"**Modeling** LTBI
What are the key issues to consider?

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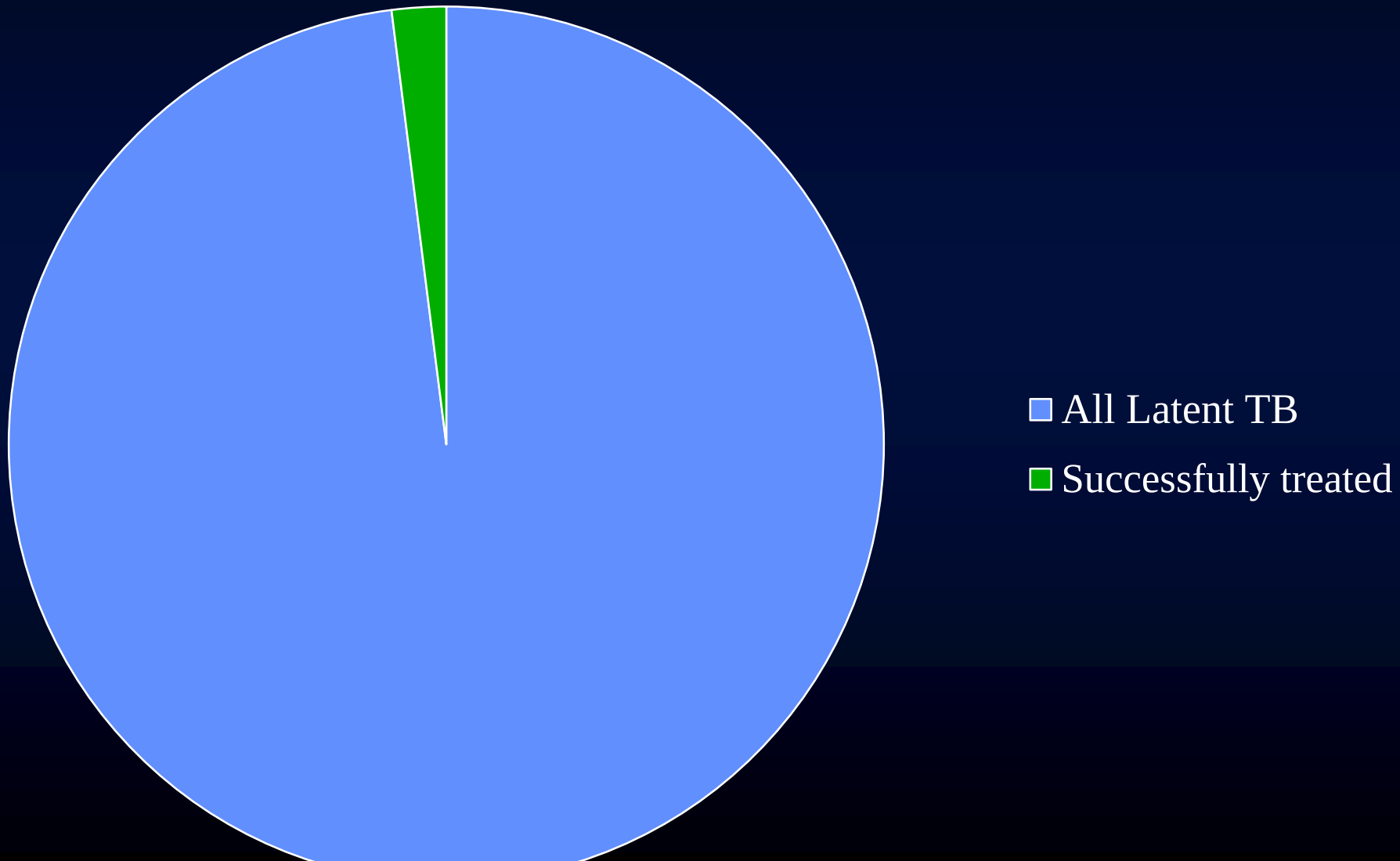
Overview

- **The problem – Treating active TB does not seem to be enough**
- **The solution: Treat Latent TB**
- **The problem(s) with that solution:**
  - **Diagnosis of LTBI**
  - **Treatment of LTBI**
  - **Health systems scale up – the Cascade of Care approach**
  - **Who should be treated?**
  - **How often should LTBI be treated?**
  - **Reservoirs and resurgences**

What is the current Global burden of LTBI?

- It is estimated that 25% of the total global population has latent TB
- That’s about 1.9 BILLION people
- If 10% will develop active TB, then about 190 million will develop TB
- How will we ever stop that????

What is the current impact of treatment on the Global burden of LTBI?



Where to start?

DIAGNOSIS OF LATENT TB

TST vs IGRA

TST

- Good Points:
  - Relatively inexpensive
  - Can be done anywhere
  - Simple to learn
  - Reproducible
- Bad points:
  - Sub-optimal specificity
  - Sub-optimal sensitivity
  - Affected by immune deficiency
  - Requires proper technique
  - OLD test

IGRA

- Good points:
  - Excellent specificity
  - No adverse effects
  - Lab-based = objective
  - NEW test
- Bad points:
  - Sub-optimal sensitivity
  - Affected by immune deficiency
  - Less accessible. Need a lab
  - More expensive
  - Not reproducible on serial testing

Incidence of active TB after a positive IGRA

(from Rangaka L, et al, Lancet ID 2015)

Country	N	Test	Incidence of active TB in IGRA+ groups
The Gambia [Hill et al. 2008]	2348	ELISPOT (in-house)	**9/1000** person-yr
Turkey [Bakir et al. 2008]	908	ELISPOT (T-SPOT.TB)	**21/1000** person-yr
S Africa [Mahomed et al. 2009]	5248	QFT	**6/1000** person-yr
Colombia [del Corral et al. 2009]	2060	In-house whole-blood CFP-10 assay	**11/1000** person-yr
Senegal [Lienhardt et al. PLoS One 2010]	2679	ELISPOT (in-house)	**14/1000** person-yr

Ability of IGRA or TST to predict TB

- Several large scale studies with IGRA and many older studies with TST completed
  - Predictive ability of IGRA somewhat better than TST.
  - But not significantly better
- **No test accurately predicts active TB**
  - HH Contacts with positive TST or IGRA: Annual risk of TB is 1-2%
  - Recent study QFT conversion – TB developed in 1.4% within 12 months
- **Makes treatment of LTBI very 'inefficient'**

Individual vs Public Health benefit

WHO SHOULD BE TREATED?

*Relative Risk for Developing Active TB by Selected Clinical Conditions**

Clinical Condition	*Relative Risk*
HIV/AIDS	*30 - 100*
Silicosis	*30*
TNF alpha inhibitors	*12 - 20*
Renal failure/hemodialysis	*10 – 25*
Solid organ transplantation:	*25 – 63*
Fibronodular Xray	*5.5 – 18*
Diabetes mellitus	*2.1 – 4.0*
Low body weight (<85% IBW)	*2.6*
Cigarette smoking	*1.5 - 3.1*
Heavy alcohol use	*2.9*

**Relative to control populations; independent of tuberculin skin test status*

Highest Population attributable fraction

Source: Lonnroth, Lancet, 2010

- Malnutrition (underweight): 27%
- Smoking (and alcohol): 20%*
- HIV infection: 14%
- Diabetes/other medical illnesses: 9%

PAF just due to smoking - ranges from:

9% in SSA to 24% in WPRO, and 28% in EER

How should Latent TB be treated?

TREATMENT OF LATENT TB

LTBI treatment – what are the options?

- **6 months of INH**
- **9 months INH**
- **3-4 months INH & RIF**
- **3 months once weekly INH& Rifapentine**
- **4 months RIFampin**

Duration of INH Therapy and efficacy/effectiveness

Eastern European trial: Patients with Fibrotic Lesions

Population	***Duration***	***Reduction in TB***
All participants	***INH 12 mo.***	***75%***
	INH 6 mo.	***65%***
	INH 3 mo.	***21%***
Completer/compliers	***INH 12 mo.***	***93%***
	INH 6 mo.	***69%***
	INH 3 mo.	***31%***

Bull WHO 1982;555-64

Mortality from INH hepatitis

Study	Years	Age	Mortality (per 100,000)
USPHS surveillance	1971-72	< 35	**0**
		> 35	**98**
IUAT trial	1969-72	35-65	**14**
CDC surveillance	1972-3	All	**54**
	1974-83	All	**14**
	1984-8	All	**6**
Salpeter survey	1983-92	< 35	**0.6**
		> 35	**2.4**

3 months once weekly INH & Rifapentine vs 9 months daily INH: Completion and Incidence of active TB *(Sterling et al NEJM 2011)*

	9INH	3HP
Randomized (MITT)	3649	3895
Completed	2536 (69%)	3190 (82%)
TB Disease - All patients	12 (0.4%)	7 (0.2%)
- Completed	5 (0.2%)	4 (0.1%)

3 months once weekly INH & Rifapentine vs 9 months daily INH: Adverse Events

(Sterling et al NEJM 2011)

	9INH	3HP
Randomized	**3649**	**3895**
Total- Grade 3-4 AE	**7.4%**	**6.0%**
Drugs stopped for AE	**3.6%**	**5.0%**
Hepatotoxicity	**2.8%**	**0.5%**
Hypersensitivity	**0.8%**	**4.0%**

A randomized trial to compare effectiveness and efficacy of 9 months Isoniazid and 4 months Rifampicin for Latent Tuberculosis infection treatment in children and adults

Diallo et al, NEJM 2018; Menzies et al NEJM 2018

Dick Menzies, Menonli Adjobimey; Rovina Ruslami; Anete Trajman; Oumou Sow; Heejin Kim; Joseph Obeng; Richard Long; Kevin Elwood; Hamdan Aljahdali; Guy Marks; Martin Gninafon; Lika Apriani; Raspati Koesoemadinata; Victoria Cook; Philip Hill; Kevin Schwartzman; Karen Hornby; Chantal Valiquette; Andrea Benedetti;

Study funded by: CIHR

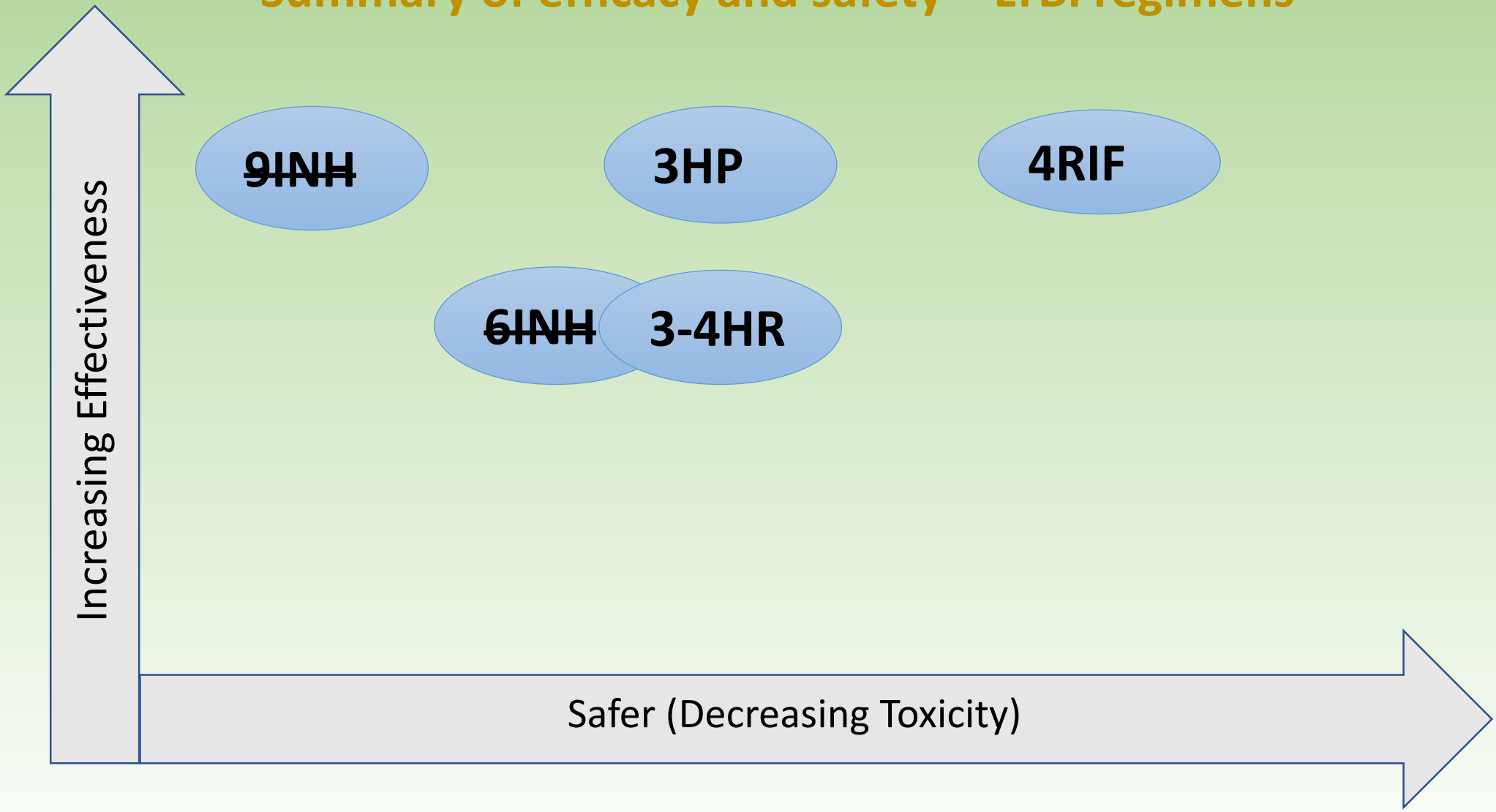
Adults: Grade 3-5 AE, Drug Stopped, and Judged By Panel as Possibly/Probably Related to Study Drug

	9INH (N=3205)	4RIF (N=3280)	Risk Difference 9H-4R
Total Drug Stopped + Grade 3-5 AE + Judged by Panel	**119 (3.7)**	**53 (1.6)**	**-**
Total Judged Probably/Possibly Related to Study Drug	**75 (2.3)**	**31 (0.9)**	**1.4 (0.8, 2.0)**
Rash or other allergy	**2 (0.1)**	**6 (0.2)**	**-0.1 (-0.3, 0.1)**
Drug Interaction	**0 (0.0)**	**2 (0.1)**	**-0.1 (-0.2, 0.0)**
Hepatotoxicity	**65 (2.0)**	**11 (0.3)**	**1.7 (1.2, 2.2)**
GI Intolerance	**1 (0.0)**	**3 (0.1)**	**-0.1 (-0.2, 0.1)**
Hematologic	**0 (0.0)**	**6 (0.2)**	**-0.2 (-0.3, 0.0)**
Pregnancy	**2 (0.1)**	**2 (0.1)**	**0 (-0.1, 0.1)**
Other	**4 (0.1)**	**1 (0.0)**	**0.1 (0, 0.2)**
Death	**1 (0.0)**	**0 (0.0)**	**0 (0, 0.1)**

Adults: Incidence of active TB – MITT analysis

	9INH	4RIF	Rate Difference (9H – 4R)
Total in MITT analysis	**3,416**	**3,443**	**-**
Total person years of follow-up	**7,853**	**7,945**	**-**
Microbiologically confirmed active TB	**4**	**4**	**-**
Clinically diagnosed (judged active TB by Review Panel)	**5**	**4**	**-**
Total Active TB (confirmed and probable)	**9**	**8**	
Incidence of confirmed active TB (per 100 person years - 95% CI)	**0.05 (0.02, 0.14)**	**0.05 (0.02, 0.14)**	**0.0 (-0.16, 0. 16)**
Incidence of all active TB - confirmed and probable clinical (per 100 person years - 95%CI)	**0.12 (0.06, 0.22)**	**0.10 (0.05, 0.20)**	**0.01 (-0.24, 0.21)**

Summary of efficacy and safety – LTBI regimens



How often? How long?

RECURRENCE OF TB AFTER TREATMENT

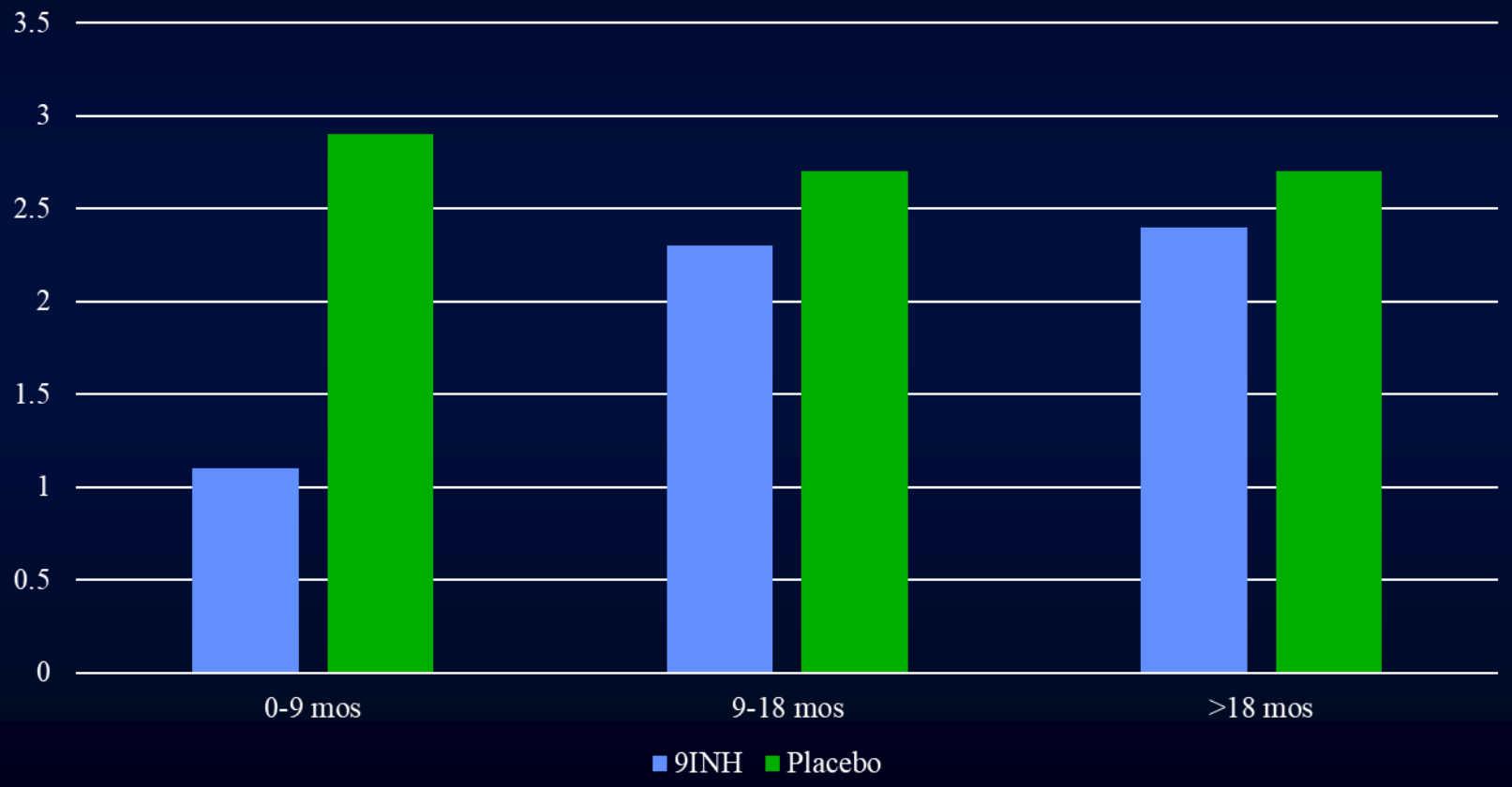
Isoniazid prophylaxis among Alaskan Eskimos: a final report of the Bethel Isoniazid studies

(*Comstock GW, Baum C, Snider DE Jr. Am Rev Respir Dis. 1979 May;119(5):827-30)*

- The protective effect of isoniazid prophylaxis among Alaskan Eskimos is shown to persist for more than **19 years** after INH was taken.
- Magnitude of effect - related to amount of isoniazid taken.
- “The results of the study are consistent with the hypothesis that the **decrease in risk of tuberculosis produced by isoniazid preventive therapy is lifelong”**

Incidence of TB per 100 PY during and after INH treatment *(HIV infected SA Gold miners)*

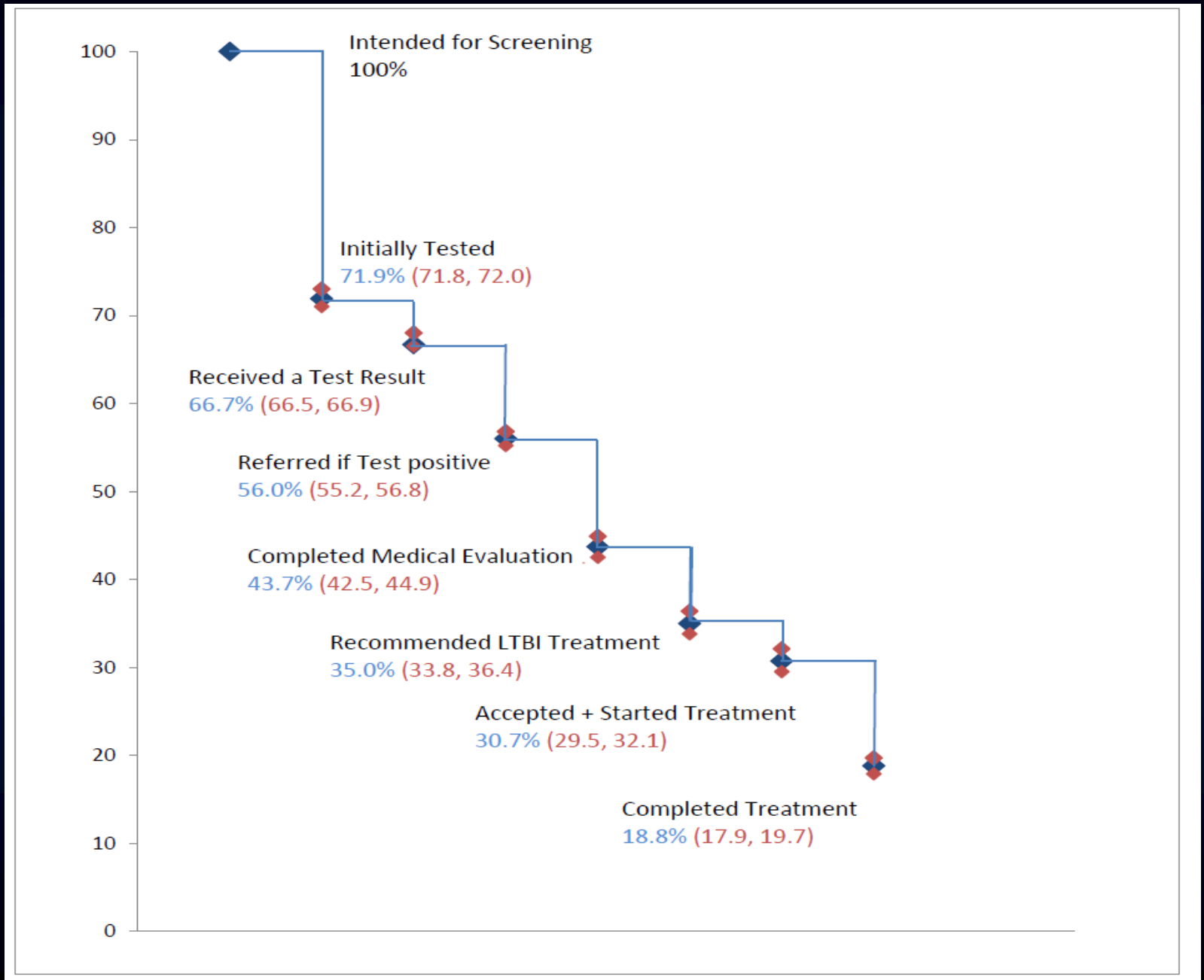
Churchyard et al, NEJM 2014



The Cascade of Care in LTBI a Health systems approach

Assuming we have the right tools to diagnose and treat Latent TB….

The Cascade of Care in Latent TB *(Alsdurf, Menzies Lancet ID 2016)*



Summary – Cascade of care review:

- Of all estimated to have LTBI: Less than 20% completed treatment
- Steps in the cascade with the greatest losses:
  - **28%** of those eligible for screening did not complete initial testing for LTBI
  - **34%** of those with positive LTBI test did not complete medical evaluation
  - **34%** of those who completed the medical evaluation were not recommended to take LTBI therapy

Conclusions and Implications

- Losses before starting LTBI therapy result in much greater reduction in public health benefit than patient non-adherence to therapy after starting
- A comprehensive ‘Cascade of Care’ approach provides a Health Systems framework to scale up LTBI management
- Modeling impact of LTBI management must account for the Cascade of care: Losses and/or Costs/Complexity

Prevention of disease

AN ALTERNATIVE APPROACH
(THINKING OUTSIDE THE BOX)

Prevention of TB without drugs or BCG: The Papworth experiment (1918-43) revisited

(Anurag Bhargava, et al. Am J Resp Crit Care Med, 2014)

- A comprehensive experiment to alter life conditions of TB patients and their families
- At least one adult had active TB
  - Children lived with their parents. Monitored for TB
- **Interventions included:**
  - **Better housing**
  - **Employment with adequiate wages**
  - **Nutrition**
  - **Careful monitoring**
- BUT – No TB drugs and no BCG

The Papworth experiment.

Study population and measurements

Two cohorts of children:

Admitted Group - Born outside Papworth. Moved there with parents in childhood

- Number=228.
- Pre-Papworth – occurrence of TB disease, Average 5 yrs
- Papworth – occurrence of Infection and disease. 7 years

Papworth-born – Born after parents admitted to Papworth.

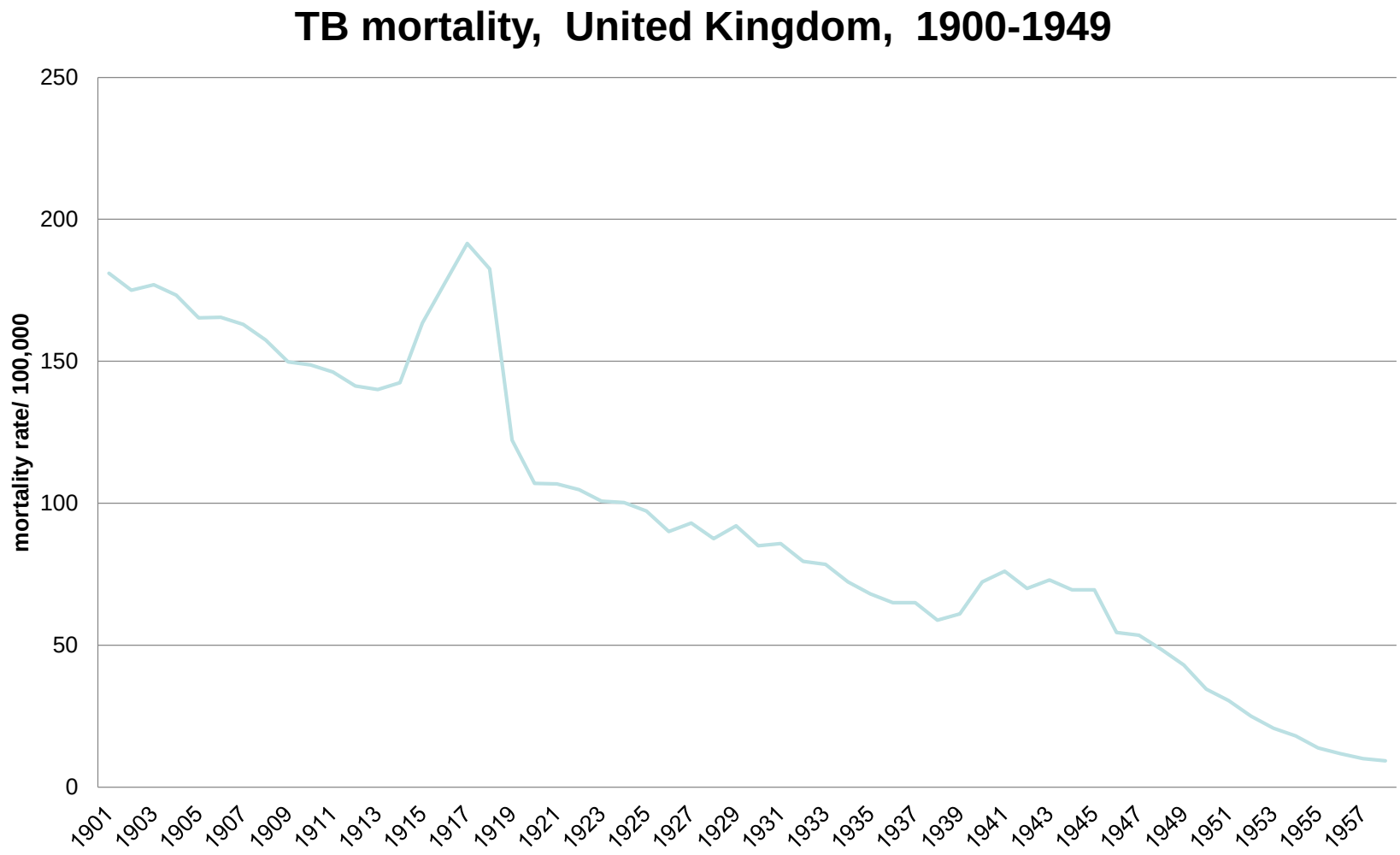
- Number = 84
- No Pre-Papworth of course
- Papworth – infection and disease. Average 7 years

SUMMARY OF DISEASE IN THE TWO GROUPS

	Admitted	Papworth-born
pre-Papworth period	**N = 231**	N = 84
No. with disease	**13**	-----
Incidence rate/10^5PYAR	**1512** (807, 2571)	-----
Papworth period	**N = 218**	**N = 84**
No. with disease	**5**	**1**
Incidence rate /10^5PYAR	**235** (76, 547)	**132** (3, 734)
Infection rate (per year)	**20%**	**21%**
Post-Papworth period	**N = 34**	**N = 3**
No. with disease	**5**	**0**
Incidence rate /10^5 PYAR	**2336** (763, 5638)	**0** (0, 14818)

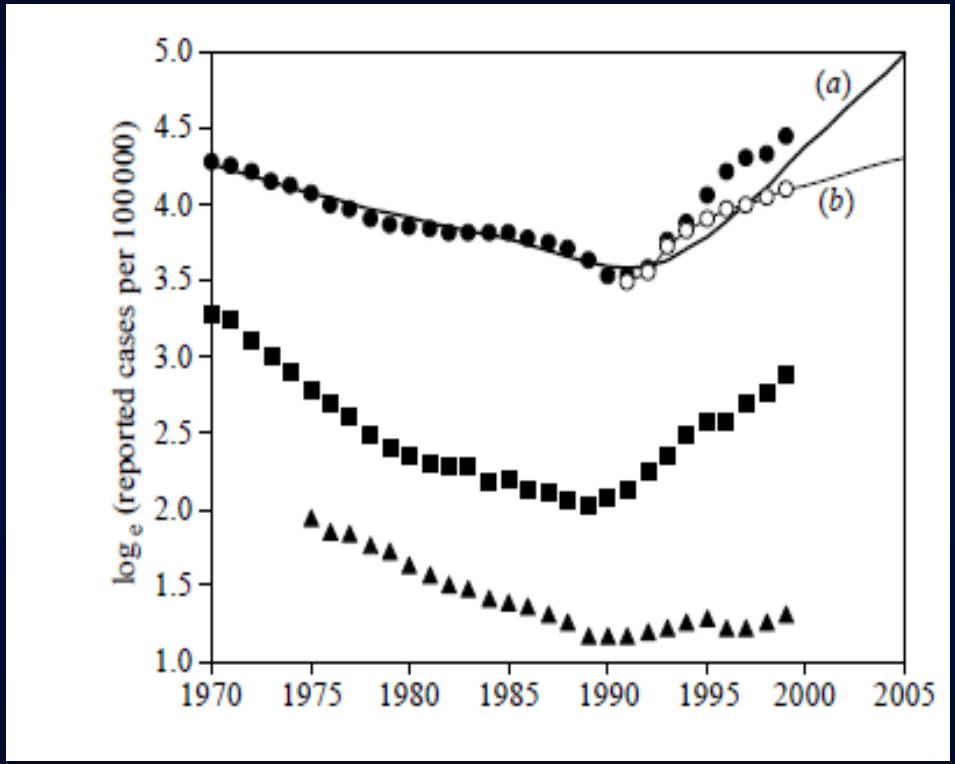
How often?

RESERVOIRS AND RESURGENCES

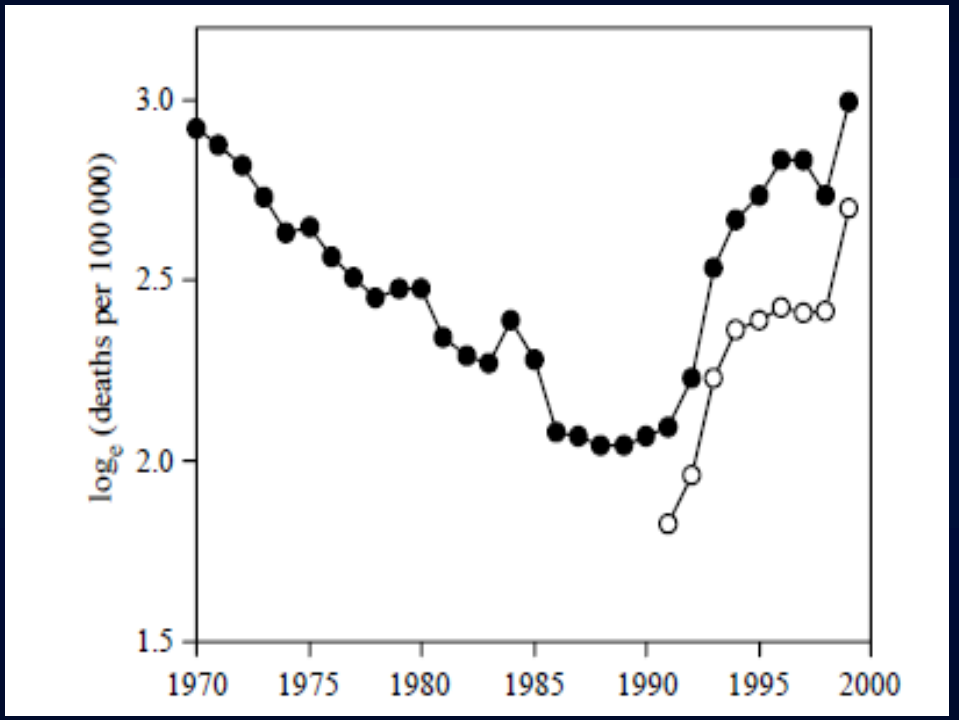


Reference: Office of National Statistics, UK, 2003

Trends in TB – Russian Federation



Trends in case notification 1970-1990 and projections to 2005



Trends in the reported TB death rate

Change in key parameters – Russian Federation and global averages

(from Oxlade et al, IJTLD, 2009)

Indicator	Mean change all Countries (N=165)	Russian Federation
Change in TB incidence rate (1990-2005) per 100,000	+37.5	+68.4
Change in Life expectancy (1990-2005)	**+2.4 yrs**	**-4 yrs**
Change in Under 5 mortality(1990-2005) rate, per 1000	-16.6	-9
Change in measles immunization coverage (1990-2005)	+8.3%	No data
Percent Change in per capita GDP(1990-2005)	+79.3%	+39%
HIV prevalence in 2005	2.2%	1.1%
Change in treatment success DOTS (1990-2005)	76.7%	58.5%

TB notification rates (per 100,000 population) from 1960 to 2014 in 6 Indigenous populations and the general population of Canada *(Dehghani et al, Lancet PH 2018)*

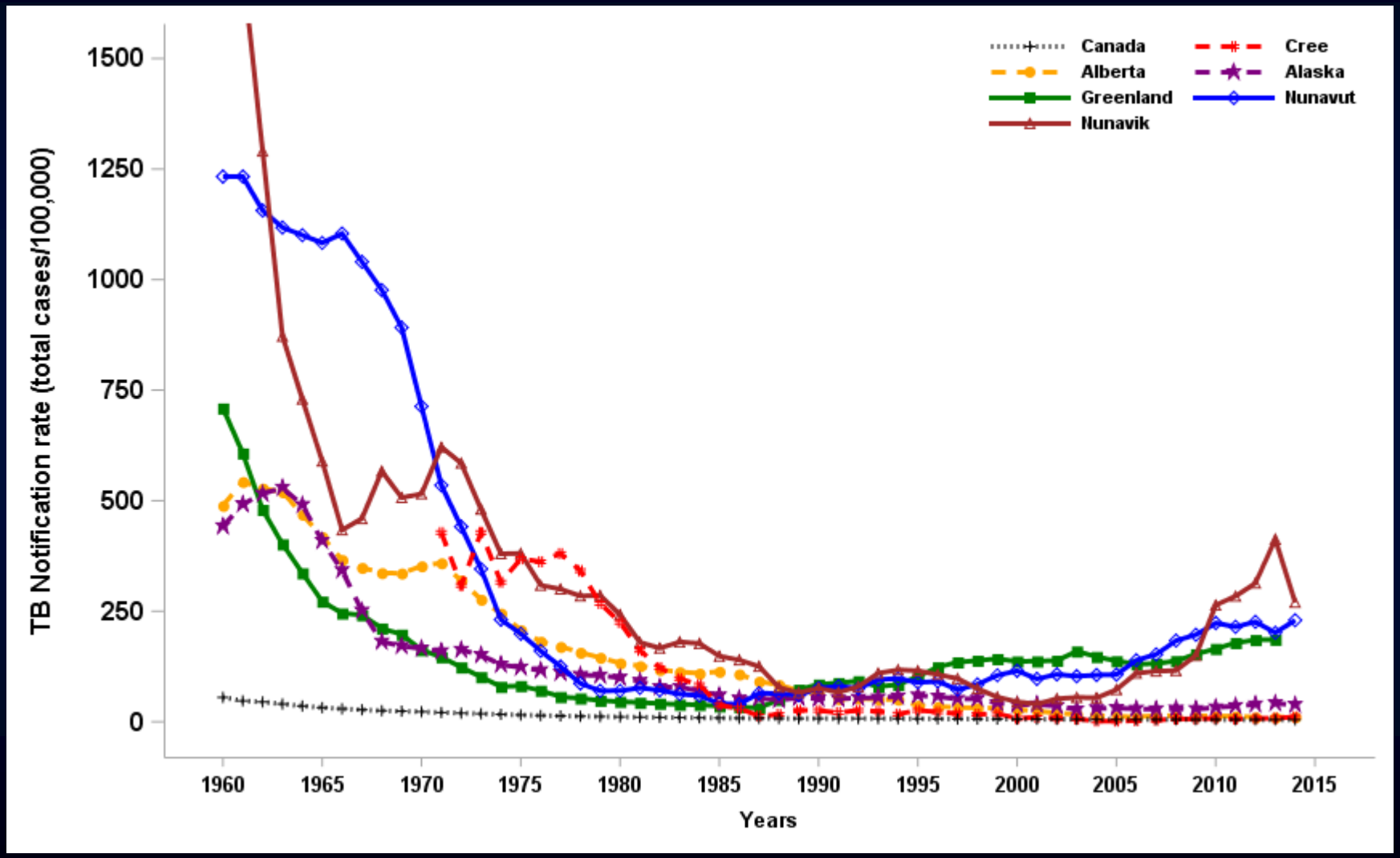
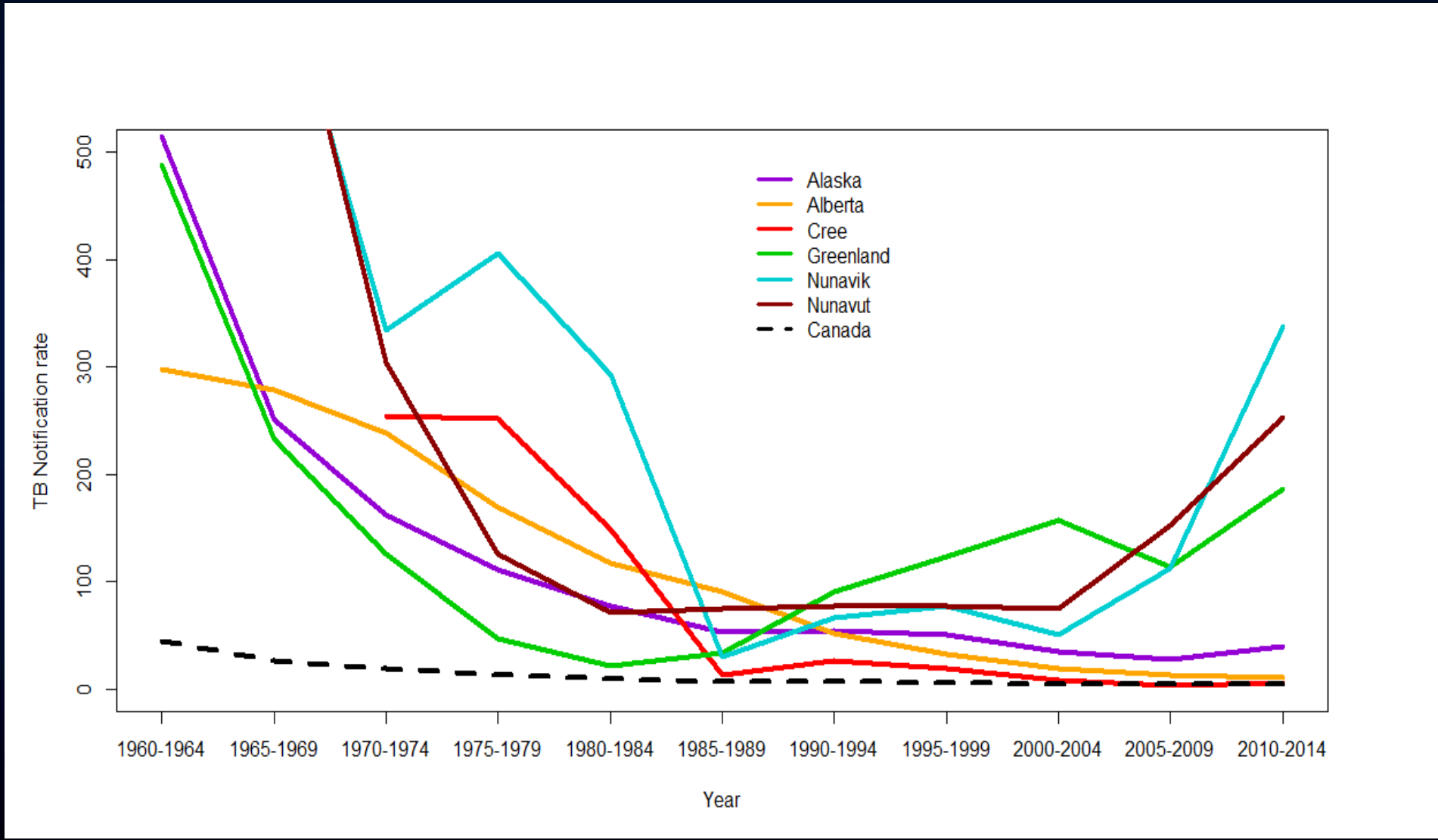


Figure 1b. *Magnified* view: TB notification rates in 6 Indigenous Populations of North America and Greenland and the Canadian general population from 1960 to 2014 ***(Dehghani et al, Lancet PH 2018)***



Final thoughts: Modeling latent TB

Underlying determinants: Important, but how to change?

Diagnosis: Poor predictive ability of current immune based tests

Who to treat: Highest risk (individual benefit) vs highest population attributable fraction (Public health benefit)

Treatment: **Forget about INH**. Rifamycin based regimens are effective, but still 3-4 months, and some risk.

Re-infection: Important to consider, but in what populations?

Cascade of care: treatment of LTBI requires broad health systems investment.

Reservoirs & resurgence – Resurgence happens (over and over) Do we really know why? **How to model what we do not understand?**