Reflections on Progress in Pediatric TB

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

Childhood Tuberculosis: What Are The Yellow Canaries Trying To Tell Us?

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Disclosures

Dr. Starke has no financial relationships to disclose.

Dr. Starke will not discuss off-label uses of medications.

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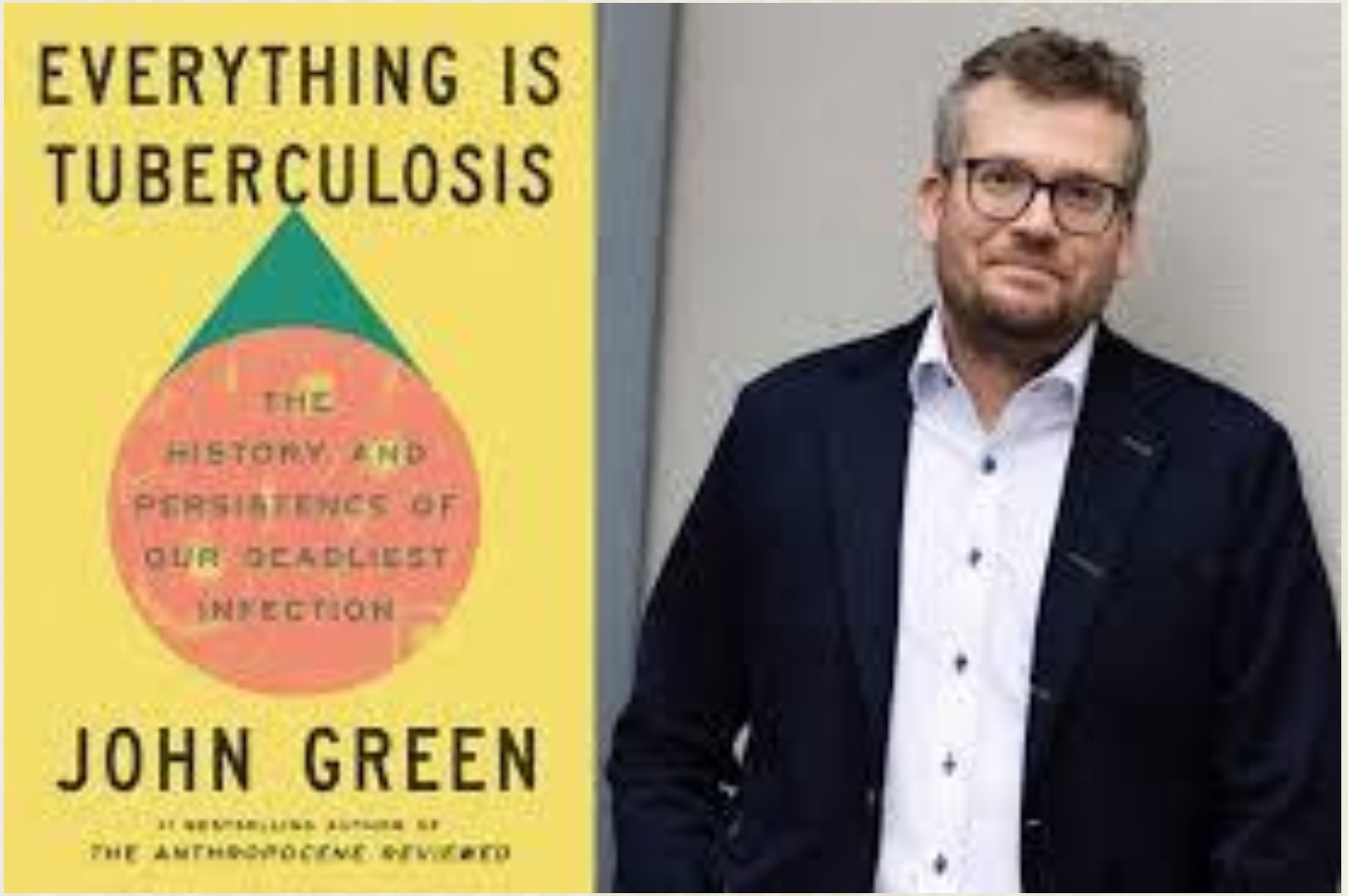
A Really Good Read



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The Most Important Thing

The detection, treatment, prevention and elimination of child tuberculosis will depend ABSOLUTELY on the maintenance of an effective and dedicated public health system!

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What is a Yellow Canary?

- The yellow canary (*Crithagra flaviventris*) is a small passerine bird in the true finch family, known for it's singing.
- A "yellow canary in a mine" means something that serves as an early warning sign of danger, like a canary bird that miners used to bring into coal mines to detect poisonous gases.

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Things I Heard From WHO Executives in the 1990s

- “Getting rid of childhood tuberculosis is easy; just get rid of adult TB!”
- “Childhood tuberculosis is a religion, and the pediatricians are the crusaders.”
- “We will do research on childhood tuberculosis when you get us the money to do it”.

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Pathophysiology of tuberculosis

- We often conceptualize TB in 3 stages: exposure, infection and disease
- However, in reality TB is a spectrum disorder that has multiple presentations on a continuum
- Childhood TB is the best example of this, and is fundamentally different from adult TB

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Pathophysiology of tuberculosis

Childhood TB is fundamentally different from adult TB

- Paucibacillary – fewer organisms to kill
- Inflammatory response is important and often harmful
- Fewer symptoms, but…
- Can develop even life-threatening disease much faster
- Totally different chest radiograph findings
- More extrapulmonary disease, esp. meningitis
- Fewer adverse reactions to TB meds

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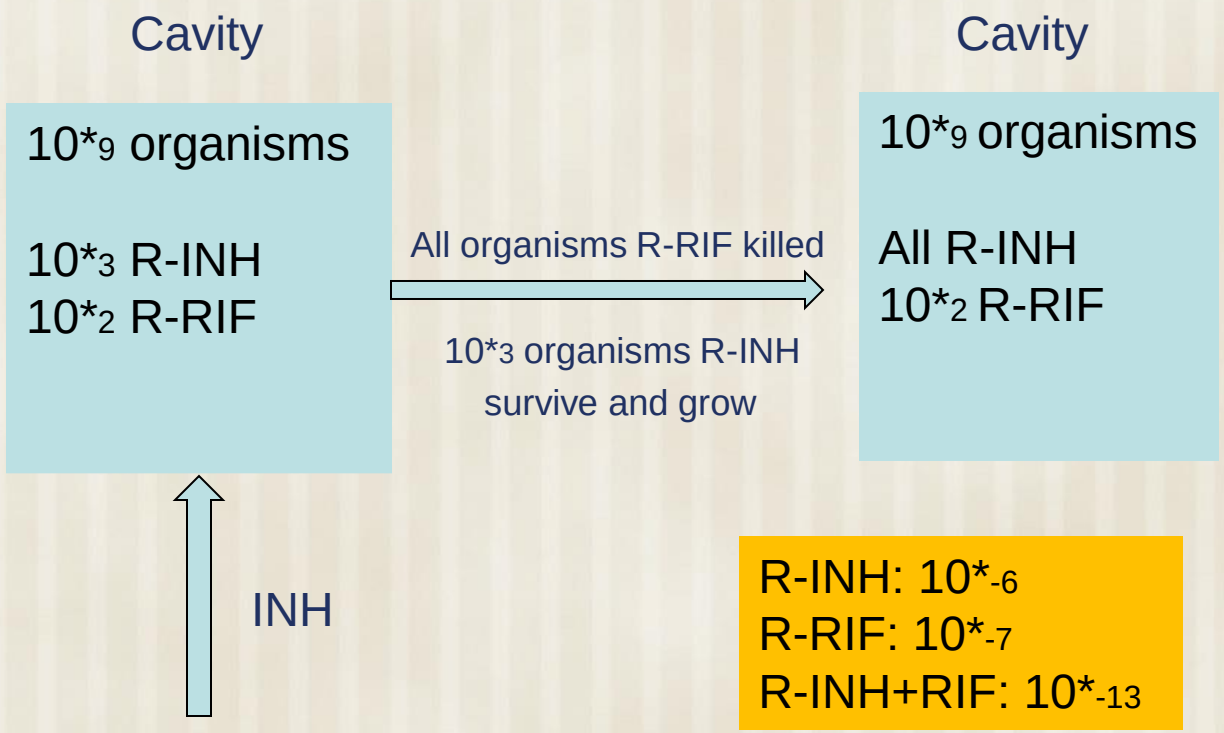
Preventing Drug Resistance in TB



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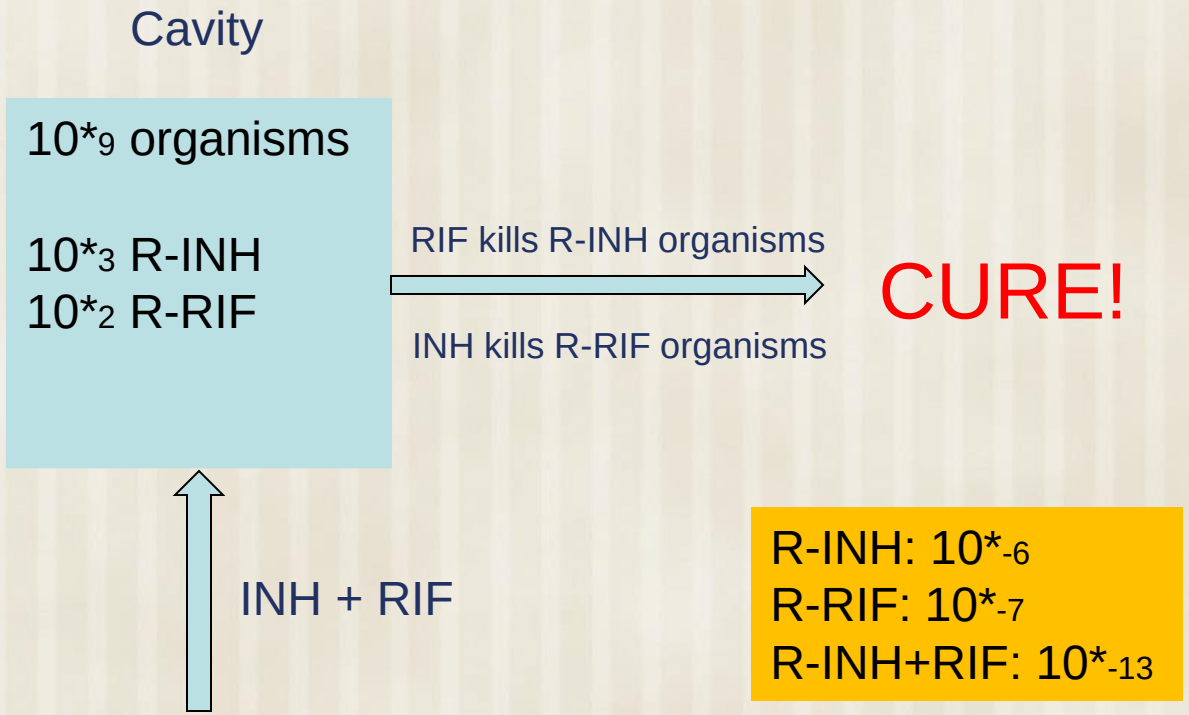
Preventing Drug Resistance in TB



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So, Where Does Childhood TB Disease Fit Into All This

- The burden of organisms is likely much lower than in adults, but this has never been measured – is it closer to TB disease in adults, or closer to TB infection?
- And when does TB infection turn into TB disease:

  Symptoms? Chest X-ray findings?

  Burden of organisms? A spectrum of findings!
- Much of what we see on the chest X-ray – and likely some of the symptoms - comes from the immunological response to the organism, not the burden of organisms

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How We Conceived TB in 1983

[Actually, the word “latent” wasn’t added until the 1990s]

Classic Concept of Tuberculosis Clinical States

Latent TB Infection	Active TB Disease
• Positive TST or IGRA	• Abnormal CXR and/or Symptoms
• Normal CXR	• Positive Culture
• No symptoms	• Positive molecular test (Xpert) unless prior disease then may be a marker of prior disease
• Non-infectious	• Infectious

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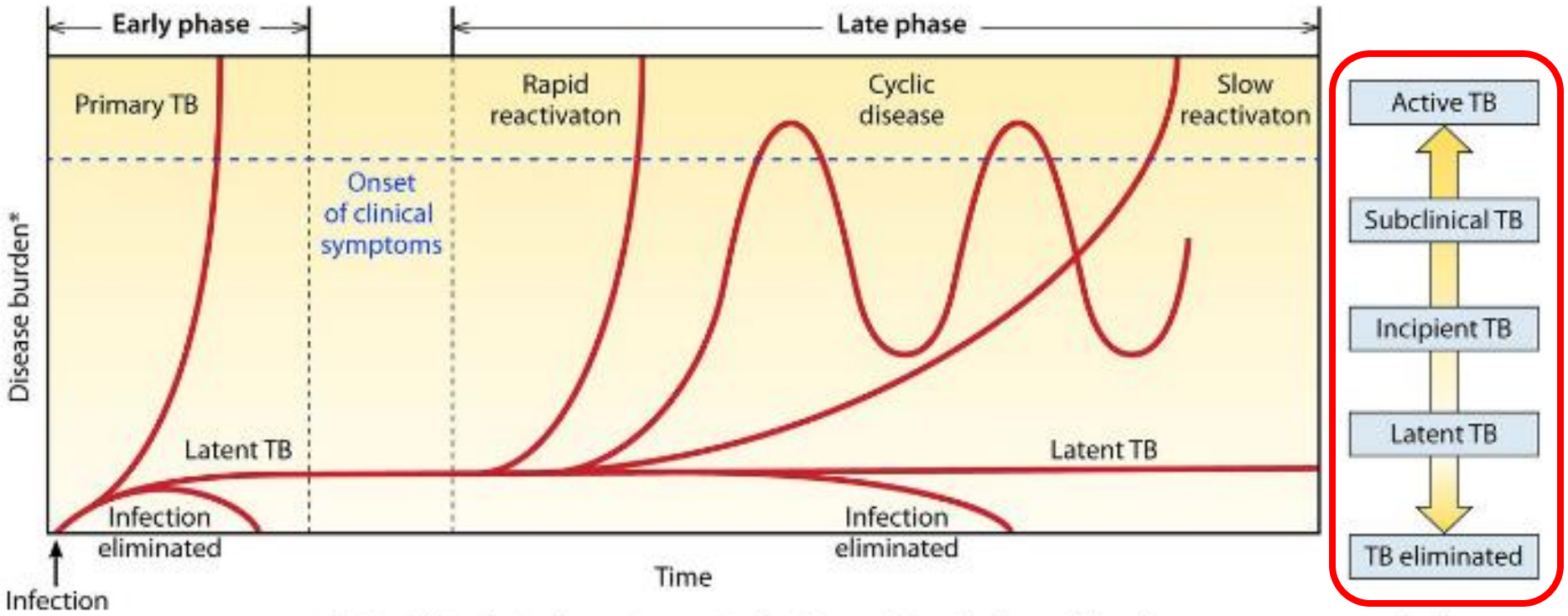
Drain et al. Clin Microbiol Rev 2018; https://doi.org/10.1128/CMR.00021-18



*Rising TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

FIG 1 Pathways of tuberculosis disease progression. After initial exposure, M. tuberculosis may be eliminated by the host immune response, persist as a latent infection, or progress to primary active disease. Following the establishment of latent infection, disease may persist in a latent form, naturally progress in a slow or rapid fashion to active tuberculosis, or cycle through incipient and subclinical states before developing into symptomatic disease or eventual disease resolution. Although not all possibilities for regression of disease burden are depicted, spontaneous recovery may occur in any of these clinical trajectories.

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Why getting all the data is so important

- Prior to 2012, the WHO gave virtually no estimates on the number of childhood tuberculosis cases – reported mostly microbiologically confirmed cases
- Child survival meeting in 2012 – “We know childhood TB is a problem, but how can we help if you can’t even tell us how big the problem is?”

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Why Are Obtaining Accurate Measures of Childhood TB So Important?

- Allocation of resources within an NTP
- Allocation of resources along the health care spectrum: community workers and programs, clinics, hospitals
- Awareness among pediatric providers
- Recognition of the issue among child survival experts and planners
- Approaching and interesting funders for both grants and programs
- Attracting the attention of researchers
- Protect the human rights of children and families

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ESTIMATES OF CHILDHOOD TUBERCULOSIS

WHO, 2013: 530,000 annual cases, 74,000 deaths in non-HIV-infected children [no estimate for HIV-infected]

- Actual notifications to WHO were 301,233

Jenkins *et al* 2014: Modeling study estimate – 999,792 cases

Dodd *et al* 2014: Modeling study estimates in 22 high burden countries: 650,977 cases; 7,591,759 children annually infected; 53,234,854 total infected children

WHO, 2023: 1.3 million annual cases; 191,000 deaths

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Children can predict the future

- Children who develop TB disease usually do so within 6-9 months of infection, often sooner
- Therefore, childhood disease is a measure of recent transmission of the organism, and a predictor of current **AND** future disease in people of all ages
- Analysis of childhood tuberculosis is a key quality indicator of a tuberculosis program

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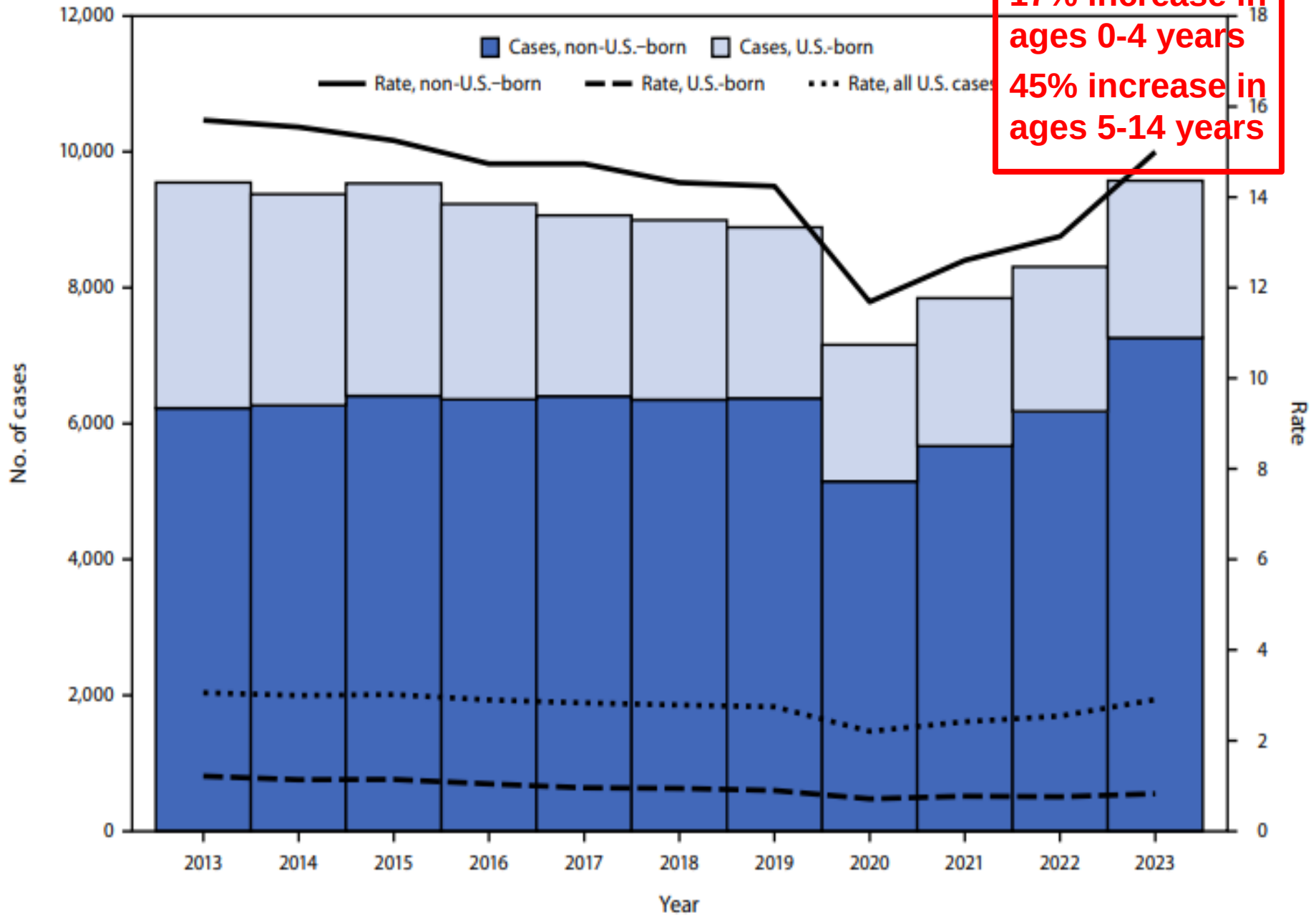
FIGURE. Annual number* and rate† of cases of tuberculosis disease, by birth origin§ — United States, 2013–2023



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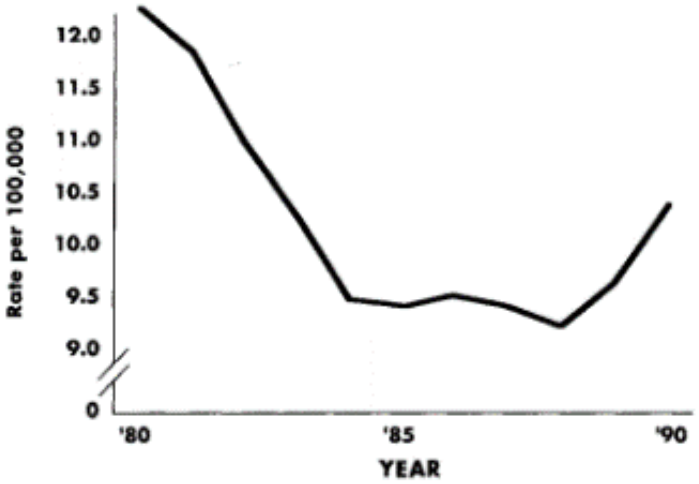
Why Did TB in Children Resurge in the United States in the 1990s?



1. **HIV/AIDS** – mostly HIV-uninfected children who got TB infection from adults living with HIV who developed pulmonary TB
2. **Congregate Settings** – schools, churches
3. **Immigration** – Prior to 2009, no testing for children < 15 yrs of age
4. **Poor Tuberculosis Control** – declined budgets, loss of expertise, lack of emphasis on prevention

0-14 years	2020 – 318 cases	2023 – 466 cases [⬆ 47%]
	1987 – 1,178 cases	1992 – 1,707 cases [⬆ 45%]
All other ages	2020 – 7,174 cases	2023 – 9,167 cases [⬆ 34%]
	1987 – 22,517 cases	1992 – 26,673 cases [⬆ 19%]

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The importance of contact tracing

- Identifies recently exposed and infected children

1) Opportunity to prevent establishment of infection
2) Prevent infection from progressing to disease
3) Detect early disease – easier to treat & cure
4) Prevent dissemination, hospitalization

- Only opportunity to determine drug susceptibility for:

1) 50% to 70% of children with disease
2) 100% of children with infection

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Ikeda et al. Epidemiology and clinical characteristics of childhood TB identified using active and passive case finding. Int J Tuberc Lung Dis 2021; 25(6):475-482.

- Retrospective cohort study of children in Houston
- 178 patients: 99 PCF, 79 ACF
- Children identified using PCF were older (mean 8.9 vs. 6.1 years, P = 0.003), more often non-US-born (OR 2.29), had more extrapulmonary disease (44.4% vs. 3.8%, OR 20.27) and severe intrathoracic findings (39.4% vs. 10.1%).
- Children identified using ACF were often asymptomatic, had isolated hilar/mediastinal adenopathy, but had more availability of drug susceptibility data from a link to a source case

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There is no substitute for trained, dedicated public health workers who understand tuberculosis

The Union | 52ND WORLD CONFERENCE ON LUNG HEALTH 19—22 OCTOBER 2021

E-Poster No. 2143

COVID-19 Impact on US Tuberculosis Programs: National Tuberculosis Controller Association Survey

Donna Wegener[1], Katelynne Gardner Toren[2], Evan Timme[3], Shu-Hua Wang[4]
[1] TB Association, [2]Seattle & King County TB Control Program, [3]Arizona TB Program, [4]The Ohio State

Background

- Early in the pandemic, efforts made to capture the effects of COVID-19 on tuberculosis (TB) elimination efforts in the US showed that resources were being diverted from central TB activities.
- The goal of this National Tuberculosis Control Association (NTCA) survey was to assess and detail the impact of COVID-19 on US TB programs, including early evidence of TB-COVID-19 Co-infections, identify strategies for addressing COVID-19 impact on TB programs, and to evaluate potential need for additional resources to TB programs.

Method

- The survey was developed by the NTCA Survey Committee and launched between January-March 2021.
- The survey was distributed to all NTCA members representing Centers for Disease Control and Prevention Cooperative Agreement programs and other local health departments.
- The survey was also promoted by the National Association of County and City Health Officials via an e-announcement to members.
- One survey was requested per jurisdiction.

Results

- A total of 46 State/ Territory/ District programs and 96 local programs (county, city, and regional levels) responded.
- Select changes in TB activities are shown in Figure 1:
  - Decreased TB program staffing and clinic hours/appointments
  - Decreased TB reporting, contact investigations and diagnostic work-ups.
  - Increased use of electronic directly observed therapy (eDOT) and telemedicine visits.

Figure 1. Changes in TB Activities due to COVID-19

		Reduced	No Change	Increased	n
Staffing and service changes	TB program staff time devoted to TB activities	120	16	1	137
	TB clinic hours	76	31	4	111
	TB clinic appointments	92	22	2	116
	Proportion of B notifications known to have arrived being evaluated				
	Proportion of close contacts being evaluated	42	70	3	115
	LTBI treatment initiation	84	43	4	131
Service delivery changes	Treatment via in-person DOT for patients with presumptive or confirmed TB	78	38	4	120
	The use of telemedicine for clinic visits	3	22	65	90
	The use of electronic DOT (eDOT)	6	26	80	112
Diagnosis and reporting change	Reporting of presumptive TB from providers	61	50	2	113
	Collection or receipt of sputum specimens to the public health laboratory for MTB testing	45	56	0	101

Conclusions

- The survey revealed the need for increased qualified staff and/or time dedicated to TB including the need for flexible and sustained funding.
- The increased use of electronic platforms has led to efforts to sustain and expand these programs and to improve reimbursement for these activities.
- Delayed and missed diagnosis required additional efforts to educate health care providers to "Think TB".
- It is important to invest in TB programs now so that we can respond to the depletion of resources and staffing and build out a solid infrastructure and knowledge base.

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Why an effective vaccine is needed

- This is an easy one…
- BCG vaccines have been given to 4-5 billion individuals
- We still have 11 million annual cases of TB in the world
- The mortality rate of childhood tuberculosis is about 20%, the same as it was in the pre-chemotherapy era [despite continued widespread use of BCG vaccines in high burden countries]
- BCG vaccines prevent some future contagious TB cases, but not enough to eradicate the disease
- No pathogen transmitted person-to-person through the air has ever been eradicated without an effective vaccine

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The need for adequate research

- Things were pretty dormant prior to the 2010s, but now…
- Supported switch from the TST to the IGRAs with gradual decrease in recommended age [now all children]
- Supported decrease in time of treatment for non-severe TB from 6 to 4 months
- Supported use of 3HP in children > 2 years of age
- Supported all-oral regimens for treating MDR- and XDR-TB in children

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The need for adequate research

Ongoing research needs:

- Better diagnostic testing for TB disease – the Holy Grail
- A better vaccine – the Holier Grail
- Earlier testing of new TB drugs in adolescents and children
- Improvement and availability or pediatric dosing forms of TB meds
- Long-term post-disease effects on children and adolescents

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The importance of national and international collaboration

- European Center for Disease Prevention and Control meeting in 2013
- Child & Adolescent Working Group of the International Union Against Tuberculosis and Lung Disease
- Lessons from pediatric oncology research
- Lessons from pediatric HIV research
- IMPAACT
- Pediatric Tuberculosis Network European Trials Group

Importance of Childhood TB Research in Low Burden Countries

- Difficult to do RCTs of treatment of TB disease because of low numbers of cases [except in large networks]
- Newer introduction of technological advancements [sometimes]
- Lack of background “noise” makes manner and modes of transmission easier to trace
- Major emphasis on prevention: finding and treating TB infection and exposure in children and adolescents
- Lack of BCG vaccination allows for better and more precise analyses of some research results

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Parents of children with tuberculosis are amazing!

I am amazed at what the parents of young children have to go through to ensure their child is adequately treated:

- Agreeing to give exposed children medication when their physical exam and CXRs are normal, the IGRA is negative and they have no symptoms
- Giving 6 month olds medications that were meant for adults
- Tolerating treating their child for 6-9 months
- Dealing with stigma [yes, it still exists]

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Adolescents have slipped through the cracks

- An example: The trial of the 4-month regimen for pulmonary TB using INH, RFP, PZA and Moxi had 2343 subjects, had only 63 adolescents ages 12-17 years split among three groups, yet the regimen was approved for use in much of this age group
- Chiang et al. Caring for adolescents and young adults with tuberculosis or at risk of tuberculosis: Consensus statement from an international expert panel. *J Adolesc Health* 2023;72:323-331.
- Chiang et al. Identifying adolescents at risk for suboptimal adherence to tuberculosis treatment: A prospective cohort study. *PLoS Glob Public Health* 2024;4(2):e0002918. doi: 10.1371/journal.pgph.0002918.
- Chiang et al. Factors driving adolescent tuberculosis incidence by age and sex in 30 high-tuberculosis burden countries: a mathematical modelling study. BMJ Glob Health 2025;10:e015368. doi:10.1136/bmjgh-2024 015368

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There is still so much we don't know

- Why some infected children get sick and others don't
- Why children ages 5-11 years are the "favored age"
- The long-term sequelae of pulmonary TB in children and adolescents
- How to get pharmaceutical companies to pay attention to children
- The mental health sequelae for a family of a TB diagnosis in a child

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The fight for human rights is essential

Opening Ceremony of The Union Annual Meeting, 2018

“Childhood Tuberculosis: At the Tipping Point”

- “While End TB has emphasized patient-centered care, for children this is not enough. For them, we need family-centered care, the consideration of the needs of the entire family when an adult is diagnosed with tuberculosis.”

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The fight for human rights is essential

"The tipping point will require the political will within the tuberculosis and child health communities, and governments, to devote the resources and energy that will be required if we are to reach our goal of tuberculosis elimination. In 2004, my friend and colleague Peter Donald stated, 'The time has come for the hidden epidemic of childhood tuberculosis to emerge from the shadow of adult tuberculosis and be seen as a neglected child health problem of considerable proportions in precisely those communities that do not have the resources to deal with it adequately'. These words remain true today, and we now have the means to do something about it. The question is: Do we have the will? Children have the same right as adults to benefit from tuberculosis care and research! It is time that we put these words into action, and the elimination of tuberculosis depends on it."

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Ten Truths About Childhood Tuberculosis

1. Adequate TB control for children requires a robust public health system.
2. We can prevent childhood TB with simple, inexpensive measures.
3. Childhood TB can be found earlier when it is easier to treat.
4. Finding and treating adults with TB is not sufficient for controlling childhood TB.
5. BCG vaccines alone cannot control childhood TB.

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Ten Truths About Childhood Tuberculosis

6. Some tests, like chest xray, are more important for children than adults.
7. Many adult TB cases arise from infection that occurred in childhood.
8. Childhood TB is a window into the effectiveness of tuberculosis control.
9. Many children with TB are still being treated with medications designed for adults.
10. Childhood TB is a neglected disease in most of the world.

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My Benediction

My career has been bookended by the pandemics of childhood HIV and SARS-CoV-2, while the pandemic of childhood tuberculosis has kept rolling along, hiding in plain sight. Unfortunately, COVID likely has set progress back by many years. Children are at the forefront of this millennia-old pandemic, and the TB pandemic will continue until we devote all the necessary resources to children, as we hopefully will do to adults. Fortunately, some really smart and dedicated young people are hard at work on all this!

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The Most Important Thing

The detection, treatment, prevention and elimination of child tuberculosis will depend ABSOLUTELY on the maintenance of an effective and dedicated public health system!

If the public health system crumbles, we will have a resurgence of childhood TB, and children and adolescents will die needlessly.

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