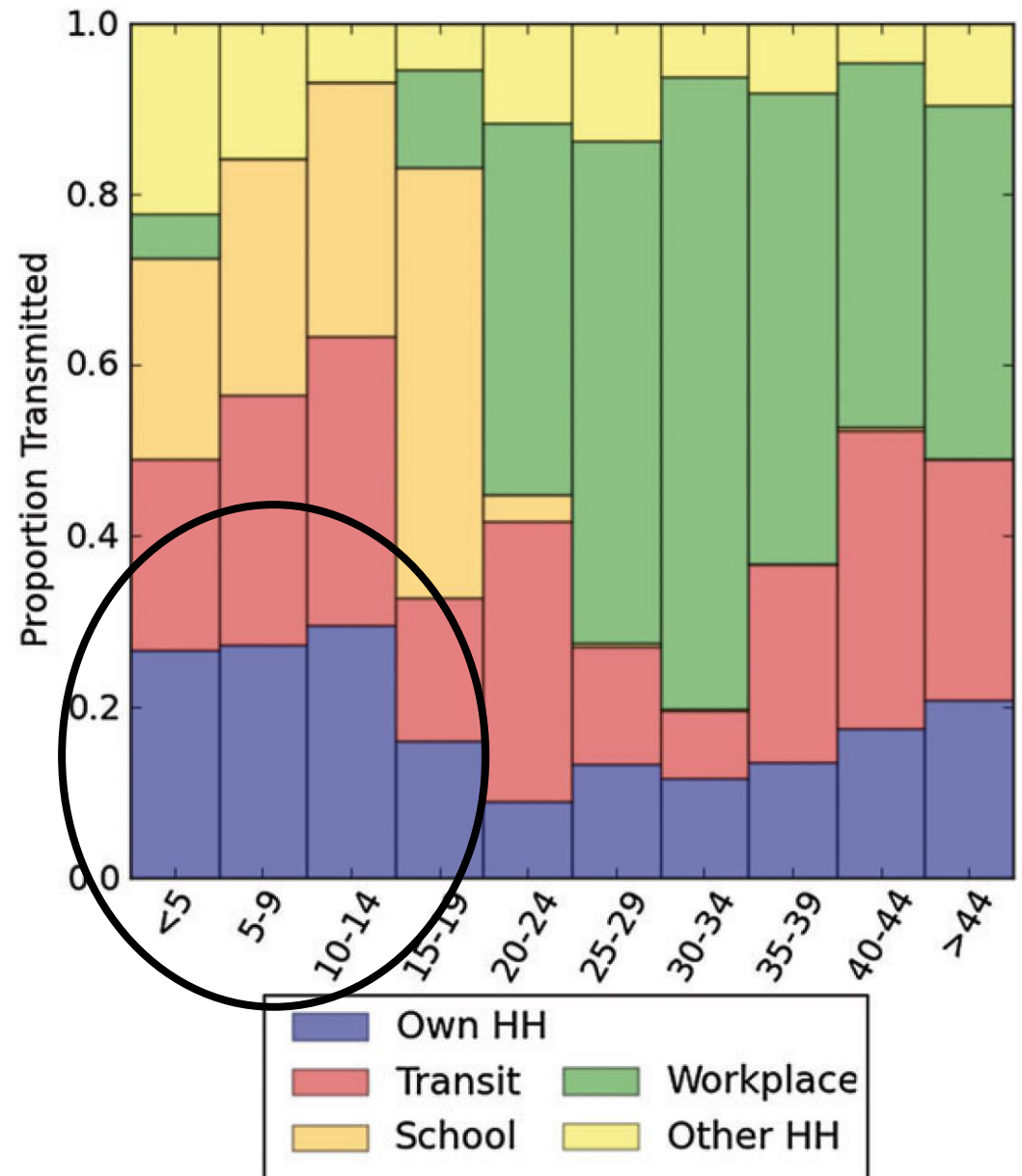
First Author, Year	Years	Age, yrs	Setting	Study Design (Sample Size)‡	Conclusions
<i>Molecular Studies</i>					
Schaaf, 2003	1993–1998	≤15	South Africa	Population-based; all culture-confirmed pediatric cases (N=35)	34% of diseased children were part of a cluster with a household tuberculosis case
Guthrie, 2018	2005–2014	<18	British Colombia	Population-based; all culture-confirmed pediatric cases (N=49)	70% of transmission occurred either in a foreign country or locally but outside the household



## Mathematical Modeling Studies



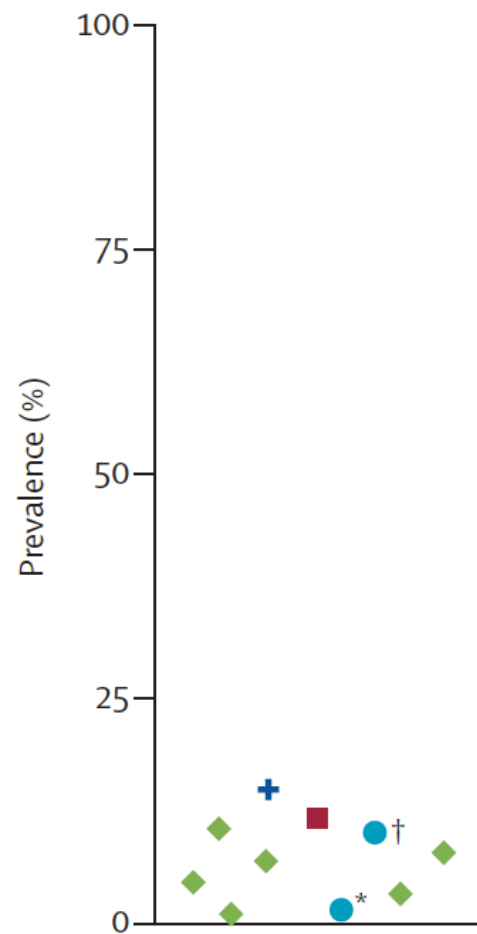
## Mathematical Modeling Studies



So, what proportion of tuberculosis transmission to children is attributable to household tuberculosis exposure?

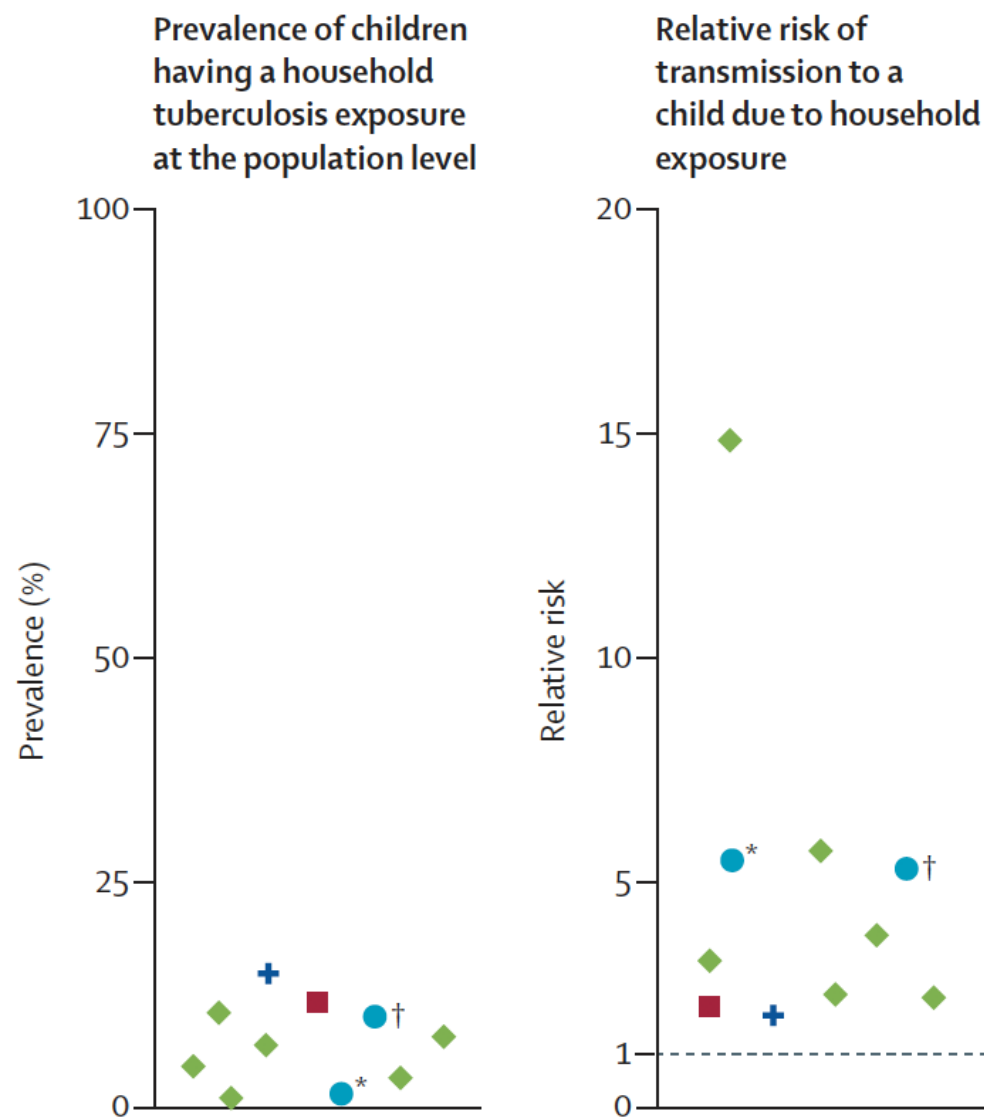
$$\text{Population-attributable fraction} = \frac{(\text{Prevalence of exposure} \times [\text{relative risk} - 1])}{(\text{Prevalence of exposure} \times [\text{relative risk} - 1]) + 1}$$

Prevalence of children  
having a household  
tuberculosis exposure  
at the population level



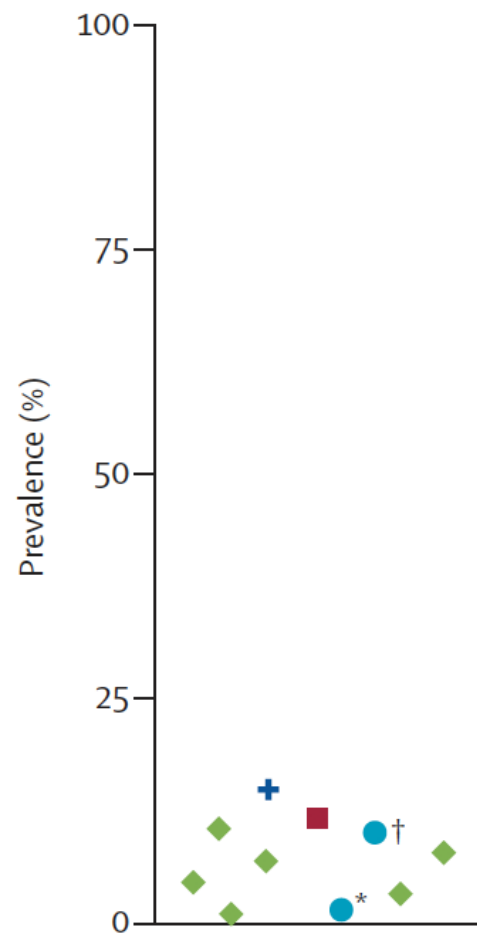
- + Prospective cohort (outcome is progression to disease)
- ◆ Tuberculosis infection survey
- Prospective cohort (outcome is TST/QFT conversion)
- Systematic review of tuberculin surveys



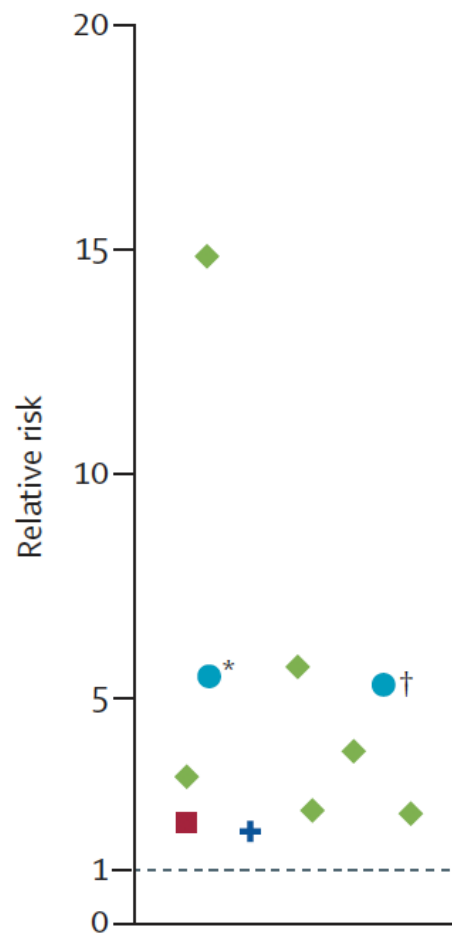


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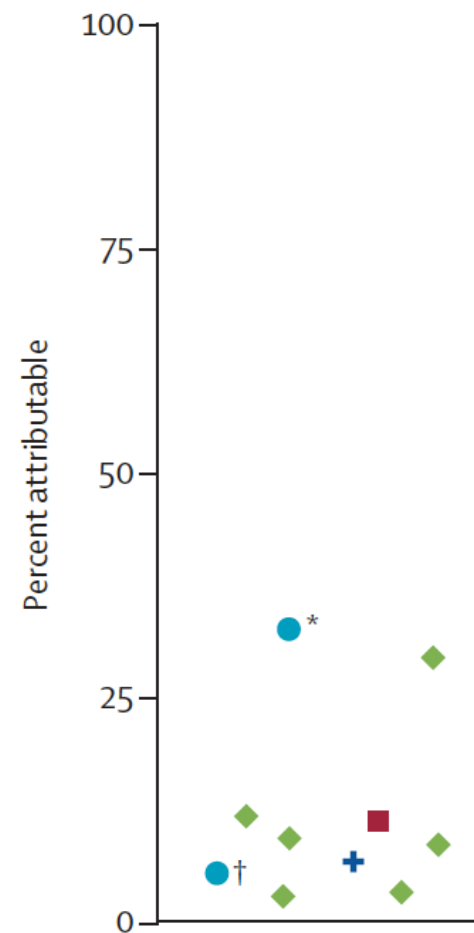
Prevalence of children having a household tuberculosis exposure at the population level



Relative risk of transmission to a child due to household exposure



Population-attributable fraction of transmission to children due to household exposure



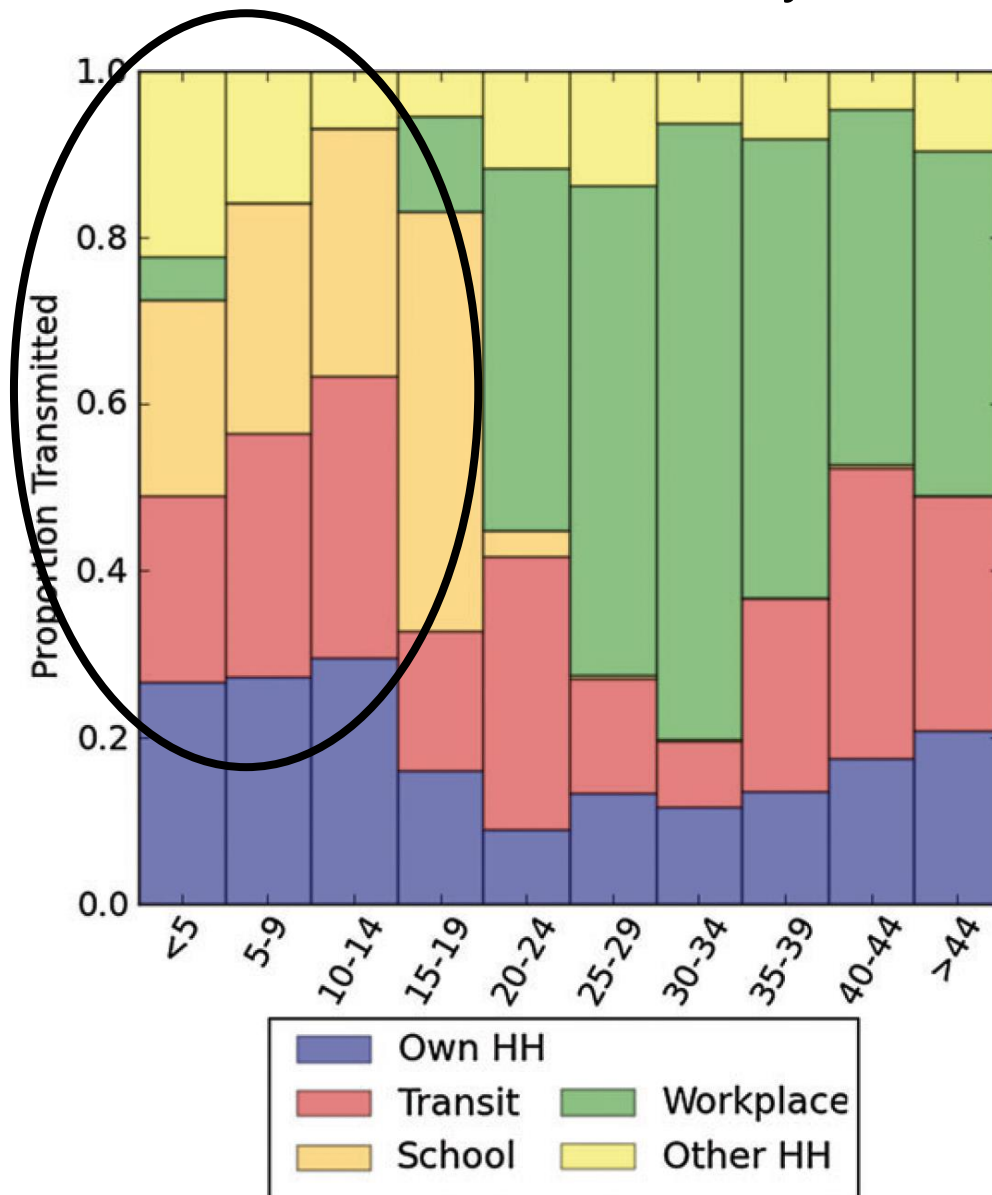
- + Prospective cohort (outcome is progression to disease)
- ◆ Tuberculosis infection survey
- Prospective cohort (outcome is TST/QFT conversion)
- Systematic review of tuberculin surveys

## Where in the Community Then?

- Almost no field intervention studies outside the household for pediatric tuberculosis
- Where outside the household?
- Entry points?



## Where in the Community Then?





# Where in the Community Then?

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<http://dx.doi.org/10.5588/ijtld.18.0025>

## Decentralisation of child tuberculosis services increases case finding and uptake of preventive therapy in Uganda

S. Zawedde-Muyanja,<sup>\*†</sup> A. Nakanwagi,<sup>\*</sup> J. P. Dongo,<sup>\*</sup> M. P. Sekadde,<sup>\*§</sup> R. Nyinoburyo,  
G. Ssentongo,<sup>§</sup> A. K. Detjen,<sup>\*\*</sup> F. Mugabe,<sup>‡</sup> J. Nakawesi,<sup>¶</sup> Y. Karamagi,<sup>¶</sup> P. Amuge,<sup>§</sup> A. Kekitiinwa,<sup>§</sup>  
S. M. Graham<sup>\*,\*\*</sup>

<sup>\*</sup>International Union Against Tuberculosis and Lung Disease, Paris, France; <sup>†</sup>The Infectious Diseases Institute, Makerere University College of Health Sciences, Kampala, <sup>‡</sup>The National Tuberculosis and Leprosy Programme, Ministry of Health, Kampala, <sup>§</sup>Baylor College of Children's Medical Foundation, Kampala, <sup>¶</sup>Mildmay Uganda, Kampala, Uganda; <sup>#</sup>United Nations Children's Fund, New York, USA; <sup>\*\*</sup>Centre for International Child Health, University of Melbourne Department of Paediatrics and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Victoria, Australia

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### SUMMARY

- A before-and-after implementation study from Uganda evaluated the effect of strengthening diagnosis, treatment, and prevention of paediatric tuberculosis at peripheral health facilities
- After implementation, a 140% increase in paediatric case notification was recorded, almost entirely driven by health-care facility interventions

# Most Tuberculosis Transmission to Children Occurs Outside the Household

- Between 10% to 20% of tuberculosis transmission to children occurs in the household
- Household contact tracing, when done perfectly at 100% implementation, may have limited impact
- A comprehensive approach that combines a set of public health, community-based screenings, in combination to household contact tracing, is necessary.



## Dogma

Most transmission in young children occurs in the household, with up to 60% of children with tuberculosis having a reported household or close contact"

### Tuberculosis transmission in HIV-endemic settings 2

#### Transmission of drug-resistant tuberculosis in HIV-endemic settings

Polansky J, Khan, Tom A, Valleron, Michael, O'Connell, Robert M, Warren, Susan, van der Horst, Anne, Padayatchi, Edward A, Ndwile, David, Mwanza, Bernard, Mathema, Neil, Gandhi, Rupert, Ezzamel, Kirsten, O'Connell, Anne, C. Valleron, Anne, Mwanza, Bernard, Padayatchi, Edward, Pym, Alexander

The emergence and expansion of the multidrug-resistant tuberculosis epidemic is a threat to the global control of tuberculosis

Review

### The transmission of *Mycobacterium tuberculosis* in high burden settings

Tom A Valleron, Polansky J, Khan, Tom A, Valleron, Michael, O'Connell, Robert M, Warren, Susan, van der Horst, Anne, Padayatchi, Edward A, Ndwile, David, Mwanza, Bernard, Mathema, Neil, Gandhi, Rupert, Ezzamel, Kirsten, O'Connell, Anne, C. Valleron, Anne, Mwanza, Bernard, Padayatchi, Edward, Pym, Alexander

Unacceptable levels of *Mycobacterium tuberculosis* transmission are noted in high burden settings and a renewed focus on infection control measures is warranted. This review reports developments in

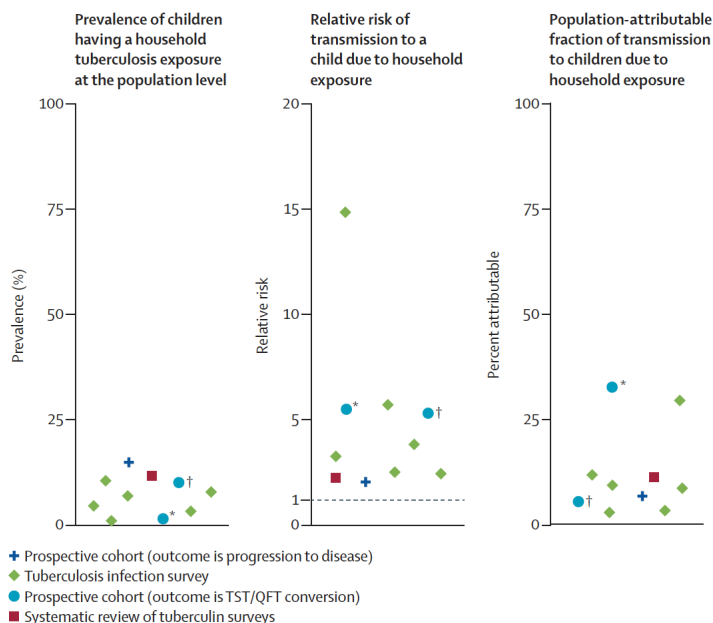
## Guidance for national tuberculosis programmes on the management of tuberculosis in children

Second edition

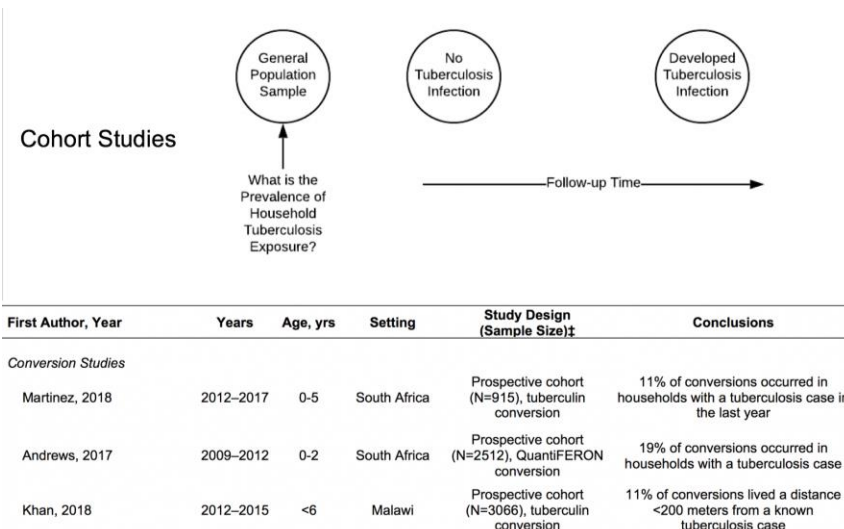
A household contact is often found to be the source of infection in children under 5 years of age with TB; infants and young children are especially likely to have contracted TB at home"

## >70% of Tuberculosis

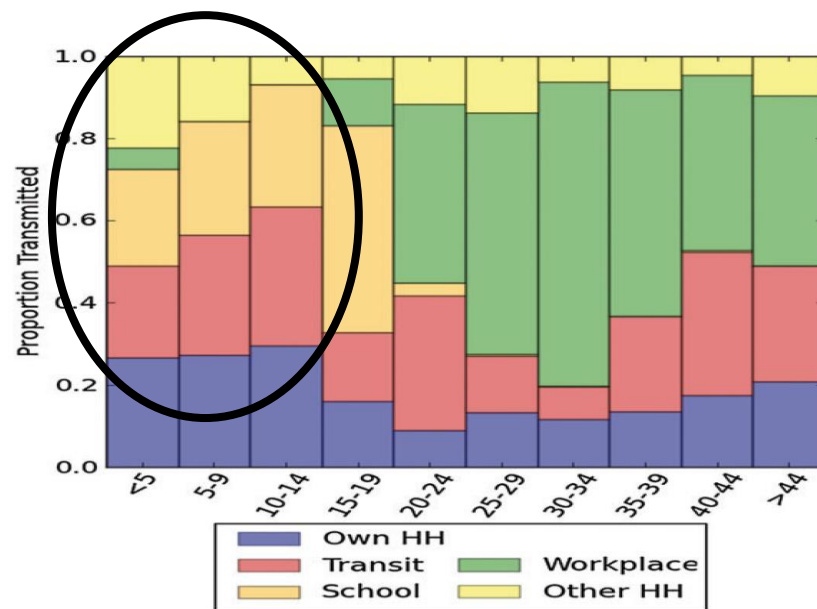
## Transmission Outside Households



## Differing Study Design Show Consistent Results



## Where transmission is occurring needs work



**Stanford University, School of Medicine**

Jason R. Andrews  
Olivia Cords  
Nathan C Lo

**Baylor University, School of Medicine**

Anna Mandalakas  
Alexander Kay

**University of Cape Town**

Heather Zar

**University of Otago**

Philip C. Hill

**Boston University**

Bob Horsburgh

**London School of Hygiene & Tropical Medicine**

Palwasha Khan

**SATVI**

Mark Hatherill



Thank you for listening.  
Questions?





Most transmission in young children occurs in the household, with up to 60% of children with tuberculosis having a reported household or close contact"

"....young children more likely to have been infected by a household member"

## Transmission of drug-resistant tuberculosis in HIV-endemic settings

**The emergence and expansion of the multidrug-resistant tuberculosis epidemic is a threat to the global control of** *Lancet Infect Dis 2014*

## Review

Tom A Yates\*, Palanisamy P Khan<sup>1</sup>, Givemini M Knight, Jonathan G Taylor, Timothy O McNulty, Isaac Lipman, Richard G White, Ted Cohen, Frank G Coburn, Robin Wood, David AJ Moore, Graham Alabaster

## Second edition

A household contact is often found to be the source of infection in children under 5 years of age with TB; infants and young children are especially likely to have contracted TB at home"

The figure consists of three scatter plots arranged horizontally, each representing a different metric related to tuberculosis. The y-axis for all plots is on the left side of each plot.

- Plot 1 (Left):** The y-axis is labeled "Prevalence (%)" and ranges from 0 to 100. The x-axis is labeled "Prevalence of children having a household tuberculosis exposure at the population level". Data points are clustered at low prevalence values (below 25%).
- Plot 2 (Middle):** The y-axis is labeled "Relative risk" and ranges from 0 to 20. The x-axis is labeled "Relative risk of transmission to a child due to household exposure". A dashed horizontal line is drawn at y=1. Data points are scattered, with some above and some below the line.
- Plot 3 (Right):** The y-axis is labeled "Percent attributable" and ranges from 0 to 100. The x-axis is labeled "Population-attributable fraction of transmission to children due to household exposure". Data points are clustered at low values (below 25%).

**Legend:**

- + Prospective cohort (outcome is progression to disease)
- ◆ Tuberculosis infection survey
- Prospective cohort (outcome is TST/QFT conversion)
- Systematic review of tuberculosis surveys

**Cohort Studies**

General Population Sample

No Tuberculosis Infection

Developed Tuberculosis Infection

What is the Prevalence of Household Tuberculosis Exposure?

Follow-up Time

The diagram illustrates a cohort study design. It begins with a 'General Population Sample' circle. Below it, an upward-pointing arrow is labeled 'What is the Prevalence of Household Tuberculosis Exposure?'. To the right, a horizontal arrow labeled 'Follow-up Time' points from a 'No Tuberculosis Infection' circle to a 'Developed Tuberculosis Infection' circle, showing the progression of the study over time.

First Author, Year	Years	Age, yrs	Setting	Study Design (Sample Size)†	Conclusions
<i>Conversion Studies</i>					
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Stacked bar chart showing the proportion of transmission by location for different age groups. The y-axis is 'Proportion Transmitted' (0.0 to 1.0). The x-axis shows age groups: <5, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, >44. The legend includes: Own HH (blue), Transit (red), School (yellow), Workplace (green), and Other HH (light yellow). A black circle highlights the first three bars (<5, 5-9, 10-14).

Age Group	Own HH	Transit	School	Workplace	Other HH
<5	0.27	0.23	0.23	0.07	0.10
5-9	0.27	0.30	0.28	0.00	0.15
10-14	0.30	0.34	0.30	0.00	0.06
15-19	0.16	0.17	0.50	0.13	0.04
20-24	0.09	0.32	0.02	0.45	0.12
25-29	0.13	0.14	0.00	0.59	0.14
30-34	0.12	0.08	0.00	0.75	0.05
35-39	0.13	0.23	0.00	0.56	0.10
40-44	0.18	0.35	0.00	0.44	0.03
>44	0.21	0.28	0.00	0.42	0.09