

Active TB case finding

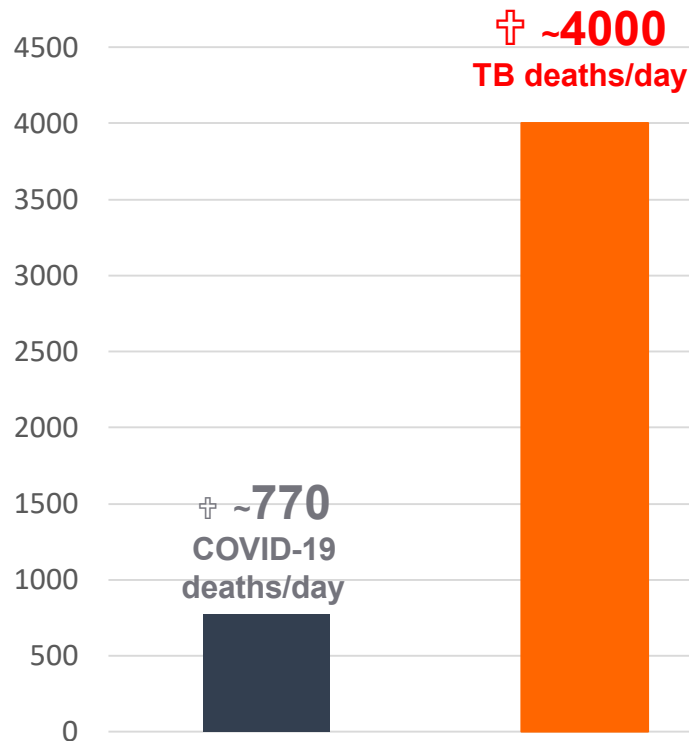
Community screening

Swiss TPH Hybrid Symposium, 21-22 March 2023

Klaus Reither MD, PhD
Swiss TPH

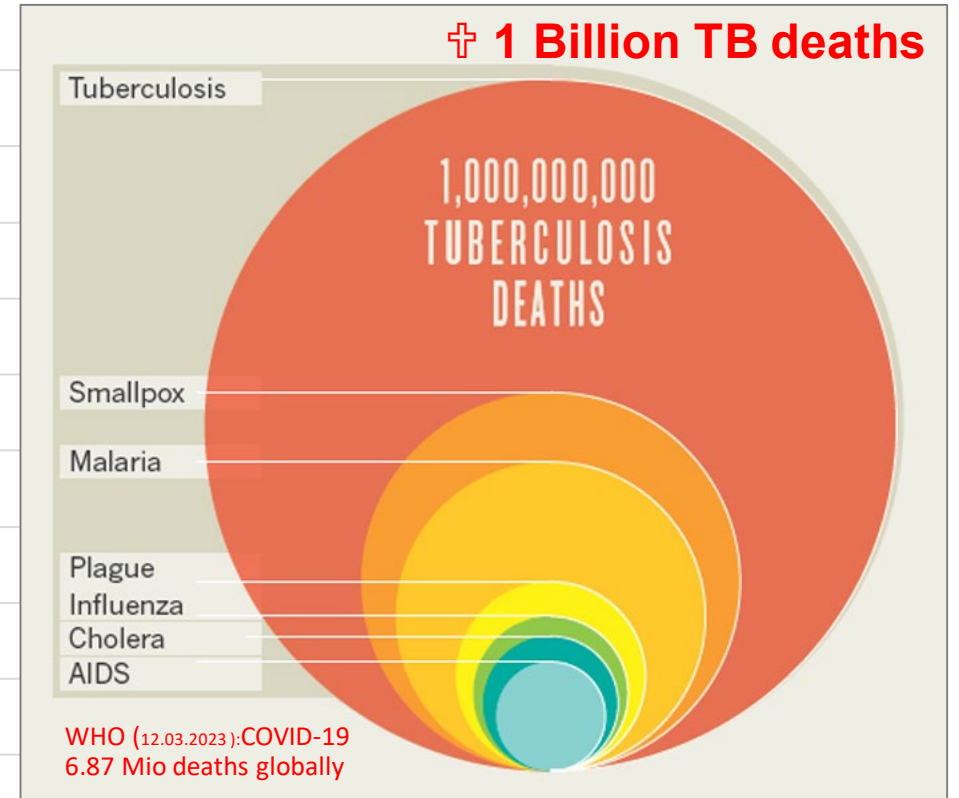
One of the deadliest infectious diseases of our time!

Example: March 11, 2023 - worldwide



WHO, 2023

During the past 200 years



Paulson T, Nature 2013

Covid-19's Devastating Effect on Tuberculosis Care — A Path to Recovery

Madhukar Pai, M.D., Ph.D., Tereza Kasaeva, M.D., Ph.D., and Soumya Swaminathan, M.D.

Urgent priority!

“**Targeted active-case-finding initiatives** (...) could help identify people with undiagnosed tuberculosis. This approach will require learning from Covid-19 testing experiences by **bringing tuberculosis testing closer to where people live and work** and engaging communities, private providers, and community-based health workers and civil-society organizations.”

Case detection strategies

Passive case finding



Routine diagnosis of symptomatic TB patients **self-presenting** to health services

Enhanced case finding



Health information or education to encourage health-seeking behaviours, with or without increasing access to diagnostic services

Active case finding (ACF)

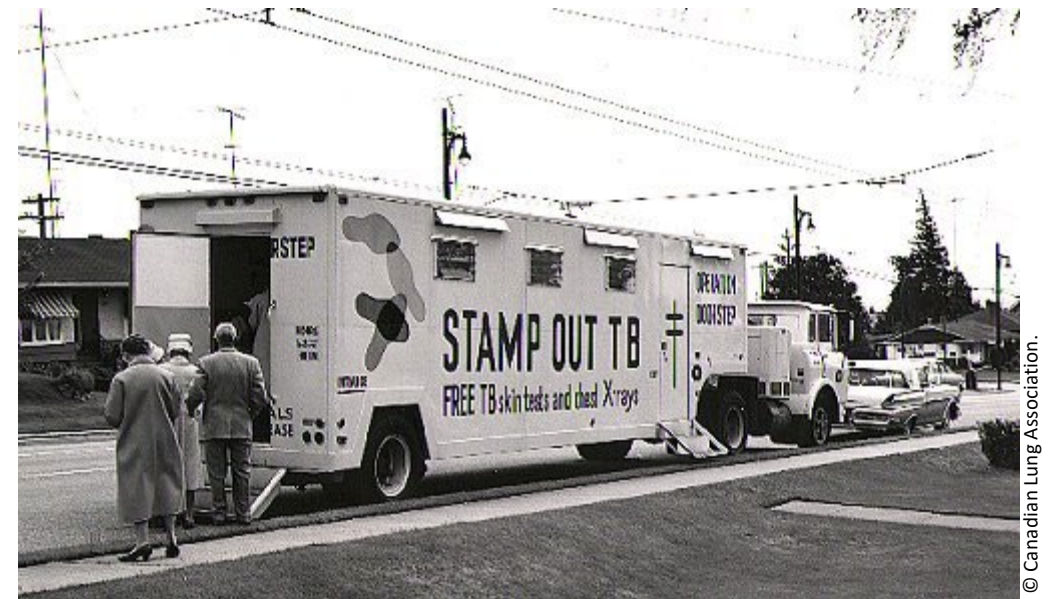


Systematic screening using any test/procedure (case-finding in communities and health facilities)

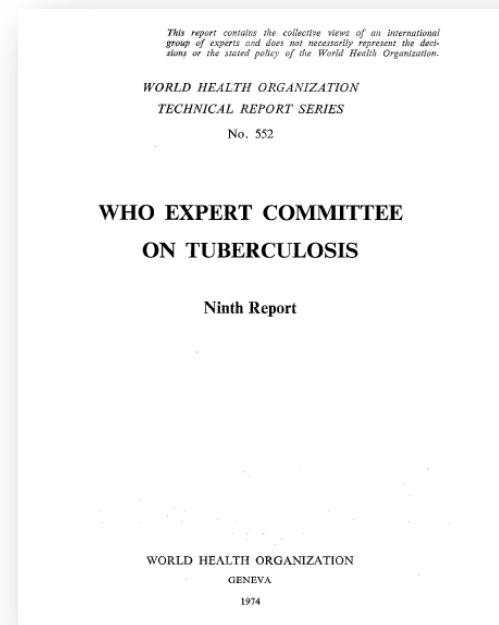


Short history of active case finding

- Example for ACF: **large scale mass radiography campaigns** in industrialized countries between the 1930s and 1960s
- Paradigm shift: focus more on **detection of symptomatic TB** patients in the 1960s
- 1974: WHO concerns about accuracy, logistics and personnel requirements for mass radiography: “indiscriminate TB case finding by mobile mass radiography **should be abandoned**”
- In the last 10 years, renaissance of active case finding; e.g. TB REACH / Stop TB Partnership, implementation of innovative case finding strategies at country level, including active case finding



© Canadian Lung Association.



WHO - Systematic TB screening

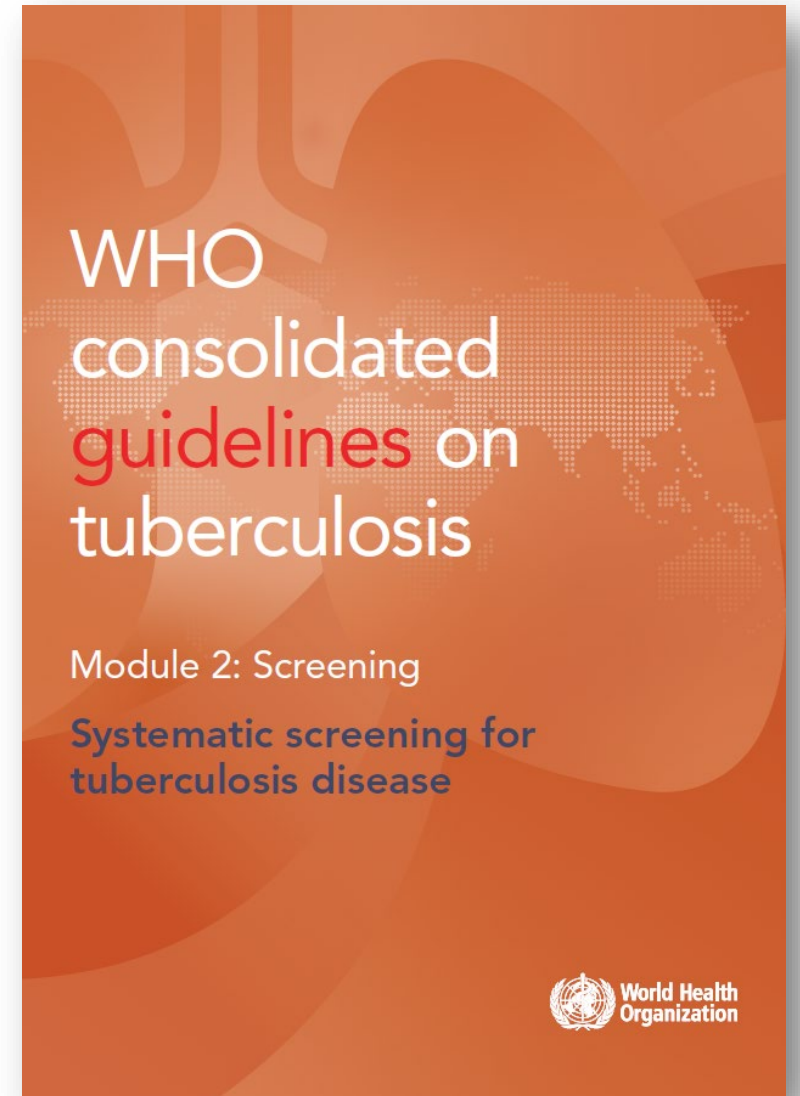
Recommendations:

General population

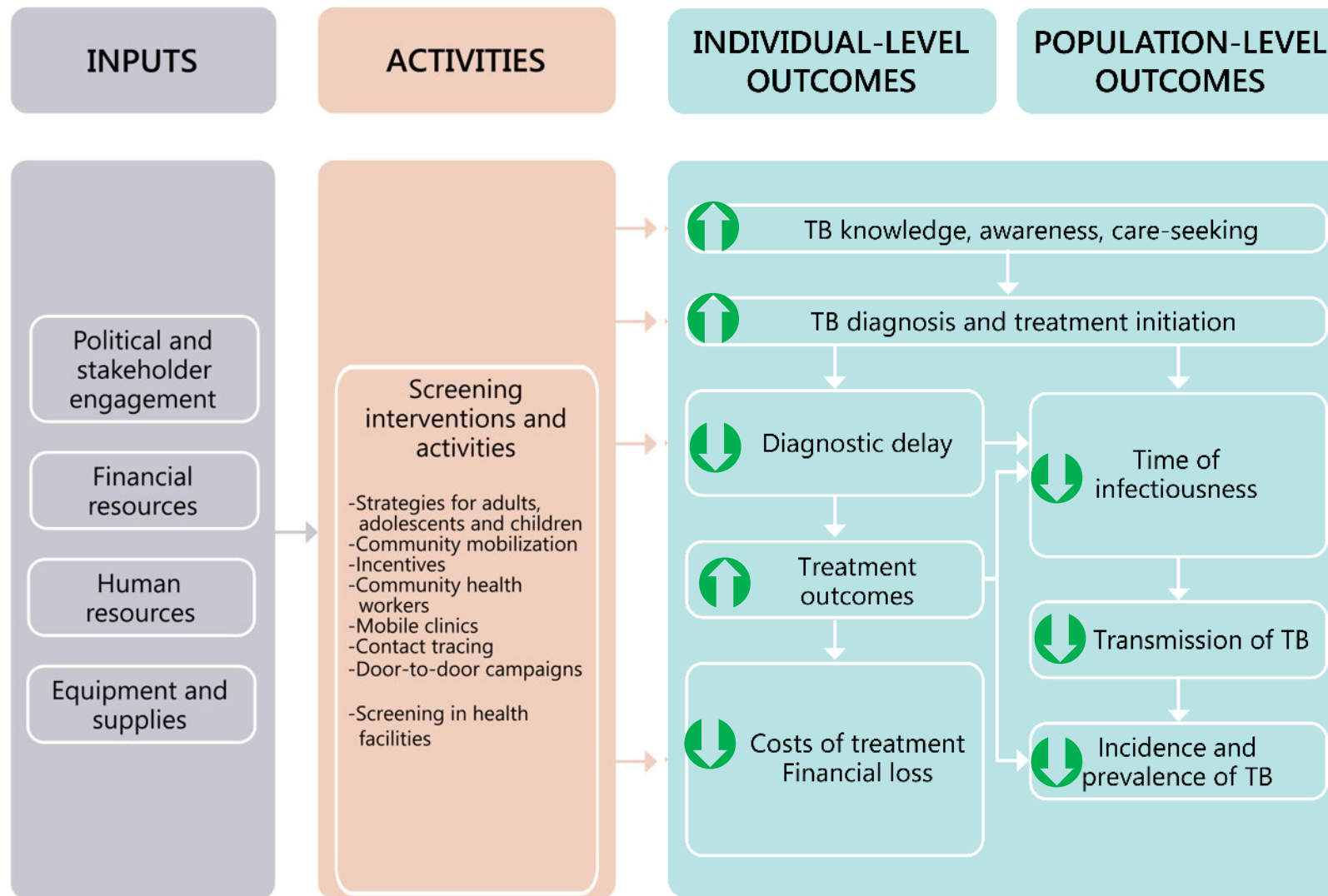
- in areas with an estimated **TB prevalence of 0.5% or higher**

Subpopulations

- with structural risk factors for TB
Such as urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care
- PLHIV
- Household contacts of TB cases (including children and adolescents)
- Prisoners
- Miners
- People with risk factors and 100/100'000 TB prevalence
- People with untreated fibrotic lung lesions



WHO - Systematic TB screening



What are the individual and community benefits of active case finding?

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<http://dx.doi.org/10.5588/ijtld.12.0743>

STATE OF THE ART

STATE OF THE ART SERIES
Active case finding/screening
Series Editor: Martien Borgdorff, Guest Editor: Knut Lönnroth
NUMBER 2 IN THE SERIES

The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review

K. Kranzer,* H. Afnan-Holmes,* K. Tomlin,* J. E. Golub,* A. E. Shapiro,* A. Schaap,* E. L. Corbett,* K. Lönnroth,* J. R. Glynn*



Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: <https://www.journals.elsevier.com/eclinicalmedicine>

Research paper

Does tuberculosis screening improve individual outcomes? A systematic review

L Telisinghe^{a,h,*}, M Ruperez^b, M Amofa-Sekyi^b, L Mwenge^b, T Mainga^b, R Kumar^b, M Hassan^{c,d}, L.H Chaisson^e, F Naufal^f, A.E Shapiro^g, J.E Golub^h, C Miller^h, E.L Corbett^{h,i}, R.M Burke^{h,i}, P MacPherson^{h,i,j}, R.J Hayes^h, V Bond^{h,k}, C Daneshvar^l, E Klinckenberg^h, H.M Ayles^{h,b}

Systematic review (2013)

“**Individual and community-level benefits from active screening for TB disease remain uncertain.**”

So far, the benefits of earlier diagnosis on patient out-comes and transmission have not been established.”

Kranzer K et al IJTLD 2013

Systematic review (2021)

“**Very limited data** on the effect of TB screening **on individual outcomes.**”

Telisinghe L et al EClinicalMedicine 2021

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

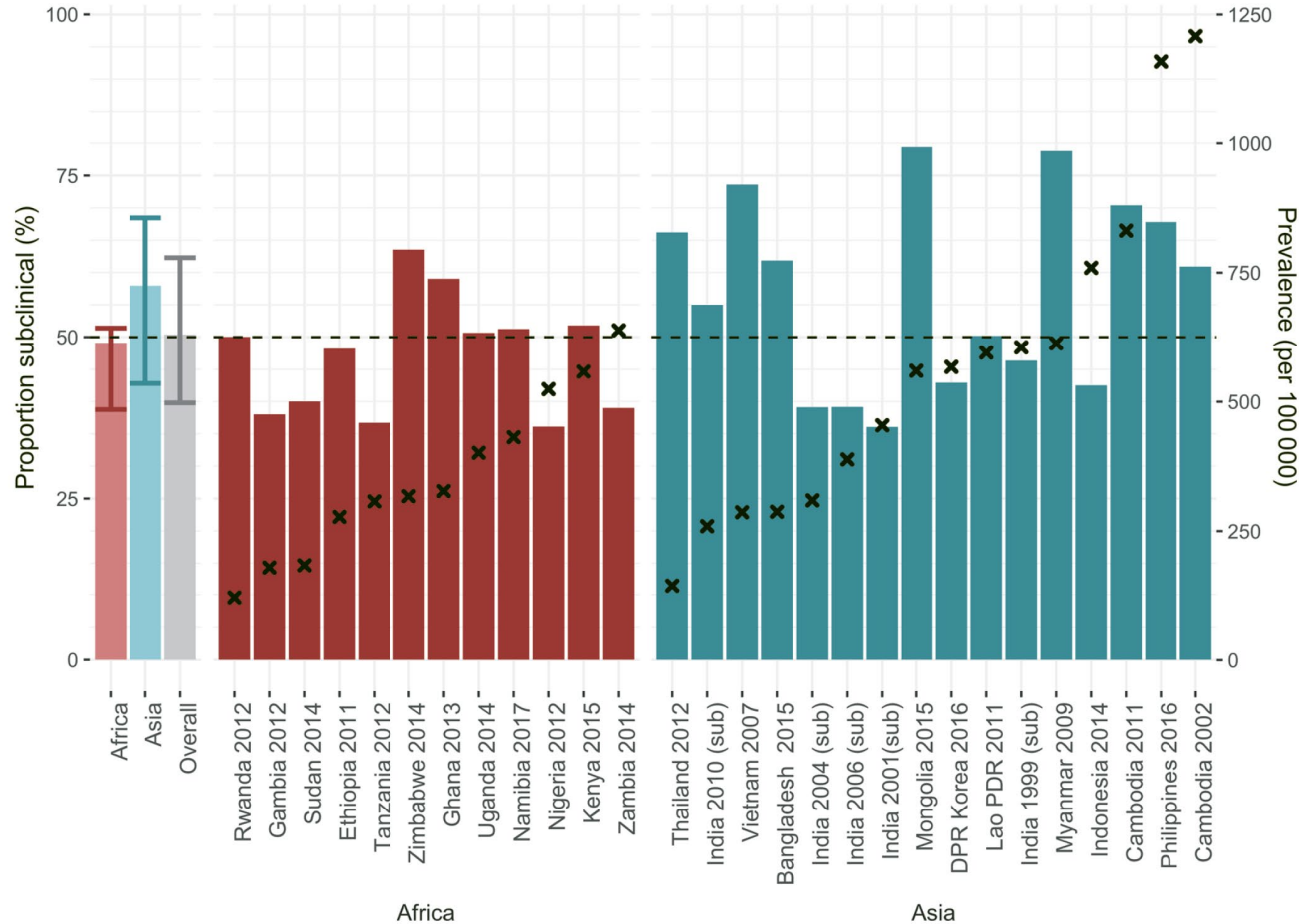
Rachel M Burke, Anisulu Pharesa, Helen Ayles, Elizabeth L Corbett, Peter MacPherson, Lily Telisinghe, Helen Ayles, Elizabeth L Corbett, Peter MacPherson

Systematic review (2021)

“Our main findings were that there is **mixed evidence** that active case-finding is effective at initially increasing tuberculosis detection when measured by case notification rates, and that active case-finding **could reduce community prevalence** of tuberculosis **if delivered with sufficient intensity and coverage.**”

Burke RM et al Lancet Public Health 2021

Why do we need to pursue active case finding?

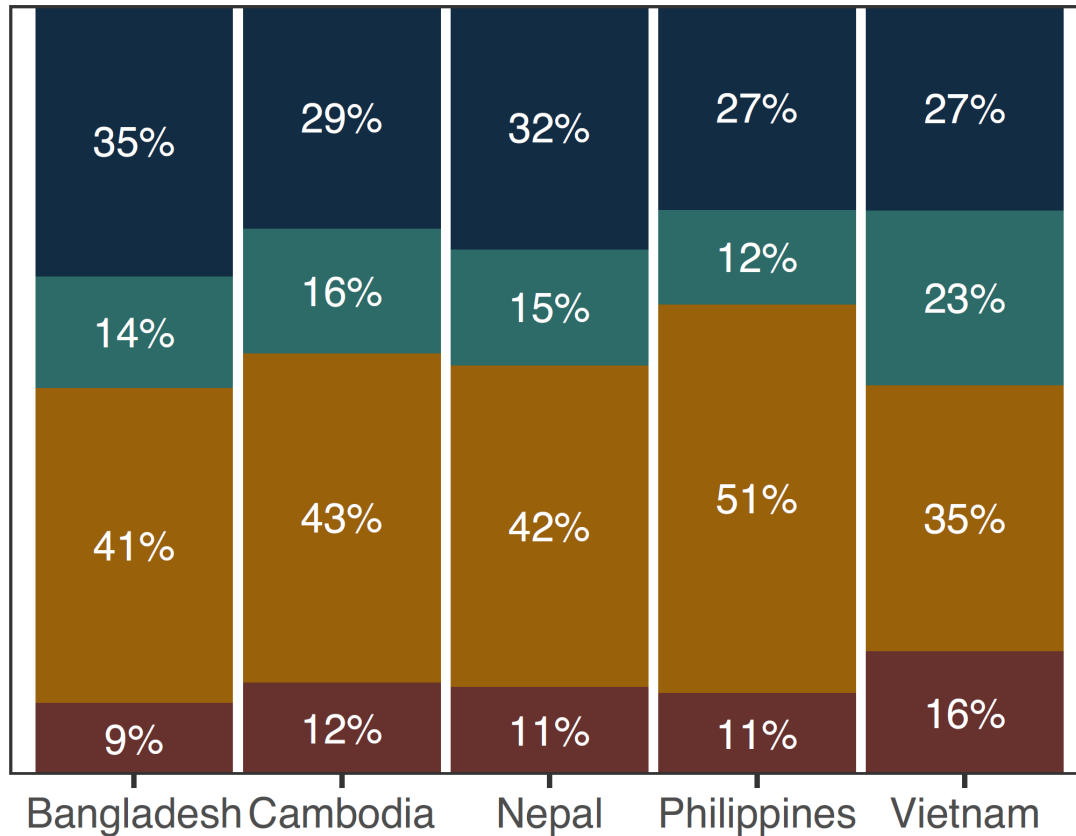


Prevalence surveys

“Between 36.1% and 79.7% (median, **50.4%**) of prevalent bacteriologically confirmed TB was **subclinical**.”

Why do we need to pursue active case finding?

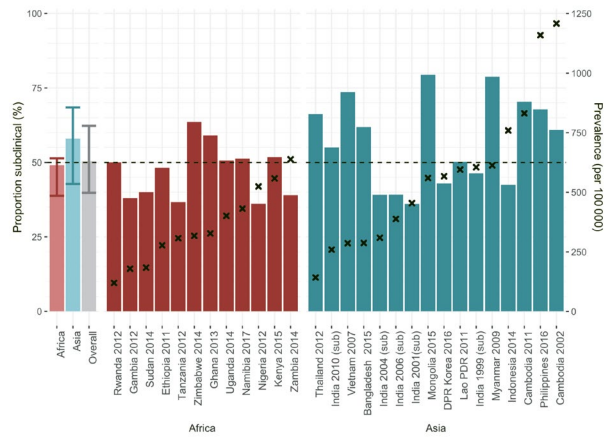
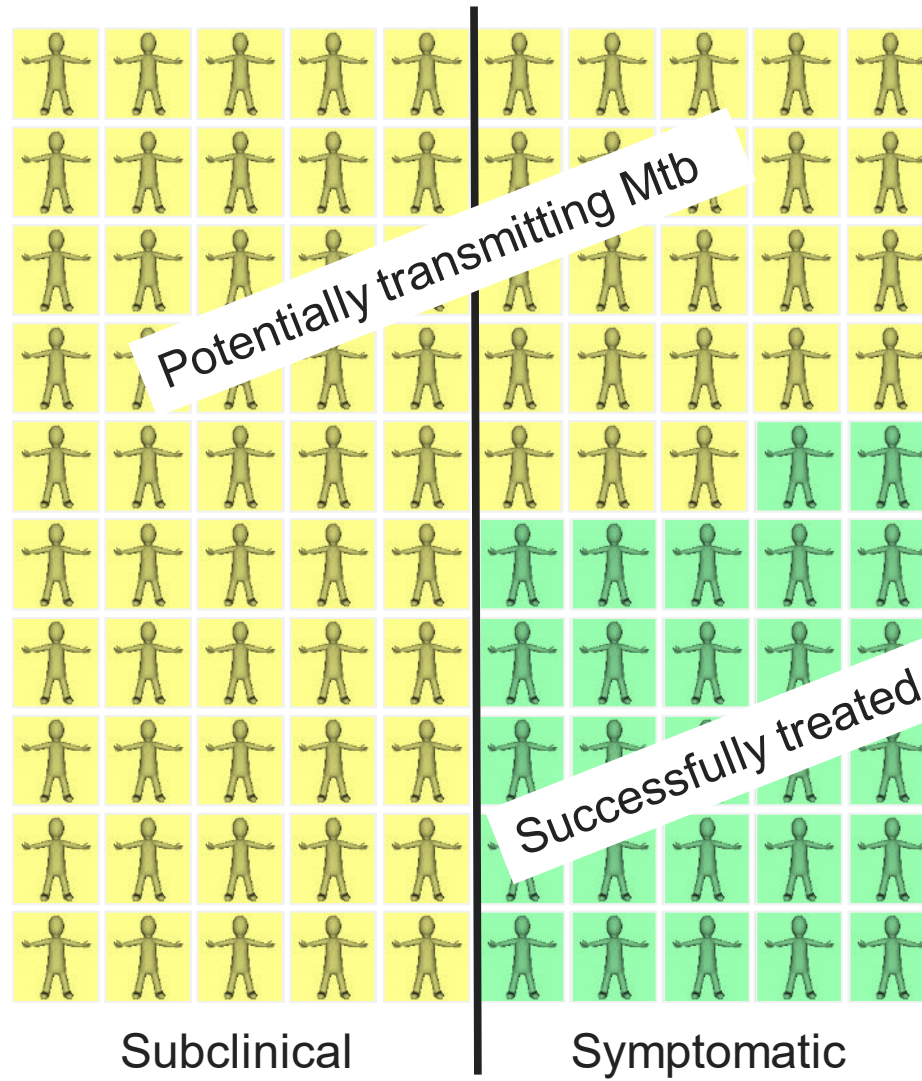
Population contribution to cumulative 5-year transmission



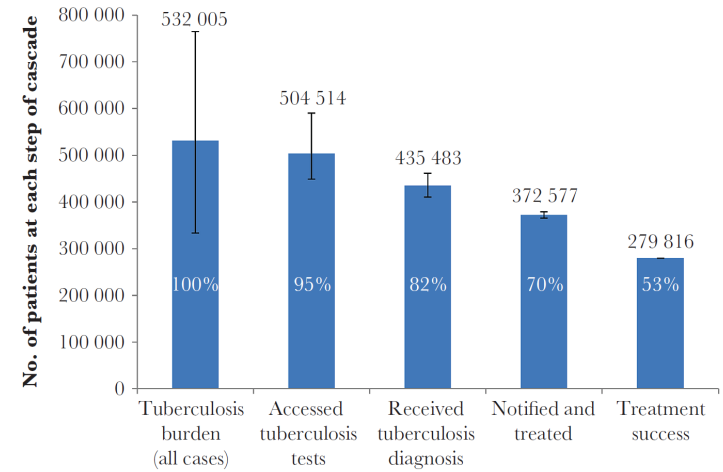
Bayesian modelling

“Despite accounting for only 11 to 19% of prevalent disease, **smear-positive subclinical TB accounted for 35 to 51% of future transmission**—a greater contribution than symptomatic or smear-negative TB.”

TB cases in the community



Frascella et al. CID 2021



Naidoo et al. JID 2017

Epidemiological approach to ending tuberculosis in high-burden countries



The burden of tuberculosis is extraordinarily unequal between countries. Incidence rates range from below 10 per 100 000 population in many mainly high-income

Promising new tools to enable active case finding for tuberculosis are available now and others are in development.⁶ In settings with a high burden of

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[https://doi.org/10.1016/S0140-6736\(22\)01433-7](https://doi.org/10.1016/S0140-6736(22)01433-7)

“We propose that substantial progress towards ending tuberculosis in high-burden settings will require **a focus on community-wide active case finding for tuberculosis with symptom-agnostic tests, followed by effective treatment to stop endemic transmission.**“

ORIGINAL ARTICLE

Community-wide Screening for Tuberculosis in a High-Prevalence Setting

Guy B. Marks, M.B., B.S., Ph.D., Nhung V. Nguyen, M.D., Ph.D.,
 Phuong T.B. Nguyen, Ph.D., Thu-Anh Nguyen, M.D., Ph.D.,
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 Paul H. Mason, Ph.D., Van-Anh T. Nguyen, Ph.D., Jennifer Ho, M.B., B.S., Ph.D.,
 Vitali Sintchenko, M.D., Ph.D., Linh N. Nguyen, M.D., Ph.D.,
 Warwick J. Britton, M.B., B.S., Ph.D., and Greg J. Fox, M.B., B.S., Ph.D.

- Ca Mau Province, Vietnam
- Screened for pulmonary TB, regardless of symptoms
- Annually for 3 years
- Intervention - **All participants (43000!)**: eligible to be tested with Xpert MTB/RIF
- Control - No active case finding

Results	Intervention TB cases; TB prevalence (Xpert pos)	Control TB cases; TB prevalence (Xpert pos)
Year 1	169; 389/100000	
Year 2	136; 308/100000	
Year 3	78; 176/100000	
Year 4	53; 126/100000	94; 226/100000

Reduction in prevalence Y1-Y4: **64%**
 (Xpert pos/Cult. pos)

	Xpert MTB/RIF actually done in intervention arm	
Year 1	23282	
Year 2	22375	→ Cost-effective?
Year 3	19890	
Year 4	18837	

84384 Xpert tests : 436 TB case

TB TRIAGE+ Project

Community-based tuberculosis triage testing
after ~~symptom screening~~ in hard-to-reach
African populations: CAD4TB versus C-
reactive protein

Call: Diagnostic tools for poverty-related diseases
Funder: EDCTP
Amount: Euro 3.19 m
Period: 4 years & 1 Year NCE
Start: January 1, 2020



EDCTP

This project is part of the EDCTP2 programme supported by the European Union



www.tbtriage.com

Partners



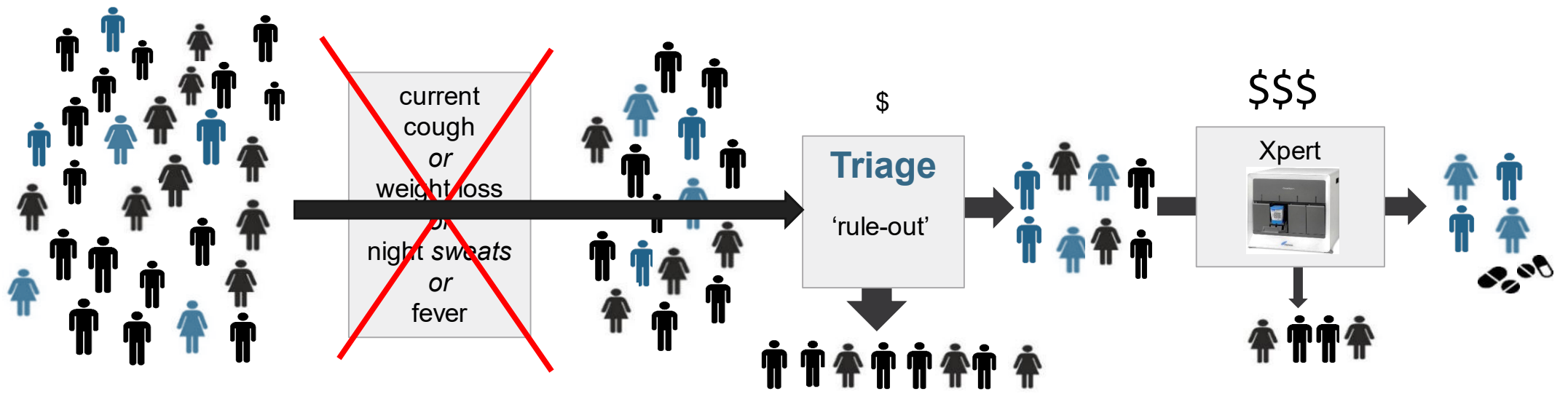
Triage testing can potentially improve active case finding in the community



Target product profiles (TPPs) for TB triage tests

Sens. >95% min: >90%
 Spec. >80% min: >70%

Low costs (<2\$), fast, simple, non-sputum



Swiss TPH 50% of infectious TB cases are asymptomatic

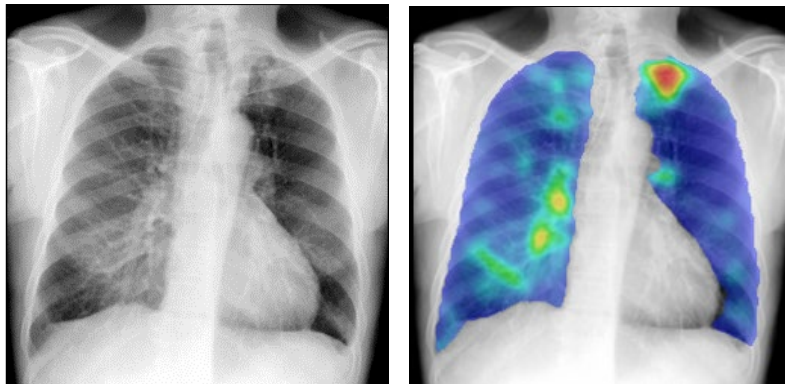
Triage test candidates

CAD4TB

Computer-aided detection of tuberculosis using digital chest radiographs

Deep Learning-Based Software

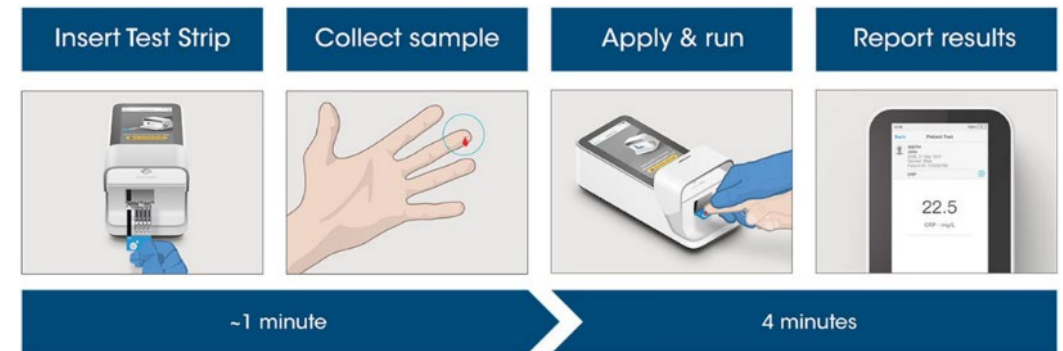
→ abnormality score (between 0 and 100)



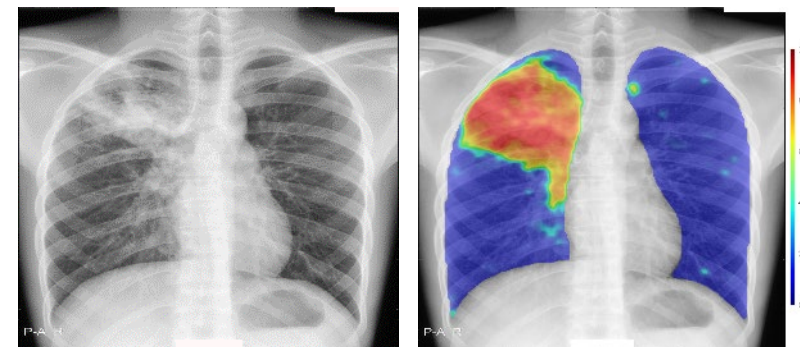
C-reactive protein (CRP)

Marker for inflammation and infection

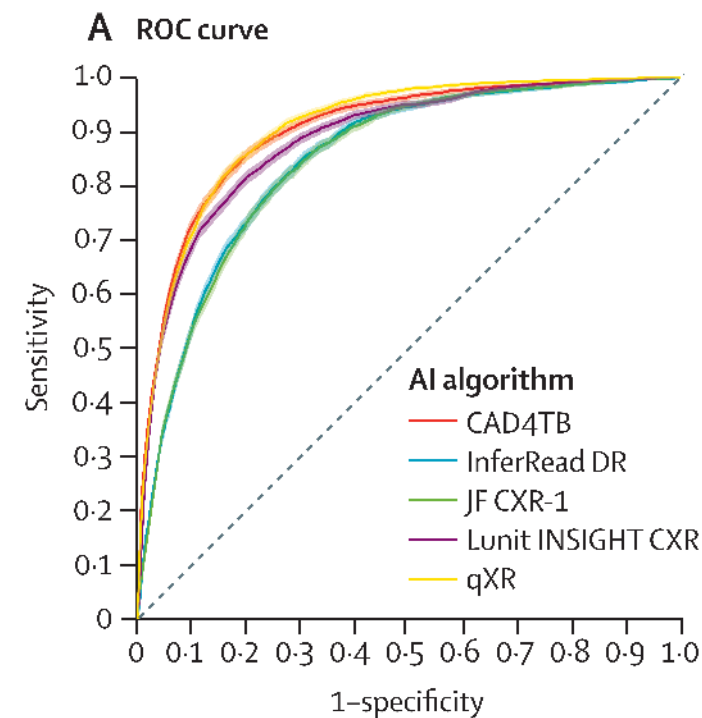
Quantitative point-of-care tests available



CAD: Computer-aided detection software



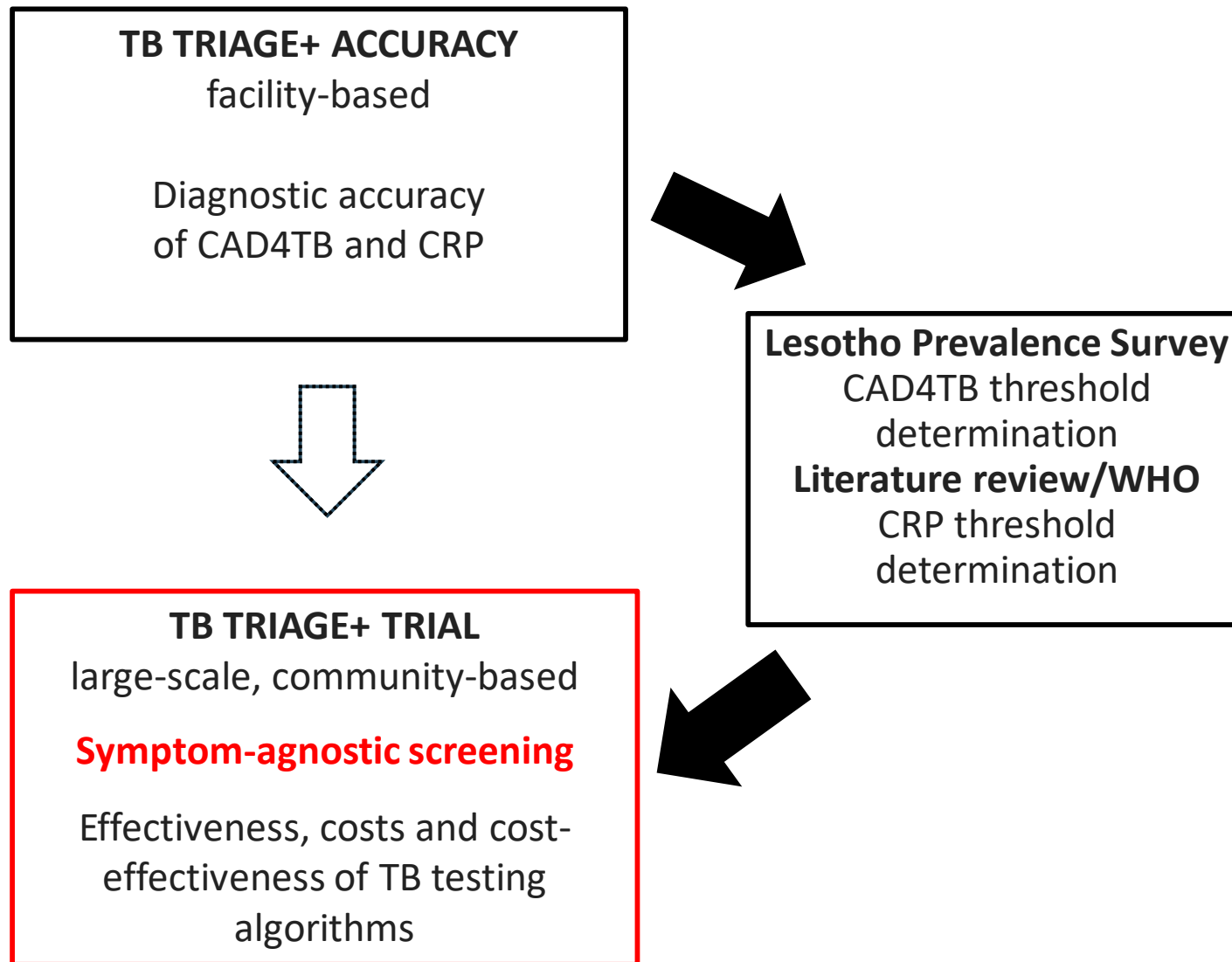
- High-sensitivity tuberculosis **rule-out test**
- CAD using newest versions of AI algorithms **outperforms experienced radiologists**
- Users need **threshold scores** identified from their own patient populations



Innovations in digital x-ray

Stationary - Mobile - Portable - Ultra-portable





Results

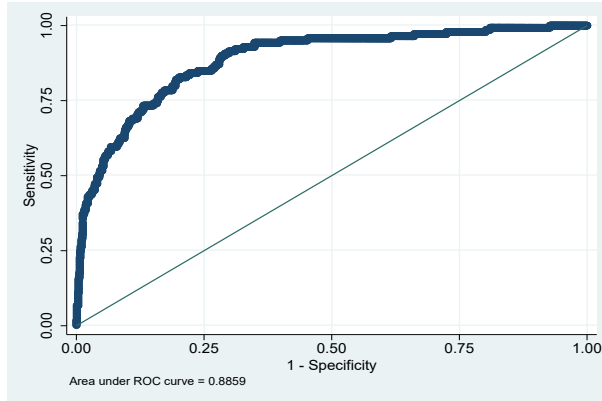
ACCURACY

Unpublished data
N=1392

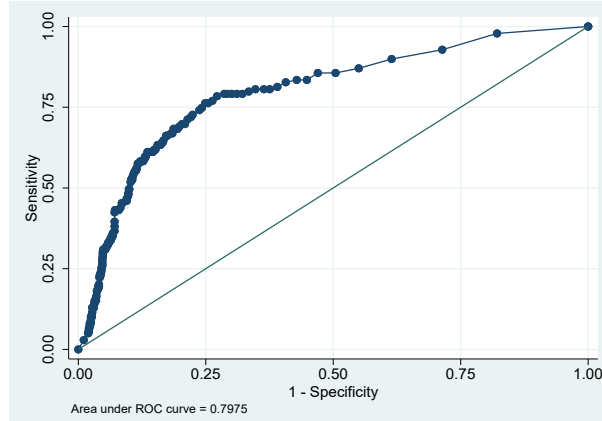
Patient characteristics

Median Age, years	45
Female	752 (54.0%)
HIV positive	676 (48.6%)
Eligible for AHD package (LS=335 / SA=341)	
CD4≤200cells/μL	20.2% / 40.6%

CAD4TBv7 meets TPP criteria



CRP does not meet TPP criteria



CRP AUC: Lesotho > SA
CAD AUC: history TB < no history TB

CRP & CAD AUC: independent of HIV status

Lesotho Prevalence Survey

Unpublished data
N=17070

Methodological approach:

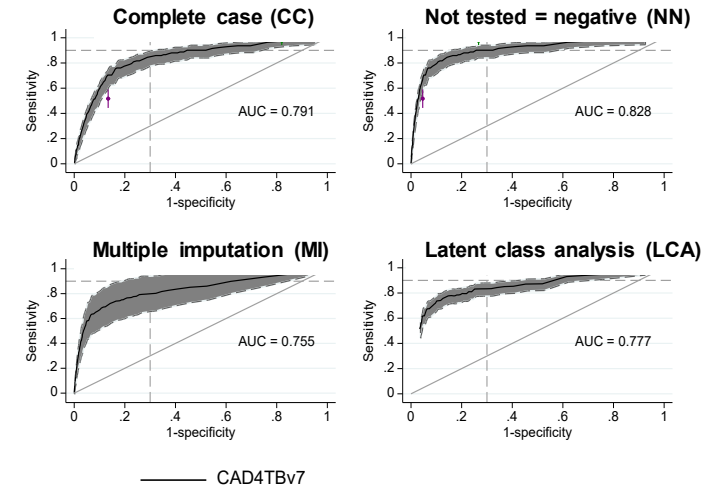
Threshold determination

Complete case (CC)

Not tested = negative (NN)

Multiple imputation (MI)

Latent class analysis (LCA)



NN approach most closely approximating the anticipated overall tuberculosis prevalence

CAD4TBv7 score with threshold 13:
sensitivity 90.1%
specificity 74.2%

→ TB TRIAGE+ TRIAL

TB TRIAGE+ TRIAL

large-scale, community-based

Lesotho and South Africa

- Community-based
- Community engagement
- Symptom-agnostic
- **20,000 individuals**
- Health economic analyses
- AHD package in community
- Hypertension and DM screening
- Same day treatment ART, CTX, TPT
- REDcap
- QGIS: geo-referencing
- Internal QC and external monitoring

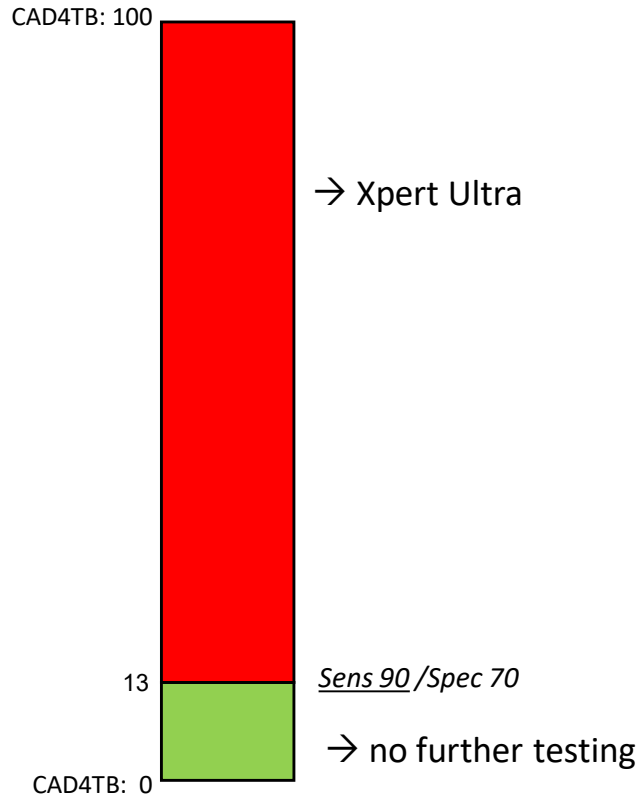


Overall aim:

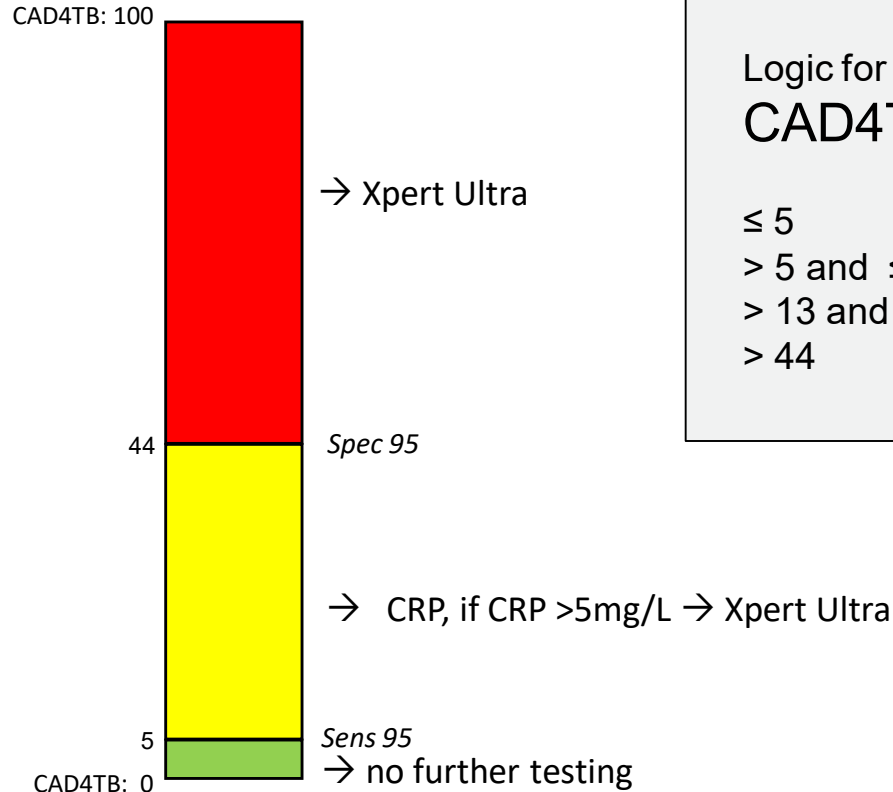
To investigate the **effectiveness, costs and cost-effectiveness** of community-based **TB triage testing** algorithms consisting of CAD4TB screening alone (approach 1) compared to CAD4TB screening with POC-CRP triage testing (approach 2), followed by Xpert MTB/RIF Ultra rapid sputum molecular testing in both approaches

TB TRIAGE+ TRIAL
large-scale, community-based

Approach 1



Approach 2



TB TRIAGE+ TRIAL

Logic for
CAD4TB v7

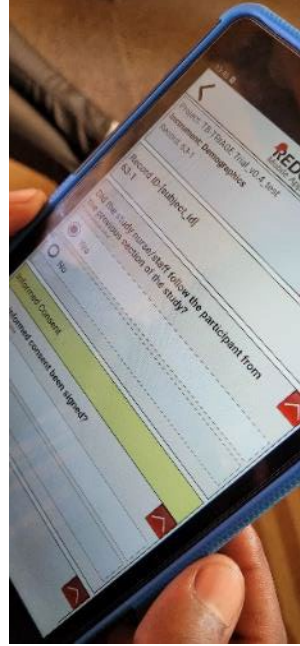
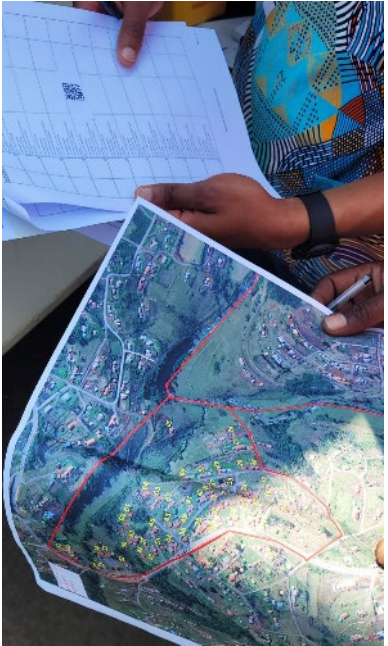
≤ 5	No further testing
> 5 and ≤ 13	CRP
> 13 and ≤ 44	CRP & Xpert Ultra
> 44	Xpert Ultra

Two diagnostic approaches in one participant: **Paired screen-positive study design**

- **Cost analysis** to assess health system and household level cost implications
- **Cost-effectiveness analysis**
- **Extended cost-effectiveness analysis (ECEA)** - impact on out-of-pocket expenditures averted and financial risk protection provided across socioeconomic groups
- **Impact of the interventions in terms of long-term health outcomes** within a simulation modeling framework

TB TRIAGE+ TRIAL
large-scale, community-based

South African site



→ Results by end of 2024

Conclusions: **Active TB case finding**

- New evidence, i.e. on subclinical TB, is fueling the discussion on the relevance of active TB case finding.
- Active community-wide, symptom-agnostic TB screening has to become a priority if we are serious about "ending TB".
- Significant financial and logistical efforts are required, which cannot be left to national TB programs alone.
- Context-specific research on screening strategies, tools and health economic analyses of active case finding for both adults and children is of key importance.

Thank you!

TB TRIAGE + Collaborators

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