The Rocky Road—the Elimination of TB

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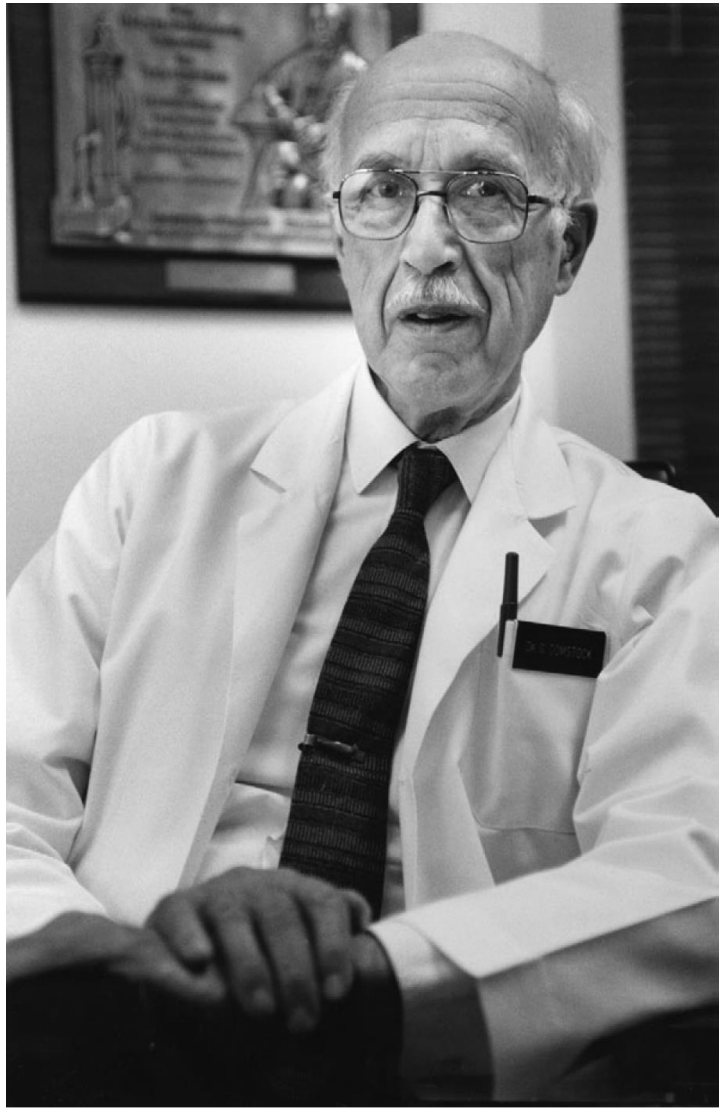
Disclaimer

- No relevant conflicts of interest to declare
- The views expressed are my own – I am not speaking on behalf of any organisation

George W. Comstock
1915 - 2007



Am J Epidemiol 2007;166:493–494

"Be ashamed to die before you have won some victory for humanity."
(Horace Mann's 1859 commencement speech at Antioch College)

Bethel, Alaska 1957

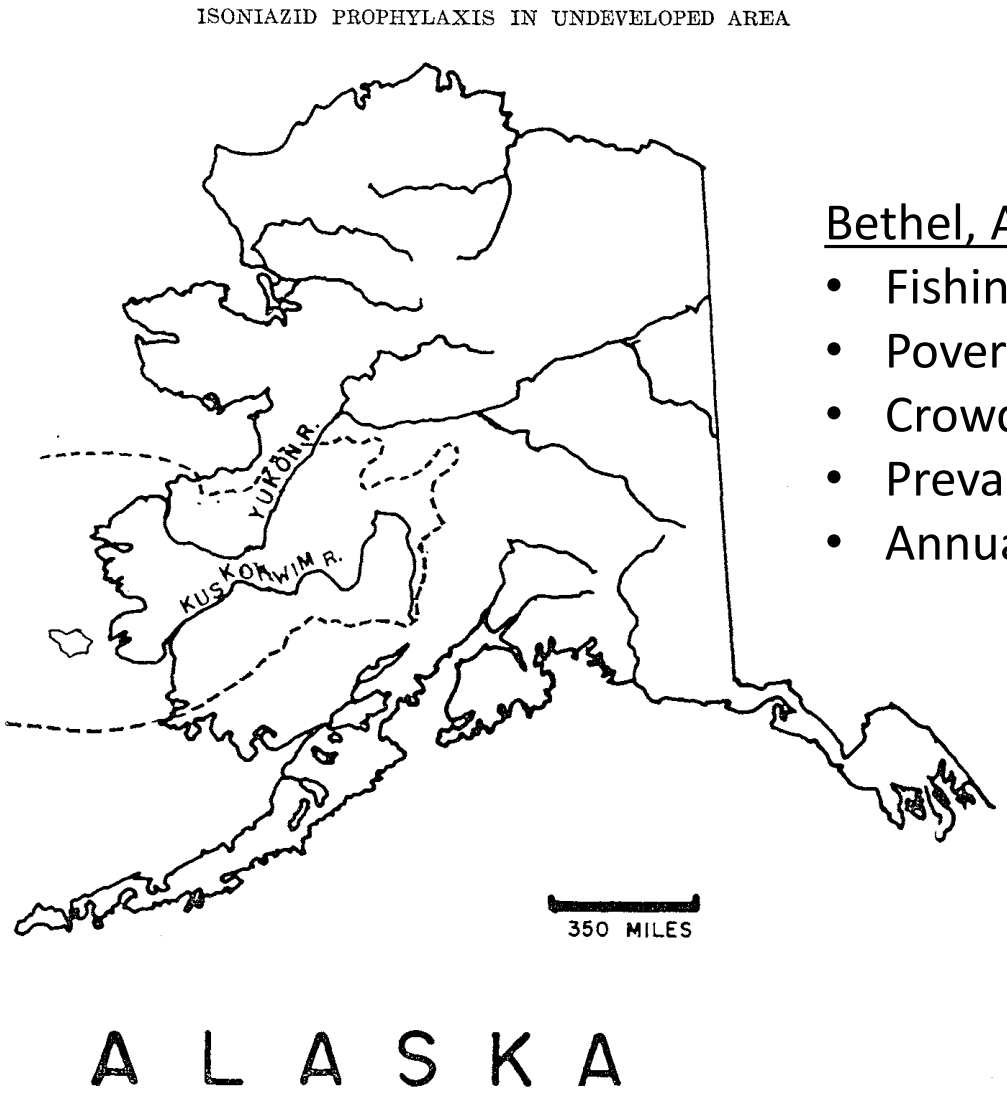


FIG. 1. Boundary of the Bethel Hospital service area is shown by the broken line.

Previous US Public Health Service Trials of INH

1. Children with asymptomatic primary TB
2. Household contacts
3. Patients in mental institutions

Bethel, Alaska

- Fishing, hunting and trapping
- Poverty
- Crowding
- Prevalence of active TB: 2%
- Annual TB infection rate: 8%

Comstock GW. Isoniazid prophylaxis in an undeveloped area. Am Rev Respir Dis. 1962;86:810-22.

Comstock G, Ferebee S, Hammes L. A controlled trial of community-wide isoniazid prophylaxis in Alaska. Am Rev Respir Dis. 1967;95:935.

Trial design

- Cluster (household) randomised, double-blind, placebo-controlled trial
- Explained trial to members of the village and they voted to participate
- Census of each household
- Isoniazid / placebo supplied in coded bottles at quarterly visits for 1 year
- All residents aged ≥ 2 months received meds (with few exceptions)
- Tuberculosis register and death register monitored for outcomes

TB infection and disease, Bethel, Alaska

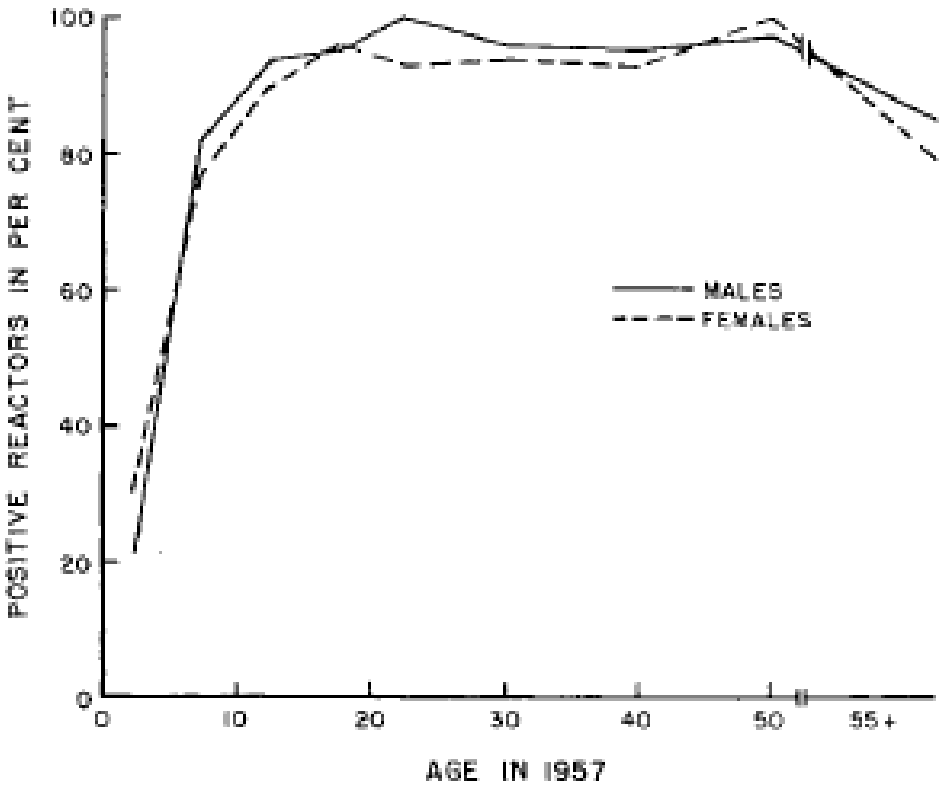


FIG. 2. Percentage of Eskimos with 5 mm. or more of induration to 5 TU of PPD-S, by sex and age in 1957.

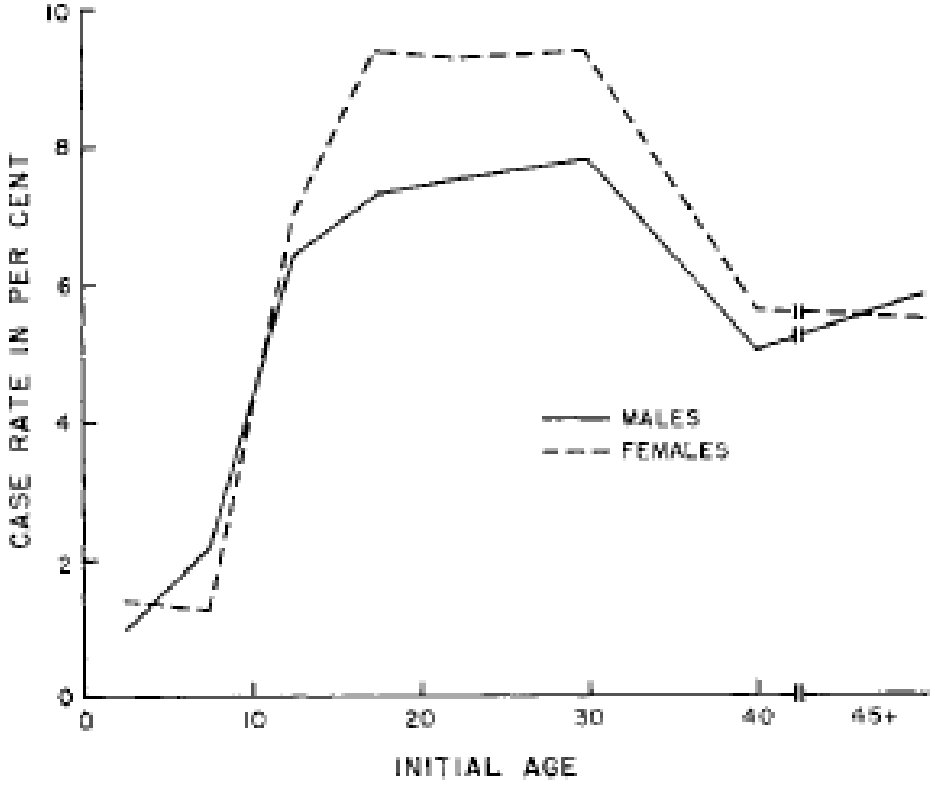


FIG. 3. Tuberculosis case rates in per cent during the study period, 1958 to 1964, among Eskimos assigned placebo by sex and age at start of trial.

Effect of isoniazid vs placebo on incidence of TB

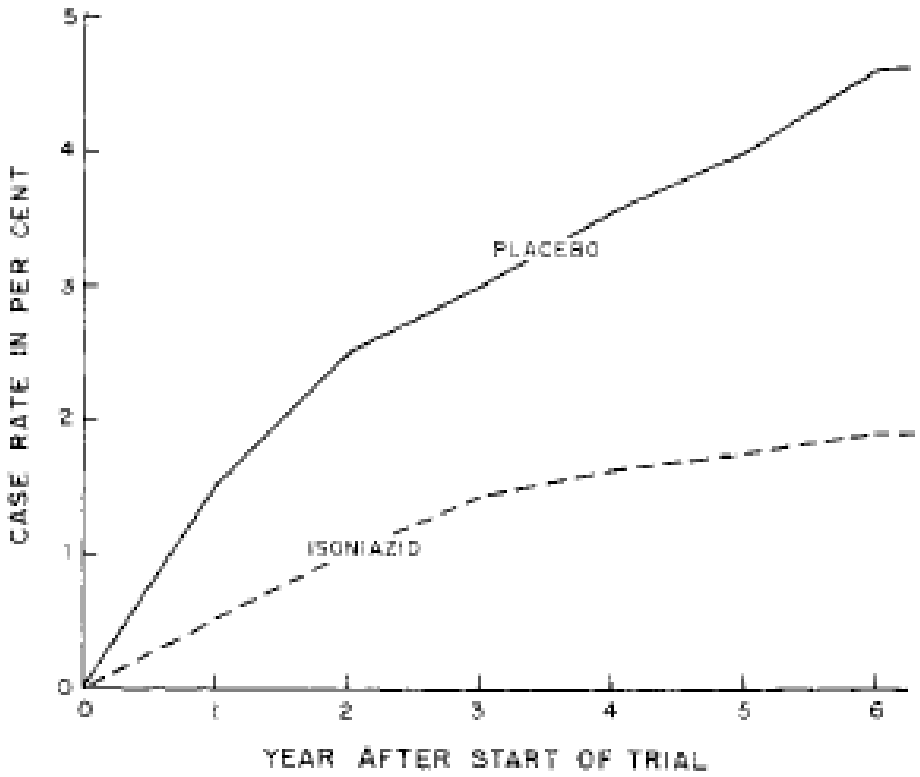


FIG. 4. Cumulative tuberculosis case rates in per cent for placebo and isoniazid groups by year after start of trial.

TABLE 4

TUBERCULOSIS CASE RATES DURING STUDY PERIOD BY MEDICATION ASSIGNED AND INITIAL TUBERCULIN STATUS[3]

Induration to 5 TU PPD-S (mm.)	Placebo			Isoniazid		
	Number Tested	Cases		Number Tested	Cases	
		Number	Per Cent		Number	Per Cent
Total	845	38	4.5	845	4	0.5
0–4	275	6	2.2	299	1	0.3
5+	570	32	5.6	546	3	0.6

Proof-of-concept for community-wide preventive therapy as strategy for TB elimination in high burden settings

A little (more) history to begin

- The causative organism for TB was identified 138 years ago
- All major diagnostic tests (radiography, AFB smear and culture, tuberculin skin test) have been available for > 100 years
- A vaccine was developed >100 years ago
- All drugs currently used in first line regimens have been available for > 50 years

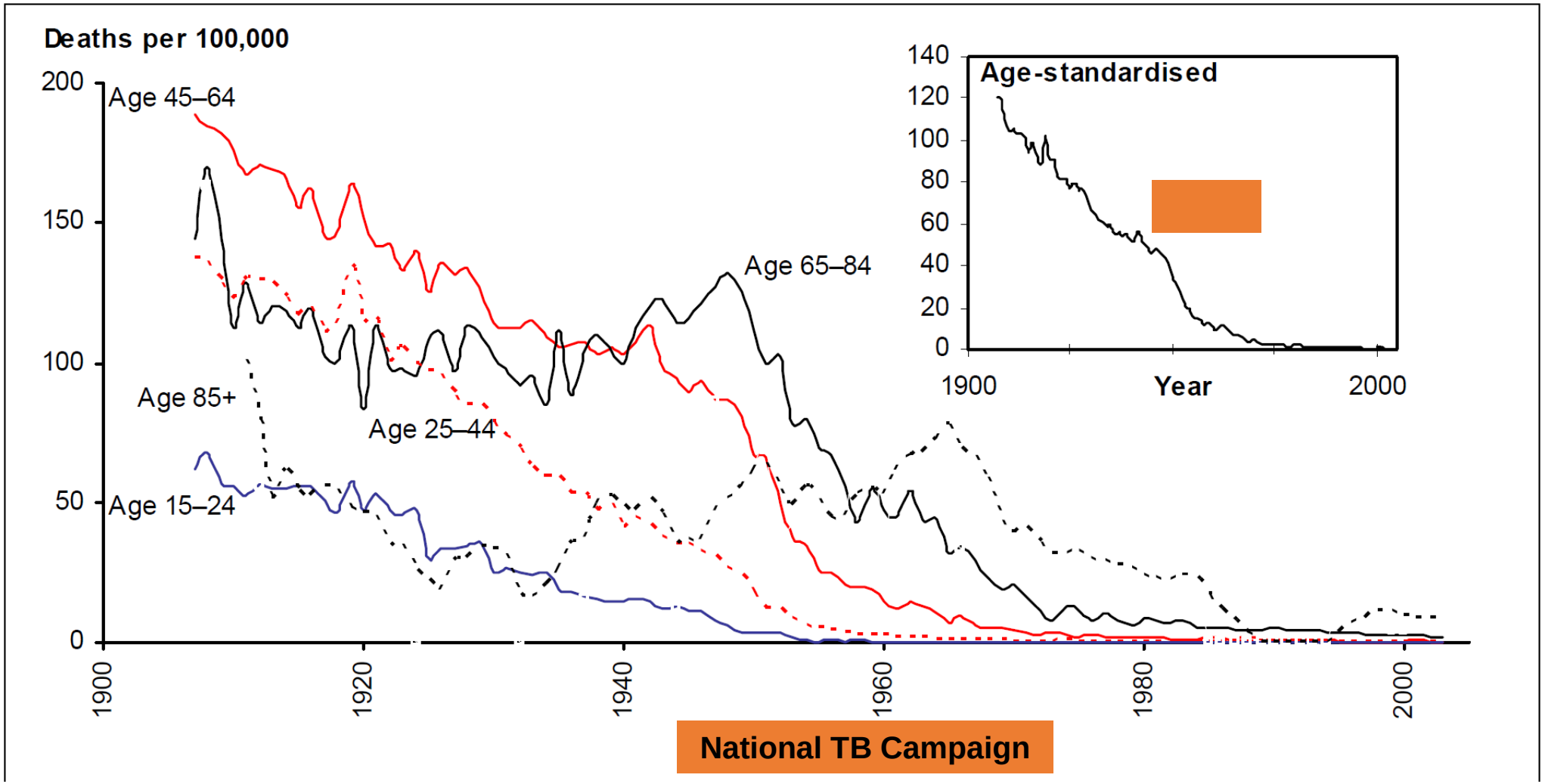
With these tools many countries have travelled the road to TB elimination

Roads Towards TB Elimination:
The Australian National Tuberculosis Campaign (1943 – 1974)

- National funding and co-ordination
- **Compulsory mass miniature chest radiography surveys**
- **Payment of tuberculosis pension** to sufferers and their dependents
- Propaganda aimed at control of the disease
- Rehabilitation facilities
- Scholarships for post-graduate study of tuberculosis
- Research training

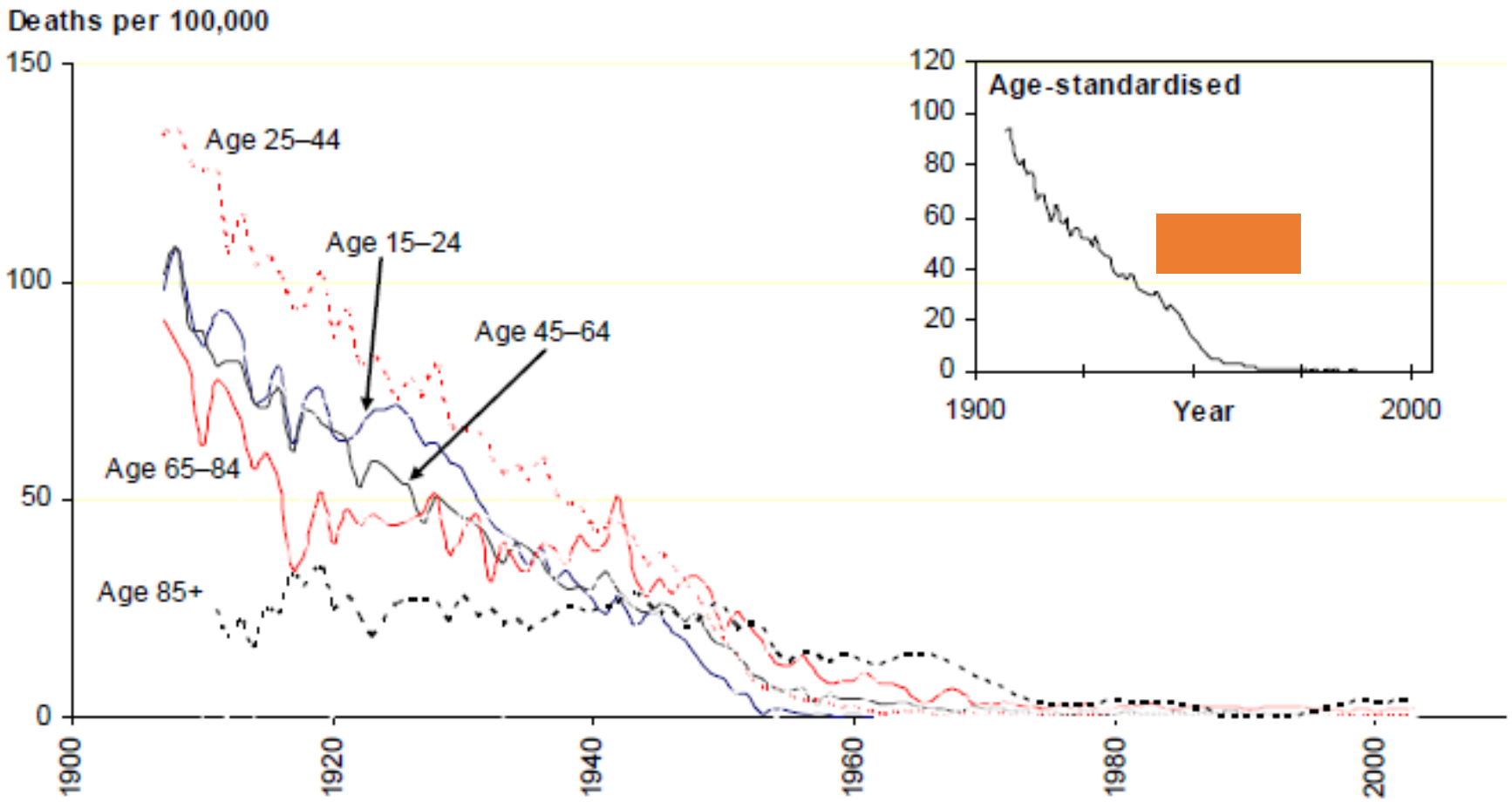
Craven B. Shoulders of Giants. Achievements in History's War on Tuberculosis. 2010. Blue Mountains Historical Society. ISBN 9780958683777

Trends in TB Deaths: Males, Australia, 1907-2003



AIHW. Mortality over the twentieth century in Australia: Trends and patterns in major causes of death. Canberra: AIHW; 2005.

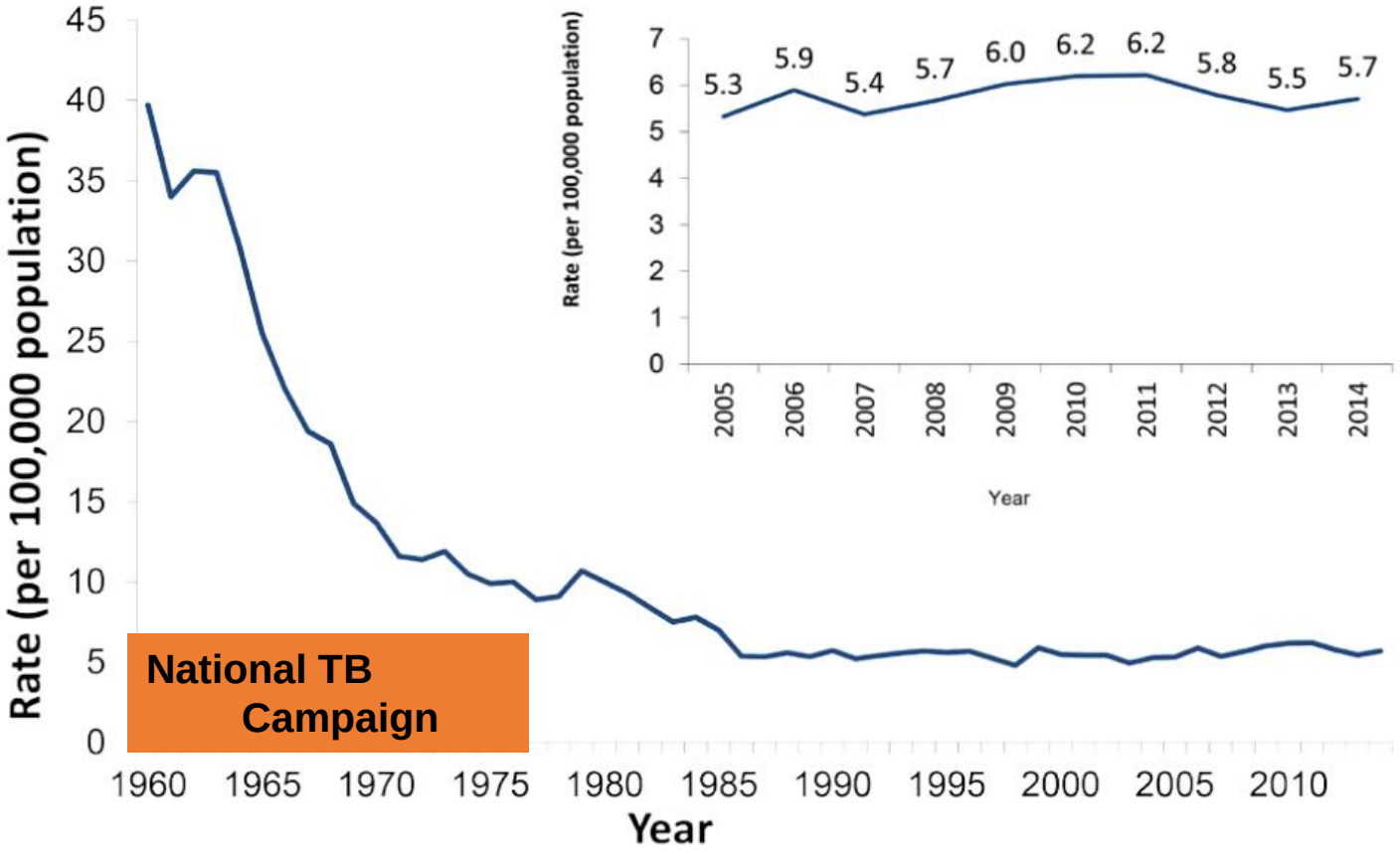
Trends in TB Deaths: Females, Australia, 1907-2003



National TB Campaign

AIHW. Mortality over the twentieth century in Australia: Trends and patterns in major causes of death. Canberra: AIHW; 2005.

Trends in the incidence of TB, Australia

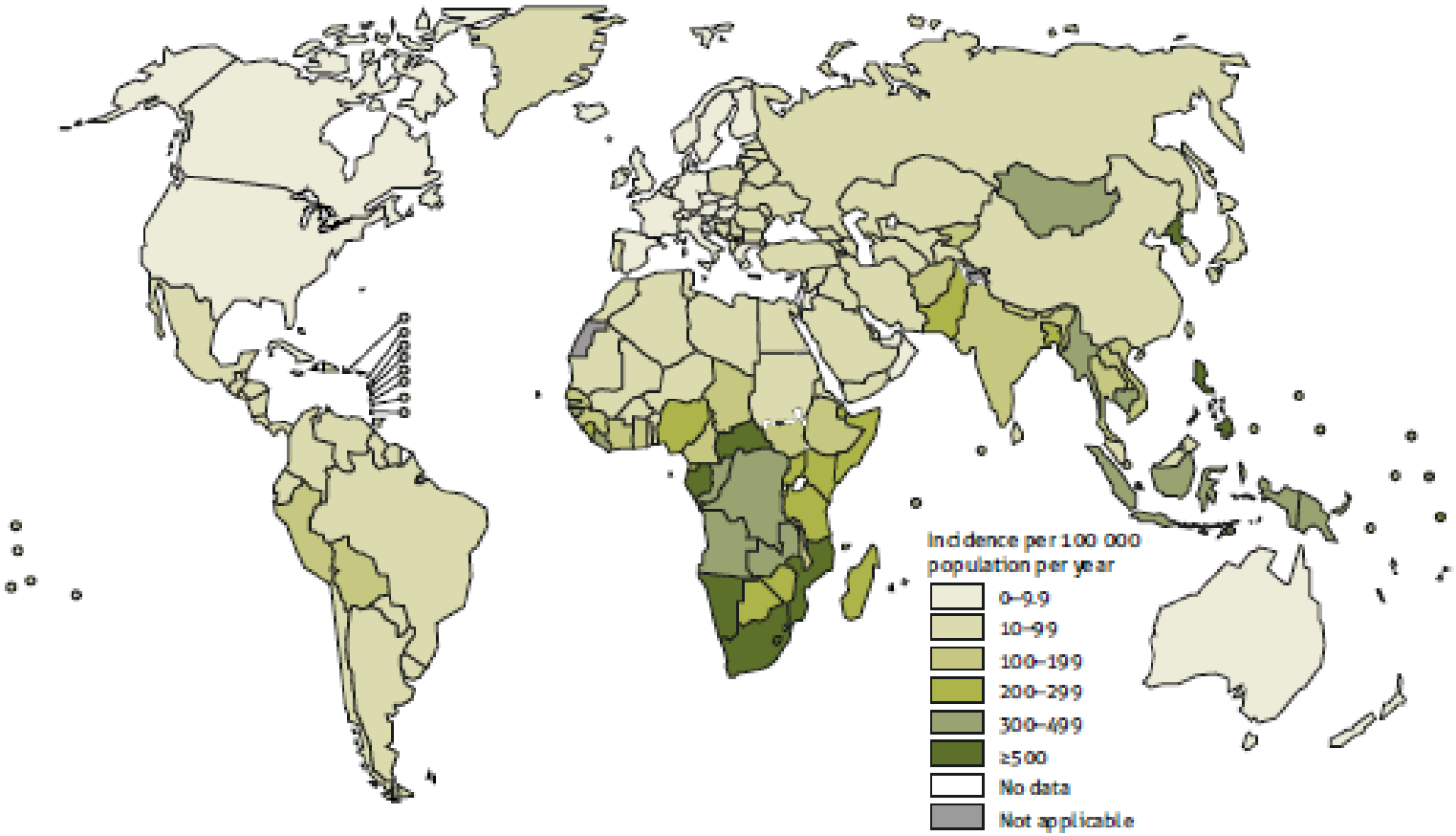


Toms C, Stapledon R, Coulter C, Douglas P, and the National Tuberculosis Advisory Committee. Tuberculosis notifications in Australia, 2014. Communicable Disease Intelligence. 2017; 41(3):E247-E63.

Yet, globally, we have a massive fail on TB

FIG. 3.4

Estimated TB incidence rates, 2018

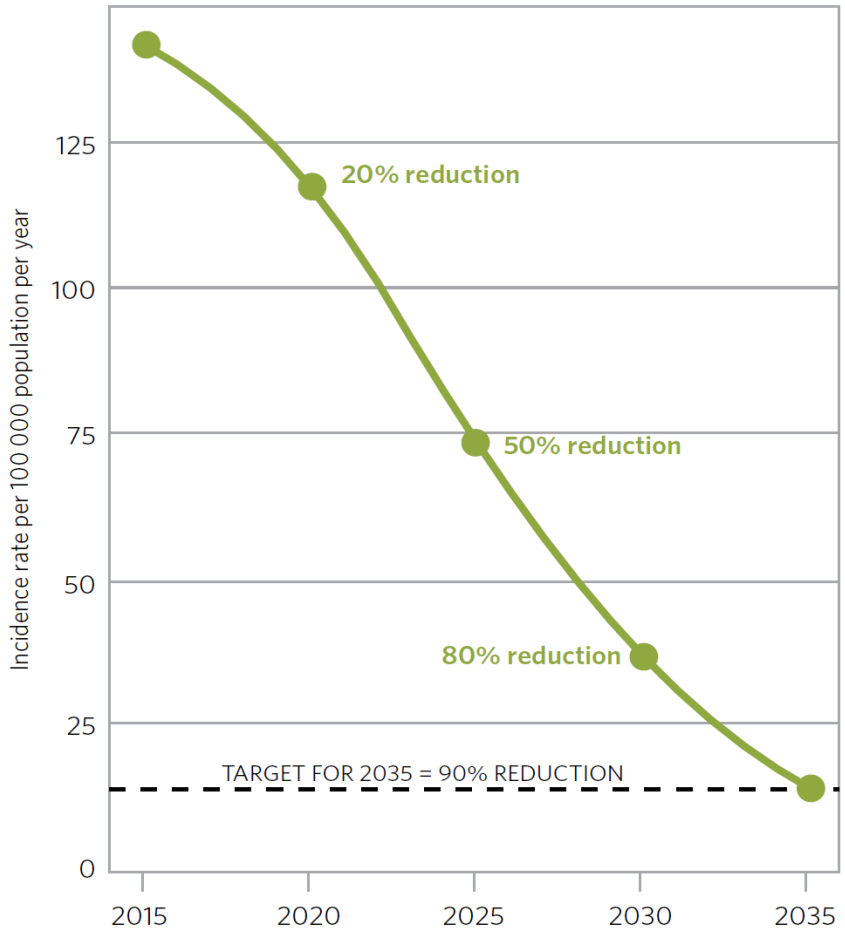


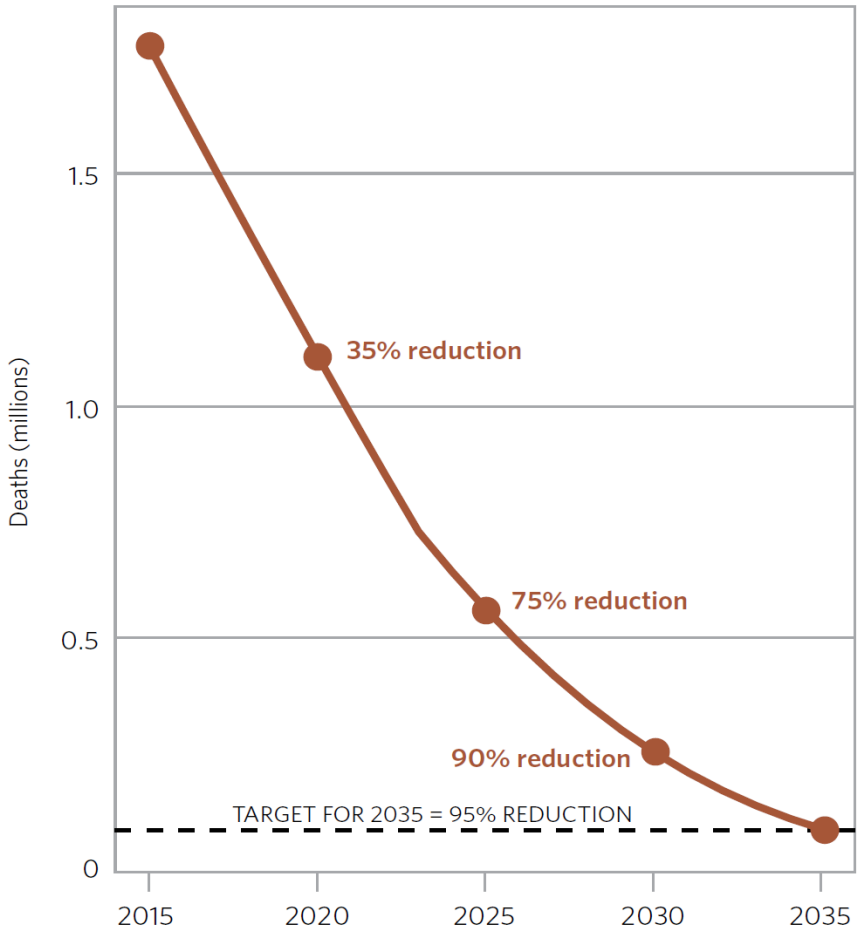
- **In 2018**
- 10.0 million new cases
- 500,000 RR-TB cases
- 1.5 million deaths

World Health Organization. Global Tuberculosis Report 2019

Ambitious global targets to END TB

Projected incidence and mortality curves that are required to reach End TB Strategy targets and milestones, 2015–2035





World Health Organization. Global Tuberculosis Report 2019

Actual global trends

FIG. 3.10

Global trends in the TB incidence rate and the absolute number of TB deaths (solid lines) compared with those required to achieve the 2020 and 2025 milestones of the End TB Strategy (dashed lines)

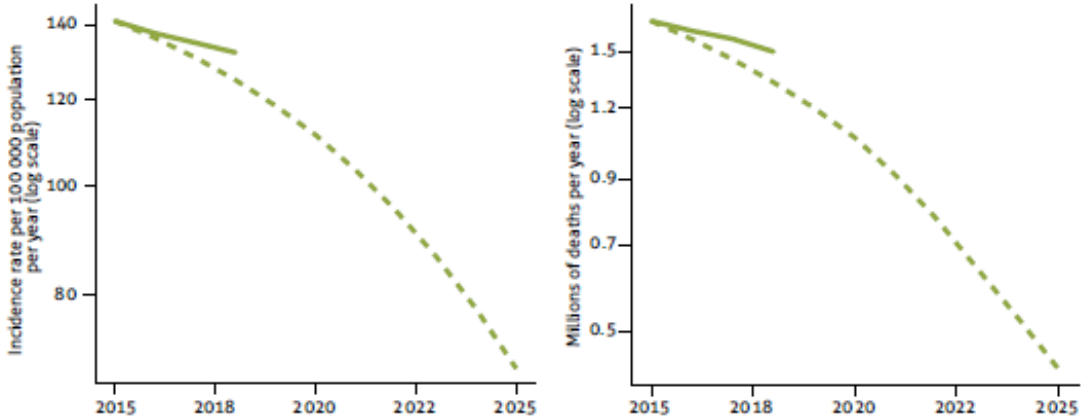
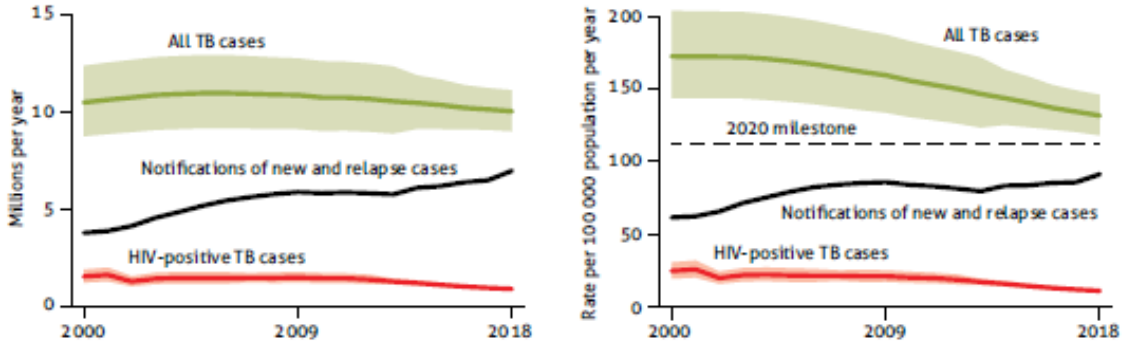


FIG. 3.9

Global trends in the estimated number of incident TB cases (left) and the incidence rate (right), 2000–2018. Shaded areas represent uncertainty intervals. The horizontal dashed line shows the 2020 milestone for incidence of the End TB Strategy.



World Health Organization. Global Tuberculosis Report 2019

We Have Stalled on the Road to Ending TB

- Failing to distinguish private goods from public goods
- Expectations are low
- Over-reliance on programs that will not, alone, lead to TB elimination
- Focus on yield over impact

Private and Public Health Goods (and Harms)

Private health
– affect only the individual

- Symptoms
- Disability
- Well-being
- Survival
- Personal lifestyle and behaviours
- Personal costs and expenditure

Public health
- consequences beyond the individual

- When one person's illness affects others
- Family and community effects
- Economic consequences beyond the individual
  - Costs of care not borne by the individual
  - Loss of productive capacity
  - Need for social support

Some illnesses are private, others public

Imagine …., a person attending this conference is diagnosed with ….

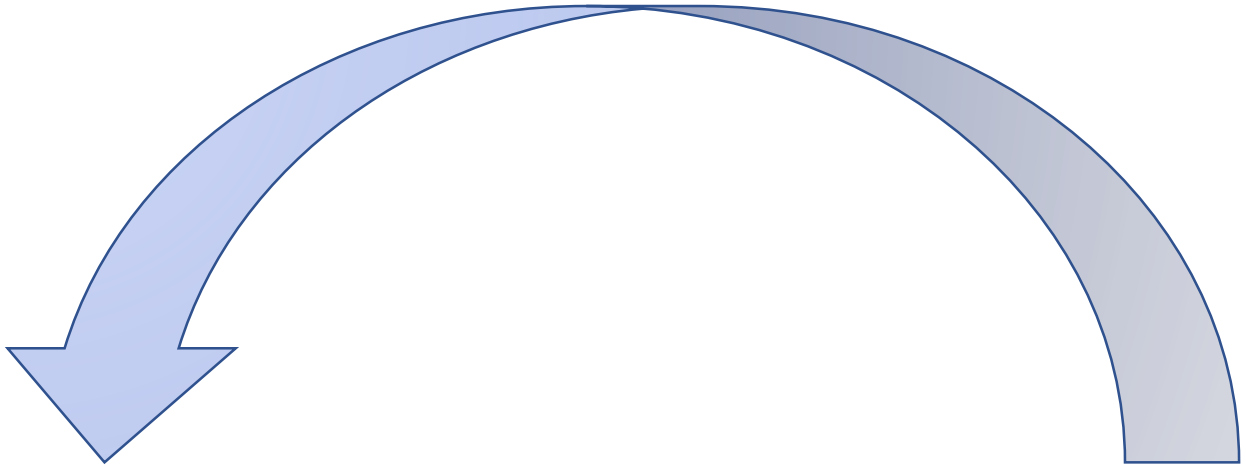
Stage 4 Lung cancer

- Surprise …
- Empathy …

CoViD-19

- Empathy? Yes
- Concern for others +++
- Concern for us +++

Tuberculosis is both private and public



Private goals

- Prevent disease
- Relieve symptoms
- Minimise side effects of treatment
- Rapid return to normal life
- Prevent death
- Reduce catastrophic costs

Public goals

- Prevent transmission
- Prevent emergence of drug resistance
- TB elimination
- Reduce economic harms

Private vs Public goals in TB Control

- Many TB programs have both public and private benefits
  - Finding and treating cases
  - Preventing transmission
  - Preventing re-activation of latent TB
- Failure to identify public and private aims sometimes means that one is subsumed
- Historically, we have tended to swing from one extreme to the other
  - Need to find a middle ground
- Ignoring public goals will distract us from the road to Ending TB

We Have Stalled on the Road to Ending TB

- Failing to distinguish private goals from public goals
- Expectations are low
- Over-reliance on programs that will not, alone, lead to TB elimination
- Focus on yield over impact

Expectations are low

- High level political commitment to target
- At implementation level there is
  - Inertia
  - Lack of ambition
  - Scepticism
  - Nihilism: TB will always be with us (treated like an NCD)
- Linking TB with poverty is a two-edged sword
- PEPFAR – ARV roll-out in Sub-Saharan Africa blazed a trail.

We Have Stalled on the Road to Ending TB

- Failing to distinguish private goals from public goals
- Expectations are low
- Over-reliance on programs that will not, alone, lead to TB elimination
- Focus on yield over impact

Many health and development strategies are important; but we cannot rely on them (alone) for Ending TB

- Health system strengthening
- Universal health coverage
- Economic development
- Managing Anti-microbial Resistance (AMR)

Necessary, but not sufficient conditions for Ending TB

Many TB programs are important; but we cannot rely on them (alone) for Ending TB

- Focus on MDR-TB
- All oral regimen
- Contact tracing
- Targeting high risk groups
- Public-private mix
- Point-of-care diagnostic testing

We Have Stalled on the Road to Ending TB

- Failing to distinguish private goods from public goods
- Expectations are low
- Over-reliance on programs that will not, alone, lead to TB elimination
- Focus on yield over impact

Focus on yield over impact

- Yield is the cost per case detected
  - Useful when the main objective is to find cases
- Our aim is to prevent cases
  - Ultimately to find no cases
  - Finding many cases is an interim goal, but must be strategically designed to prevent transmission
- We should measure cases prevented – and pay for this!

There are many roads to PREVENTION for Ending TB

1. Find and effectively treat infectious cases
2. Reduce transmission from infectious cases
3. Reduce risk that latent TB will become active

1. Find and effectively treat infectious cases

- Find
  - Enhance passive case detection
  - Targeted active case finding
  - General – community wide active case finding
- Effectively treat
  - DOTS
  - Adherence enhancement
  - Combination tablets

2. Reduce transmission from infectious cases

- Improved social conditions
  - Less crowding
  - Better ventilation
- Increased social distancing
- Vaccine

3. Reduce risk that LTBI will become active

- Preventive therapy
  - Targeted
  - General community
- Vaccine
- Improved constitutional resistance to re-activation
  - General health
  - Treat or prevent specific risks: HIV, diabetes, renal failure, cancer, silicosis

Case Finding for Prevention

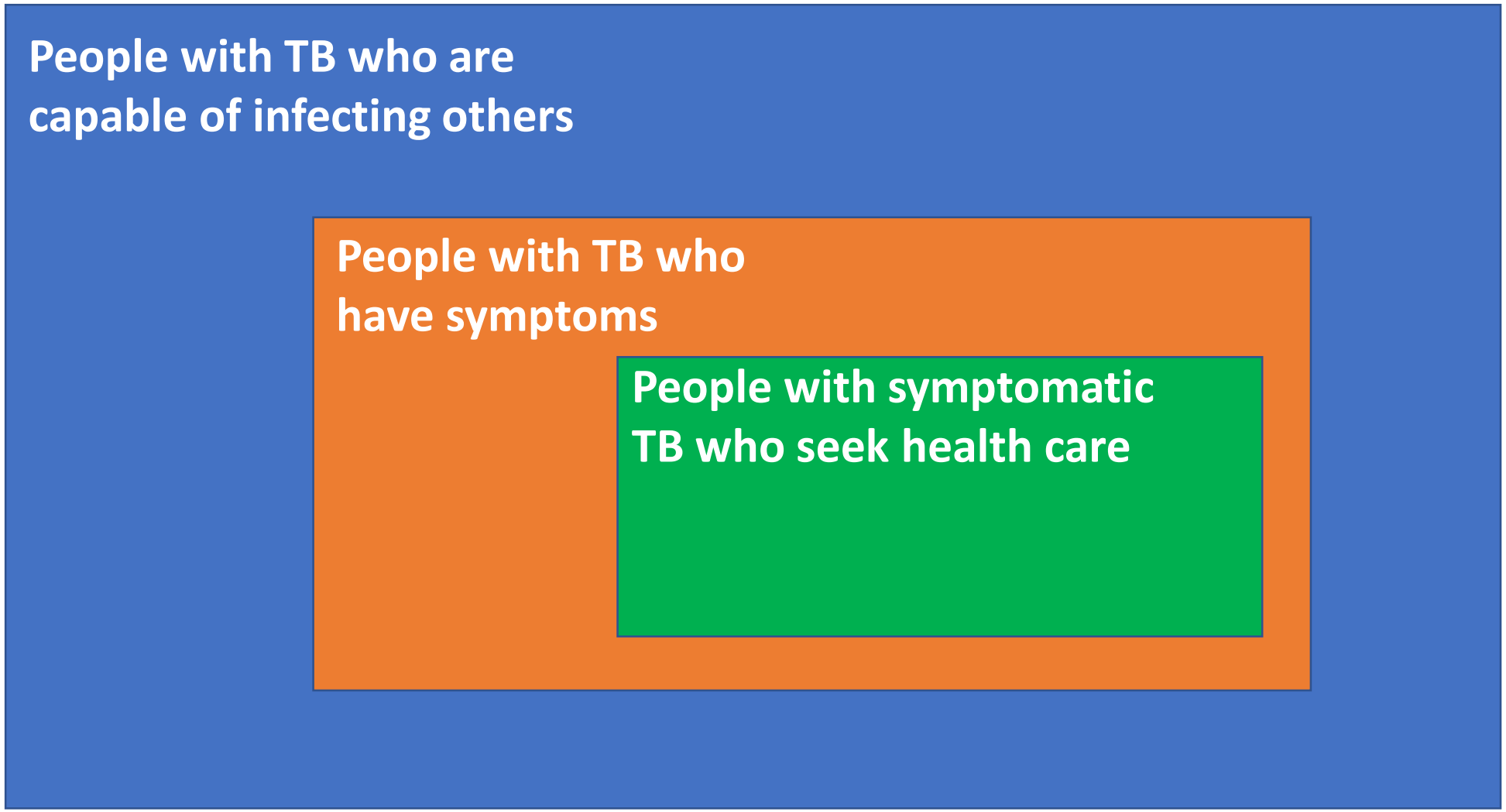
What are the benefits?

- Private benefits for individual who is found
  - Prevention of morbidity and risk of death due to progressive disease
  - Relevant to both communicable and noncommunicable diseases
- Public benefits for community in which individual case is found
  - Prevention of transmission of infection to others
    - At scale, can end the epidemic
  - ONLY relevant to communicable diseases
  - This is well recognised
    - For acute infectious diseases (Ebola, CoViD-19, influenza)
      - Does not even require effective treatment (maybe even for TB)!
    - For tuberculosis in low burden settings
  - **Seems to be forgotten for TB in high burden settings**

Limitations of passive case finding

- Many patients with TB
  - Do not have “typical” symptoms of TB
    - Just 53% of people with prevalent TB in Vietnam in 2006/07 had persistent productive cough (Hoa et al., Bull WHO, 2010)
  - Delay or do not seek health care

- Many health systems suffer from structural weakness
  - Difficult for patients with TB to navigate the cascade of care


People with TB who are capable of infecting others
People with TB who have symptoms
People with symptomatic TB who seek health care

Active case finding

- Now widely recognised value in both high and low burden settings
- Mainly targets high risk groups:
  - Contacts
  - PLHIV
  - Homeless, prisoners, other congregate settings
  - Medical high risk-groups (diabetes, renal disease, cancer etc)
- Conventional approach
  - Symptoms and/or radiology as first stage screening tool

Limitations of current approaches to active case finding

- High-risk groups
  - In high-burden settings, most people with TB are not in “high-risk” groups
  - Hence, little impact on prevention of transmission
- Symptom-based screening
  - Many people with TB do not have typical, or even any, symptoms
- X-ray screening
  - Accessibility
  - Radiation
  - Reliability and validity of interpretation

Community-wide active case finding using sputum Xpert testing (ACT3)

Goal: Proof-of-concept for this intervention as a strategy for TB elimination

Does community-wide active case finding reduce:

- The prevalence of active TB
- The prevalence of TB infection in children (i.e. prevent transmission)

Setting: Ca Mau

Population: 1.23 million

Districts: 9

Communes: 101

Sub-communes Ap: 948

Main industries: fishing, shrimp farming, forestry and rice cultivation

TB cases reported: 114 / 100,000

AFB+ cases: 80 / 100,000

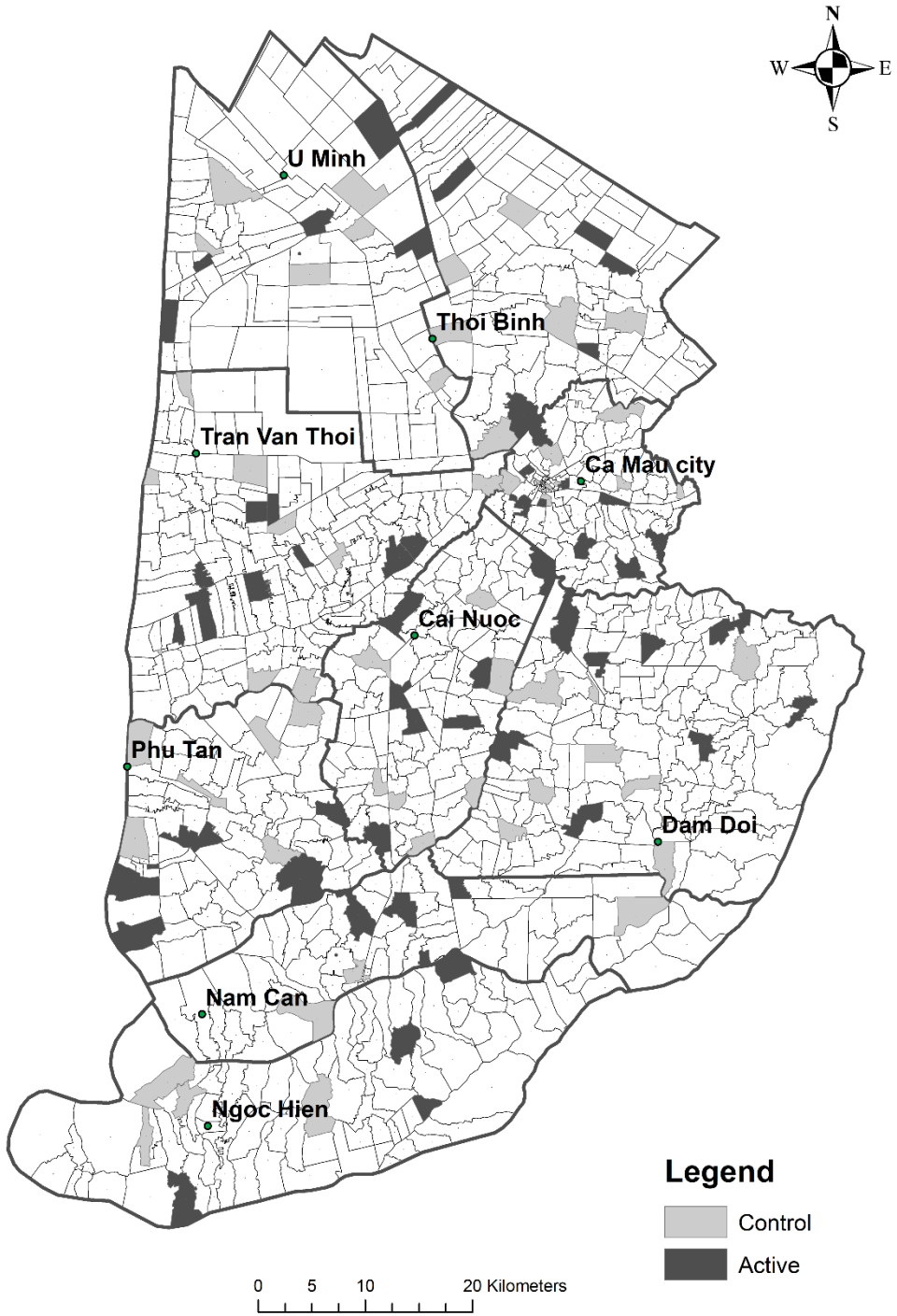
Active Case finding for Tuberculosis (ACT3)

Population: all persons aged ≥ 15 years

Intervention: annual screening for TB, regardless of symptoms, by testing a single spontaneously expectorated sputum using Xpert MTB/RIF

Comparison: usual care, that is, passive case finding

Outcome: prevalence of TB in fourth year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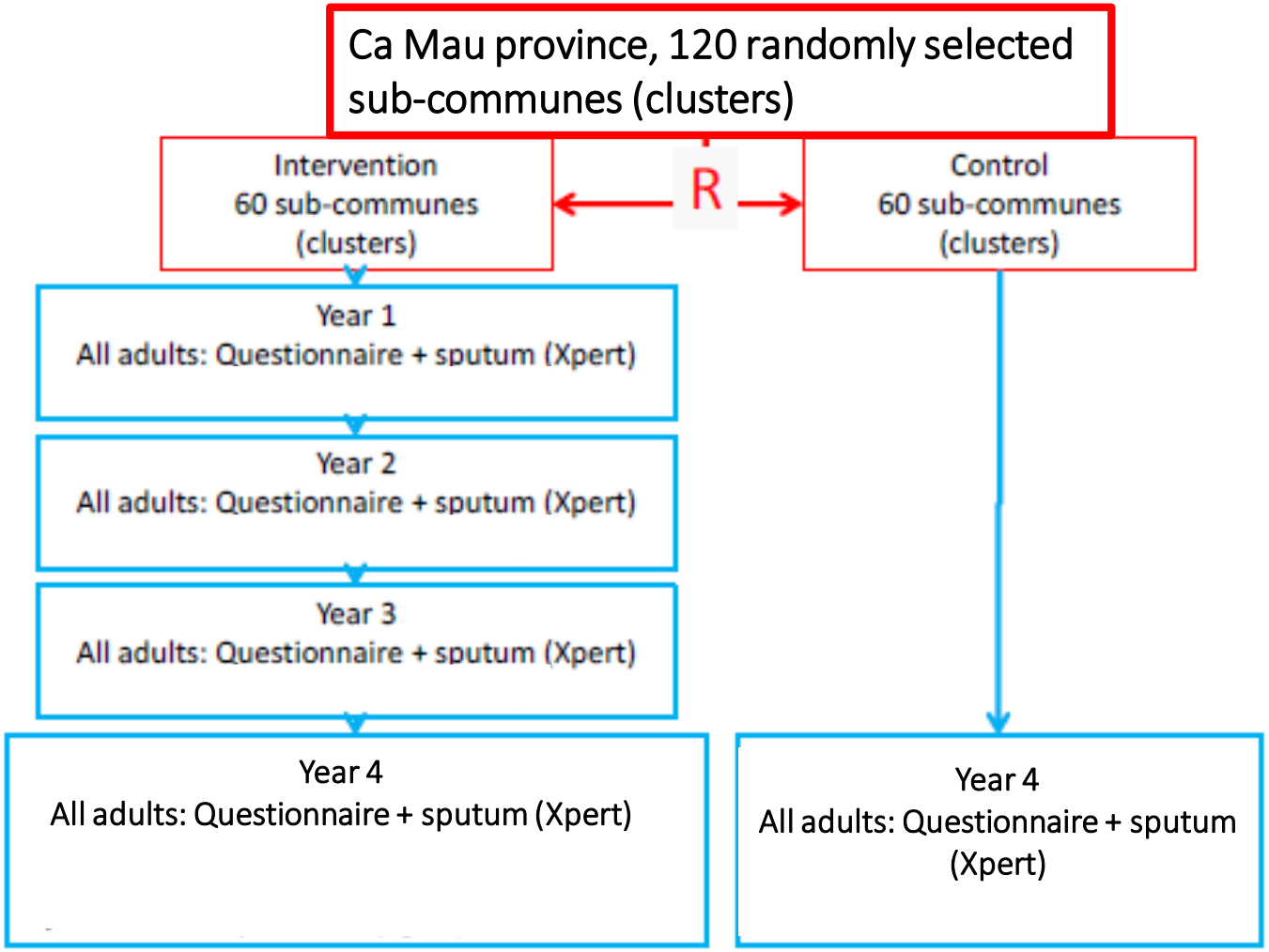
Cluster randomised controlled trial



Procedure for screening intervention in sub-communes

Community engagement

Enumeration of adult population
Informed consent

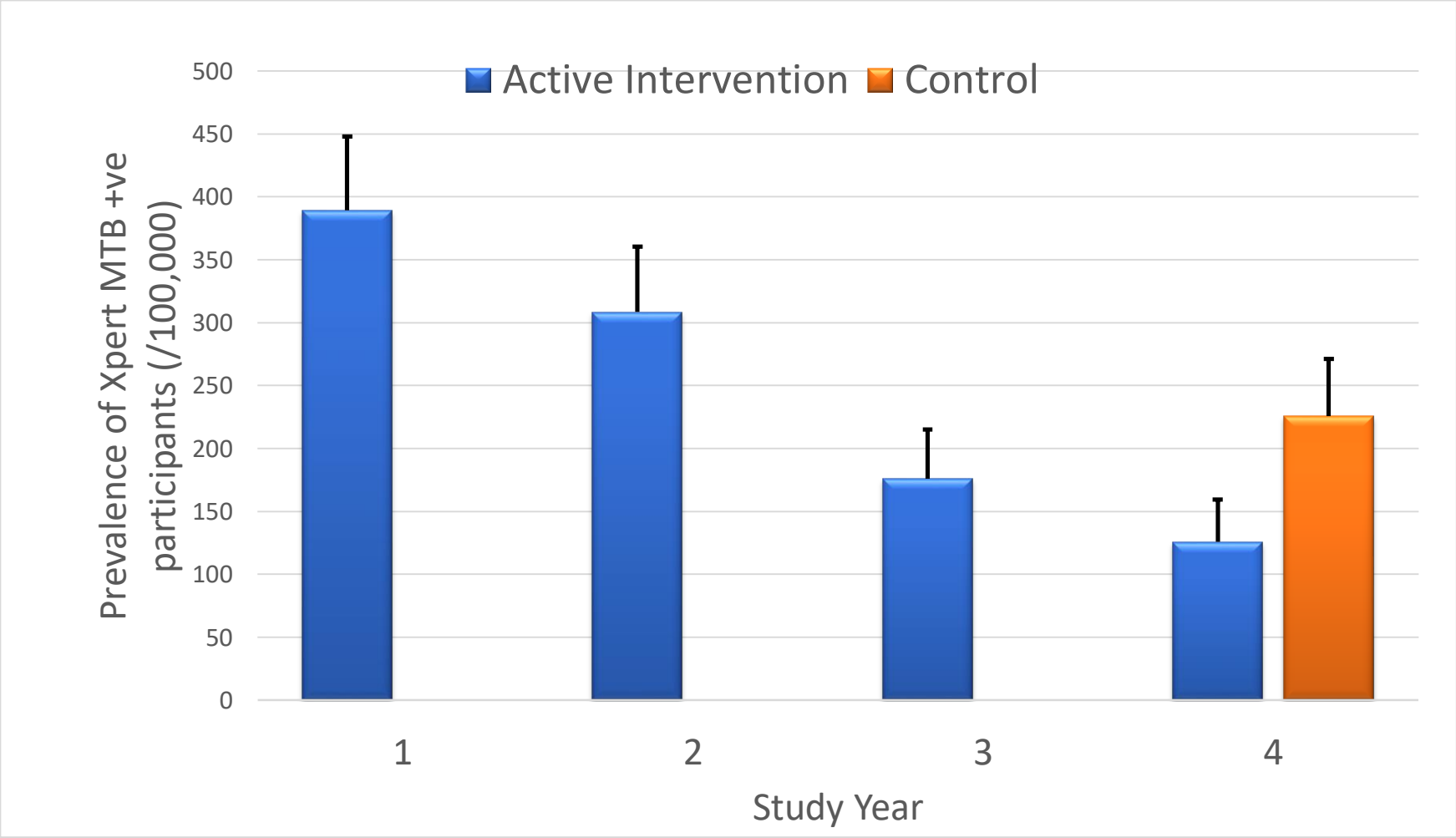
Screening: collection of spontaneously expectorated sputum

Testing sputum specimens with Xpert MTB/RIF

Sputum Collection

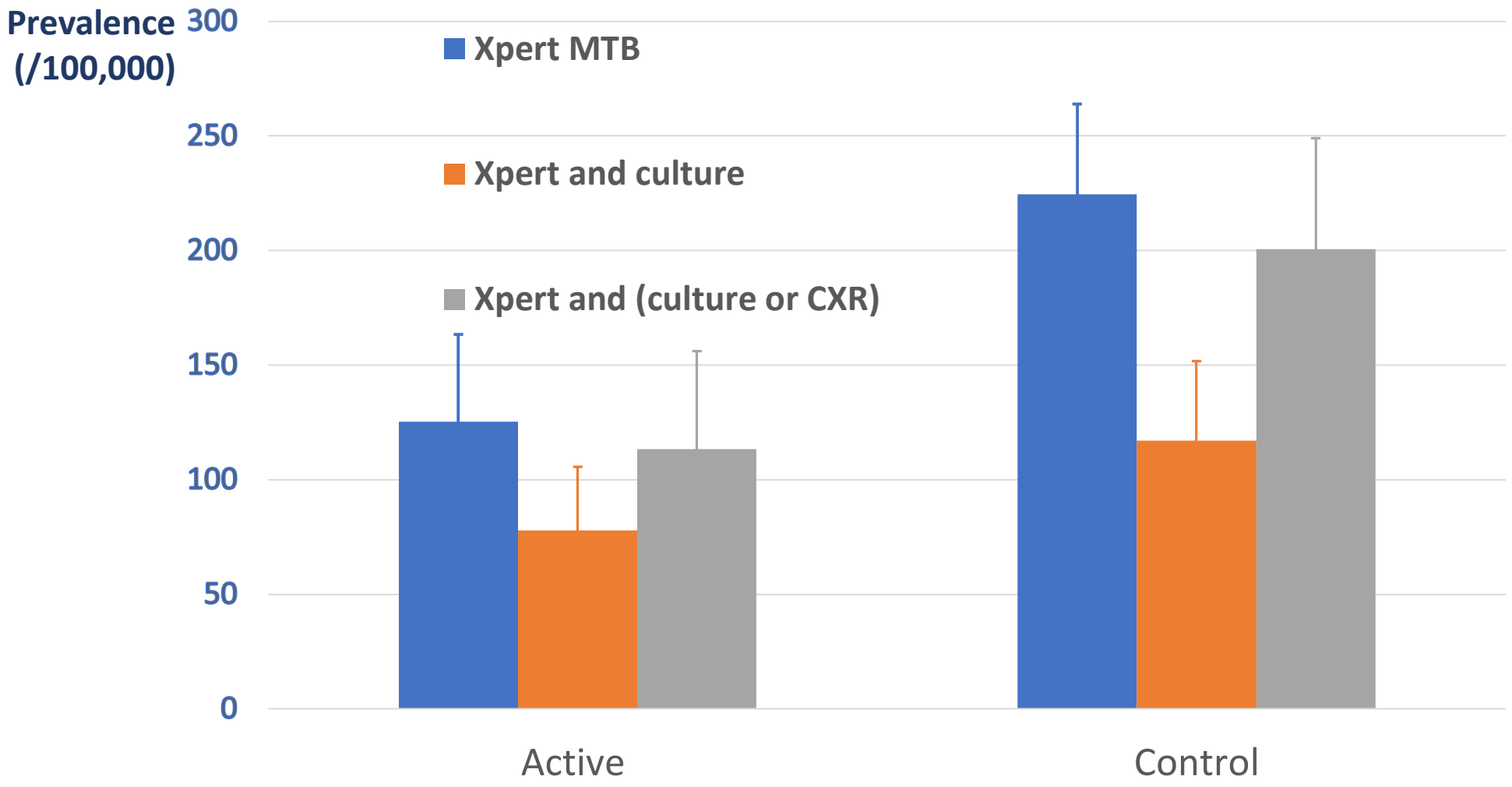

HIEP THANH PLASTIC

Prevalence of Xpert MTB positive by year and group



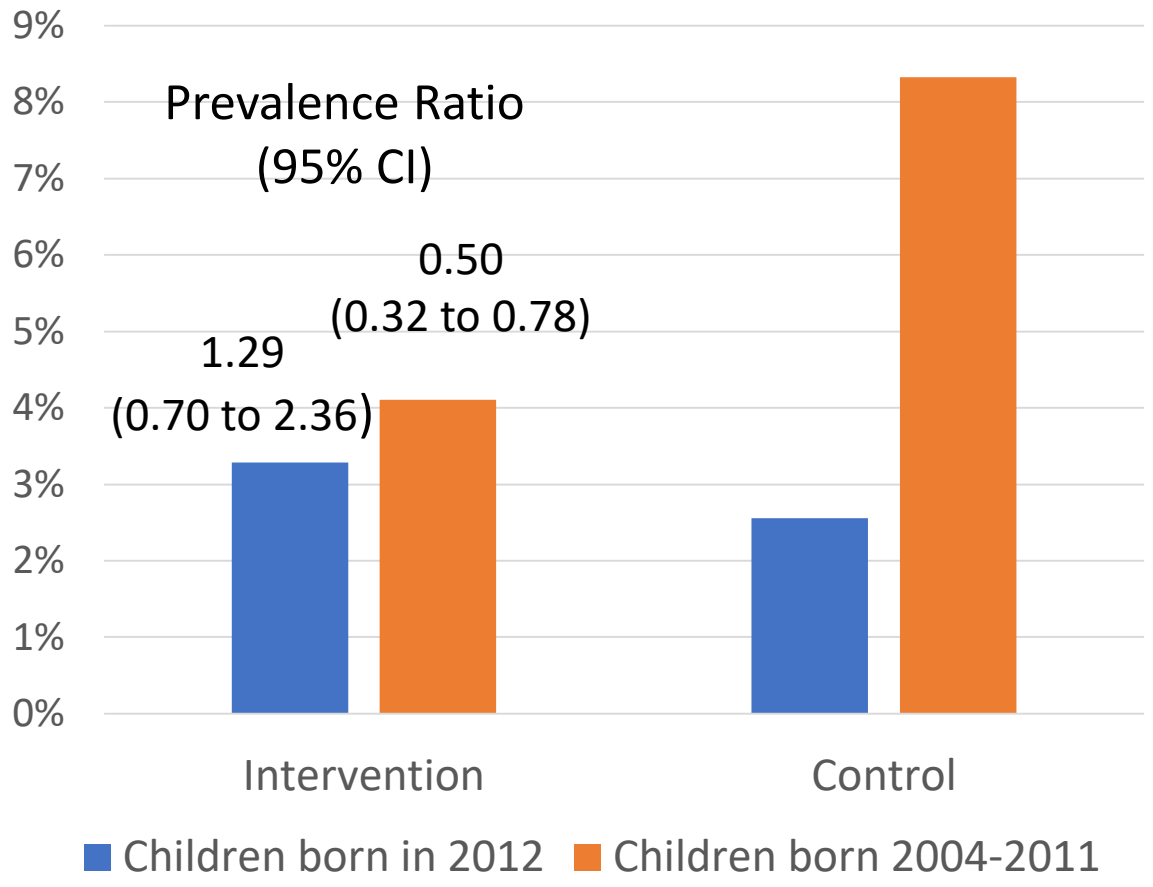
Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. N Engl J Med. 2019;381(14):1347-57.

Prevalence of TB by group, year 4



Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. N Engl J Med. 2019;381(14):1347-57.

Prevalence of +ve IGRA in children, by intervention status



Marks GB, Nguyen NV, Nguyen PTB, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. N Engl J Med. 2019;381(14):1347-57.

Conclusions from ACT3

- Community-wide active case finding can reduce
  - The prevalence of TB
  - The prevalence of TB infection in children
- May play a role in the elimination of TB
- Many questions remain prior to scale-up


Dasani

Australian Government

National Health and Medical Research Council

NHMRC

Moving from proof-of-concept to Ending TB

What are the key drivers for Ending TB in high-burden settings?

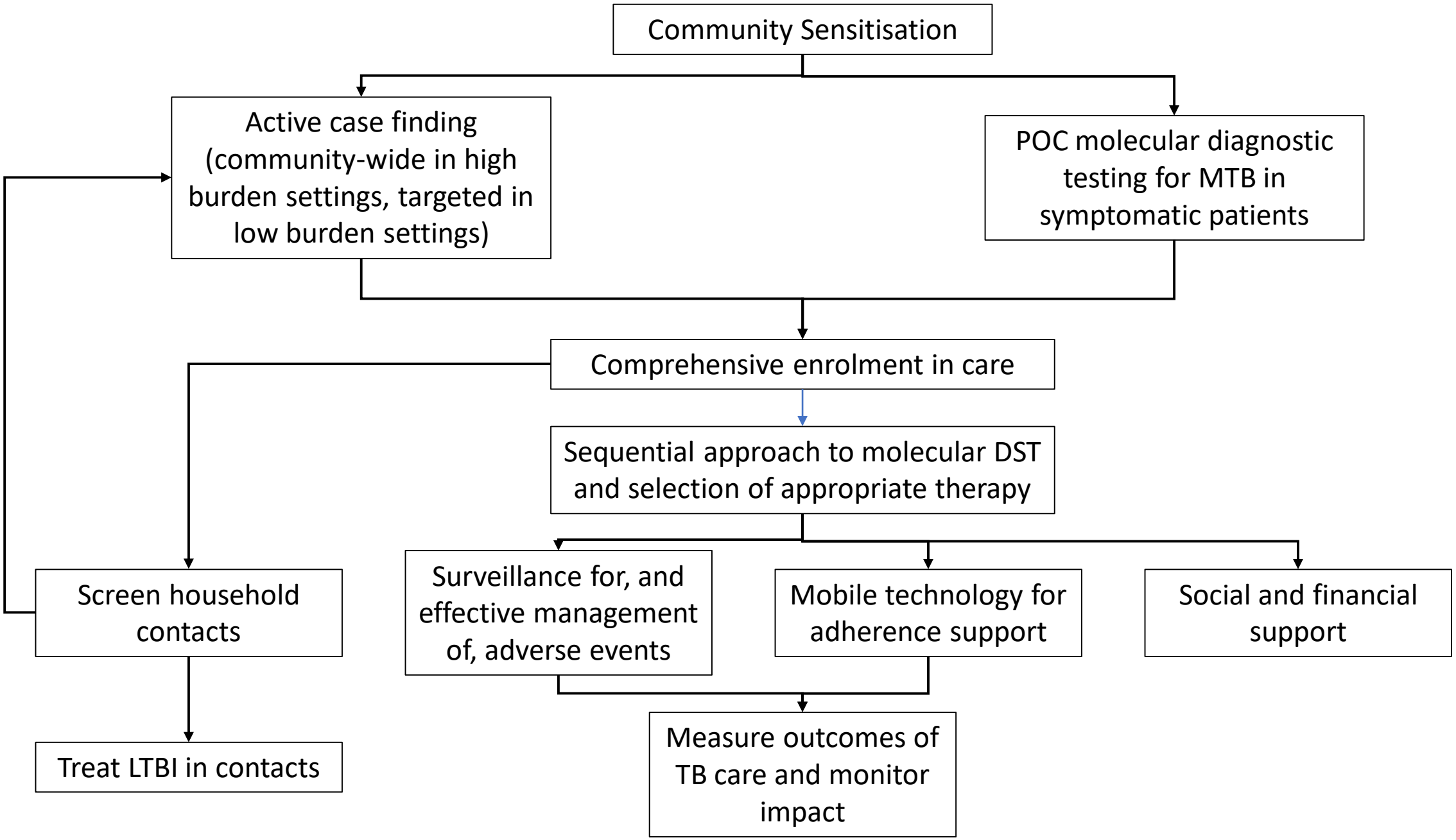
- Ongoing transmission due to prevalent, undiagnosed, infectious cases
  - Many are asymptomatic or do not seek care
  - ACT3 study was directed at this driver
- Barriers to commencing and completing effective treatment

We need to focus on interventions that target these drivers

Beginning to End TB — scaling up effective interventions

1. Community sensitisation and advocacy
2. Community-wide active case finding
   - leaving no-one behind
3. Comprehensive enrolment in care
   - for those diagnosed with TB
4. Algorithmic - sequential approach to molecular DST
   - to ensure that appropriate therapy is administered from the beginning of therapy

5. Effective surveillance for, and management of, AEs
   - to maximise safety and adherence
6. Social and financial support during therapy
7. Mobile technology to assist in adherence promotion
8. Screening household contacts
   - for active TB and treatment of LTBI
9. Monitoring outcomes


Community Sensitisation
Active case finding (community-wide in high burden settings, targeted in low burden settings)
POC molecular diagnostic testing for MTB in symptomatic patients
Comprehensive enrolment in care
Sequential approach to molecular DST and selection of appropriate therapy
Screen household contacts
Surveillance for, and effective management of, adverse events
Mobile technology for adherence support
Social and financial support
Treat LTBI in contacts
Measure outcomes of TB care and monitor impact

- We have a problem
- We have targets
- We have advocacy and seek political commitment
- We have tools that work
- We need to chart a course
  - Walk the walk
    - Ride the rocky road to TB elimination