



University
of Glasgow

Responding to Rapidly Changing HIV and Tuberculosis Epidemiology in Africa

Prof Peter MacPherson

World TB Day 2023

Swiss Tropical & Public Health Institute

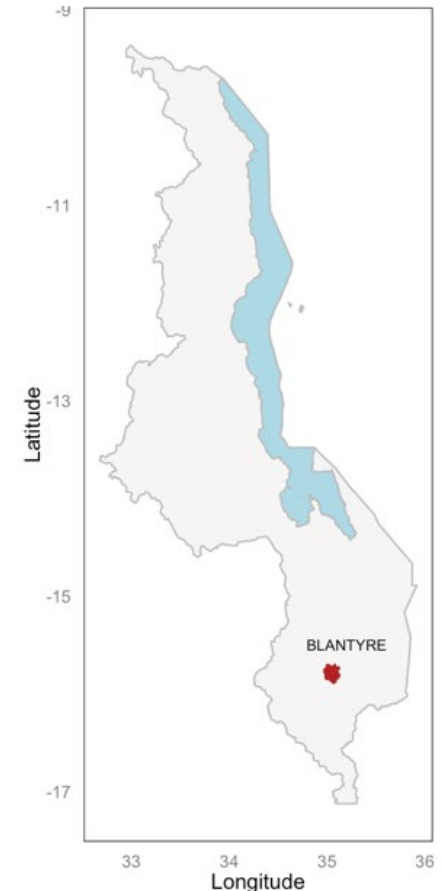
**WORLD
CHANGING
GLASGOW**

**A WORLD
TOP 100
UNIVERSITY**



Overview of presentation

- 1.** Emerging shifts in tuberculosis epidemiology
Particularly in high HIV prevalence countries in Africa
- 2.** Renewed focus on community-based active case finding
Delivering smarter, more effective and efficient interventions?
- 3.** New tools for finding the missing millions
But how to measure impact?





1. Emerging shifts in tuberculosis epidemiology
Particularly in high HIV prevalence countries



TB incidence declining in many high HIV prevalence countries

Percentage of TB incidence that is HIV-associated

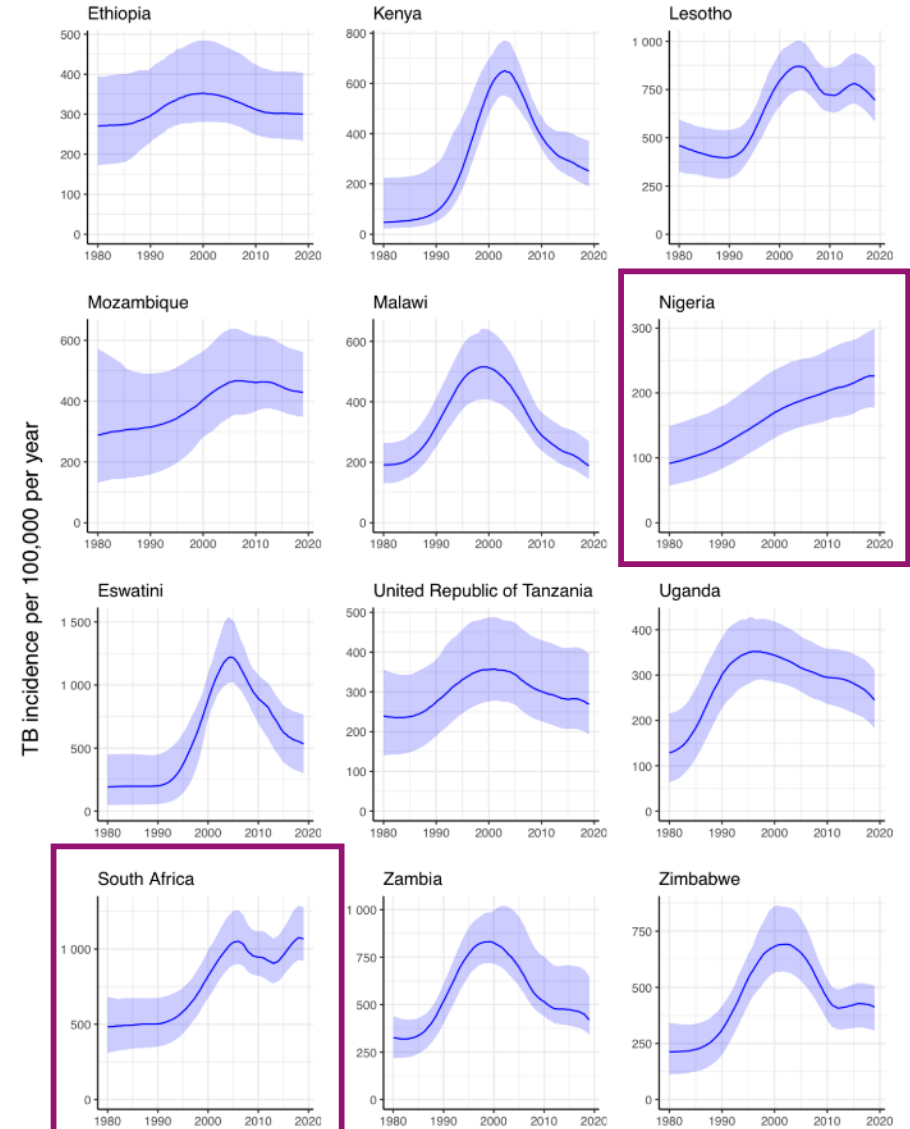
47%

2000



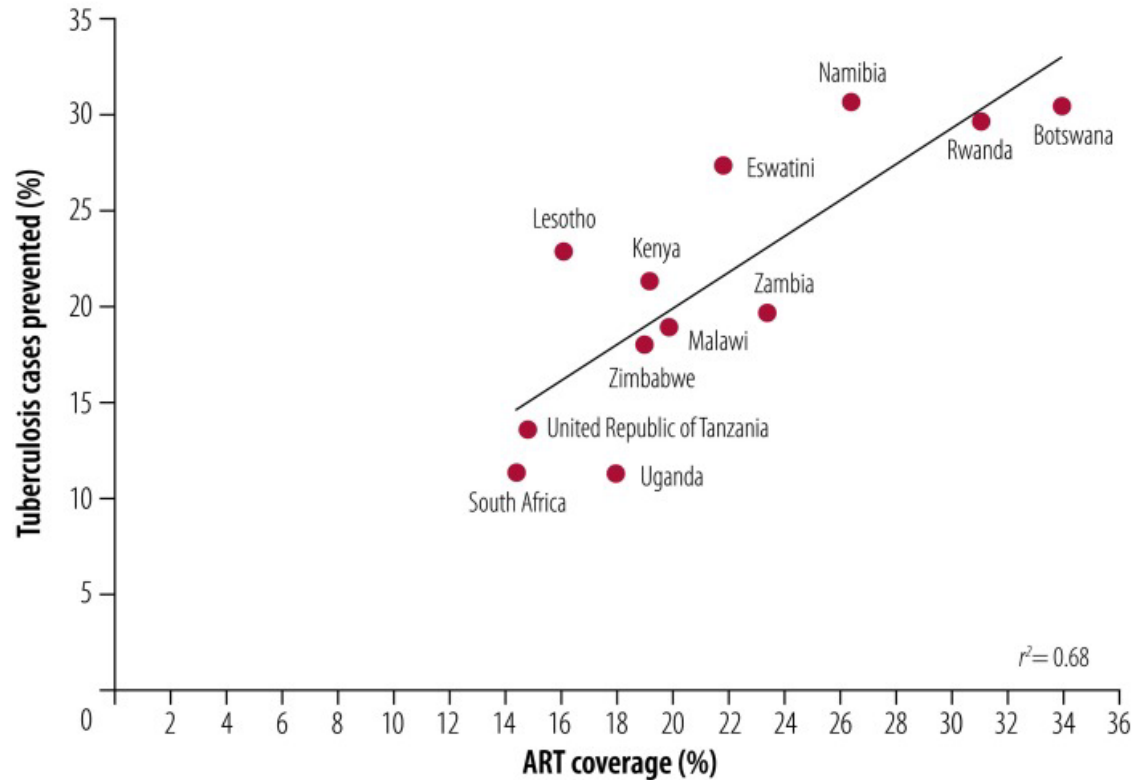
41%

2019



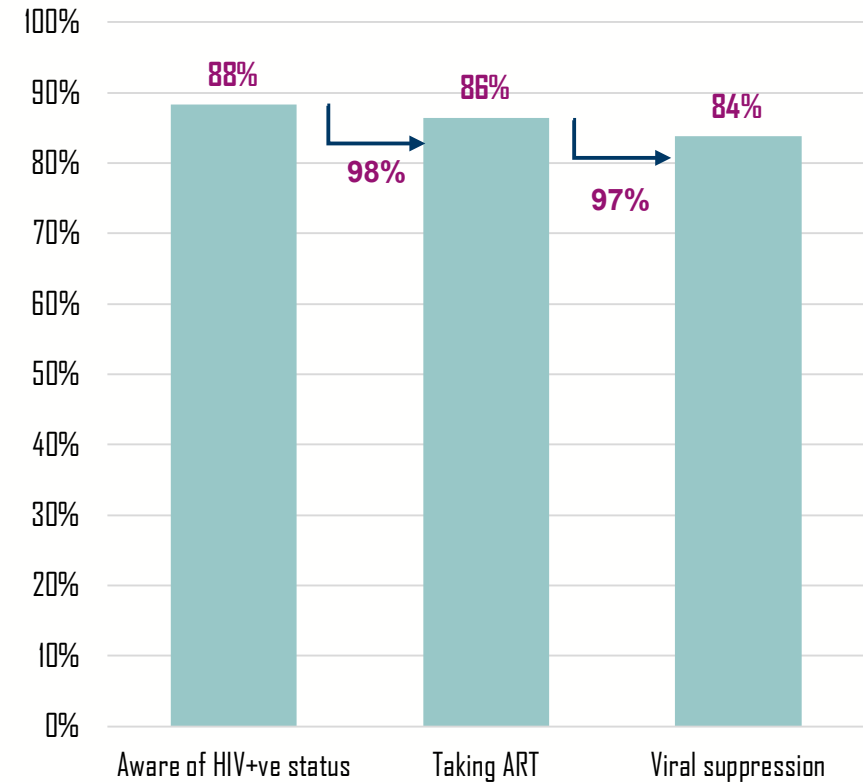
What is driving changes in TB epidemiology?

Association between antiretroviral coverage and tuberculosis incidence in people living with HIV



12 countries in the WHO African Region, 2003–2016

HIV testing and treatment cascade
Malawi: 2020-2021





Changes accelerated at city-level

Blantyre City, Malawi

Population: 1.1 million



Marriott Nliwasa



Rachael Burke



McEwen Khundi

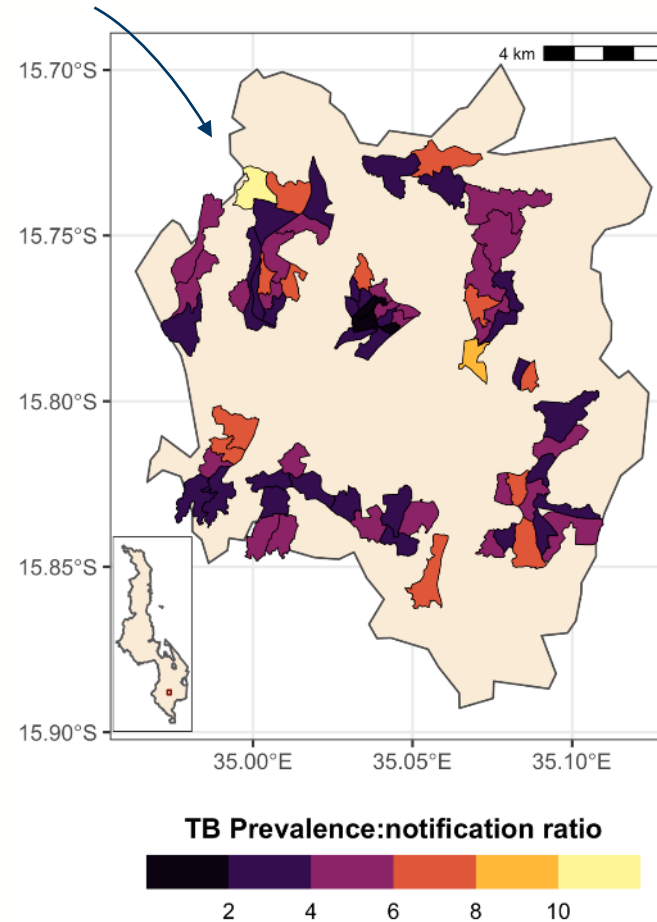


James Carpenter

Blantyre City TB case notification rates (n=25,202)



Underdiagnosis concentrated in informal settlements



Blantyre City TB prevalence

~1088 per 100k (2014)

80% reduction

215 per 100k (2021)

- Khundi et al PLOS One 2022
- Khundi et al Epidem & Infect 2021
- Nwaza-Soko et al Emerg Infect Dis 2021
- Ku et al BMC Medicine 2021
- MacPherson et al BMC Med 2019



Ageing and concentrating HIV epidemic



Jeff Eaton



Augustine Choko

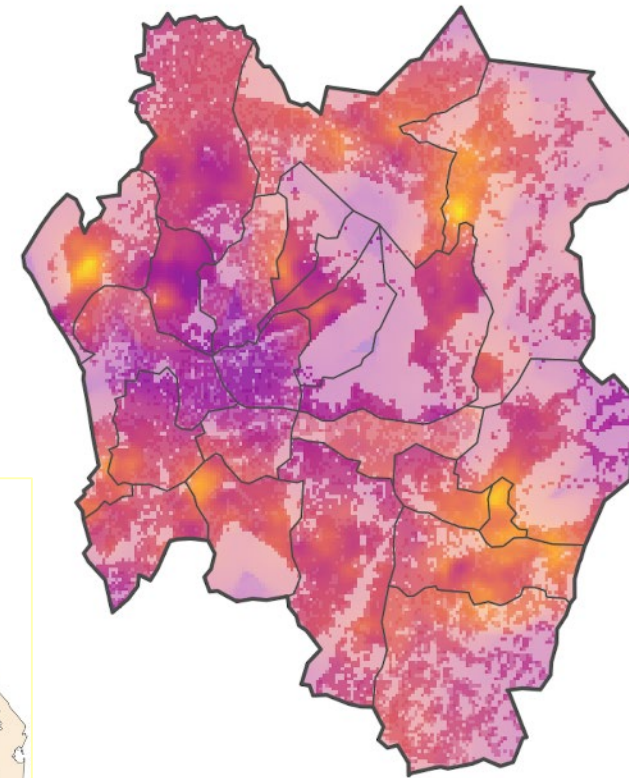
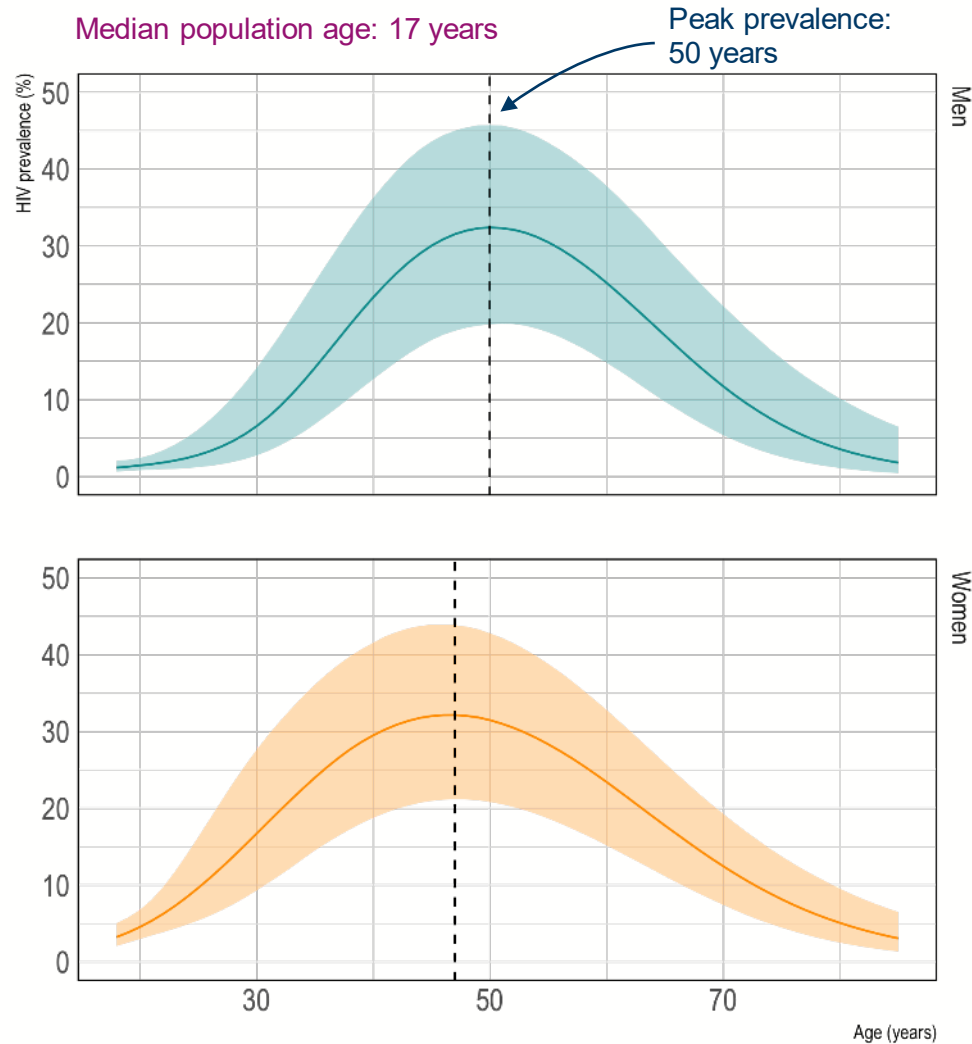


Rachael Burke

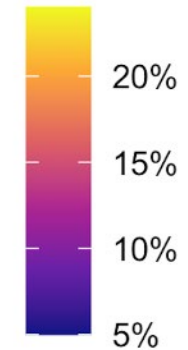


Rebecca Nwaza

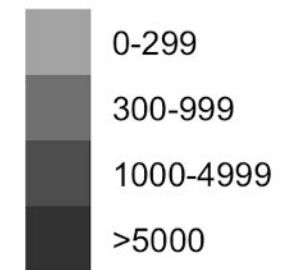
Blantyre City, Malawi (Population: 1.1 million)



HIV prevalence, age 15-49y



Population density per km²



Threats: Impact of COVID-19 on TB notifications in Blantyre



Pete Dodd



Rachael Burke



Rebecca Nwaza-Soko



333 fewer TB notifications
(95% CI: 291 to 376)

24% reduction
(95% CI: 21 to 26%)



University
of Glasgow

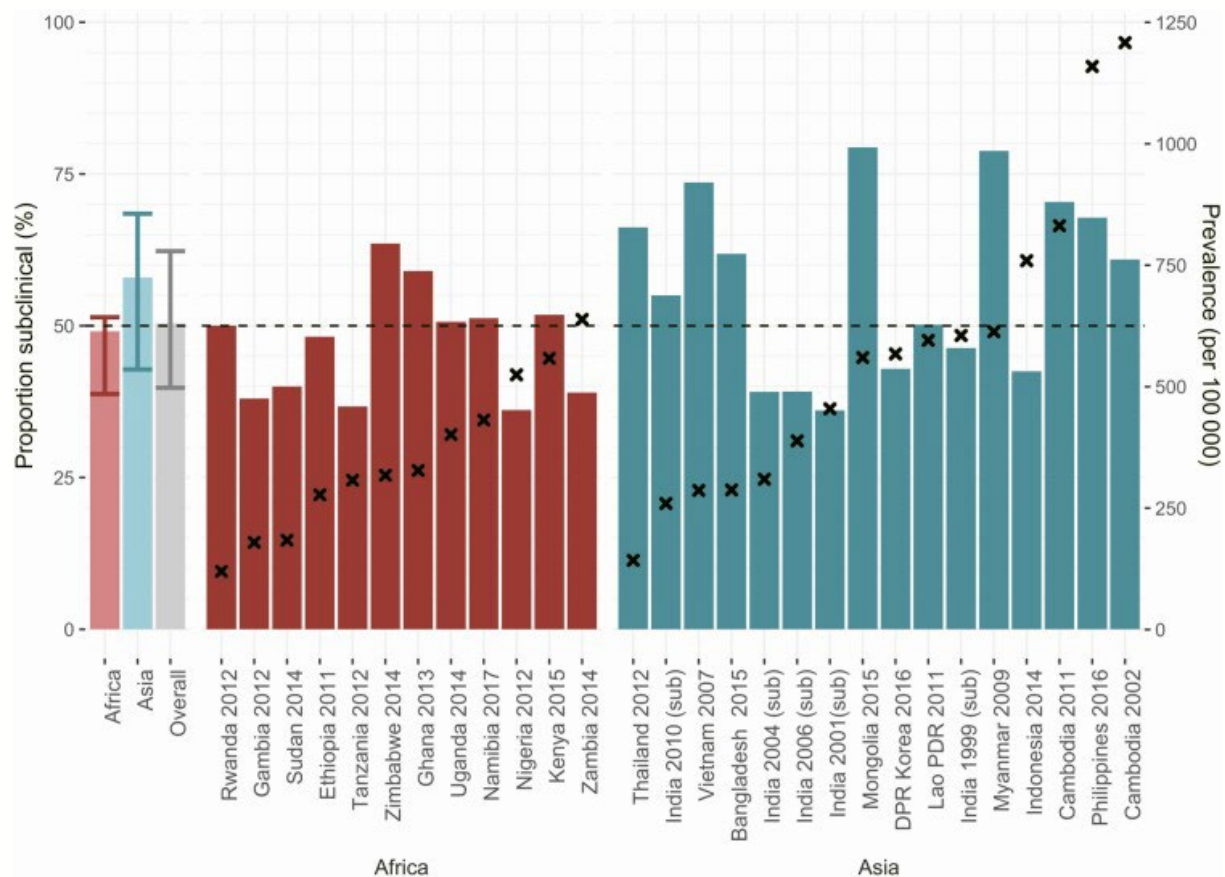
Threats: Impact of climate crisis on TB care and prevention



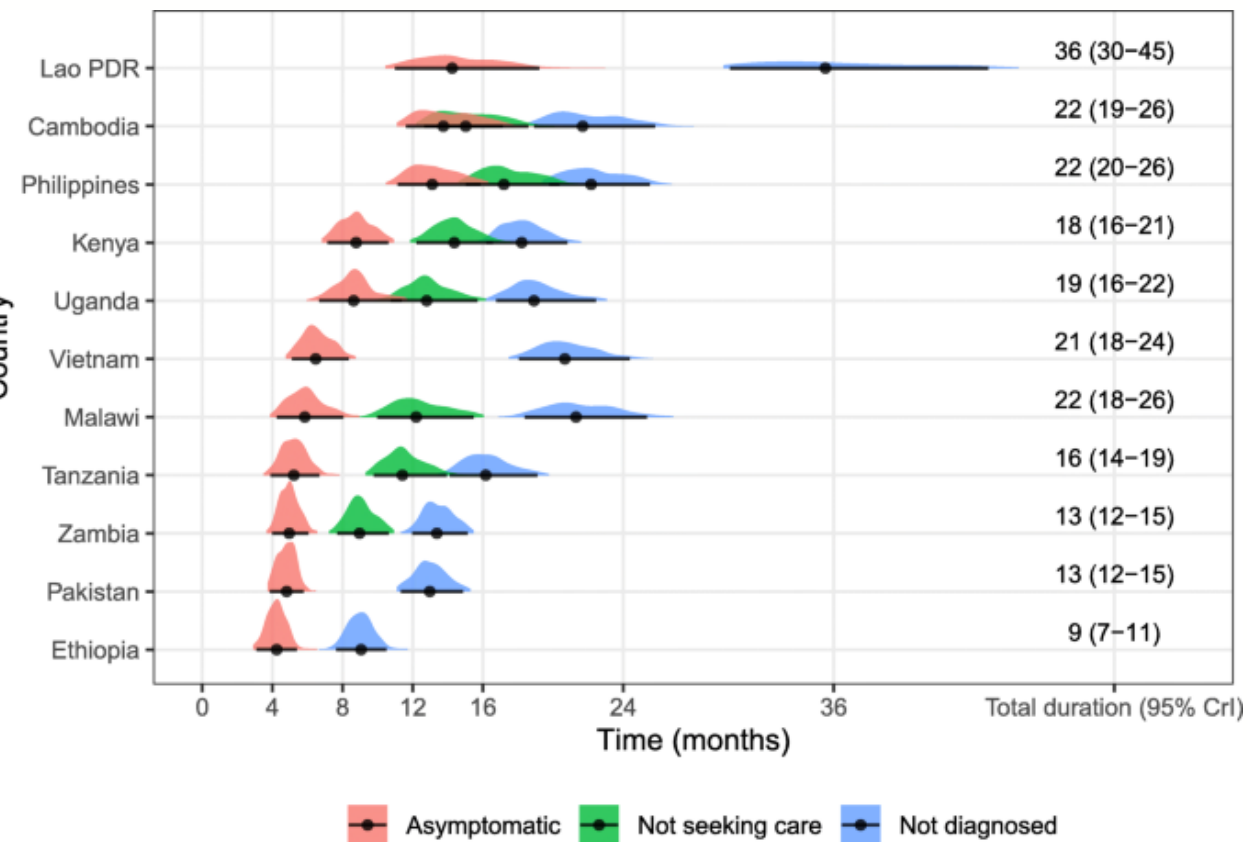
Cyclone Freddy: Blantyre, Malawi March 2023

New insights into subclinical TB: implications for TB programmes

50% of bacteriologically-confirmed TB was subclinical



Asymptomatic TB disease typically lasts around 6 m





Subclinical TB – back to the future?

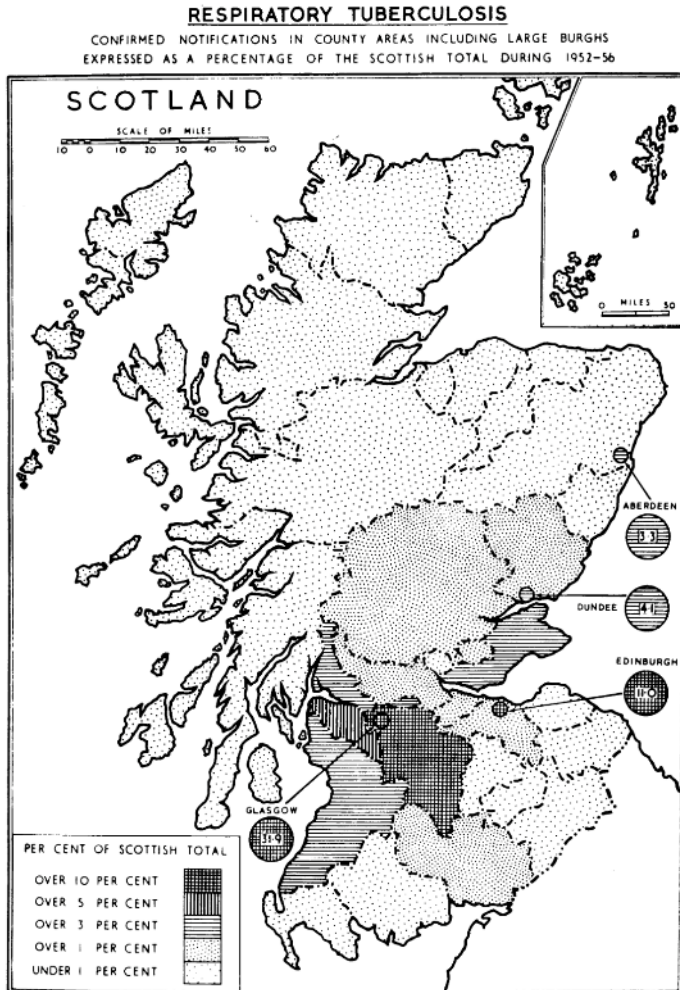
Scottish Mass Radiography Campaign 1957-1958

>40% of entire adult population screened in 60 weeks

Previous ACF interventions in:

- USA, Denmark,
- Locally (Wales, Northumberland, Stockholm, Liverpool)

Where reported, substantial fraction of bacteriologically-positive TB was asymptomatic



		Adults resident in survey areas		Difference A/E Per cent.
		Estimated	Actual 1957-58	
Attendance		1,200,000	1,639,957	+ 37
Active tuberculosis	New cases	2,400	3,988	+ 66
	Rate/1000	2.0	2.43	+ 22
Observation tuberculosis	New cases	7,200	7,235	-
	Rate/1000	6.0	4.35	- 27



Implications of changing TB epidemiology in high HIV prevalence settings

1

TB epidemics are concentrating: spatially, and within harder-to-reach priority groups

2

Need to focus on high-quality, targeted screening programmes, that minimize harms, and maximize benefits and efficiencies

3

New screening tools, approaches, and ways of measuring impact urgently needed



2. Renewed focus on community-based active case finding Smarter, more effective and efficient interventions?



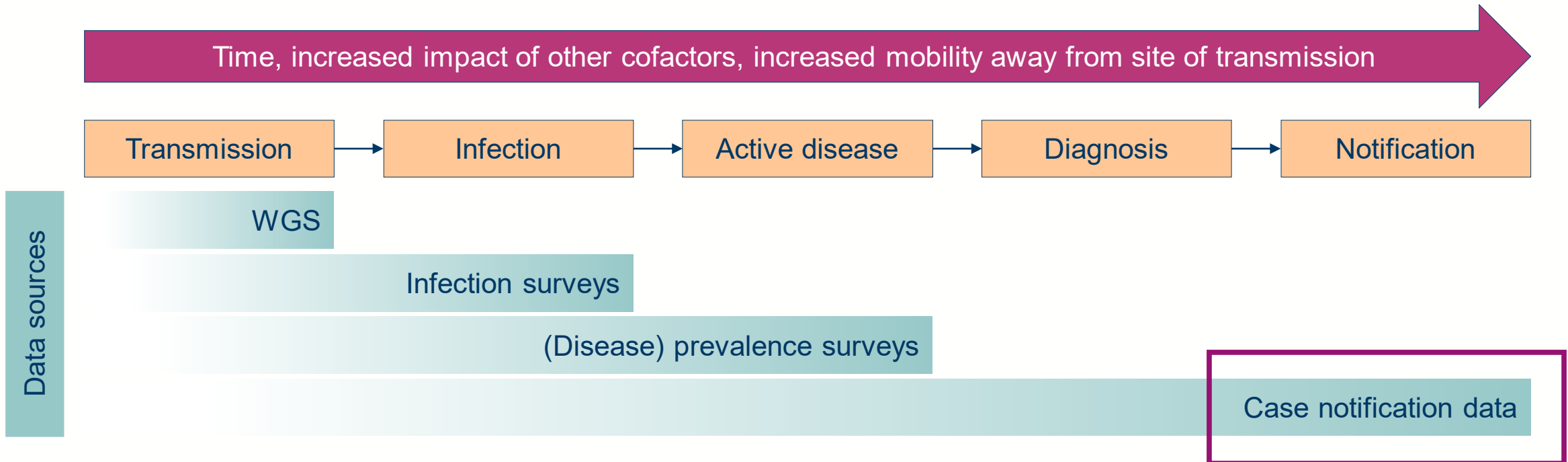
Epidemiological targets of active case finding programmes



Mphatso Phiri



Hannah Rickman

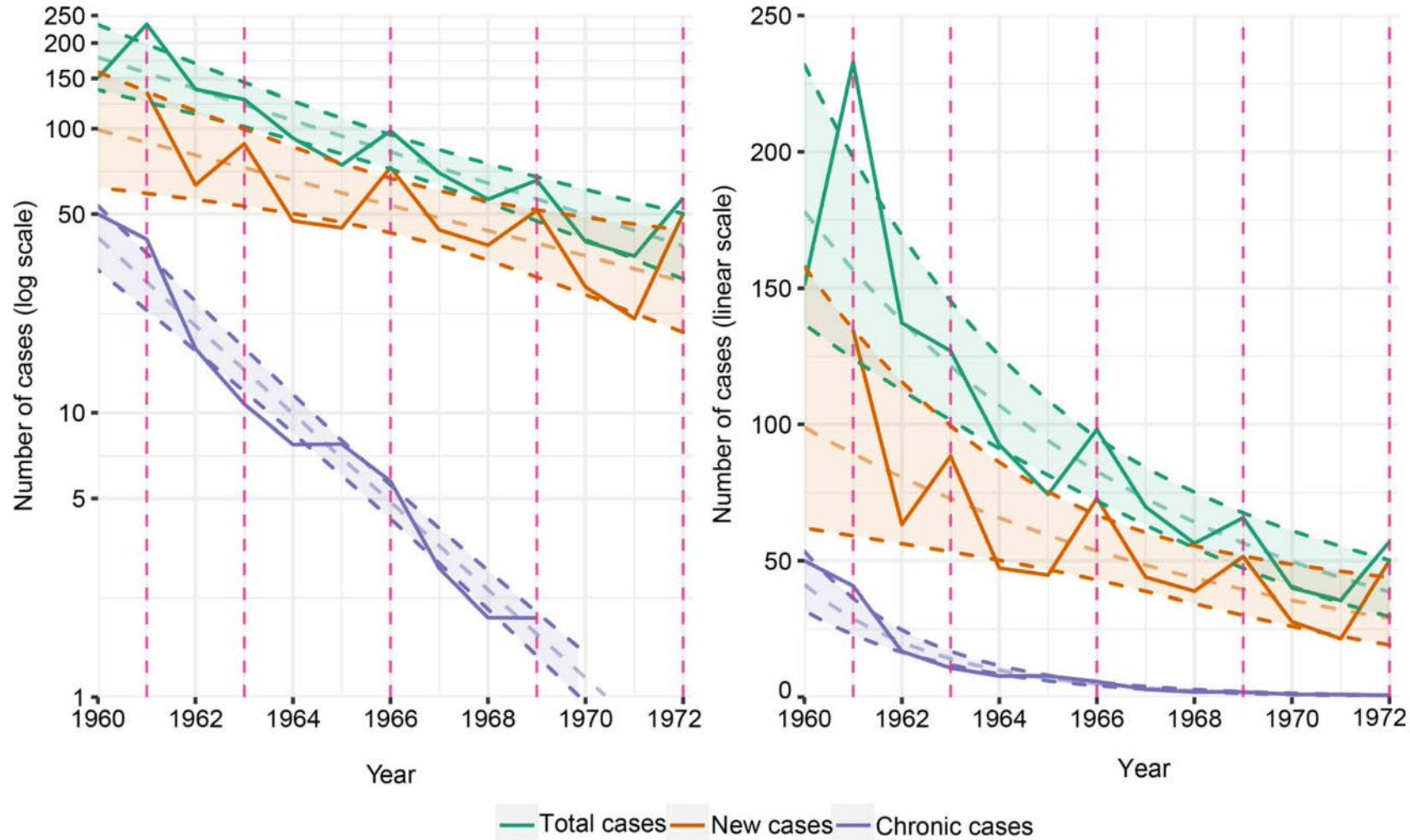




Active case finding: impact on case notification rates

What should we expect to see?

TB notifications in Kof in, Czechoslovakia, 1960–1972 (Schwalb et al IJTLD 2022)

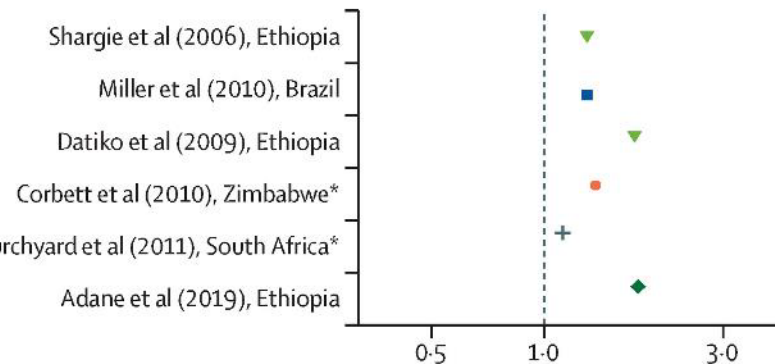


Community-based TB active case finding: impact on case notification rate ratios



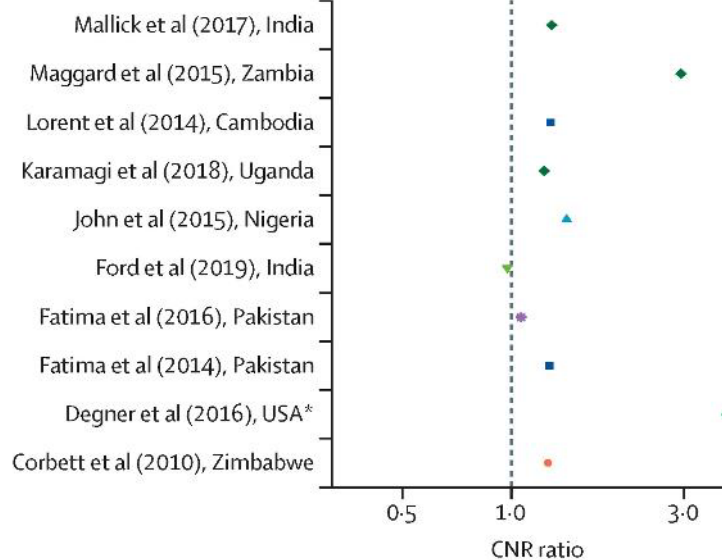
Rachael Burke

Randomised controlled trial

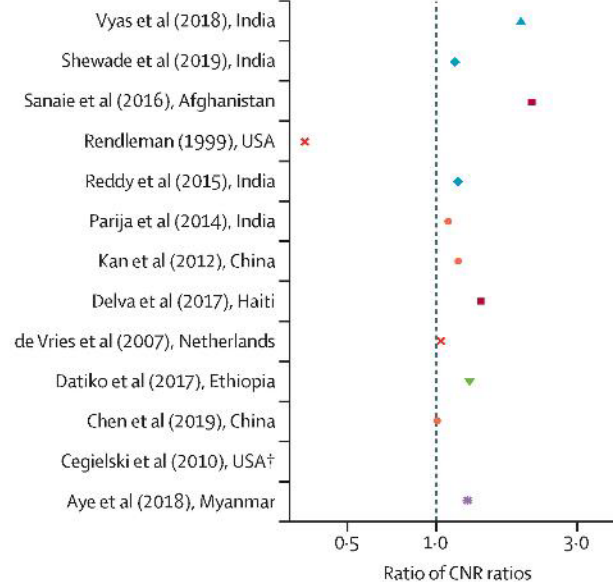


1980-2020: >100 million years of person follow-up

Before-after without control group



Controlled before-after



Articles

Community-based active case-finding interventions for tuberculosis: a systematic review

Summary

Background Community-based active case-finding interventions might identify and treat more people with tuberculosis disease than standard case detection. We aimed to assess whether active case-finding interventions can affect tuberculosis epidemiology in the wider community.

Methods We did a systematic review by searching PubMed, Embase, Scopus, and Cochrane Library for studies that compared tuberculosis case notification rates, tuberculosis disease prevalence, or tuberculosis infection prevalence or incidence in children, between populations exposed and unexposed to active case-finding interventions. We included studies published in English between Jan 1, 1990, and April 31, 2020. Studies of active case-finding in the general population, in populations perceived to be at high risk for tuberculosis, and in closed settings were included, whereas studies of tuberculosis screening at healthcare facilities, among household contacts, or among children only, and studies that covered fewer than 1000 people were excluded. To estimate effectiveness, we extracted or calculated case notification rates, prevalence of tuberculosis disease, and incidence or prevalence of tuberculosis infection in children, and compared rates of these outcomes between groups that were exposed or not exposed to active case-finding interventions.

Results 27183 abstracts were screened and 948 articles underwent full-text review. 28 studies contributed data for analysis of tuberculosis case notification, nine for prevalence of tuberculosis disease, and two for incidence or prevalence of tuberculosis infection in children. In one cluster-randomised trial in South Africa and Zambia, an active case-finding intervention based on community mobilisation and sputum drop-off did not affect tuberculosis prevalence, whereas, in a cluster-randomised trial in Vietnam, an active case-finding intervention based on sputum tuberculosis tests for the purpose of reducing tuberculosis prevalence in the community. We found no evidence, low-quality evidence that active case-finding might increase the number of cases of tuberculosis notified in populations with structural risk factors for tuberculosis.

Interpretation Community-based active case-finding for tuberculosis might be effective in changing tuberculosis epidemiology and thereby improving population health if delivered with high coverage and intensity. If possible, active case-finding projects should incorporate a well-designed, robust evaluation to contribute to the evidence base and help decide which delivery methods and diagnostic strategies are most effective.

Funding WHO Global TB Programme.

Copyright © 2021 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Tuberculosis is the leading infectious cause of death worldwide. An estimated 1 million people with active tuberculosis were notified in 2019, but many were not notified through national reporting systems in 2019. The notified incidence of people with undiagnosed or untreated active tuberculosis at risk of death and severe illness, and who transmit tuberculosis to others in their households and communities. Evidence in global tuberculosis burden has been slow and, at the rate of current progress, an unlikely to meet the WHO End TB Strategy target to reduce incidence by 95% and tuberculosis deaths by 95% to 2035. Therefore, more intensive, evidence-based strategies that can increase diagnosis and treatment of tuberculosis, and potentially reduce tuberculosis transmission, are urgently required.

Community-based tuberculosis screening, delivered through active case-finding interventions, has been widely implemented throughout the high and low-income, but with varying levels of intensity between regions and over time. However, tuberculosis care and prevention interventions that rely primarily on passive case detection within their households and communities. Evidence in global tuberculosis burden has been slow and, at the rate of current progress, an unlikely to meet the WHO End TB Strategy target to reduce incidence by 95% and tuberculosis deaths by 95% to 2035. Therefore, more intensive, evidence-based strategies that can increase diagnosis and treatment of tuberculosis, and potentially reduce tuberculosis transmission, are urgently required.

Community-based tuberculosis screening, delivered through active case-finding interventions, has been widely implemented throughout the high and low-income, but with varying levels of intensity between regions and over time. However, tuberculosis care and prevention interventions that rely primarily on passive case detection within their households and communities. Evidence in global tuberculosis burden has been slow and, at the rate of current progress, an unlikely to meet the WHO End TB Strategy target to reduce incidence by 95% and tuberculosis deaths by 95% to 2035. Therefore, more intensive, evidence-based strategies that can increase diagnosis and treatment of tuberculosis, and potentially reduce tuberculosis transmission, are urgently required.

Active case-finding encompasses a wide range of interventions that range in intensity from health promoter visits and community mobilisation, through to systematic

WHO consolidated guidelines on tuberculosis

Module 2: Screening

Systematic screening for tuberculosis disease

World Health Organization

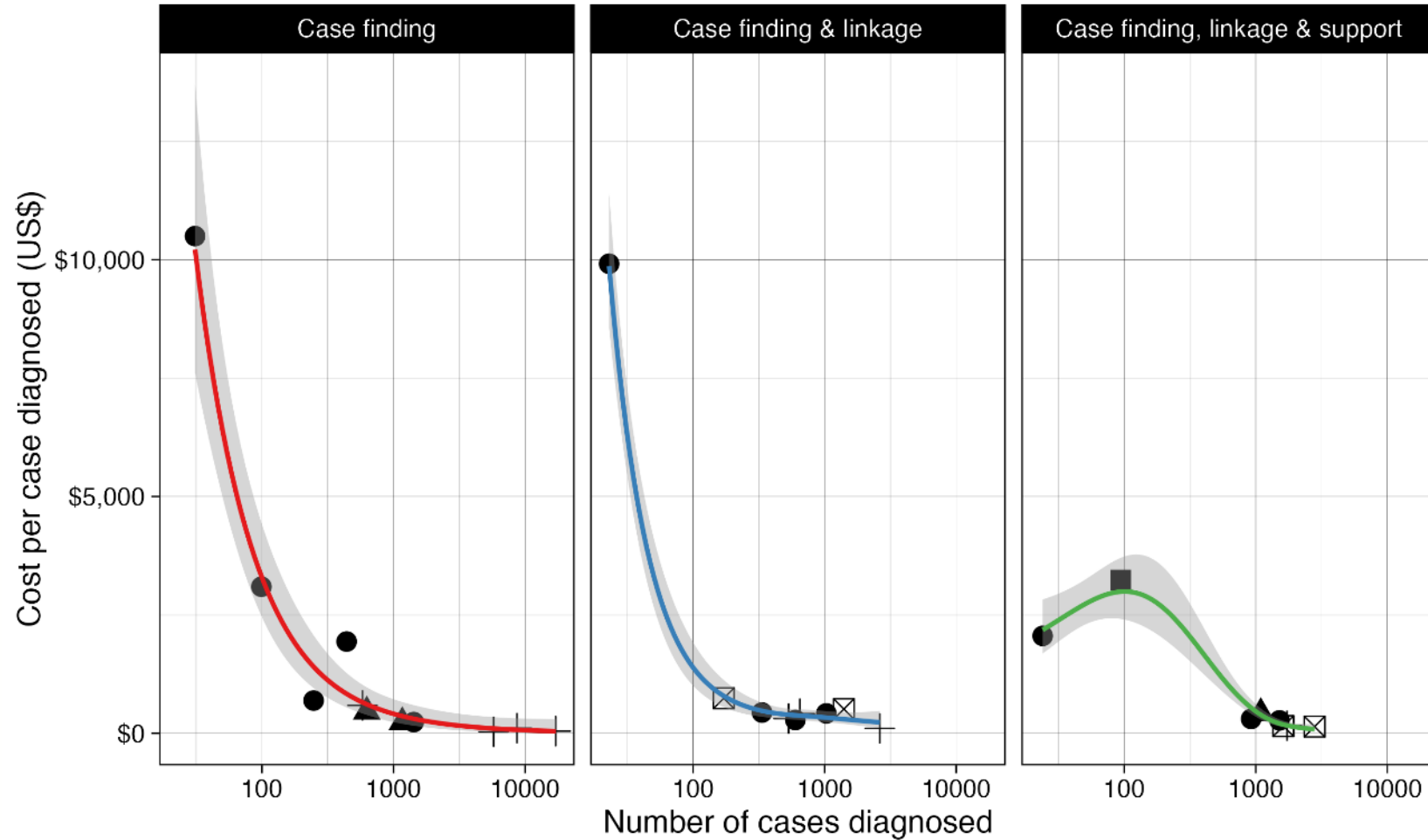
ACF impact on TB disease prevalence / infection

Study	ZAMSTAR Ayles 2013	ACT3 Marks 2019	TREATS Ayles 2021	Hit-TB Corbett unpublished	Cain unpublished	SCALE Corbett unpublished
Countries	Zambia & South Africa	Viet Nam	Zambia & South Africa	Malawi	Kenya	Malawi
ACF approach	Symptom screen -> smear	Xpert for all	Symptom screen -> Xpert/smear	Symptom screen -> smear	?	Symptom screen/CXR -> smear
Total population	447,228	42,150	49,557	34,456	?	~520,000
Effect on adult TB prevalence (aRR)	1.09 (0.86-1.40)	0.55 (0.39-0.77)	1.15 (0.67-1.95)	?	?	?
Effect on incidence/prevalence of TB infection (aRR)	1.36 (0.59-3.14)	1.29 (0.70-2.36)*	1.45 (0.97-2.15)	?	?	?

“Community-based active case-finding for tuberculosis might be effective in changing tuberculosis epidemiology if delivered with high coverage and intensity”



Cost and efficiency of TB active case finding interventions

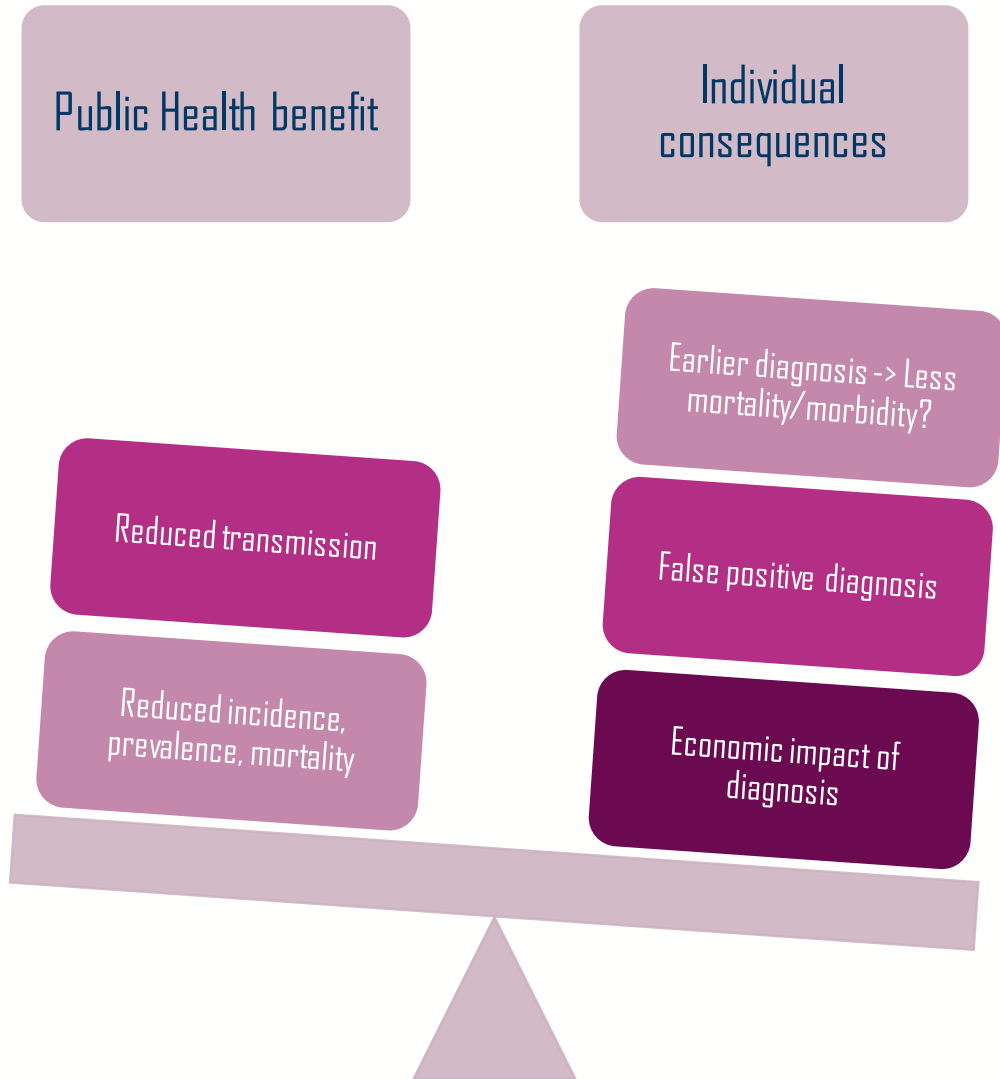


N=32 TB Reach Round 5 studies

● AFR ▲ EMR ■ PAR + SEAR ☒ WPR



Does TB active case finding improve individual outcomes?

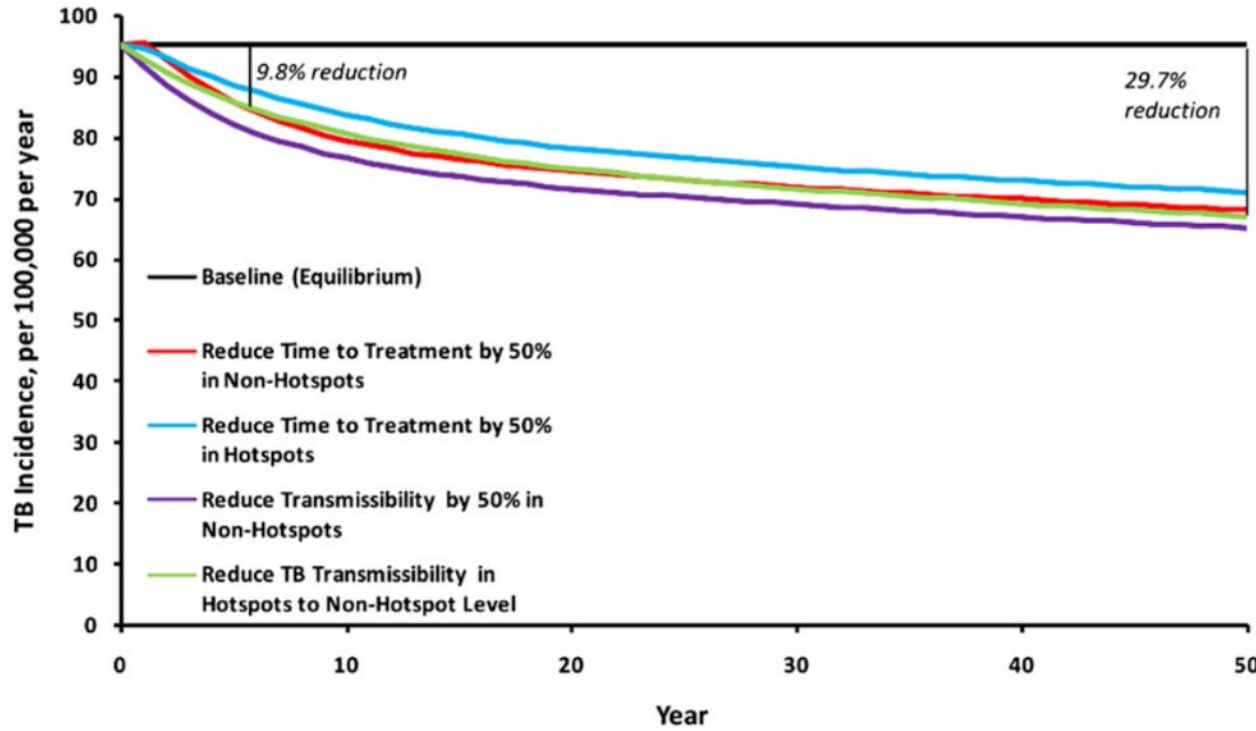


"We found **very limited data** on the effect of TB screening on individual outcomes.

Routine/research programmes **must prioritise collecting and reporting this data.**"



How should active case finding interventions be targeted?



Open access Original research

BMJ Open Effectiveness of spatially targeted interventions for control of HIV, tuberculosis, leprosy and malaria: a systematic review

Yvonne Hilland, James R Curran, Meredith Mueser, Ted Cohen, Elizabeth L Condit, Peter Muir-Pierson

ABSTRACT
Background: Spatially targeted interventions for HIV, tuberculosis, leprosy and malaria have been proposed as a means of reducing the burden of these diseases in high-burden settings. However, the effectiveness of these interventions remains unclear. This systematic review synthesises the evidence on the effectiveness of spatially targeted interventions for HIV, tuberculosis, leprosy and malaria.

Search and selection of the study
We searched Medline, Embase, Cochrane, and other databases for studies published between 1980 and 2019. We included studies that evaluated the effectiveness of spatially targeted interventions for HIV, tuberculosis, leprosy and malaria in high-burden settings. We excluded studies that did not report on the effectiveness of these interventions or that were not in English.

INTRODUCTION
The need for more targeted approaches to controlling HIV, tuberculosis (Tb), leprosy and malaria is becoming increasingly apparent. These diseases are major causes of morbidity and mortality in high-burden settings, and their control remains a major public health challenge. Spatially targeted interventions have been proposed as a means of reducing the burden of these diseases in high-burden settings. However, the effectiveness of these interventions remains unclear. This systematic review synthesises the evidence on the effectiveness of spatially targeted interventions for HIV, tuberculosis, leprosy and malaria.

- Key findings:
- Very few studies
 - Methods to define hotspots need advancing
 - How should impact be measured?

Tuberculosis transmission in HIV-endemic settings 3

Spatially targeted screening to reduce tuberculosis transmission in high-incidence settings

Background: Tuberculosis (Tb) is a major cause of morbidity and mortality in high-burden settings, and its control remains a major public health challenge. Spatially targeted interventions have been proposed as a means of reducing the burden of Tb in high-burden settings. However, the effectiveness of these interventions remains unclear. This systematic review synthesises the evidence on the effectiveness of spatially targeted interventions for Tb in high-burden settings.

INTRODUCTION
Tuberculosis (Tb) is a major cause of morbidity and mortality in high-burden settings, and its control remains a major public health challenge. Spatially targeted interventions have been proposed as a means of reducing the burden of Tb in high-burden settings. However, the effectiveness of these interventions remains unclear. This systematic review synthesises the evidence on the effectiveness of spatially targeted interventions for Tb in high-burden settings.

SEARCH AND SELECTION OF THE STUDY
We searched Medline, Embase, Cochrane, and other databases for studies published between 1980 and 2019. We included studies that evaluated the effectiveness of spatially targeted interventions for Tb in high-burden settings. We excluded studies that did not report on the effectiveness of these interventions or that were not in English.



How to target active case finding interventions?

Epidemiological data

- Spatiotemporally-resolved CNRs
- Stratified by age, sex, HIV status
- Case fatality rates
- HIV care cascade data

Healthcare utilization and access data

- Clinic distance, opening
- Clinic screening uptake and positivity
- Laboratory throughput and positivity

Community/stakeholder perspectives

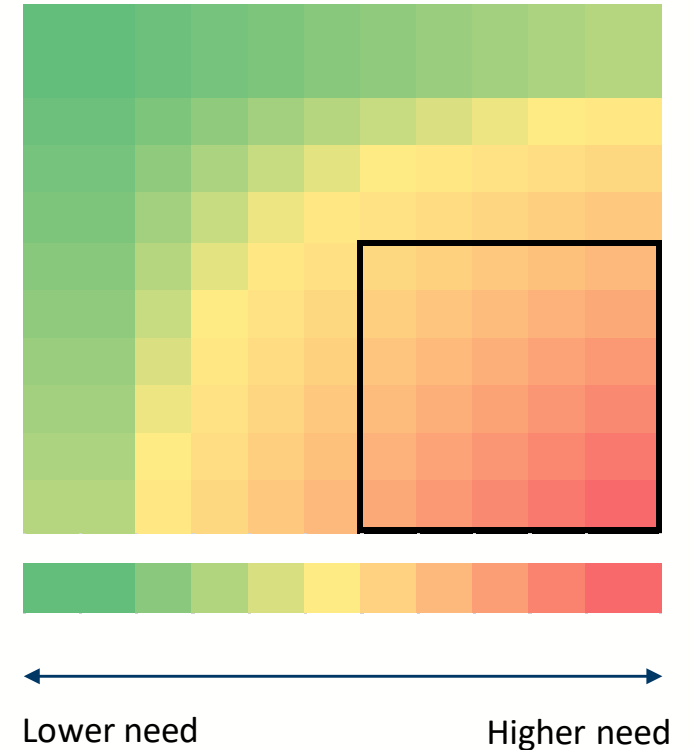
- Perceived barriers
- intersectional barriers
- Community norms and expectations

Resourcing and sustainability

- Financing
- Political support
- Management, monitoring and evaluation

Public health needs assessment

Targeted ACF





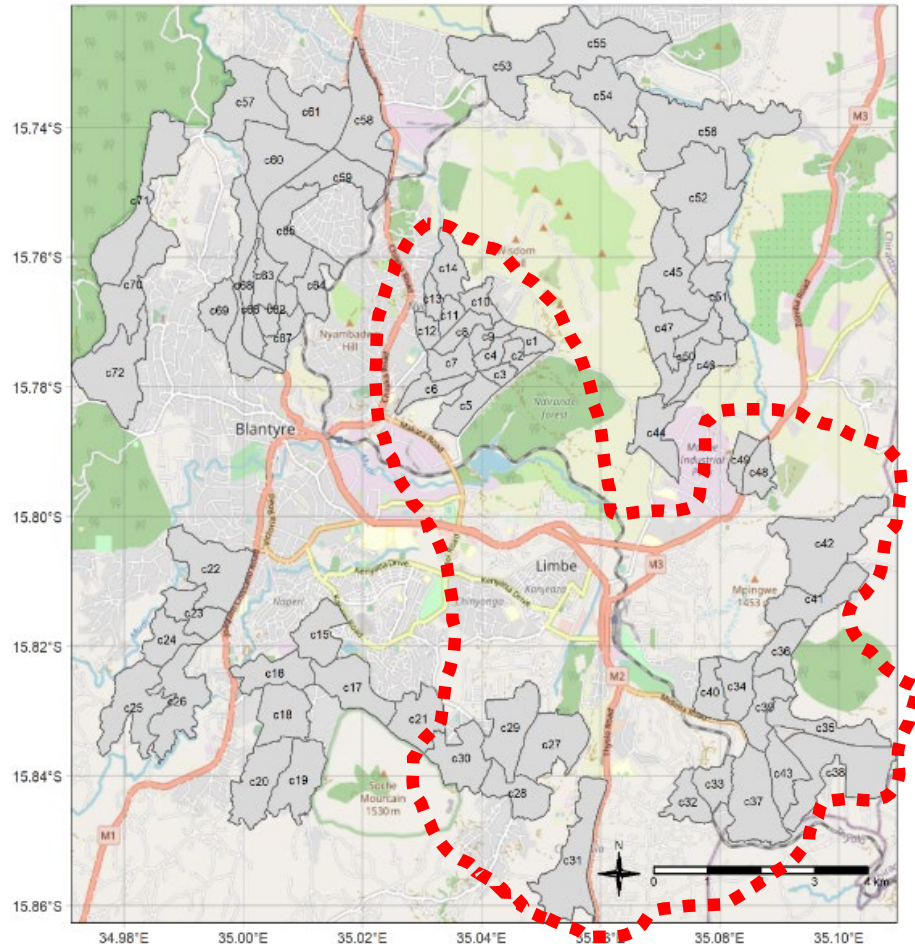
Convenience sampling for TB infection



Mphatso Phiri

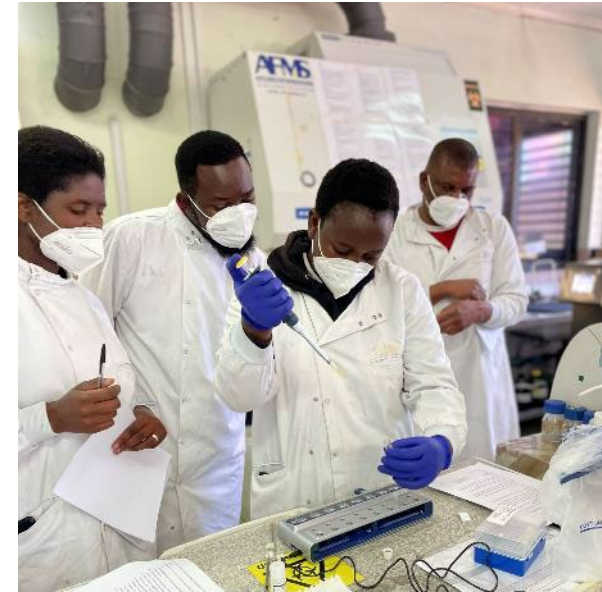


Hannah Rickman



Timasamala Study

- Testing 6,000 healthy U5s in Blantyre for TB immunoreactivity
- QFT+ IGRA
- Recruiting from:
 - 1) Cross-sectional household sample
 - 2) Convenience sampling in PHCs
- Additional cohort: 4000 adolescent and adult household members





Mphatso Phiri



Moses Kumwenda



Liz Corbett



Katherine Horton



Bertie Squire

Kenya, Malawi, Uganda, Nigeria



Focus on engaging men in TB care

488 per 100,000

231 per 100,000



2.21



1

M:F prevalence ratio in bacteriological confirmed TB





3. New tools for finding the missing millions But how to measure impact?



Computer-aided x-ray diagnosis of TB

PLOS MEDICINE

RESEARCH ARTICLE

Computer-aided X-ray screening for tuberculosis and HIV testing among adults with cough in Malawi (the PROSPECT study): A randomised trial and cost-effectiveness analysis

Peter MacPherson^{1,2,3*}, Emily L. Webb⁴, Wala Kamchedzera⁵, Elizabeth Joeke⁶, Gugu Mjoli⁷, David G. Lalloo⁸, Titus H. Divya^{9,10}, Augustine T. Choko^{11,12}, Rachael M. Burke¹³, Hendramoorthy Maheswaran¹⁴, Madhukar Pais¹⁵, S. Bertel Squire¹⁶, Marriott Nilwasa^{17,18}, Elizabeth L. Corbett^{2,3}

1 Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom, 2 Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi, 3 Clinical Research Department, London School of Hygiene and Tropical Medicine, London, United Kingdom, 4 MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London, United Kingdom, 5 Department of Radiology, Chris Hani Baragwanath Hospital, Soweto, South Africa, 6 Helse Nord TB Initiative, College of Medicine, University of Malawi, Blantyre, Malawi, 7 Department of Public Health and Policy, University of Liverpool, Liverpool, United Kingdom, 8 McGill International TB Centre, McGill University, Montreal, Canada

* peter.macpherson@lstm.ac.uk



OPEN ACCESS

Citation: MacPherson P, Webb EL, Kamchedzera W, Joeke E, Mjoli G, Lalloo DG, et al. (2021) Computer-aided X-ray screening for tuberculosis and HIV testing among adults with cough in Malawi (the PROSPECT study): A randomised trial and cost-effectiveness analysis. PLoS Med 18(9): e1003752. <https://doi.org/10.1371/journal.pmed.1003752>

Academic Editor: Ruanna V. Bumbusa, University of Washington Department of Global Health, UNITED STATES

Received: December 10, 2020

Accepted: August 3, 2021

Published: September 9, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pmed.1003752>

Copyright: © 2021 MacPherson et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

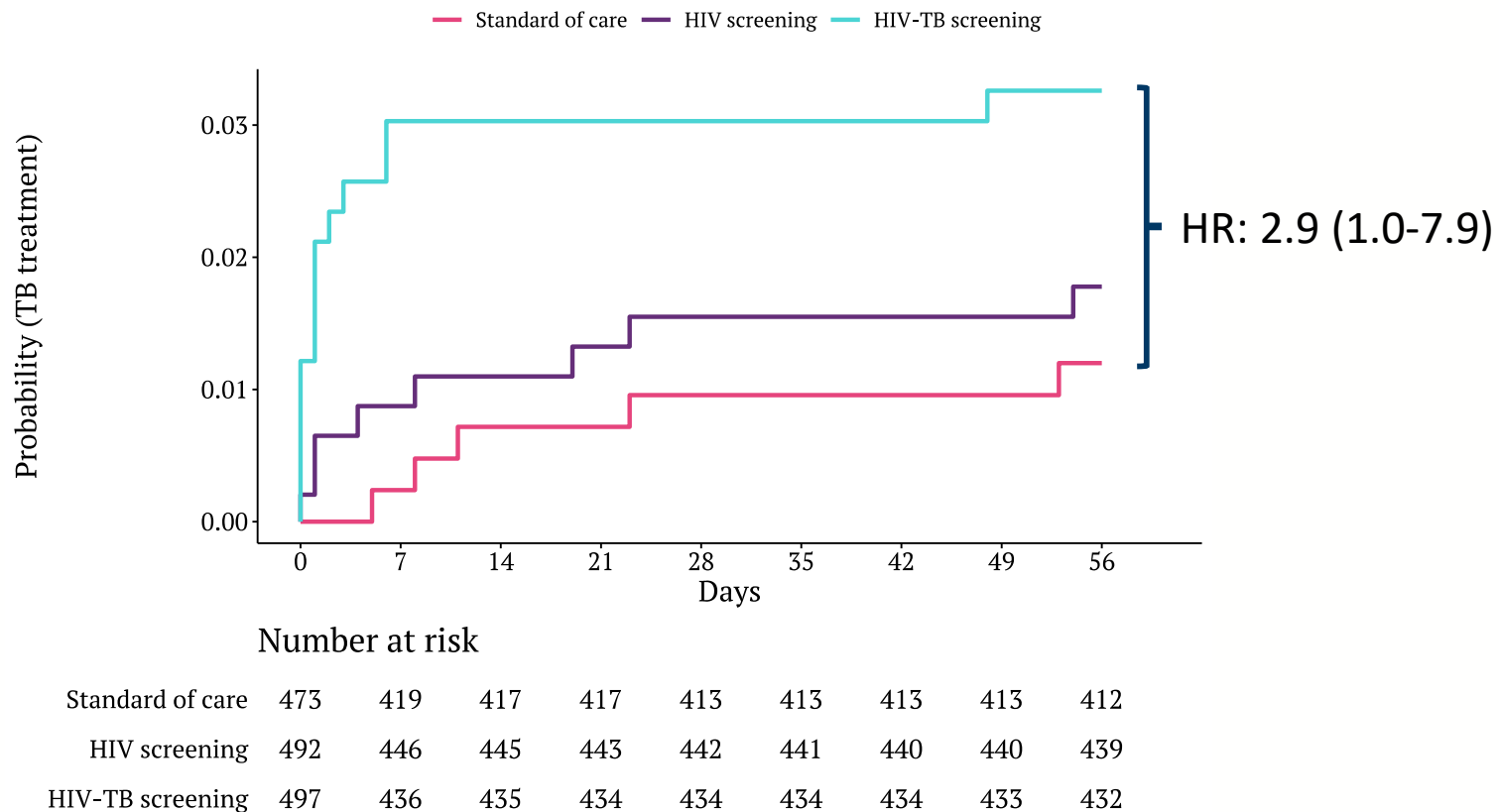
Abstract

Background

Suboptimal tuberculosis (TB) diagnostics and HIV contribute to the high global burden of TB. We investigated costs and yield from systematic HIV-TB screening, including computer-aided digital chest X-ray (DCXR-CAD).

Methods and findings

In this open, three-arm randomised trial, adults (≥18 years) with cough attending acute primary services in Malawi were randomised (1:1:1) to standard of care (SOC; oral HIV testing (HIV screening) and linkage to care; or HIV testing and linkage to care plus DCXR-CAD with sputum Xpert for high CAD4TBv5 scores (HIV-TB screening)). Participants and study staff were not blinded to intervention allocation, but investigator blinding was maintained until final analysis. The primary outcome was time to TB treatment. Secondary outcomes included proportion with same-day TB treatment; prevalence of undiagnosed/untreated bacteriologically confirmed TB on day 56; and undiagnosed/untreated HIV. Analysis was done on an intention-to-treat basis. Cost-effectiveness analysis used a health-provider perspective. Between 15 November 2018 and 27 November 2019, 8,236 were screened for eligibility, with 473, 492, and 497 randomly allocated to SOC, HIV, and HIV-TB screening arms; 53 (11%), 52 (9%), and 47 (9%) were lost to follow-up, respectively. At 56 days, TB





First RCT of artificial intelligence in medicine

First WHO pre-qualification of software as a medical device

WHO consolidated guidelines on tuberculosis

Module 2: Screening

**Systematic screening for
tuberculosis disease**

Box 1. Main changes to the guidance in the current update

- Community-wide systematic screening using an accurate screening and diagnostic algorithm may be used in settings with a TB prevalence of 0.5% and higher, based on new evidence of public health benefit.
- Computer-aided detection (CAD) is being recommended for the first time as an alternative to human interpretation of digital chest X-ray (CXR) for screening and triage for TB. Its use should be limited to the interpretation of plain CXRs for pulmonary TB in individuals aged 15 years or older.

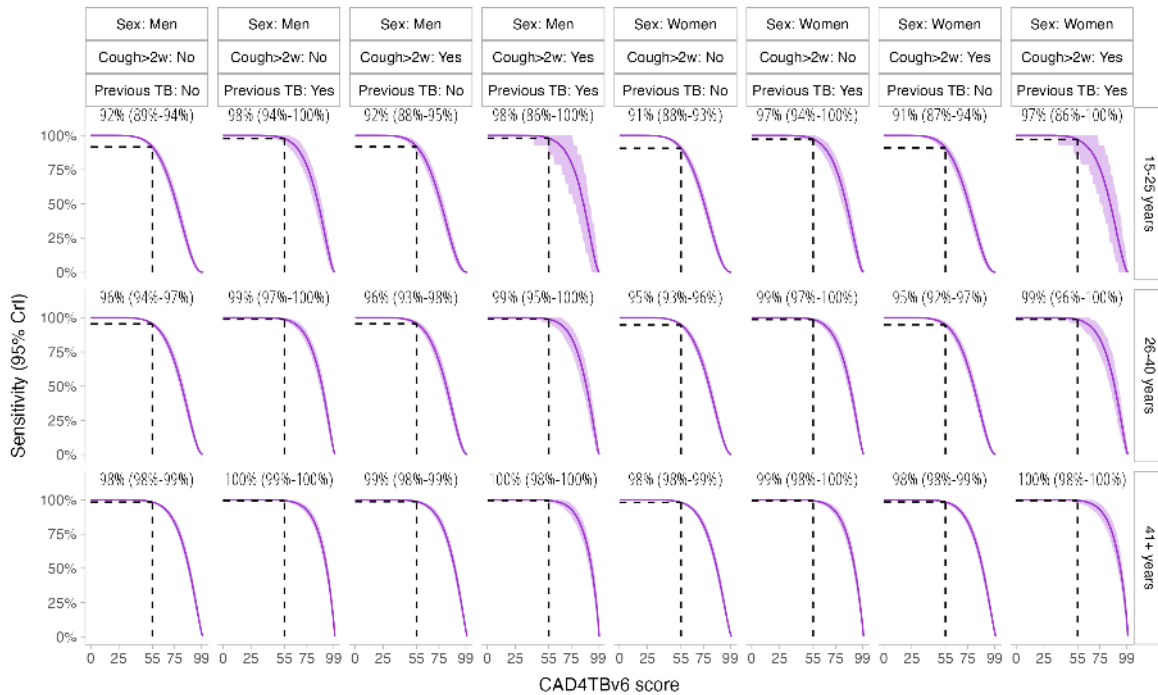
Adaptive thresholds for CAD required?



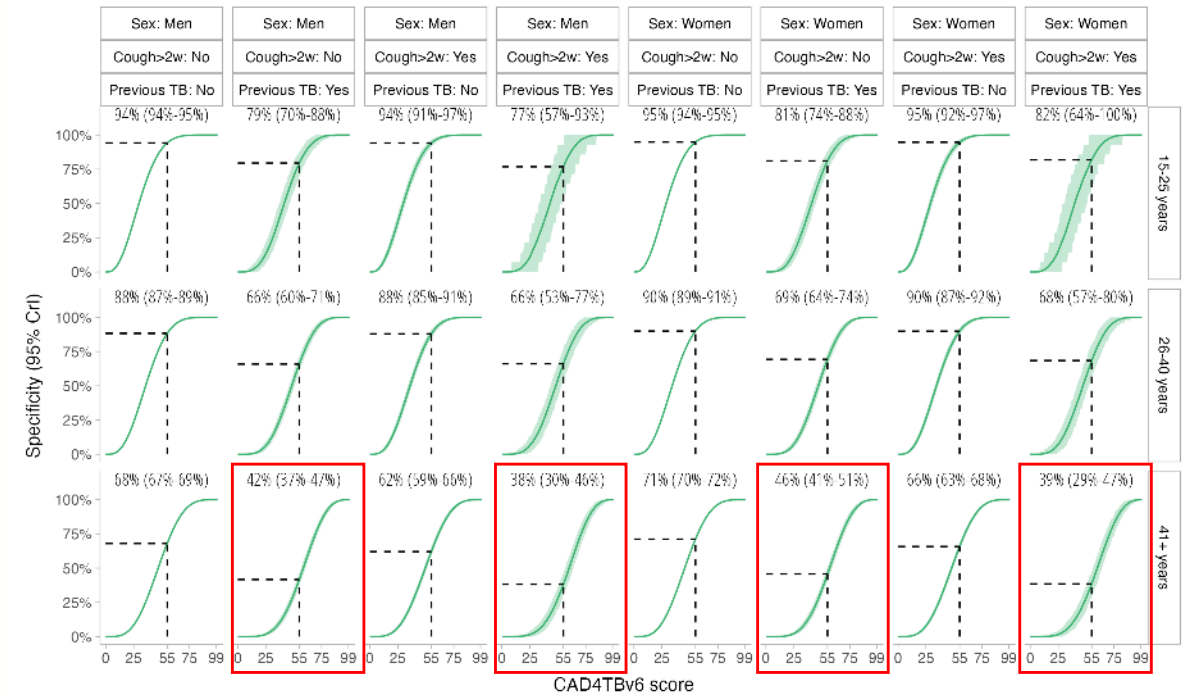
Brenda Mungai

Kenya national TB prevalence survey (n=61,484)

Sensitivity



Specificity





Conclusions

1

We are entering a new era in TB epidemiology in high HIV prevalence countries.
Our approaches to finding the missing millions must adapt

2

Precision-public health approaches using all available sources of data are required
Programmes must be targeted to where benefit (individual and population) will be greatest

3

New screening tools are emerging
Need to be rigorously evaluated in randomized trials for population an individual benefit and harms



University
of Glasgow

Thank you

#UofGWorldChangers



@UofGlasgow