Pediatric Tuberculosis Transmission and Pathogenesis/ Testing and Evaluation of Child Contacts

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October 26, 2022

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Disclosures

- I have no relevant financial conflicts of interest

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Agenda

Part I –
- **Epidemiology**
- **Significance of pediatric TB**
- **Pathogenesis**

Dr. Campbell – TB testing, TB infection

Part II –
- Diagnostic challenges
- TB infection therapy, special considerations
- TB disease therapy
- Pandemic challenges
- Role of telehealth

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TB Epidemiology

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WHO, 2020 – TB disease
(est 1.7b w/ TB infection)

Table 2.1.1 Global and regional estimates of TB incidence, numbers (in thousands) and rates (per 100 000 population) in 2020

Low and high are the 5th and 95th percentiles of the uncertainty interval (UI).

		Number of cases (in thousands)						Rate per 100 000 population					
		Total			HIV-positive			Total			HIV-positive		
Region or country group	Population	Best estimate	Low	High	Best estimate	Low	High	Best estimate	Low	High	Best estimate	Low	High
African Region	1 120 000	2 460	2 190	2 750	579	497	668	220	195	245	24	19	28
Region of the Americas	1 020 000	291	270	314	29	26	31	29	26	31	9.9	8.8	11
South-East Asia Region	2 020 000	4 270	3 420	5 210	98	77	122	112	89	138	1.9	1.3	2.8
European Region	933 000	231	201	264	29	22	36	25	22	28	12	9.2	16
Eastern Mediterranean Region	731 000	821	649	1 010	16	11	21	211	169	258	2.3	1.7	3.1
Western Pacific Region	1 940 000	1 800	1 480	2 140	37	28	47	93	76	110	2.1	1.5	2.7
High TB burden countries	4 800 000	8 500	7 520	9 540	649	563	740	177	157	199	7.7	6.3	9.1
Global	**7 770 000**	**9 870**	**8 880**	**10 900**	**787**	**701**	**879**	**127**	**114**	**140**	**8.0**	**6.8**	**9.3**

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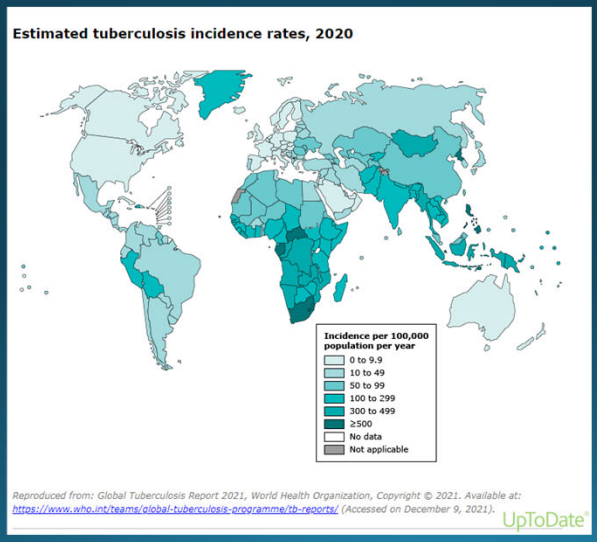
WHO, 2020 – TB Disease



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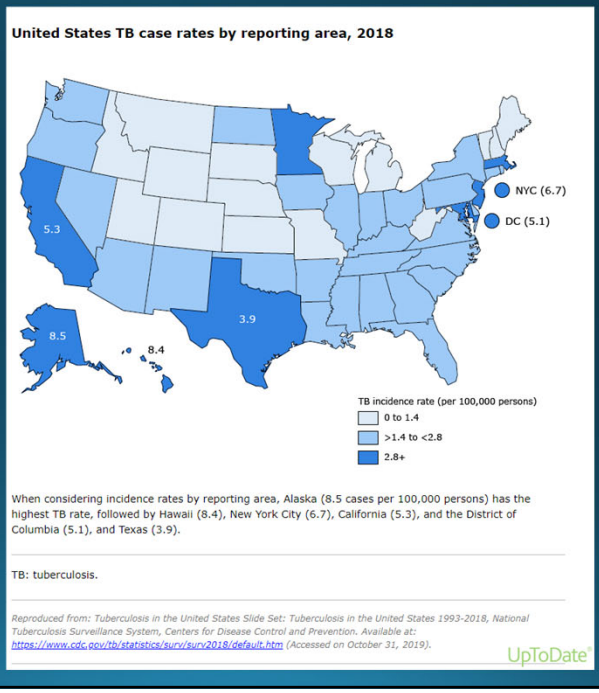
CDC, 2019



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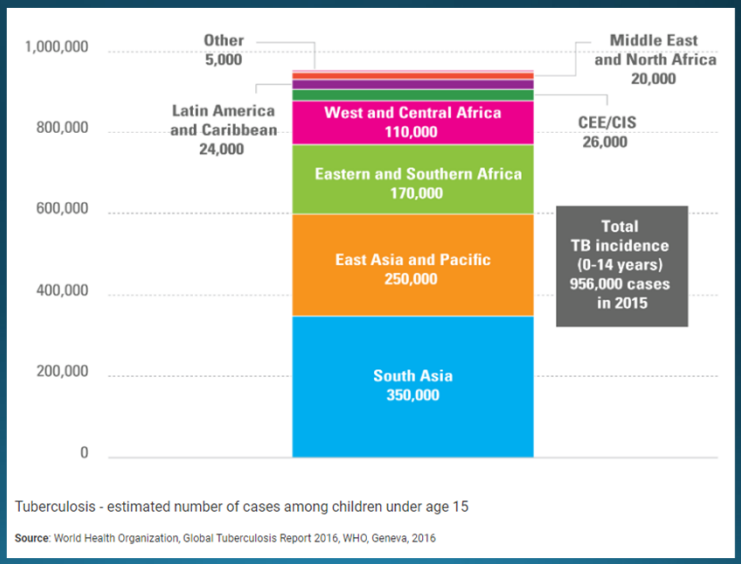
WHO, 2016



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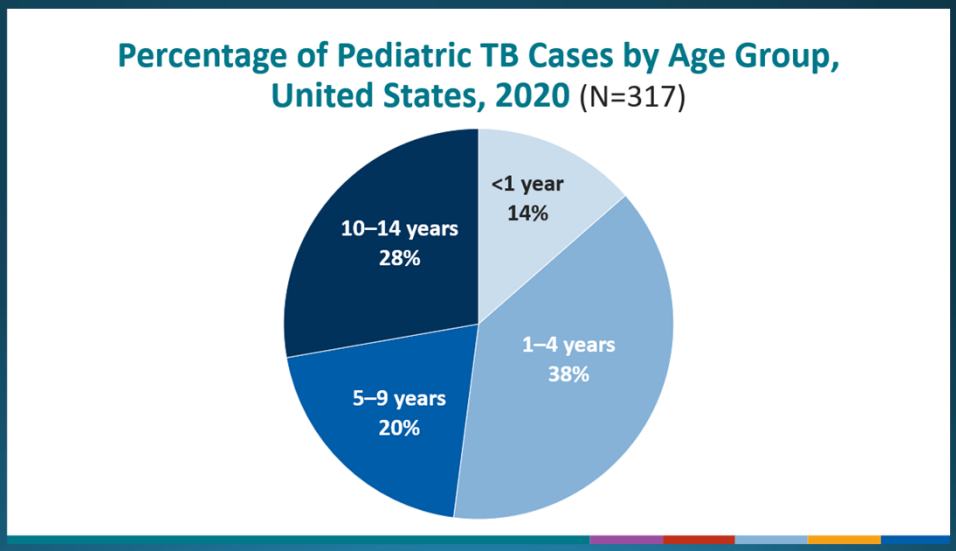
CDC, 2021



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Why is pediatric TB important?

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Significance of Tuberculosis in Children

- Personal Health: High rates of morbidity and mortality compared to adults
- Public Health: Diagnosis of TB infection or disease in a child is considered a "sentinel public health event" = recent transmission of TB

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Risk of Progression to TB Disease

- Immunocompetent adults
  - 5-10% lifetime risk of developing disease after infection
- Adults with TB infection and untreated HIV infection
  - 5-10% annual risk of developing disease
- Children and the risk of TB disease….

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Risk of Progression to TB Disease by Age

	Risk of disease following primary infection			Comments
	Disseminated tuberculosis/ tuberculosis meningitis	Pulmonary tuberculosis	No disease	
<1 years	10–20%	30–40%	50%	High rates of morbidity and mortality
1–2 years	2–5%	10–20%	75–80%	High rates of morbidity and mortality
2–5 years	0·5%	5%	95%	..
5–10 years	<0·5%	2%	98%	"Safe school years"
>10 years	<0·5%	10–20%	80–90%	Effusions or adult-type pulmonary disease

Adapted from reference 30.

Table 1: Risk of pulmonary and extrapulmonary disease in children following infection with *Mycobacterium tuberculosis*

Newton S, et al Lancet ID 2008 after Marais BJ, et al. Int J Tuberc Lung Dis 2004

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High-Risk Groups (Pediatrics)

- Age groups:
  - Infants and young children
  - Post-pubertal adolescents
- **Recent infection:**
  - **Highest risk in first 6 months after infection**
  - **Remains high for 2 years**

- Recent immigration
- Immunodeficiency:
  - HIV infection, Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition
  - Immunosuppressive drugs: prolonged or high-dose corticosteroid therapy, chemotherapy, tumor necrosis factor (TNF-alpha) antagonists

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BCG vaccine

- Many different formulations around the world
  - Most common BCG-Denmark, BCG-Japan, BCG-Russia
- Not given in US (availability for research, bladder cancer)
- NEONATAL vaccine
  - Prevents severe miliary and CNS TB disease in first year+ of life
- Other benefits (reduced mortality from other infectious causes)
- Variable impact on TB infection (interpretation of tests?)

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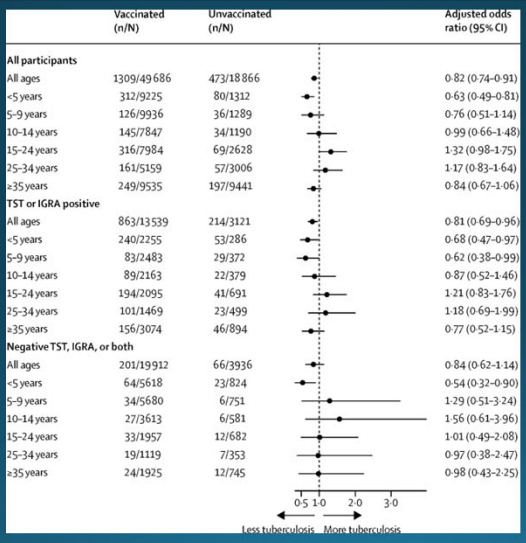
Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis



	Vaccinated (n/N)	Unvaccinated (n/N)	Adjusted odds ratio (95% CI)
All participants			
All ages	1309/49 686	473/18 866	0·82 (0·74–0·91)
<5 years	312/9225	80/1312	0·63 (0·49–0·81)
5–9 years	126/9936	36/1289	0·76 (0·51–1·14)
10–14 years	145/7847	34/1190	0·99 (0·66–1·48)
15–24 years	316/7984	69/2628	1·32 (0·98–1·75)
25–34 years	161/5159	57/3006	1·17 (0·83–1·64)
≥35 years	249/9535	197/9441	0·84 (0·67–1·06)
TST or IGRA positive			
All ages	863/13 539	214/3121	0·81 (0·69–0·96)
<5 years	240/2255	53/286	0·68 (0·47–0·97)
5–9 years	83/2483	29/372	0·62 (0·38–0·99)
10–14 years	89/2163	22/379	0·87 (0·52–1·46)
15–24 years	194/2095	41/691	1·21 (0·83–1·76)
25–34 years	101/1469	23/499	1·18 (0·69–1·99)
≥35 years	156/3074	46/894	0·77 (0·52–1·15)
Negative TST, IGRA, or both			
All ages	201/19 912	66/3936	0·84 (0·62–1·14)
<5 years	64/5618	23/824	0·54 (0·32–0·90)
5–9 years	34/5680	6/751	1·29 (0·51–3·24)
10–14 years	27/3613	6/581	1·56 (0·61–3·96)
15–24 years	33/1957	12/682	1·01 (0·49–2·08)
25–34 years	19/1119	7/353	0·97 (0·38–2·47)
≥35 years	24/1925	12/745	0·98 (0·43–2·25)

The Lancet Global Health 2022 10e1307-e1316DOI: (10.1016/S2214-109X(22)00283-2)

L. Martinez et al. 2022

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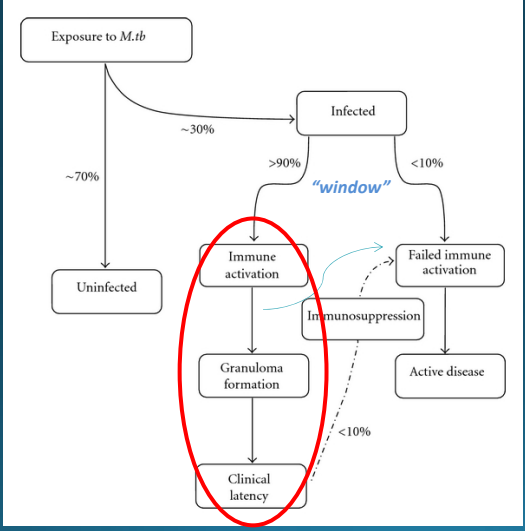
Pathogenesis



Adapted from: Shaler, CR, *et al.* Clin Dev Immunol. 2012

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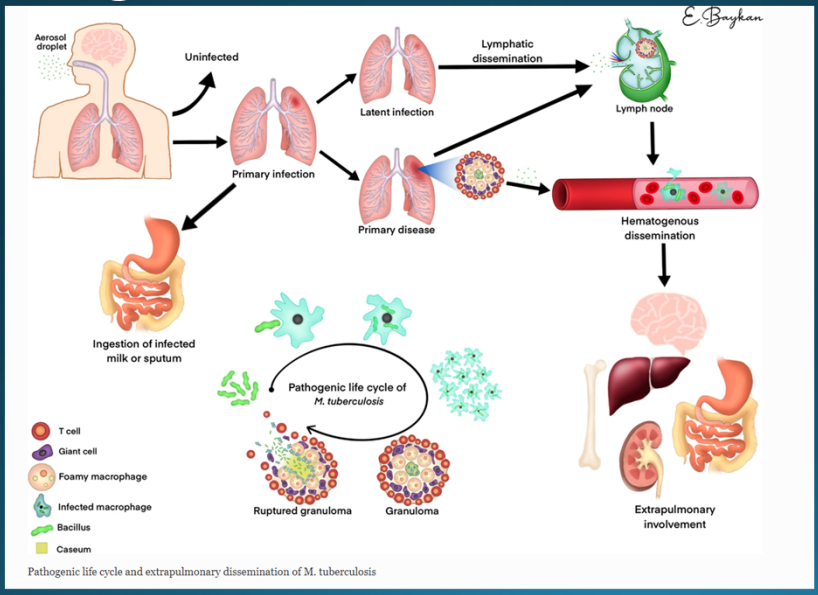
Pathogenesis



Baykan *et al. Insights Imaging* **13**, 39 (2022).

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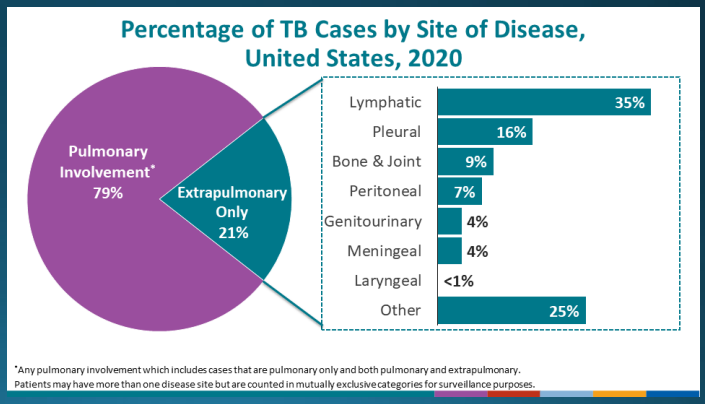
Extrapulmonary TB

Massachusetts Data (2021)

Clinical Presentation Primary site of disease	
Pulmonary	82 (54%)
Extra-pulmonary	46 (30%)
Both	23 (15%)

US Data (2010-20)



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Extrapulmonary TB

But remember much higher risk in youngest children

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End of Part I

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