What Can A Low-Burden TB Setting Contribute To Global Childhood TB Care and Prevention?

Jeffrey R. Starke, M.D.
Professor of Pediatrics
Baylor College of Medicine

Texas Children's Hospital

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Tuberculosis in Adults

Pulmonary TB in adults is diagnosed by:

- Sputum microscopy [60 – 70%]
- Sputum Xpert [75 – 85%]
- Sputum culture [85 – 95%]

- Therefore, the basis for counting adult cases of TB is microbiologic, detection of the organism
- Only ~10% of cases are extrapulmonary

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Tuberculosis in Children

Pulmonary TB in children is diagnosed by:

- Sputum microscopy [< 10%]
- Sputum Xpert [~15%]
- Sputum culture [~30%]

- Therefore, using microbiology to count cases misses most childhood cases
- Most children with pulmonary TB don't even produce sputum!
- 30% of cases are extrapulmonary!

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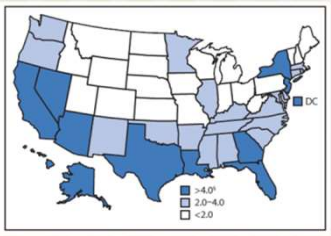
Some Aspects of TB Control for Children - Low Burden Countries



- Elimination of background “noise” – TB as a collection of outbreaks
- Value of contact tracing
- Value of reverse contact tracing [“Associate Investigation”]
- Identifying less common modes and locations of transmission
- Effectiveness of preventive chemotherapy
- Infectiousness of children with pulmonary TB

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Childhood TB Control Strategies in the U.S.

- Never used a BCG vaccine
- Slow, steady decline [~5%/Yr] until the mid-1980s when it recurred with a vengeance
- Strategy of universal periodic testing [TST] for TB infection began in the late 1950s and continued until the 1990s
- Universal testing replaced with screening for risk factors and testing for risk
- Heavy use of INH treatment for TB exposure and LTBI
- Specific recording and reporting of childhood TB cases – each case is a “sentinel event”

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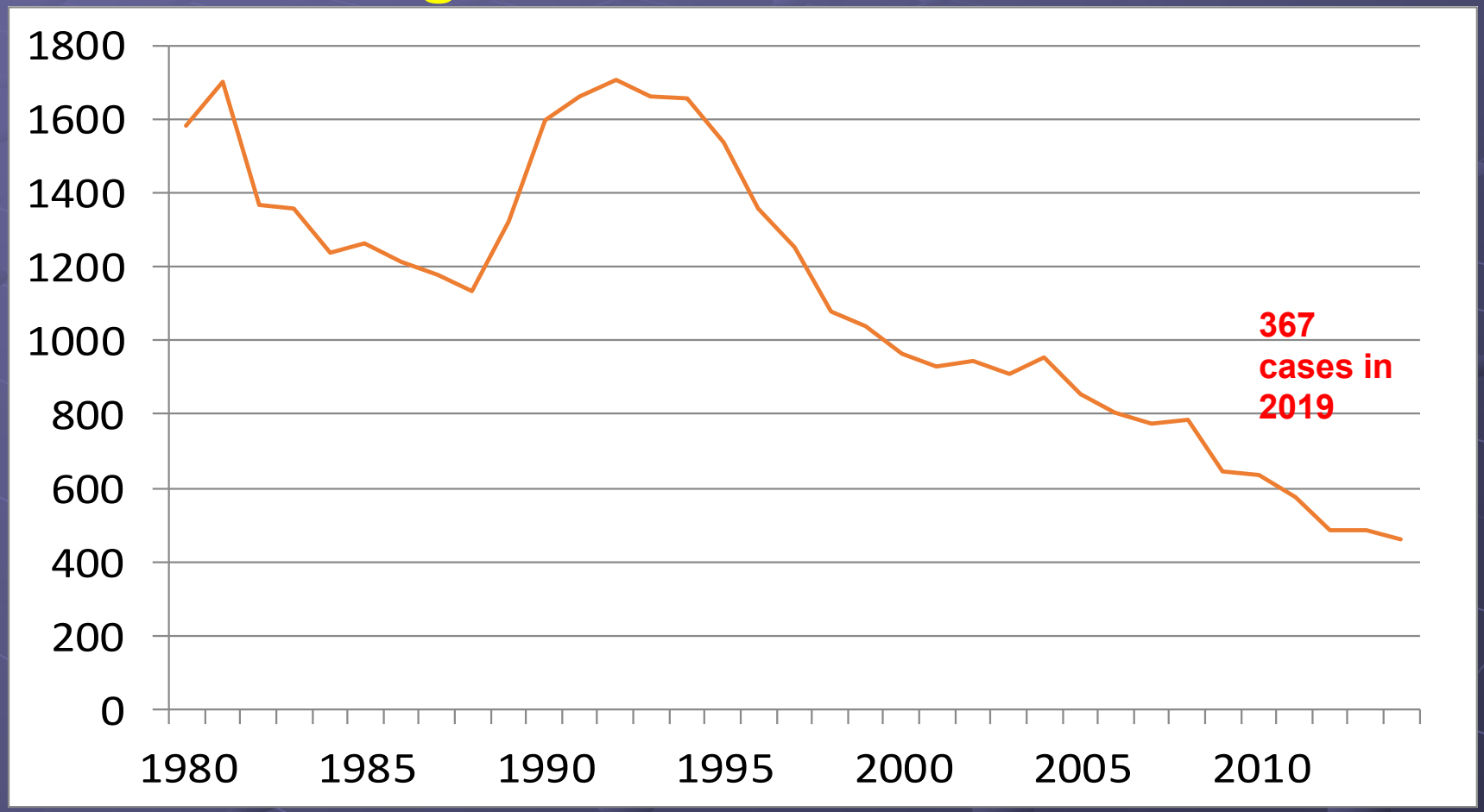
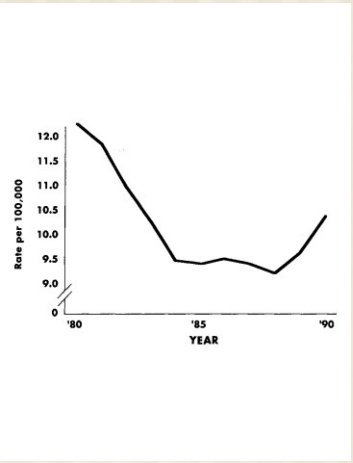
Tuberculosis Cases in Children 0-14 Years of Age, 1980-2016 – United States



Why Did TB in Children Resurge in the United States?



1. HIV/AIDS – mostly HIV-uninfected children who got TB infection from HIV-infected adults with pulmonary TB
2. Congregate Settings – schools, churches
3. Immigration – Prior to 2009, no testing for children < 15 yrs of age; now looking only for TB disease, not infection
4. Poor Tuberculosis Control – declined budgets, loss of expertise, lack of emphasis on prevention

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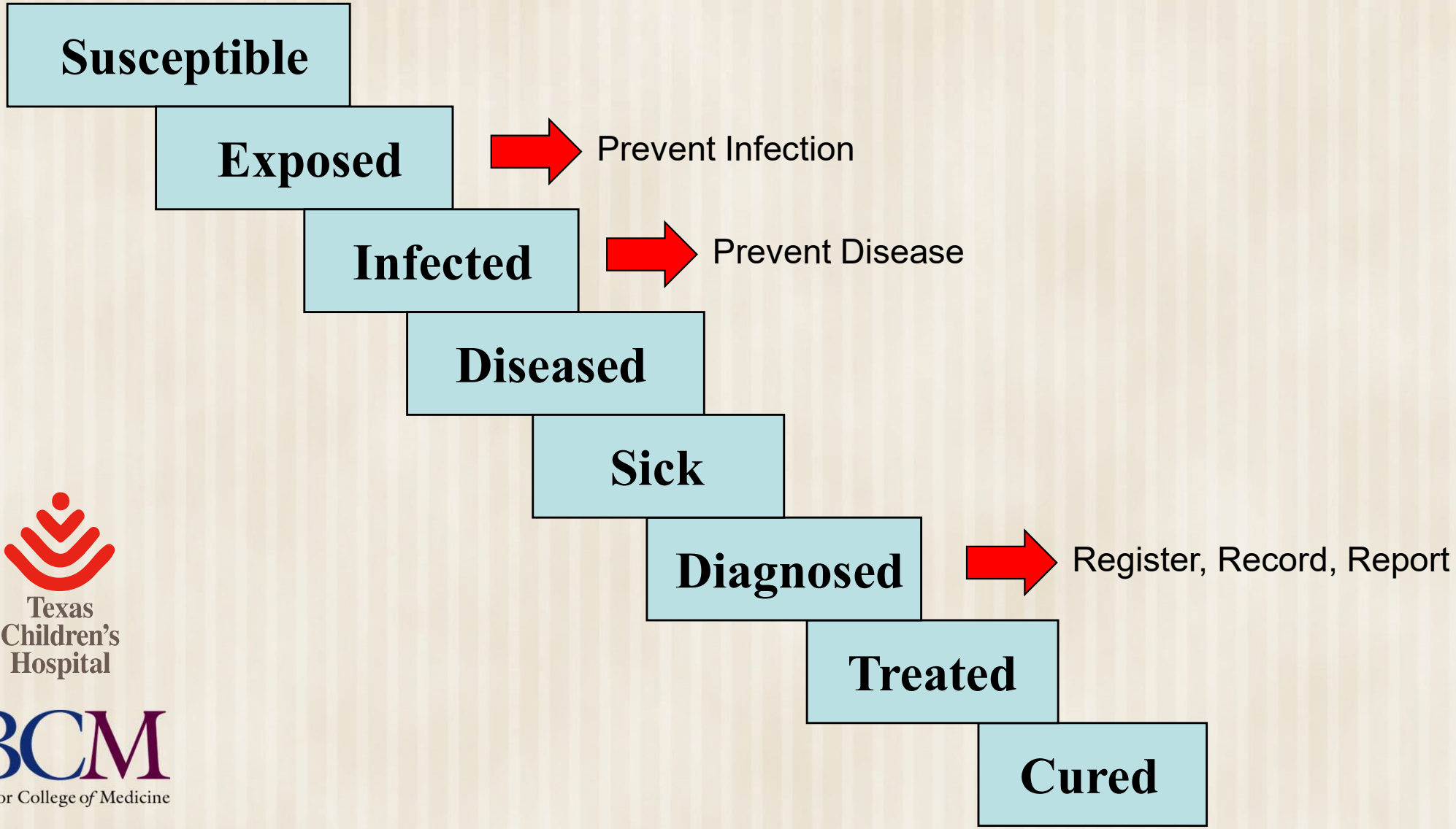
TRANSITIONS IN TUBERCULOSIS



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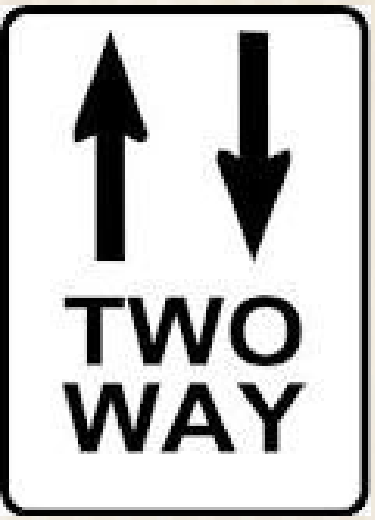

There are only two ways a child in a community can come to have TB infection:

1. Acquired within the community
   [Contact Tracing]
2. Acquired elsewhere and brought into a community
   [Screening for Risk]

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Katherine HK Hsu, M.D.

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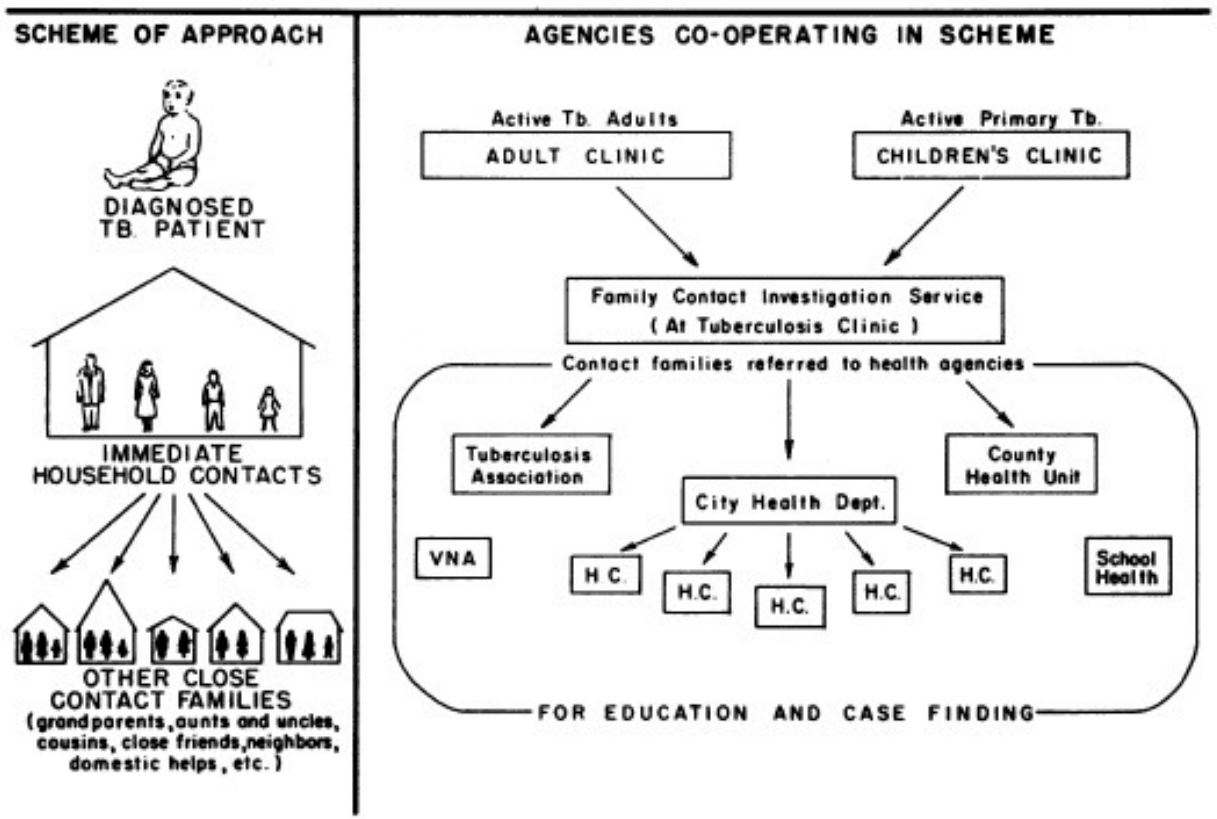

Figure 1—The Scheme for Tuberculosis Contact Investigation

Hsu KHK: Contact investigation: A practical approach to tuberculosis eradication. *AJPH* 53;1751, 1963.

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The findings of a study of 205 family groups for tuberculosis and tuberculosis contacts are reported. These show that tuberculosis exists in "pools" involving large numbers of cases. Public health efforts should be directed to these pools of infection, and contact investigation has proved very efficient in finding pools. Intensive contact investigation will permit wide chemoprophylaxis amid children and young adults.

What Does Family Centered Contact Tracing Do?

- 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 S, Cruz AT, Starke JR. Epidemiology and clinical characteristics of childhood TB identified using active and passive case finding. *Int J Tuberc Lung Dis*, in press.

- Childhood Tuberculosis (TB) can be found via active case finding (ACF), discovering a child through contact tracing and passive case finding (PCF), diagnosing a symptomatic child
- As contact tracing is introduced to high burden settings, knowing characteristics of the 2 groups is important so that cases can be recognized faster, and effective treatment begun earlier
- **Aim:** Compare the characteristics of epidemiological, clinical, microbiologic and radiographic findings in pediatric TB patients diagnosed through ACF and PCF

Demographics

Variable	Active case finding 79 (44.4%) N (%)	Passive case finding 99 (55.6%) N (%)	OR (95% CI)
Age in years (median, IQR)	4.11 (IQR 8.73)	10.12 (IQR 14.53)	
Female N (%)	43 (54.4)	50 (50.5)	0.85 (0.47-1.55)
Race/ethnicity N (%)			
Hispanic	42 (53.2)	49 (49.5)	REF
Non-Hispanic Black	20 (25.3)	23 (23.2)	0.99 (0.48-2.0)
Asian	10 (12.7)	22 (22.2)	1.89 (0.8-4.4)
Non-Hispanic White	5 (6.3)	4 (4.0)	0.69 (0.17-2.72)
Multiracial	2 (2.5)	1 (1.0)	0.43 (0.04-4.9)
Region of birth			
US	65 (82.3)	67 (67.7)	REF
Non-US born	14 (17.7)	32 (32.3)	2.22 (1.09-4.5)
Source case known	65 (82.3)	26 (26.3)	0.08 (0.04-0.16)
Source case found after the patient	2/65 (3.1)[d]	14/26 (53.8)	36.75 (7.38-182.95)

Clinical Manifestations

	Active Case Finding (N=79) N (%)	Passive Case Finding (N=99) N (%)	OR (95% CI) or p-value for Fisher exact
Symptoms			
Asymptomatic	43 (54.4)	0	p=1.0
Fever	16 (20.3)	53 (53.5)	4.54 (2.31-8.92)
Cough	30 (38)	54 (54.5)	1.96 (1.07-3.58)
Hemoptysis	0	8 (8.1)	p=0.001
Weight loss	3 (3.8)	22 (22.2)	7.24 (2.08-25.19)
Night sweats	2 (2.5)	7 (7.1)	2.93 (0.59-14.51)
Decreased energy	2 (2.5)	21 (21.2)	10.37 (2.35-45.73)
Lymphadenopathy	2 (2.5)	25 (25.3)	13.01 (2.98-56.87)
Type of disease			
Intrathoracic only	76 (96.2)	55 (55.6)	0.05 (0.01-0.17)
Extrathoracic only	1 (1.3)	28 (28.3)	30.76 (4.08-231.98)
Both Intra- and Extrathoracic	2 (2.5)	16 (16.2)	7.42 (1.65-33.34)

Conclusion

- Children diagnosed via ACF were younger and more likely to be US born
- Almost all the severe and extrathoracic cases were seen in the PCF group
- **Early diagnosis via ACF prevents more serious forms of TB disease**
- **Availability of source case culture and drug susceptibility results for ACF patients allowed for more tailored empiric mycobacterial therapy**
- Clinicians need to be aware that the common epidemiological, clinical and radiographic presentations in children differ between PCF and ACF

ASSOCIATE INVESTIGATION ["Reverse Contact Tracing"]

Identification and evaluation of close contacts of children and adolescents with LTBI or TB disease

- can be considered a form of targeted testing
- Index Case → Source Case
- yield of finding cases of tuberculosis may be low
- yield of finding LTBI is 30% to 40% in the U.S.
- *effective only if index child with LTBI was tested because of risk*

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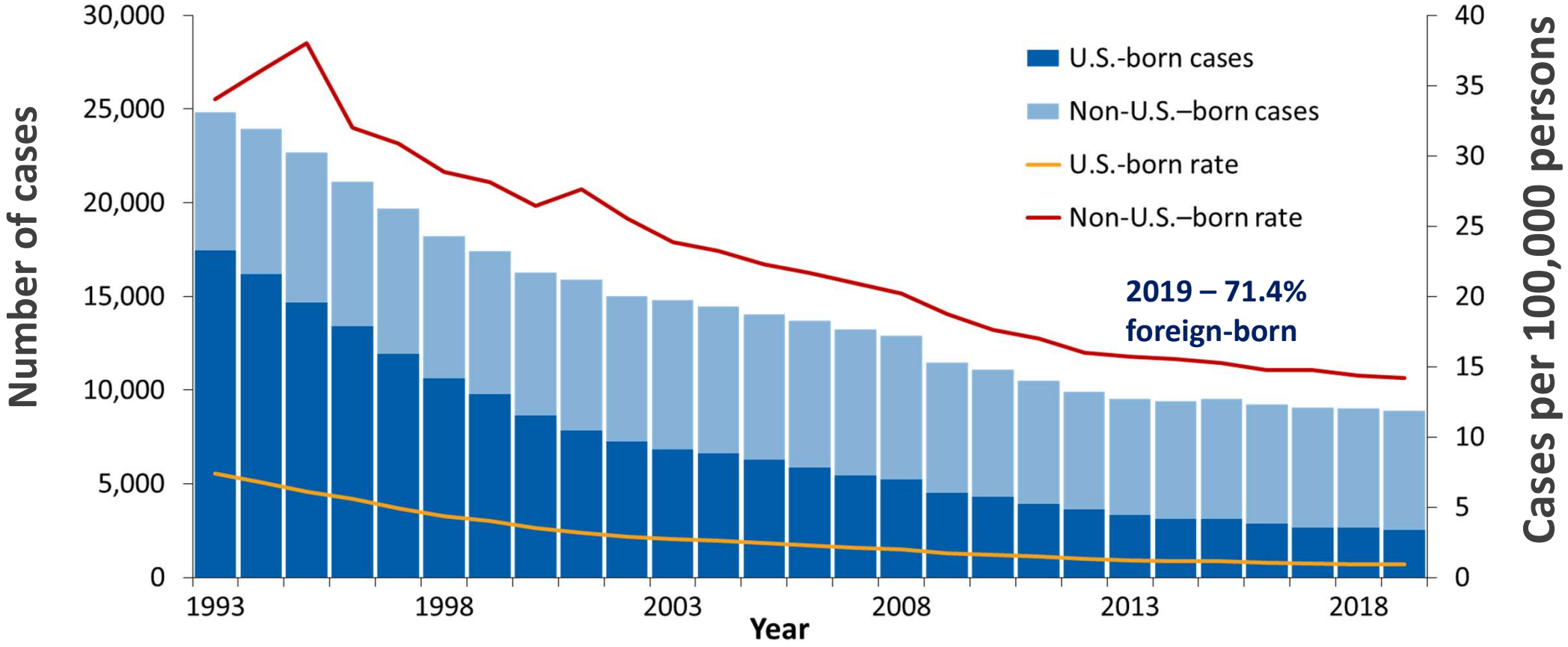
ASSOCIATE INVESTIGATIONS FOR CHILDREN WITH LTBI

Location	Year	# of associates	# (%) positive TST	TB cases
San Francisco	1986	831	330 (40)	3
NYC	1993-5	659	210 (32)	0
NYC	1996-8	668	198 (30)	3
San Diego	2001-2	713	292 (41)	0
Ft. Worth	1999-01	87	31 (35)	2

TB Cases and Rates Among U.S.-born versus Non-U.S.–born Persons, United States, 1993–2019



Greenaway et al. CMAJ 2010; 183: E939

Table 1: Incidence of tuberculosis/100 000 population for immigrants and refugees after arrival in high-income countries

Country of origin	Overall rate	Time since migration; incidence per 100 000 population		
		≤ 1 yr	> 1–5 yr	≥ 5 yr
All world regions				
All foreign-born*† [8,32,33]	35	128	37	17
Refugees received by US‡ [37]		504		
Latin America and Caribbean				
All foreign-born† [8,32,33]	17	76	26	10
Mexico [8]	19	75	22	11
Haiti [8]	55	428	98	28
Guatemala [8]	32	173	58	12
Peru [8]	47	233	90	23
Eastern Europe and Central Asia				
All foreign-born† [8,32,33]	17	65	19	13
Former Yugoslavia [33]	80	240	50	27
Refugees received by US [37]		162		
Middle East and North Africa				
All foreign-born [8,32]	8	47	15	5
Sub-Saharan Africa				
All foreign-born† [8,32,33]	133	1120	120	48
Ethiopia [8]	159	1515	189	59
Somalia [33]	710	1540	560	433
Refugees received by US [37]		1107		
South Asia				
All foreign-born [8]	36	179	52	22
India [8]	40	150	51	21
Pakistan [33]	240	530	255	157
East Asia and Pacific				
All foreign-born† [8,32,33]	53	284	58	33
Philippines [8]	52	543	66	30
Vietnam [8,33]	87	602	112	51
China [8,32]	28	129	27	19
South Korea [8]	51	158	67	32
Refugees received by US [37]		877		
Low-incidence countries [8,32]	1.7	3.0	2.0	1.6

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Childhood TB in the U.S. Effect of Immigration

Lobato and Hopewell. *ARRCCM* 1998; 158:1871

- Children living in a household that had a visitor from a high prevalence country were 2.4 times more likely to have LTBI

Winston and Menzies. *Pediatrics* 2012; 130:e1425

- 31% of children diagnosed with TB in the U.S. in 2008 – 2010 were foreign-born [61% for all ages]
- Among U.S.-born children with TB, 66% had a foreign-born parent [over 3 times the U.S. average]
- Only 25% of U.S.-born children with TB did not have an international connection

Foreign-born children in the U.S. are not treated for LTBI prior to immigration, are less likely to have health insurance and a medical home, more likely to not be in school

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Cruz and Starke. Safety, adherence and efficacy of twice-weekly therapy for childhood tuberculosis exposure or infection. *IJTLD* 2013; 17:169.

Treatment was twice weekly DOT: INH 20-30 mg/kg or RIF 15-20 mg/kg
Treatment was by the same health workers who treated the source case
855 children had household exposure: 62 had conversion of TST from negative to positive; no child developed TB disease

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Table 3: Estimated Efficacy of Intermittent Preventive Therapy in Children with Latent TB Infection

Age Range (years)	# in Age Subgroup	Risk of Progression to Disease if Untreated†	# Estimated to Progress to Disease if Untreated	# Progressing to Disease Who Received Intermittent Preventive Therapy	Efficacy of Intermittent Preventive Therapy
0-<1	22	50%	11	0	100%
1-<2	52	20-25%	10-13	0	100%
2-4	168	5%	8	0	100%
5-10	138	2%	3	1	67%
>10	68	10-20%	7-14	0	100%
Total	**448**	-	**44**	**1**	**98%**

Cruz and Starke. Increasing adherence for latent tuberculosis infection therapy with health department-administered therapy. *PIDJ* 2012; 31:193.

Variable	Subcategory	All Patients N (%)*†	Completed N (%)*‡	Defaulted N (%)*‡
Total		248	186 (75%)	62 (25%)
Age, y	Mean	7.4	7.2 (6.5–7.8)	8.2 (7–9.4)
	Median	7	7	7
Race/ethnicity	Hispanic	145 (58%)	108 (74%)	37 (26%)
	Asian	58 (23%)	43 (74%)	15 (26%)
	Non-Hispanic Black	38 (15%)	30 (79%)	8 (21%)
	Non-Hispanic White	7 (3%)	5 (71%)	2 (29%)
Region of country of origin	United States	91 (37%)	73 (80%)	18 (20%)
	Latin America	48 (19%)	34 (71%)	14 (29%)
	Asia	33 (13%)	24 (73%)	9 (27%)
	Africa	17 (7%)	10 (59%)	7 (41%)
	Middle East	7 (3%)	3 (43%)	4 (57%)
	N.D.	47 (19%)	37 (79%)	10 (21%)
No. medications used	1 drug	245 (99%)	184 (65%)	61 (25%)
	2 drugs	3 (1%)	2 (67%)	1 (33%)
	INH	242 (98%)	183 (76%)	59 (24%)
	RIF	1 (0.4%)	1 (100%)	0
	PZA + FQ	3 (1%)	2 (67%)	1 (33%)
	Changed from INH to RIF§	2 (0.8%)	0	2 (%)
How medications administered	Self-medicated	99 (40%)	49 (49%)	50 (51%)
	ESAT	20 (8%)	17 (85%)	3 (15%)
	DOPT	129 (52%)	120 (93%)	9 (7%)
	ESAT or DOPT	149 (60%)	137 (92%)	12 (8%)
How identified	Contact investigation	82 (33%)	75 (91%)	7 (9%)
	Other	166 (67%)	111 (67%)	57 (34%)

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ARE YOUNG CHILDREN WITH TUBERCULOSIS EVER CONTAGIOUS?

- Difficult to answer in the community
- Orphanages – caretaker with TB led to transmission; a child with TB did not
- Schools – only 2 reported “epidemics” caused by children <13 years old
- Children’s Hospitals – rare case reports of transmission, all with special circumstances; none has been patient - to - patient

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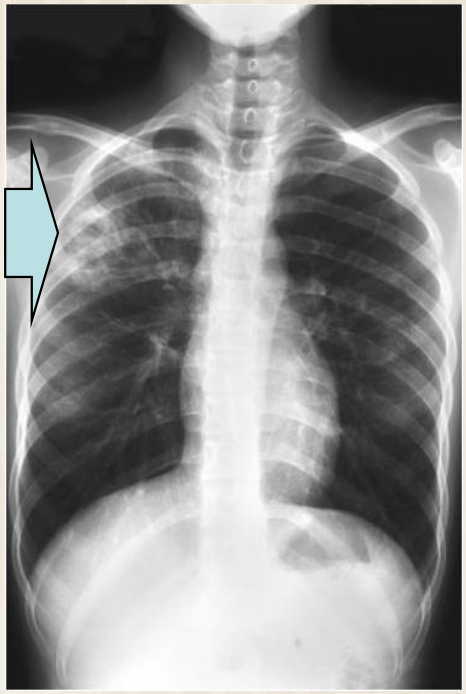
Methods



- From January, 2003 to December, 2009, all children at TCH with suspected TB were admitted to a private room
- Negative pressure rooms were used only if the child had characteristics of infectious TB [cavity, extensive apical infiltrate, sputum production, intubation], if a caregiver was ill or had an abnormal chest radiograph, or if there were delays in obtaining a chest radiograph for a caregiver
- Chest radiographs were obtained ASAP at TCH at the hospital's expense for up to 3 caregivers per patient. Children and caregivers were confined to the patient's room until all the chest radiographs were cleared by a radiologist
- Other visitors were not allowed unless they could show proof of a negative chest radiograph performed elsewhere within the past 2 weeks.

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Results

- During the 7 year study period, 153 children suspected by the treating physician of having TB disease were admitted to TCH
- Ultimately, 59 (39%) had confirmed TB; 2 additional children were treated for 2 months before an alternative diagnosis was established
- 5 children had miliary TB [of which 3 were intubated], 1 had cavitary TB and 1 adolescent had extensive apical disease; 5 of these 7 patients were AFB sputum smear positive
- Diagnoses in the 94 children found not to have TB included: CAP [42],malignancy [9],parapneumonic effusion [9], NTM disease [8], CF with NTM [6], pyogenic lung abscess [6], viral pneumonitis [5], other [9]

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Results

Caregivers

- 254 chest radiographs were obtained [mean 1.7 per child]
- Among the 59 children ultimately diagnosed with TB, 10/59 families [16.9%] and 9/110 caregivers [9.1% or 9,100 per 100,000] had abnormal chest radiographs and each caregiver was confirmed to have pulmonary TB
- Of the 10 caregivers with TB, 4 were fathers, 3 were mothers, 2 were grandmothers and 1 was an aunt
- Overall rate of abnormal caregiver chest radiographs was 8% of families and 12/254 [5%] of caregivers

Health Care Workers

- No TST conversions among those who cared for TB patients

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Childhood TB: Lessons From a Low Burden Environment

- Prevention of TB in children requires a system with central coordination and community activity
- Linking a child to a source case improves the accuracy of diagnosis and effectiveness of treatment
- Analysis of childhood tuberculosis is a window into the effectiveness of TB control – “yellow canaries”
- Most childhood TB can be prevented with very little cost but better organization and emphasis
- Migrating children at high risk and have difficulty accessing central and community services
- Young children with tuberculosis are rarely infectious to others

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SOME REASONS WHY CHILDHOOD TUBERCULOSIS HAS BEEN NEGLECTED

- Inadequate data
- Difficulty confirming the diagnosis
- Children are rarely contagious
  [public health “dead end”]
- Perception from TB policy makers that treating adults is enough
- Government programs fail to address children
- Lack of family centered contact tracing
- Perceived lack of scientific study and scrutiny
- Misplaced faith in the BCG vaccines
- Lack of industry support
- Inadequate advocacy by pediatricians

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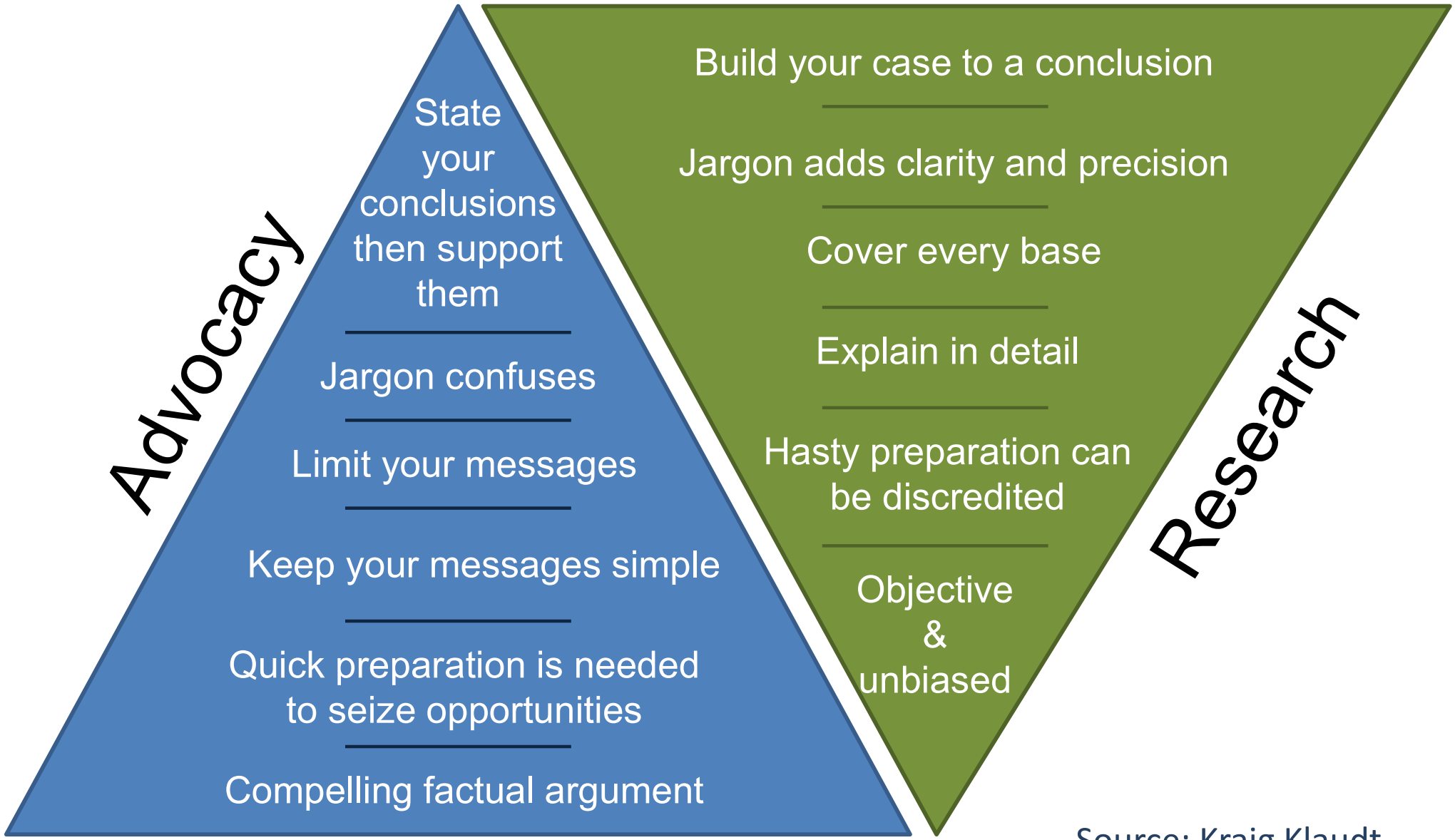
Advocacy vs Research Communication



Source: Kraig Klaudt