Modeling Pediatric Tuberculosis: Missing Puzzle Pieces

Leonardo Martinez

Olivia Cords

Bob Horsburgh

Jason Andrews

Stanford University

School of Medicine

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Overview

- More pediatric modeling recently
- What parameters are critical drivers and require better understanding?
- How can existing studies be utilized to support the pediatric tuberculosis modeling community?

Background

- Pediatric tuberculosis is a major global health problem.

- Kids are at high-risk for disease progression after recent exposure and infection; their mortality risk is also high

- Historically considerable amount of modeling in the adult world but there's been a paucity of models in children

Several recent high-profile modeling studies have begun to fill this gap

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

Jenkins et al, *The Lancet* 2014

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Pediatric Tuberculosis Burden in 22 High-Burden Countries
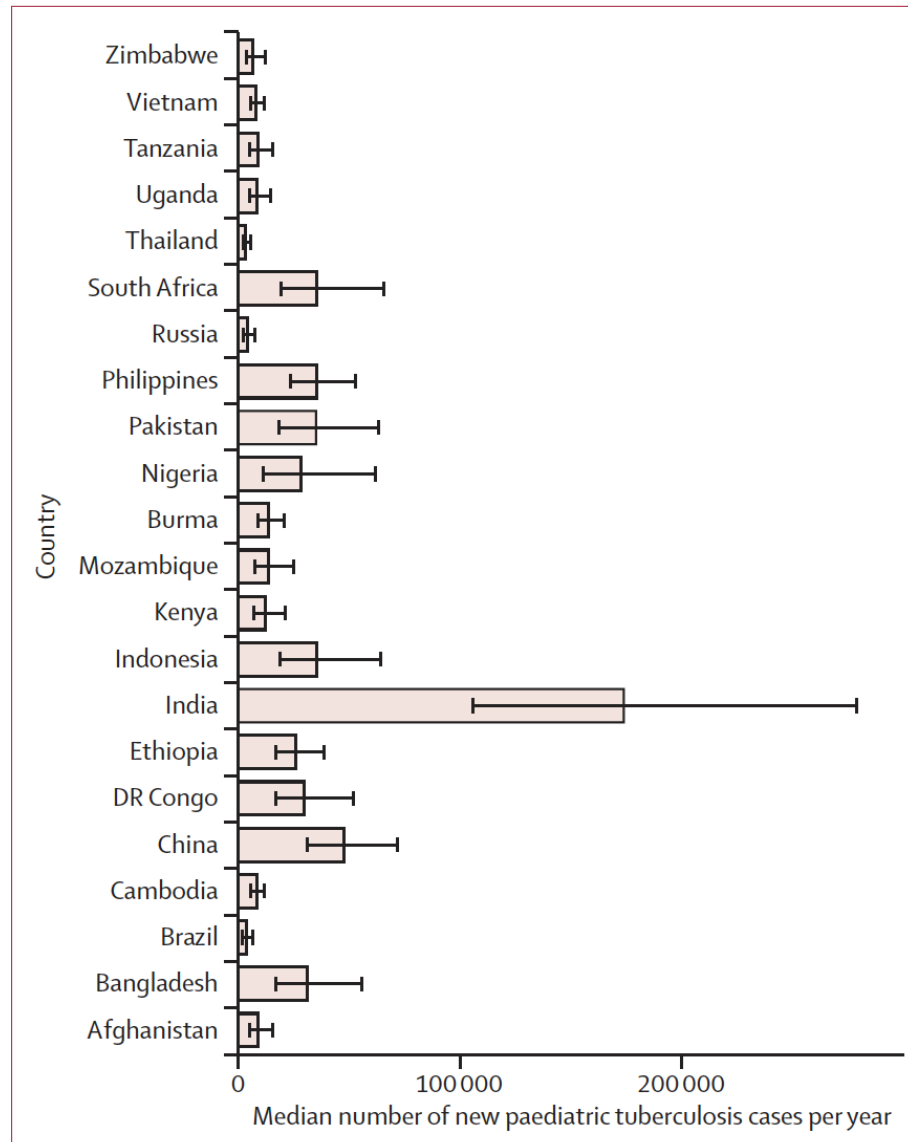
Figure 4: Numbers of new paediatric tuberculosis cases in 2010, by country

Dodd et al, *The Lancet Global Health* 2014

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Global Pediatric Mortality
Due to Tuberculosis
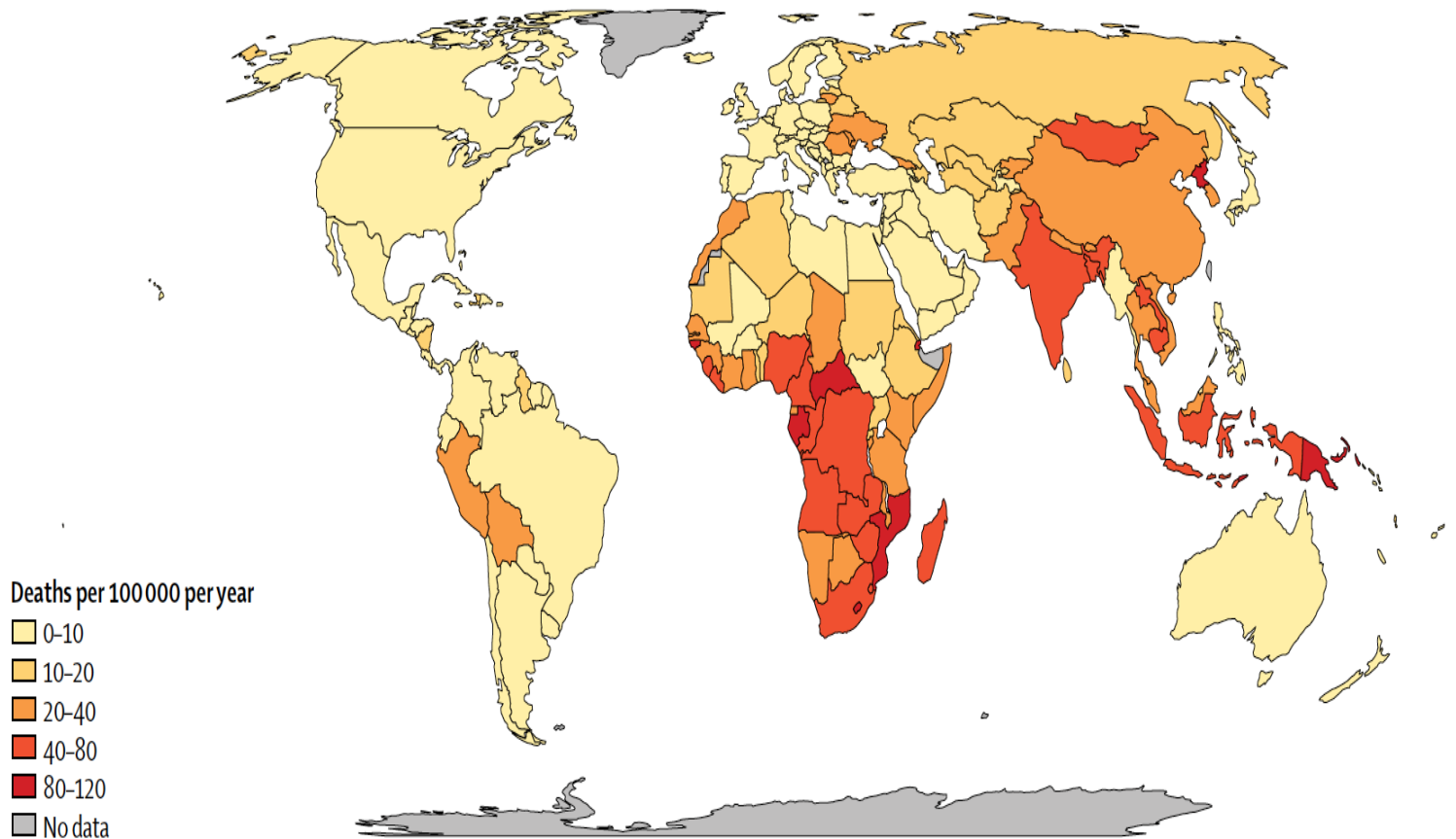
Enthusiasm, Energy, Effort

EDITORIAL

Children with TB: neglected no more . . . .

NOVEMBER 20TH 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.[6] 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

Counting children with tuberculosis: why numbers matter

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

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) in countries that have high rates of child mortality.[1] The

death and not contributory causes to WHO, vital registration data cannot be used to estimate the number

Lancet 2014; 383: 1605–07

Reid and Goosby, *IJTLD,* 2016
Seddon et al, *IJTLD,* 2015
Graham et al, Lancet, 2014

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What Parameters are We Working With?

- Our understanding of pediatric tuberculosis lags behind adult tuberculosis

- Some of our best data are old

Old Tuberculosis Literature is Rich

Manifestation-time of Primary Tuberculosis after infection.

Wallgren, *Tubercle,* 1948

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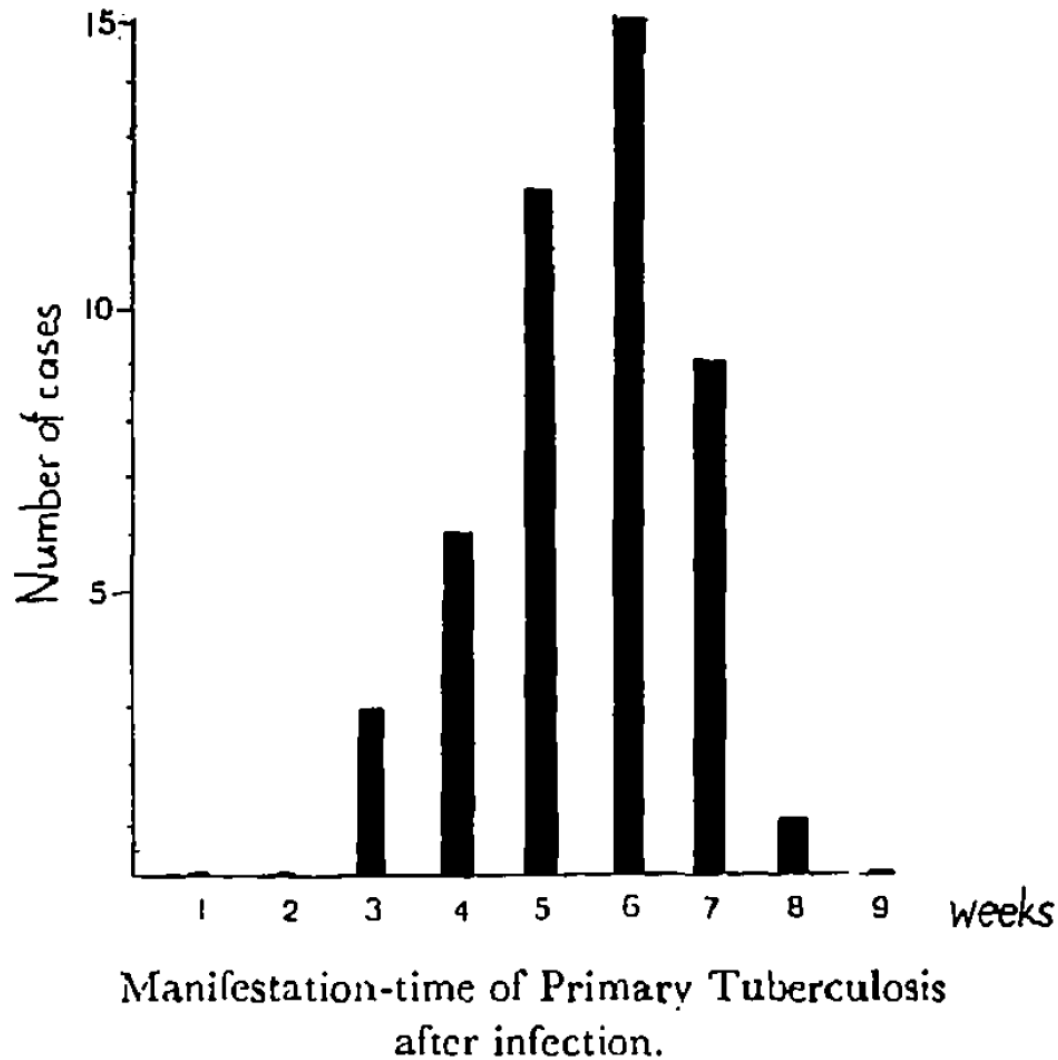
Old Tuberculosis Literature is Rich

TABLE 25
RISK OF CONTACTS DEVELOPING TUBERCULOSIS DURING FIRST YEAR AFTER DIAGNOSIS OF INDEX CASE, BY AGE AND INITIAL INFECTION STATUS

Initial Characteristic	Population Receiving Placebo	Cases				Total Rate per 1,000
		Total	Pulmonary	Extra-pulmonary	Primary	
Total...........................	12,594	107	62	16	29	8.5
Age in years						
Less than 5........................	2,174	28	—	7	21	12.9
5–9...............................	2,570	6	1	—	5	2.3
10–14.............................	2,216	10	4	4	2	4.5
15–19.............................	1,262	17	15	1	1	13.5
20–24.............................	651	9	9	—	—	13.8
25–29.............................	549	8	6	2	—	14.6
30–34.............................	588	7	7	—	—	11.9
35–39.............................	553	6	6	—	—	10.8
40–44.............................	468	6	6	—	—	12.8
45 or more........................	1,563	10	8	2	—	6.4
Infection status*.................						
Tuberculin reaction (mm.)						
Less than 5......................	6,496	32	10	6	16	4.9
5–9.............................	1,445	12	3	4	5	8.3
10–14...........................	2,240	23	18	2	3	10.3
15–19...........................	1,280	16	12	—	4	12.5
20 or more......................	801	16	11	4	1	20.0
Abnormal roentgenogram..........	308	8	8	—	—	26.0
Total infected†................	6,074	75	52	10	13	12.3

* Excludes 24 persons whose initial infection status was not established.
† Includes contacts with tuberculin reactions of 5 mm. or more and those with abnormal roentgenograms.

Ferebee et al, *Am Rev Respir Dis*, 1962

Risk of Pediatric Tuberculosis Progression After Primary Infection

Age at primary infection	Immune-competent children (dominant disease entity indicated in brackets)	Risk of disease following primary infection %
<1 year	No disease	50
	Pulmonary disease (Gnon focus, lymph node, or bronchial)	30–40
	TBM or miliary disease	10–20
1–2 years	No disease	70–80
	Pulmonary disease (Gnon focus, lymph node, or bronchial)	10–10
	TBM or miliary disease	2–5
2–5 years	No disease	95
	Pulmonary disease (lymph node, or bronchial)	5
	TBM or miliary disease	0.5
5–10 years	No disease	98
	Pulmonary disease (lymph node, bronchial, effusion or adult-type)	2
	TBM or miliary disease	<0.5
>10 years	No disease	80–90
	Pulmonary disease (effusion or adult-type)	10–20
	TBM or miliary disease	<0.5

TBM = tuberculous meningitis.

Marais et al IJTLD, 2004

The Epidemic Has Changed

- HIV
- BCG vaccination coverage
- Preventive therapy
- Drug-resistant tuberculosis
- Disease treatment
- Diagnostics have improved

Need for New Parameters

- "Risks of progression were based on reports from the early 20th century in white people and might not fully apply to populations that we assessed, which can differ systematically in factors affecting risks of progression…"
    -- Dodd et al, 2014

- "Studies from the pre-treatment era were done in Canada, Europe, and the USA, which might limit the generalizability of their finding to untreated populations today as a result of geographical and temporal differences in socioeconomic conditions, nutrition, burden of disease, and other factors…"
    -- Jenkins et al, 2017

Looking Forward for Modelers

- We'd love to hear from modelers about what else they would like to know

- Collaborations

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Wellcome Centre for Clinical Tropical Medicine, Imperial College London; Universidad Peruana Cayetano Heredia, Department of Public Health, Unit of General Epidemiology and Disease Control, Institute of Tropical Medicine, Antwerp, Belgium; Bacterial Diseases Programme, Medical Research Council (MRC) Laboratories, Banjul, The Gambia; Boston University, Section of Infectious Diseases, Dept of Medicine, Boston Medical Center and Boston University School of Medicine; Núcleo de Doenças Infecciosas, Universidade Federal do Espírito Santo, Vitória, Brazil; Department of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, Hsin-Chu, Taiwan; National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei,Taiwan,; Centers for Disease Control, Department of Health, Taipei, Taiwan; Department of Pediatrics, Sardjito Hospital and Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia; Centre for International Child Health, University of Melbourne Department of Paediatrics; Desmond Tutu Tuberculosis Centre, Tygerberg, South Africa; University Research Co. Branch in Georgia, USAID Georgia TB Prevention Project, Tbilisi, Georgia; Respiratory Diseases Center, Fukujuji Hospital, Kiyose City, Japan; Division of Clinical Microbiology and Molecular Medicine, All India Institute of Medical Sciences, New Delhi, India; Unidad de Investigacion en Tuberculosis de Barcelona del Servicio de Epidemiolog´ıa de la Agencia de Salud Publica de Barcelona, Barcelona, Spain; Faculty of Health Sciences, Federal University of Grande Dourados, Brazil; Swiss Lung Association, Berne, Switzerland; Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; Victorian Tuberculosis Program, Melbourne Health, Melbourne, Victoria, Australia; Center for Disease Control and Prevention of Jiangsu Province, Department of Chronic Communicable Disease; Grupo de Epidemiologıa, Universidad de Antioquia, Medellın, Colombia; Department of Infectious Diseases, Public Health Service, Amsterdam, The Netherlands; Department of Internal Medicine, All India Institute of Medical Sciences, New Delhi, India; Institut de Recherche pour le Developpement, Programme Tuberculose, Dakar, Senegal; Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, New York

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Thank you for listening
Questions?

Leonardo Martinez
Email: Leomarti@Stanford.edu