

**Programmatic and clinical
issues arising from national
tuberculosis prevalence
surveys:**

“All we know about TB is wrong”

Philip Hopewell

**Curry International Tuberculosis Center
University of California, San Francisco**

George W. Comstock



“Although I seem to be generally associated with tuberculosis, a review of my publications will show that my research interests have been very broad. The common thread through most of these studies has been that they are based on local communities—Muscogee county, GA; Bethel area of Alaska; and Washington County, Maryland.”



George W. Comstock

- [Lancet Oncol.](#) 2013 Sep;14(10):1009-19. doi: 10.1016/S1470-2045(13)70301-2. Epub 2013 Jul 24.

Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies.

- [Am J Epidemiol.](#) 2008 Oct 1;168(7):841-4. doi: 10.1093/aje/kwn271.

Prostate-specific antigen levels and subsequent prostate cancer: potential for screening.

- [Am J Epidemiol.](#) 2008 Oct 1;168(7):831-40. doi: 10.1093/aje/kwn328.

The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acids, carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity.

- [Am J Epidemiol.](#) 2008 Oct 1;168(7):827-30. doi: 10.1093/aje/kwn327.

Effects of repeated freeze-thaw cycles on concentrations of cholesterol, micronutrients, and hormones in human plasma and serum.

- [Am J Epidemiol.](#) 2008 Oct 1;168(7):819-26. doi: 10.1093/aje/kwn326.

Church attendance and health.

George W. Comstock

Series: History of epidemiology

School of Hygiene and Public Health,

Johns Hopkins University, Hagerstown, MD

Soz.- Präventivmed. 46 (2001) 007–012

© Birkhäuser Verlag, Basel, 2001

Cohort analysis: W.H. Frost's contributions to the epidemiology of tuberculosis and chronic disease

Wade Hampton Frost: prevention, case-finding, and social protection

To Frost's credit, it should be pointed out that he realised that isolation of cases and surveillance of contacts could impose major hardships on patients and their families. "If we are to require the isolation of open tuberculosis as a matter of public protection, it becomes a public responsibility to bear not only the cost of medical care, but the whole cost to the patient's family, or as large a share as may be required. Moreover, it should be recognised that what is needed is not bare maintenance on a minimum or average 'relief' standard, that it is not sufficient merely to prevent their dropping lower in the economic scale; it may often be necessary to

Comstock on Frost

His second priority was preventive treatment for noninfectious cases, a procedure which has since been demonstrated to be highly effective though not yet universally applied.

Unless greater emphasis is placed on prevention of the second stage of tuberculosis—i.e., the development of disease among infected persons, tens of thousands will be needlessly afflicted.

WHO Global Tuberculosis Programme:

TB Monitoring and Evaluation

**Katherine Floyd, Philippe Glaziou, Irwin
Law, Ikushi Onozaki, Babis Sismanidis**

Surveys 1990–2017

1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
China	Thailand			Myanmar	R. Korea		Philippines		
R. Korea									
2000	2001	2002	2003	2004	2005	2006	2007	2008	
China		Cambodia		Eritrea	Indonesia		Philippines	BNG	
							Viet Nam		
2009	2010	2011	2012	2013	2014	2015	2016	2017	
Myanmar	China	Cambodia	Gambia	Ghana	Indonesia	Mongolia	DPR Korea	Myanmar	
		Ethiopia	Nigeria	Malawi	Zambia	Uganda	Mozambique		
		Lao PDR	Rwanda	Sudan	Zimbabwe	Bangladesh	Nepal		
		Pakistan	Tanzania			Kenya	South Africa		
			Thailand			Philippines	Viet Nam		

- Completed (16*) **since Task Force subgroup active*
- Field operations completed, analysis ongoing (1)
- Field operations ongoing (3)
- Planned (8)

27 surveys between 2009 and 2015/16

- 20/22 global focus countries (not Mali or Sierra Leone)
 - + 7 more: Lao PDR, Gambia, Sudan, Zimbabwe, Mongolia, DPR Korea, Nepal



INDEPENDENT ASSESSMENT OF NATIONAL TB PREVALENCE SURVEYS
CONDUCTED BETWEEN 2009–2015

“Tb prevalence surveys represent the most ambitious and complex health surveys in the world.”

“The surveys have been game-changers and are universally valued in the TB world. At the same time, however, the surveys are highly complex, expensive, require massive external technical assistance, and are subject to problems with radiography, laboratory testing, data management and analysis.”



USAID
FROM THE AMERICAN PEOPLE

Indonesia prevalence survey: Sampling scheme



General Lessons from prevalence surveys

1. Generally, TB is more prevalent than estimated.
2. Cough is an insensitive indicator of TB.
3. Microscopy sensitivity is widely variable, ~30-70% compared with culture or Xpert.
4. False-positive smears are common.
5. Many “smear positive cases” cannot be confirmed by culture. (Is problem with smear or with culture?)
6. Non-tuberculous mycobacteria (NTMs) are relatively common in some countries (up to ~15% of isolates).
7. There is often broad disagreement on interpretation of CXRs.
8. Many cases are treated in the private sector, often with diagnostic and treatment delays and poor monitoring and evaluation of outcomes.

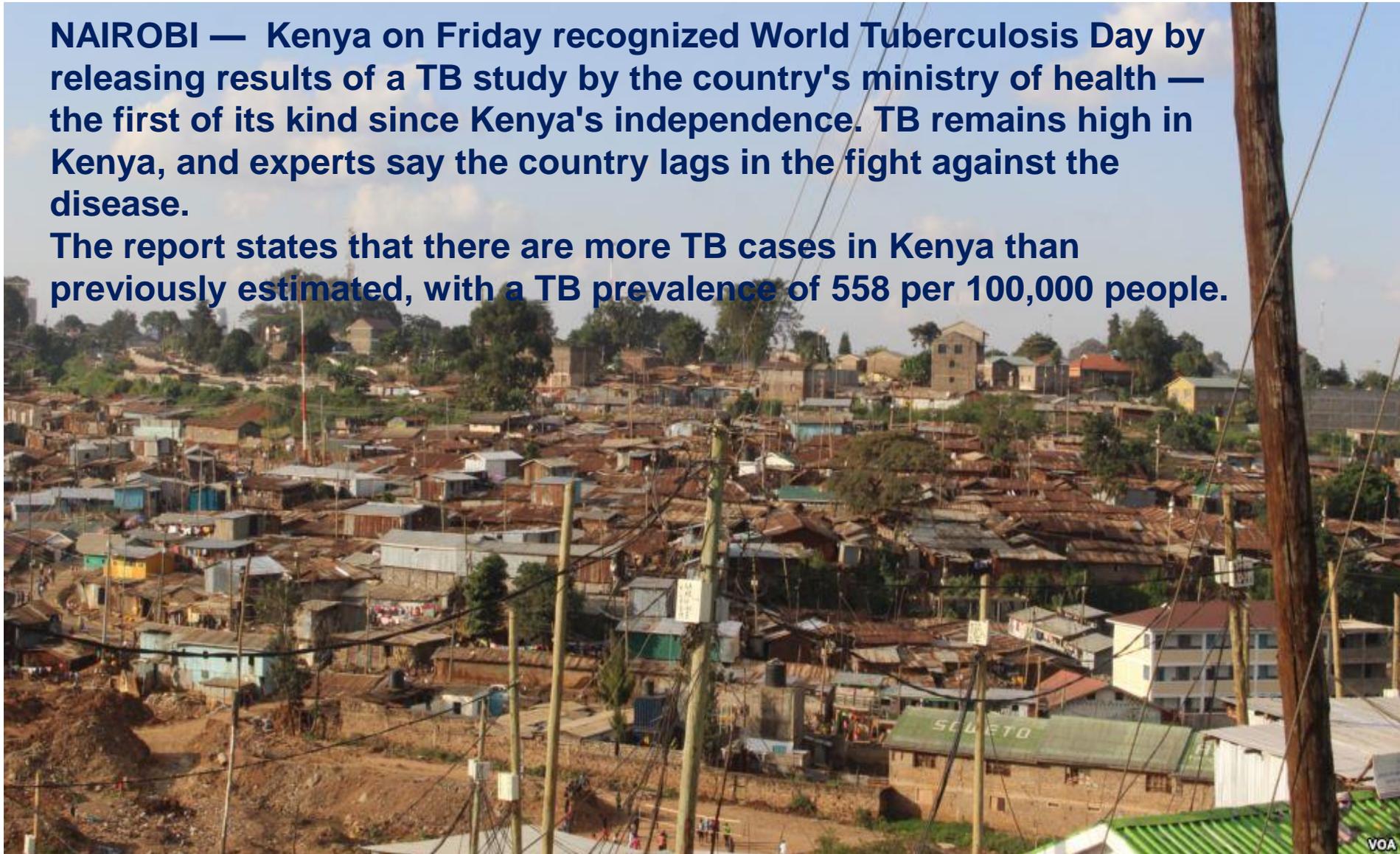
WHO calculations of prevalence provide a reasonably accurate estimate of the case load.

Prevalence may be 2-3X greater than estimated

Kenya Releases Results of National TB Prevalence Survey: March 24, 2017

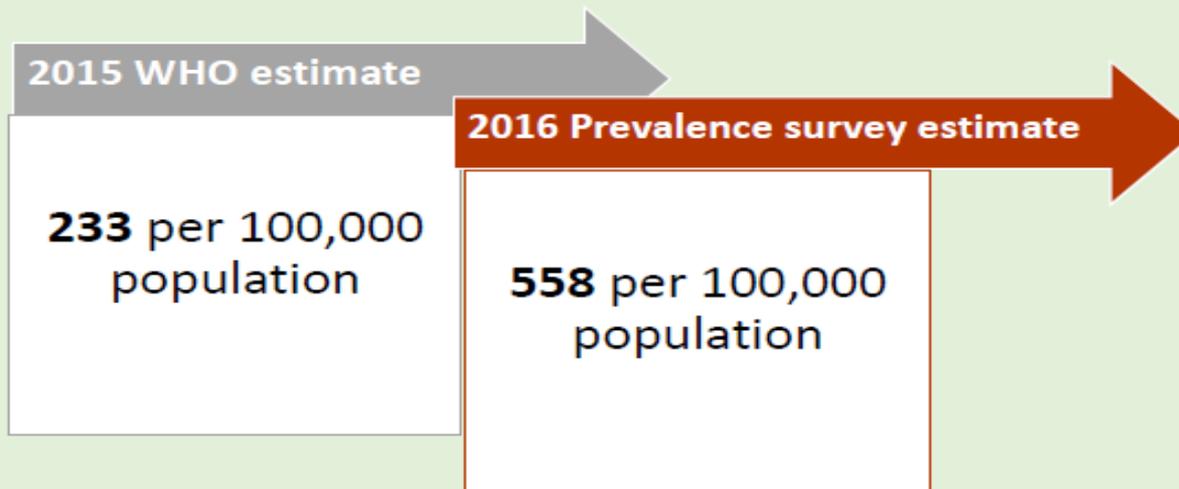
NAIROBI — Kenya on Friday recognized World Tuberculosis Day by releasing results of a TB study by the country's ministry of health — the first of its kind since Kenya's independence. TB remains high in Kenya, and experts say the country lags in the fight against the disease.

The report states that there are more TB cases in Kenya than previously estimated, with a TB prevalence of 558 per 100,000 people.



Prevalence survey, Kenya

There's More TB In Kenya Than We Thought



Translates to approx. 138,105 incident cases/year compared with 81,518 reported 2015 (40% missing)

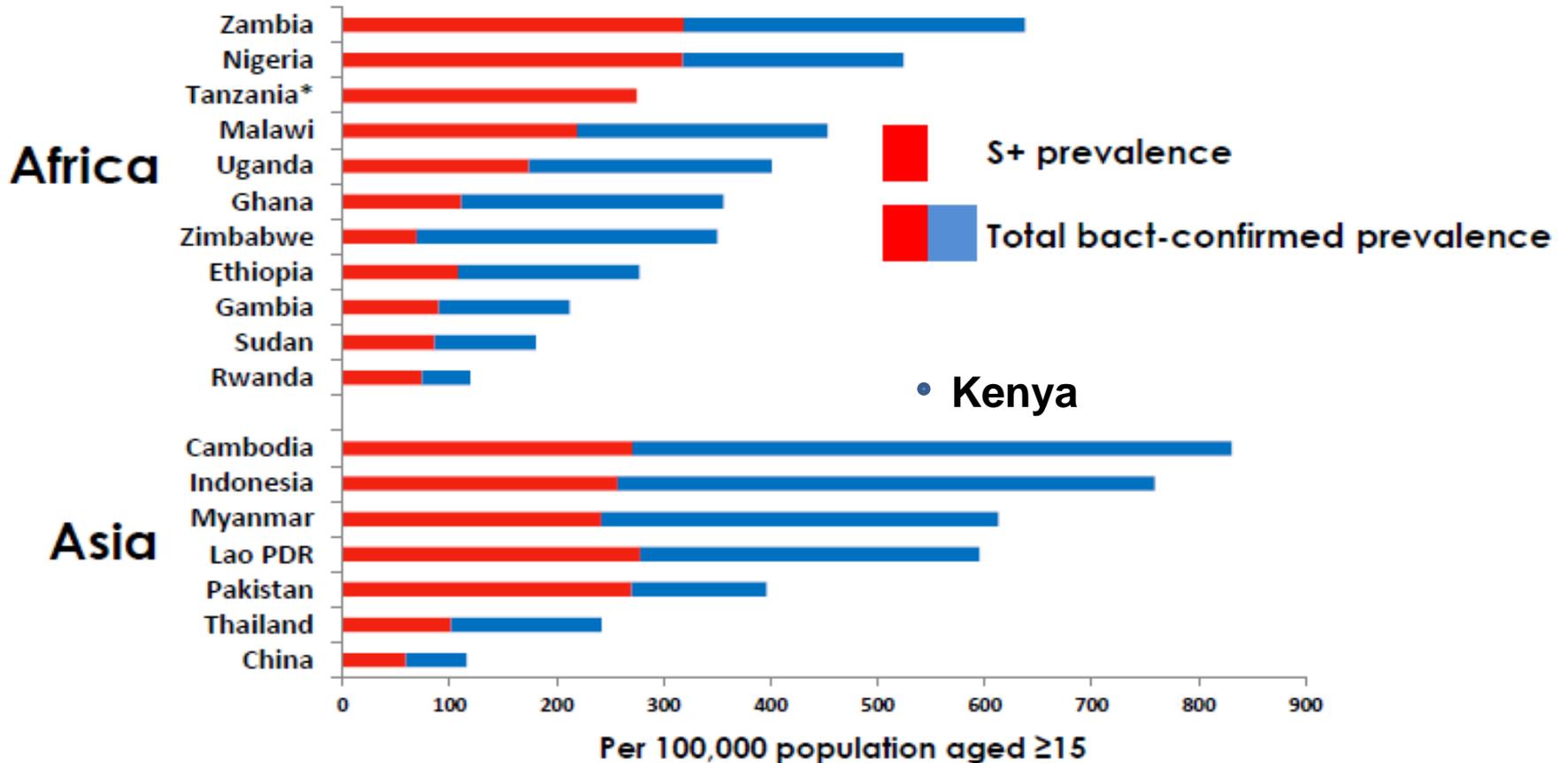


KENYA TUBERCULOSIS PREVALENCE SURVEY 2015 – 2016

Assessing Kenya's TB Burden
REACH, TREAT, CURE EVERYONE



Overall prevalence: Africa and Asia

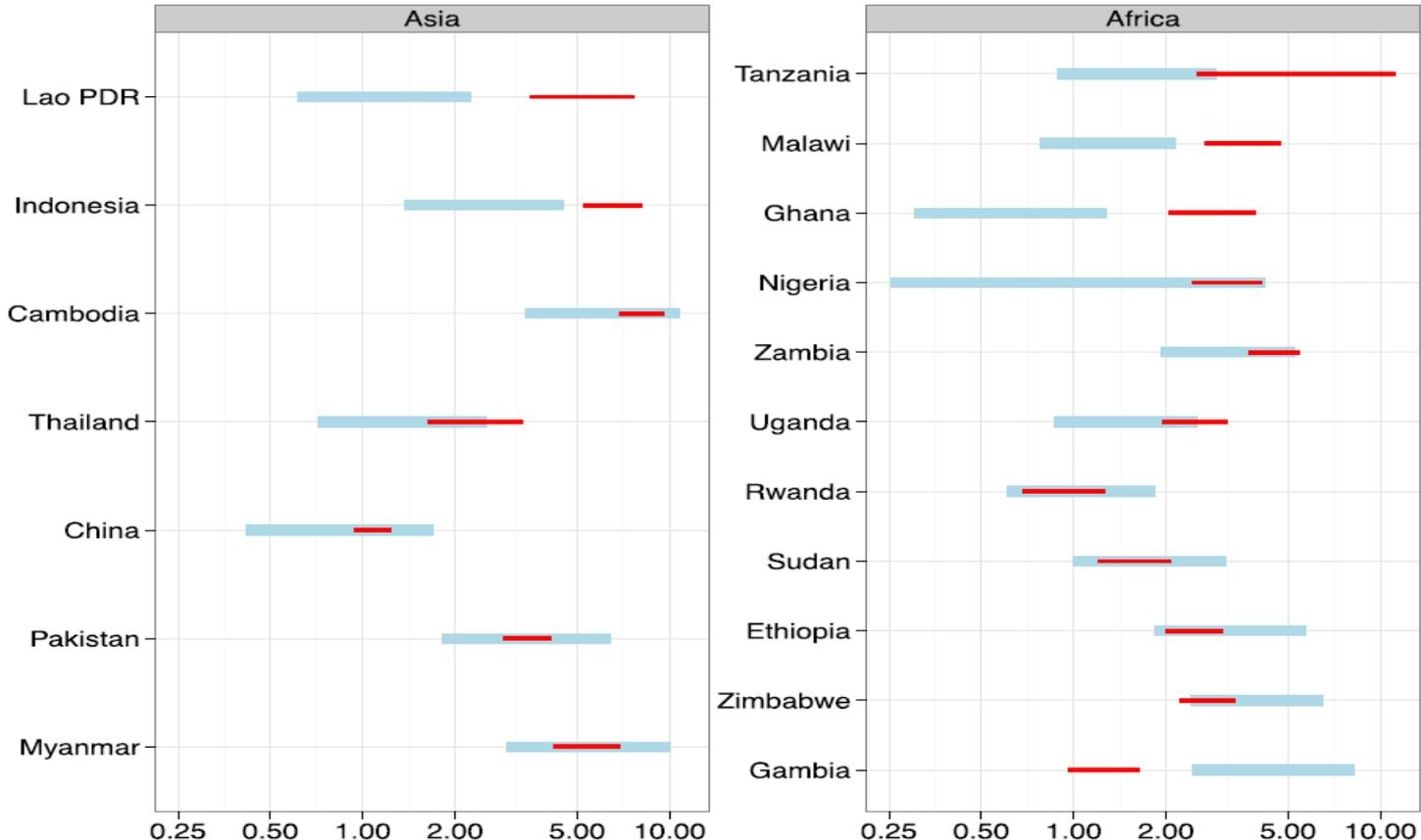


- Considerable variation among countries, highest in Asia
- High proportion of cases that are bact-confirmed but smear-negative

*Tanzania: bacteriologically confirmed cases could not be verified

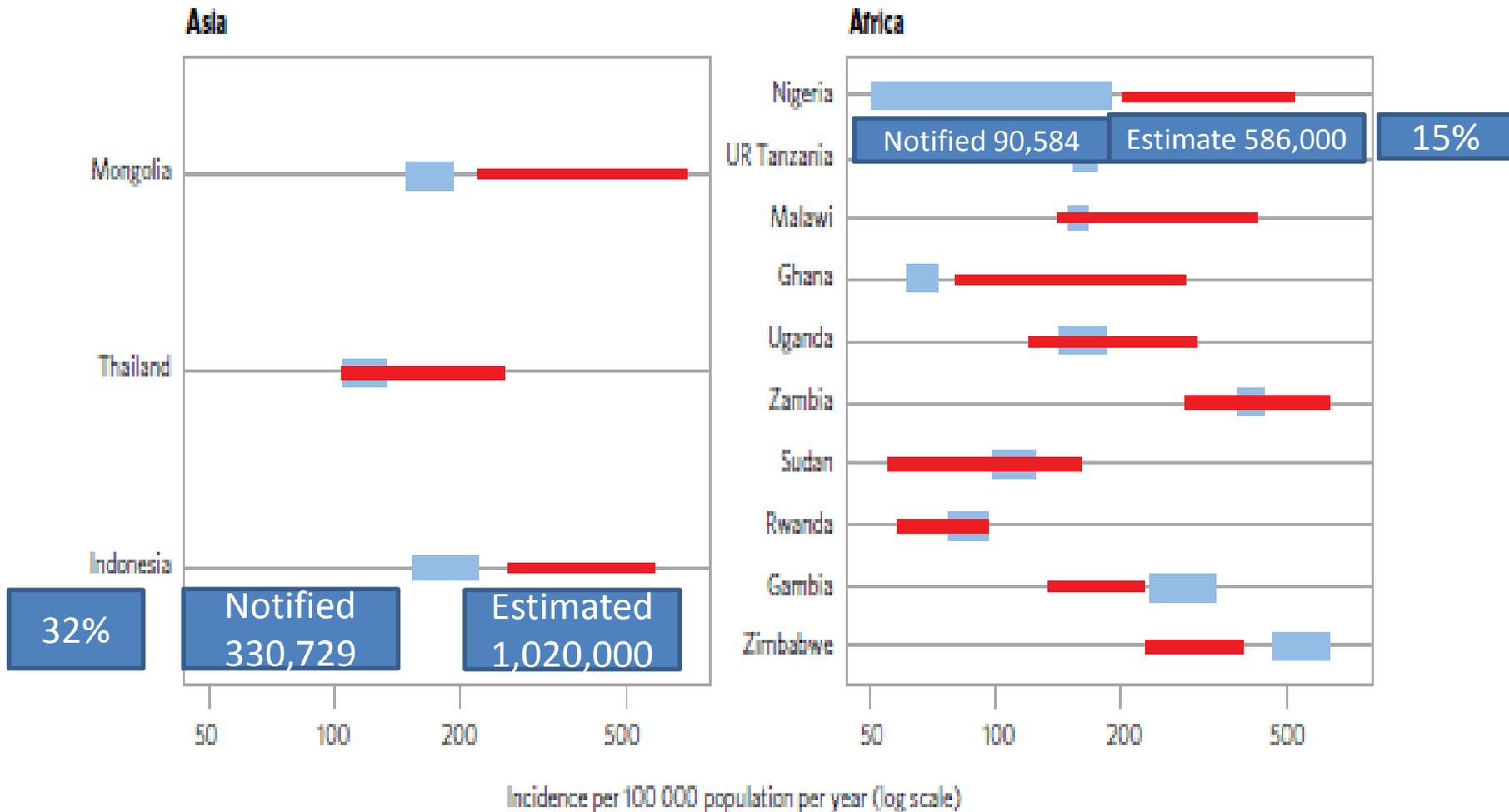
Pre and post-survey estimates

All forms, all ages



Pre-survey prevalence (range of uncertainty)
Post-survey prevalence (range of uncertainty)

Incidence estimates **before** and **after** surveys 2012-2015

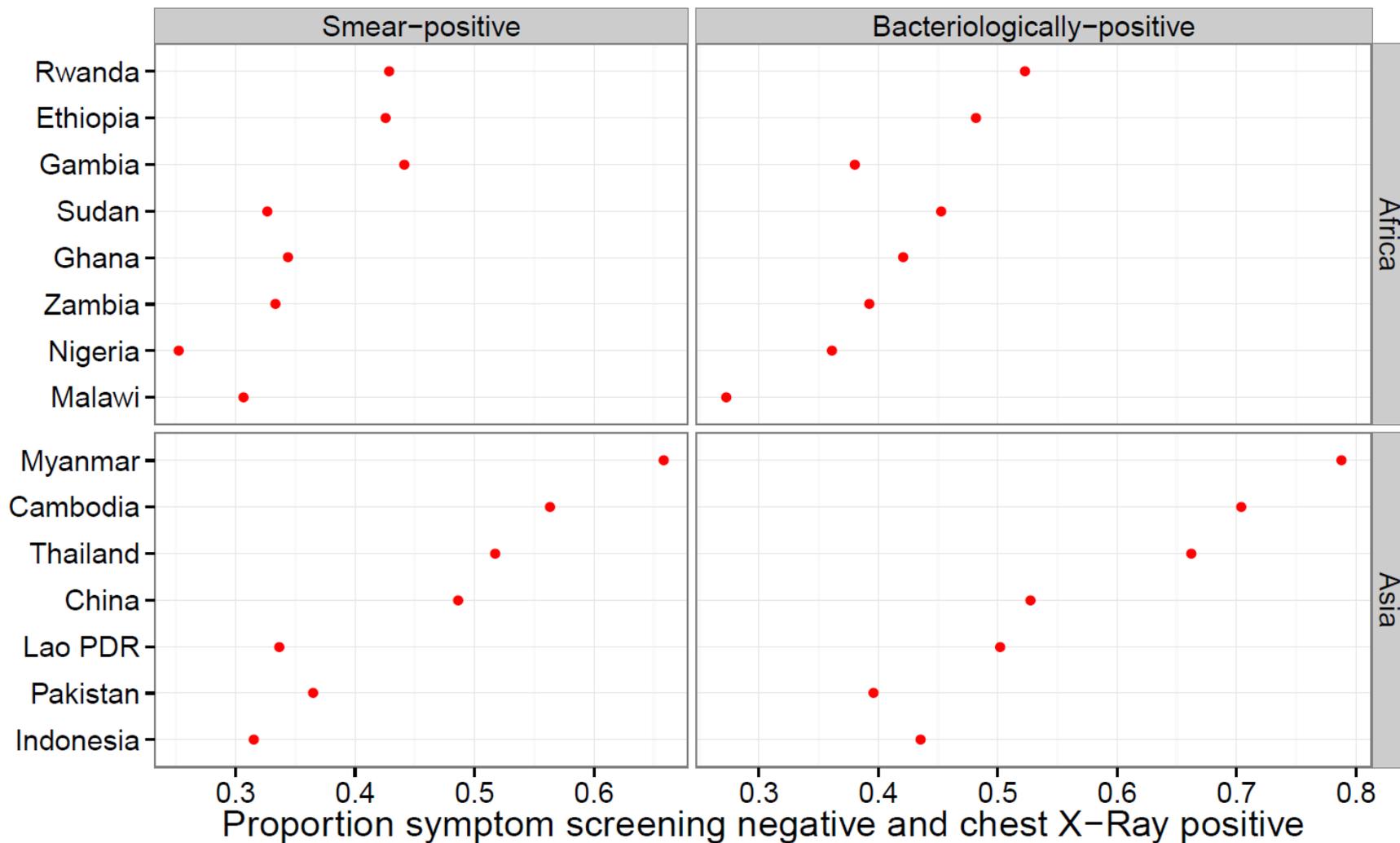


Case-finding should be passive, based on evaluation of patients seeking care because of cough.

Cough is an insensitive indicator of TB.

Many persons with cough don't seek care

Many prevalent cases don't report cough



Indonesia prevalence survey: Care-seeking for Cough

Place of treatment	Male		Female		Total	
	n	%	n	%	n	%
Public hospital	141	2.8	112	3.2	253	3.0
Private hospital	53	1.1	52	1.5	105	1.2
Public primary health facility	440	8.7	485	13.9	925	10.8
Private practitioner/clinic	283	5.6	284	8.1	567	6.6
Nurse or midwife	168	3.3	213	6.1	381	4.5
Pharmacy, drug store, shops etc	1 575	31.1	1 061	30.4	2 636	30.8
Did not seek treatment	2 404	47.5	1 281	36.7	3 685	43.1
TOTAL	5 064	100	3 488	100	8 552	100

Prevalence of symptoms among cases: Kenya

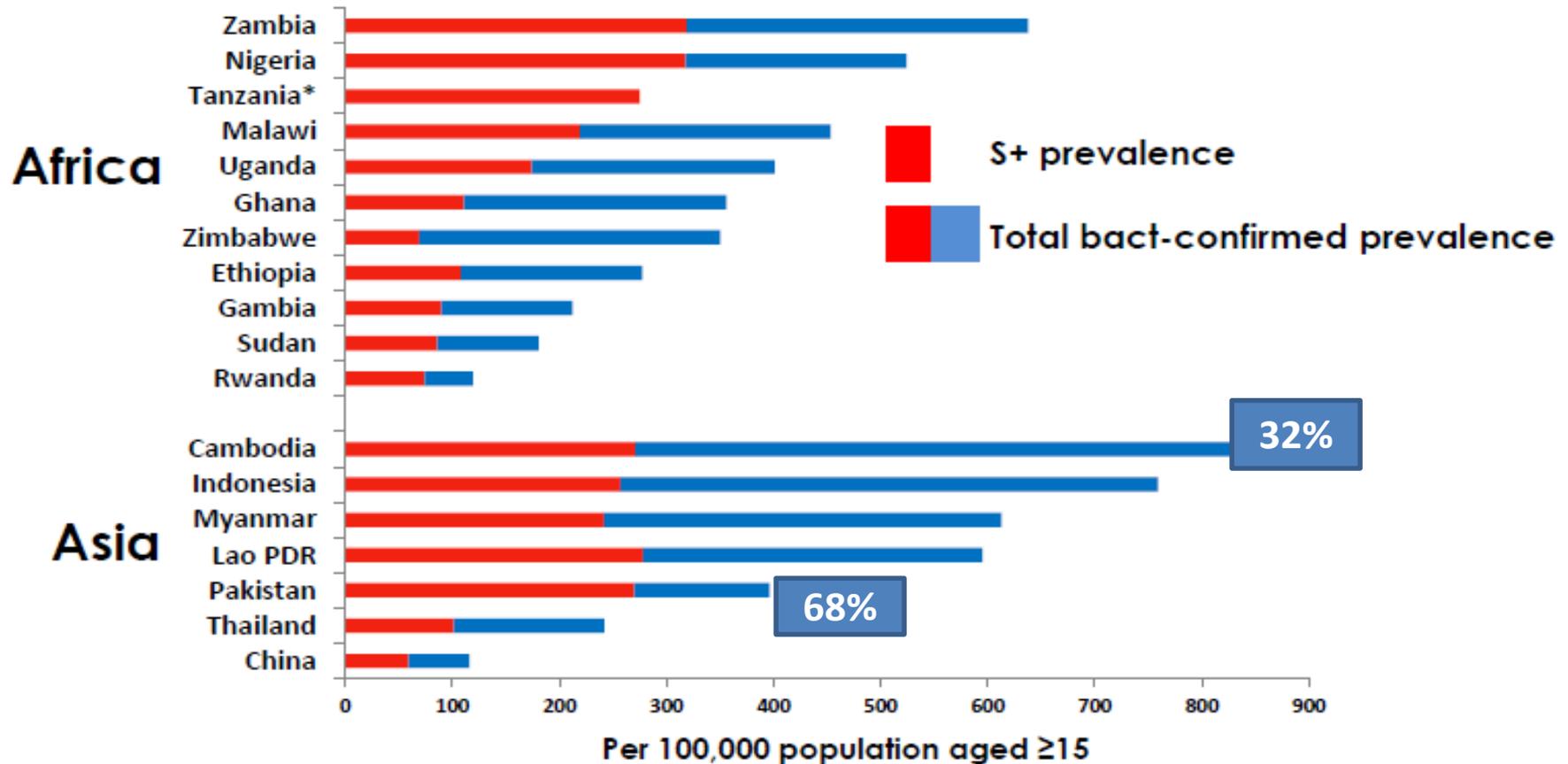
Symptom	Cases	Proportion
Cough > two weeks only	147	48%
Night sweats only	85	28%
Fever only	62	20%
Weight loss only	41	13%
Weight loss or fever or night sweats or cough more than two weeks	181	59%
Any coughing or fever or weight loss or night sweats or fatigue or other symptoms or breathe shortness or chest pains (At least one symptom)	225	74%
Total	305	100%

Diagnosis should be based on sputum smear microscopy:

- insensitive but highly specific**
- culture is the gold standard**

- Microscopy is <50% sensitive (compared with culture and/or Xpert)**
- False-positive smears are common**
- Culture is problematic in many countries**

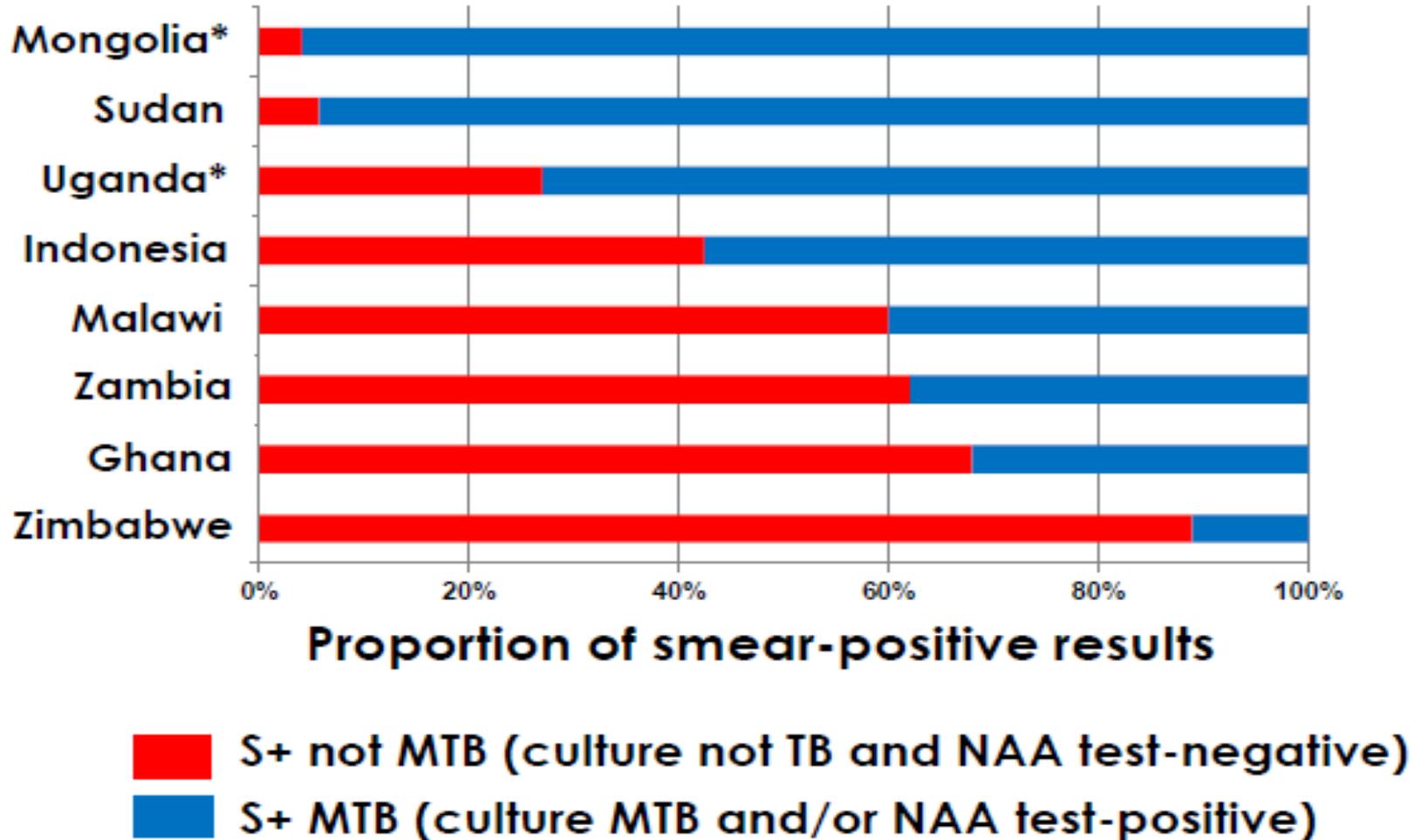
Sensitivity of microscopy



Range ~30-70% sensitivity

*Tanzania: bacteriologically confirmed cases could not be verified

False-positive smears are common



Indonesia prevalence survey: False positive smears

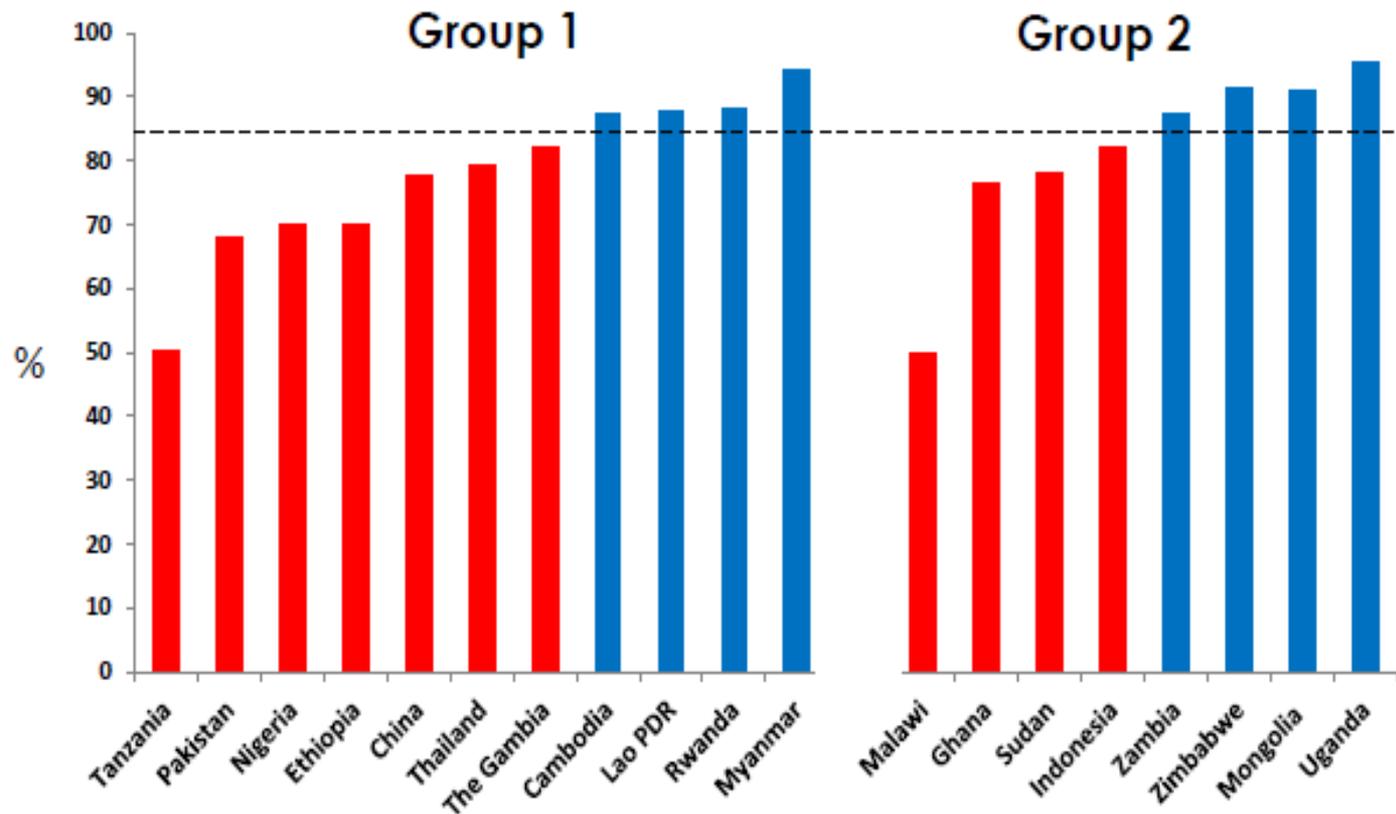
Result	Culture						TOTAL
	Negative	MTB	NTM	Contamination	NA		
Positive	18	133	1	5	0	157	
Negative	105	5	13	1	0	124	
NA	6	3	0	0	1	10	
TOTAL	129	141	14	6	1	291	

Xpert MTB/RIF

Smear

118/291 (42%) false positive smears
13/291 (4.5%) NTMs

>50% of surveys had problems with culture: Low culture confirmation among smear-positive TB cases (<85%)



Group 1: Classical definition of smear-positive TB based on culture and CXR

Group 2: Since 2013, new definition of smear-positive TB based on culture and Xpert/LPA

Non-tuberculous mycobacteria (NTMs) are uncommon in most countries and, thus, are unlikely to cause a positive smear

Non-tuberculous mycobacteria (NTMs) are relatively common in some countries (but are unlikely to cause a positive smear)

Indonesia prevalence survey: Isolation of M Tb and NTMs

Culture results	Spot		Morning		Combined	
	n	%	n	%	n	%
Number of specimen collected	4 534	100	14 619	100	15 141	100
Number of specimen examined	4 433	97.8	14 569	99.7	15 109	99.8

Culture results:

MTB	133	3.0	358	2.5	400	2.7
NTM	79	1.8	334	2.3	405	2.7

Of 334 morning specimens positive for NTMs only 9 (3%) were smear positive

**Chest radiography has no role
in the diagnosis of tuberculosis:
expense, lack of facilities, lack
of trained readers, poor
specificity**

Substantial disagreement between “field”
readers and central readers

- Largely over-reading in the field
- Minimal(4%) missed by field readers

Indonesia: Agreement between field and central CXR interpretation

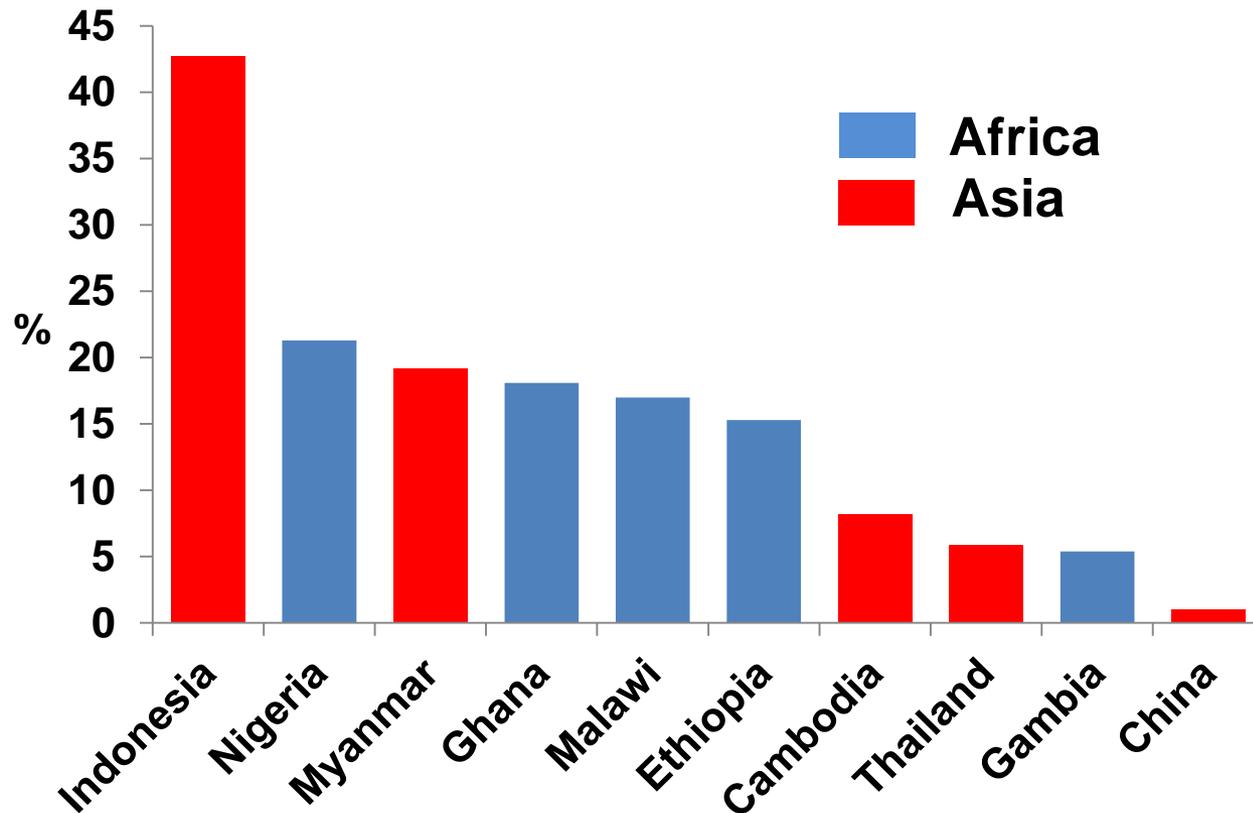
Central Reader	Field Reader							
	Normal	%	Abnormal TB	%	Other Abnormalities	%	Total	%
Normal	5,121	92%	1,616	60%	1,388	66%	8,125	78%
Abnormal TB	220	4%	771	28%	209	10%	1,200	12%
Other Abnormalities	242	4%	314	12%	500	24%	1,056	10%
Total	5,583	54%	2,701	26%	2,097	20%	10,381	

4% of CXR read “normal” in field were “abnormal TB” by central reader.
60% of CXR read as “abnormal TB” in field were “normal” by central reader

Many cases are treated in the private sector or initially seek care in private facilities/providers.

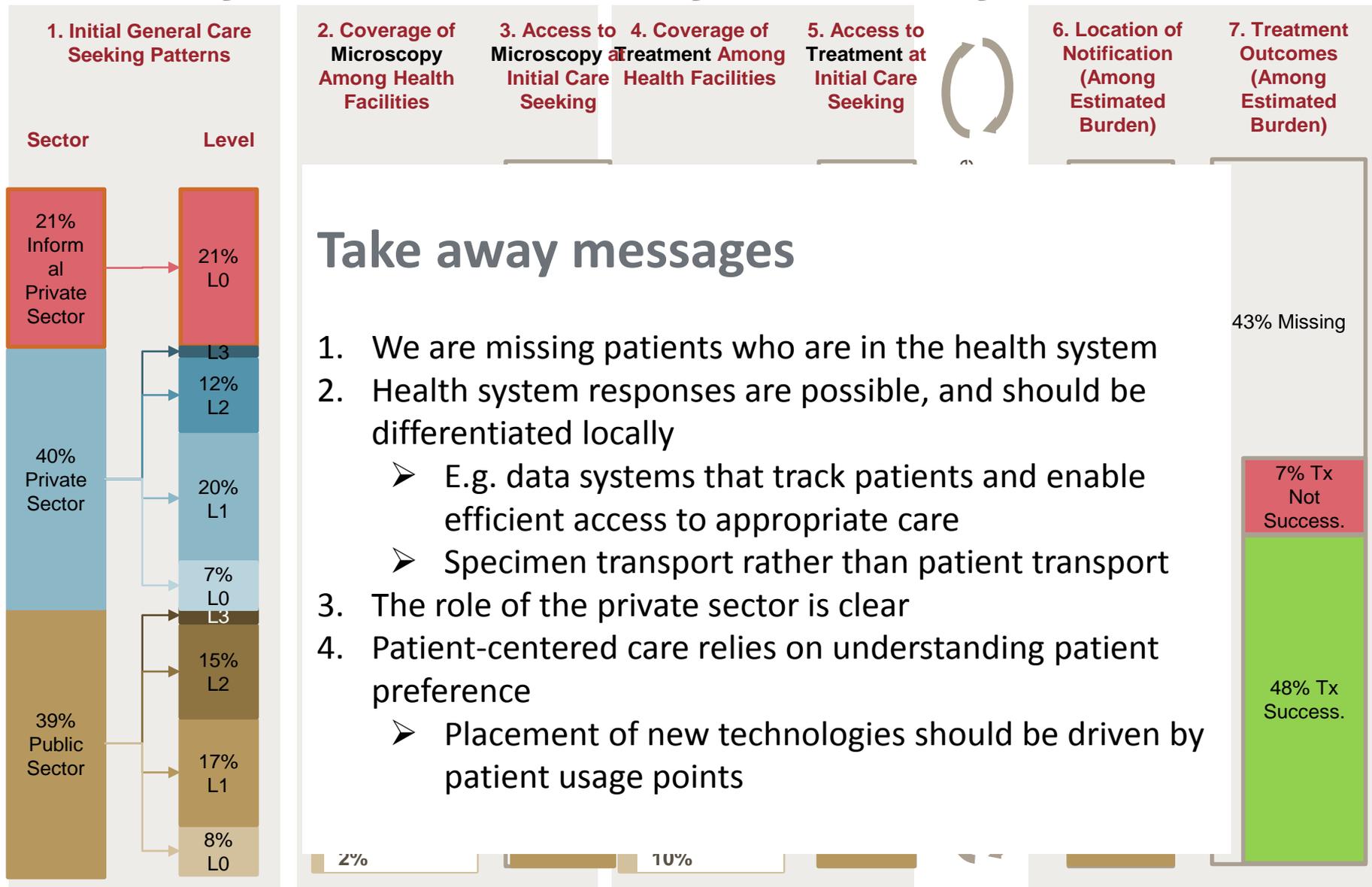
This is correct

High proportion of patients being treated in private sector



*Those currently on TB treatment at the time of the survey (excluding unknown location)

Country Patient Pathway Summary



Preventive treatment of LTBI has no place in tuberculosis control

Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy (6). The efficacy of currently available treatments ranges from 60% to 90% (1). The potential benefit of treatment should, however, be carefully balanced against the risk for drug-related adverse events. Mass, population-wide LTBI testing and treatment are not feasible because the tests are imperfect, there are risks of serious and fatal side-effects, and the cost would be high, for an unproven public health impact. For infected individuals in population groups in which the risk for progression to active disease significantly exceeds that of the general population, however, the benefits are greater than the harm. Management of LTBI involves a comprehensive package of interventions: identifying and testing those individuals who should be tested, delivering effective, safe treatment in such a way that the majority of those starting a treatment regimen will complete it with no or minimal risk of adverse events, and monitoring and evaluation of the process.

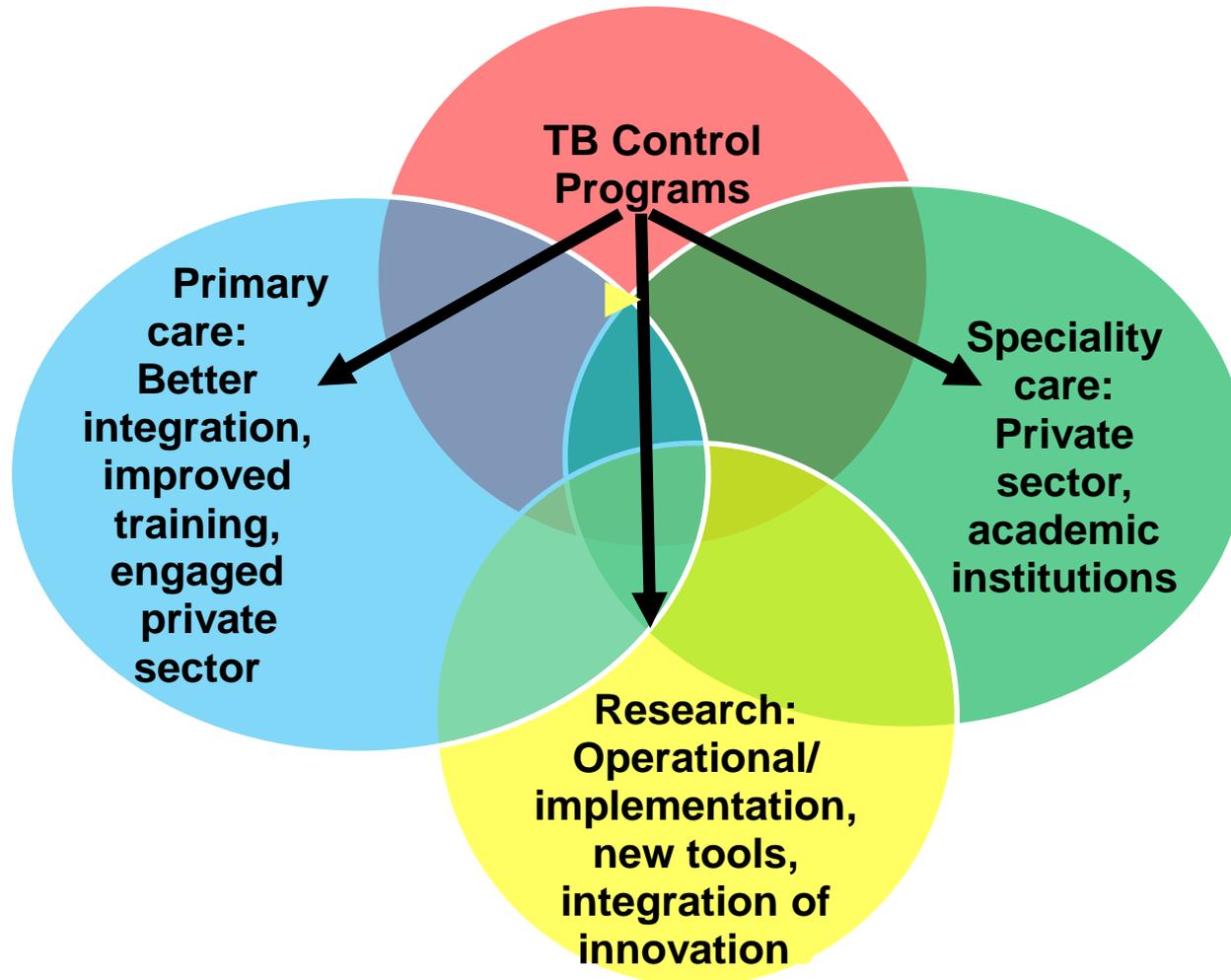
Prevalence surveys: What are the programmatic issues?

- Awareness of symptoms/insensitivity of symptom screening
- Access to high quality care
- Integration of care/strong primary care (IMAI)
- Appropriate diagnostic evaluations
- Appropriate use of screening tests and algorithms
- Poor performance of conventional microbiological tests: (?Xpert more sensitive than culture in practice)
- Appropriate use of radiological evaluation (difficulties with field reading)
- Epidemiological impact of “asymptomatic TB”

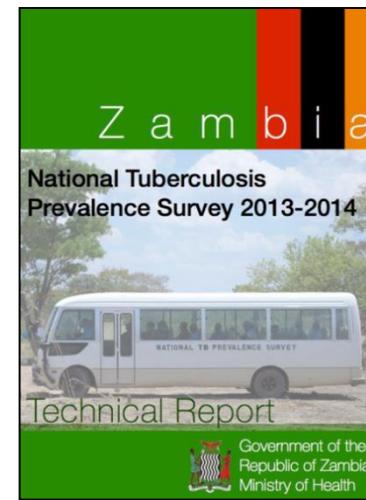
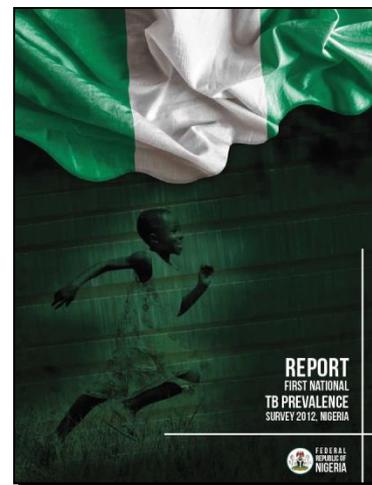
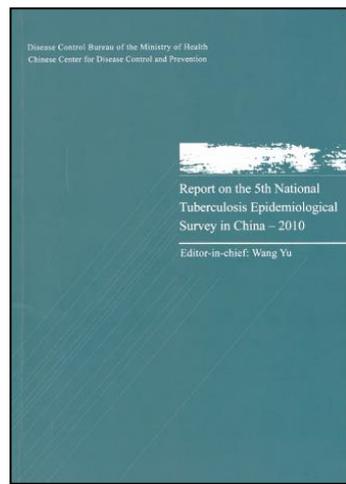
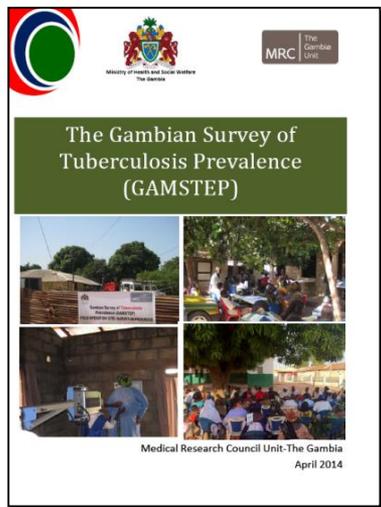
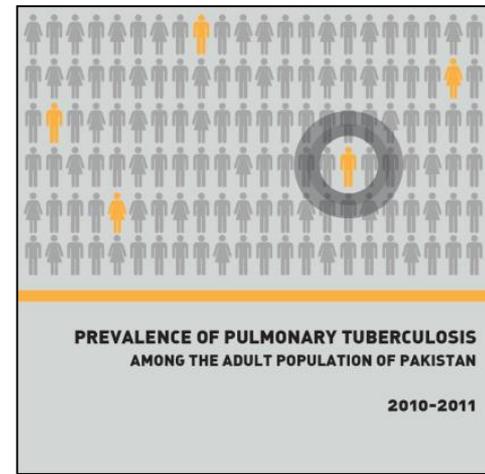
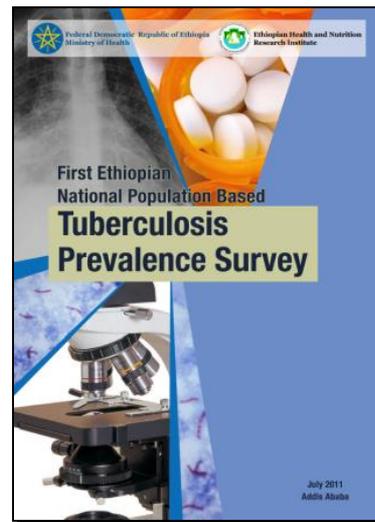
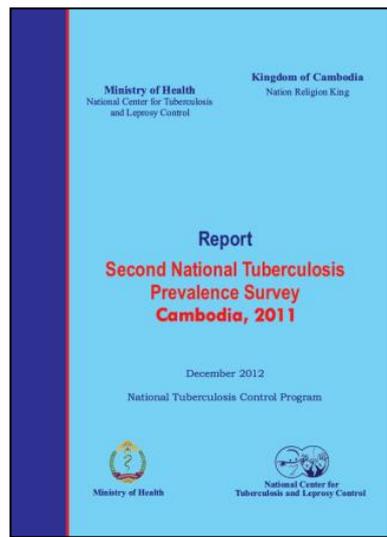
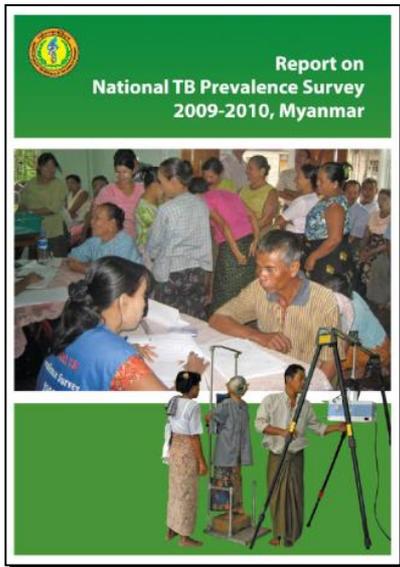
Prevalence surveys: Implications for clinicians

- Clinical suspicion for TB must be increased, especially among those with risks in high incidence settings.
- Symptom screening should include any cough, fever, night sweats, weight loss.
- Where possible patients with symptoms should be evaluated with a chest x-ray.
- Radiographic abnormalities suggestive of TB should be evaluated with a rapid molecular test (Xpert MTB/RIF).
- Communication and collaboration between public and private sectors is essential.

Collaboration and coordination is essential



Publications from individual surveys



Prevalence survey, Indonesia: 2013-14

Indonesia

**Tuberculosis Prevalence Survey
2013–2014**



Ministry of Health, Republic of Indonesia

National Institute of Health Research and Development

In collaboration with

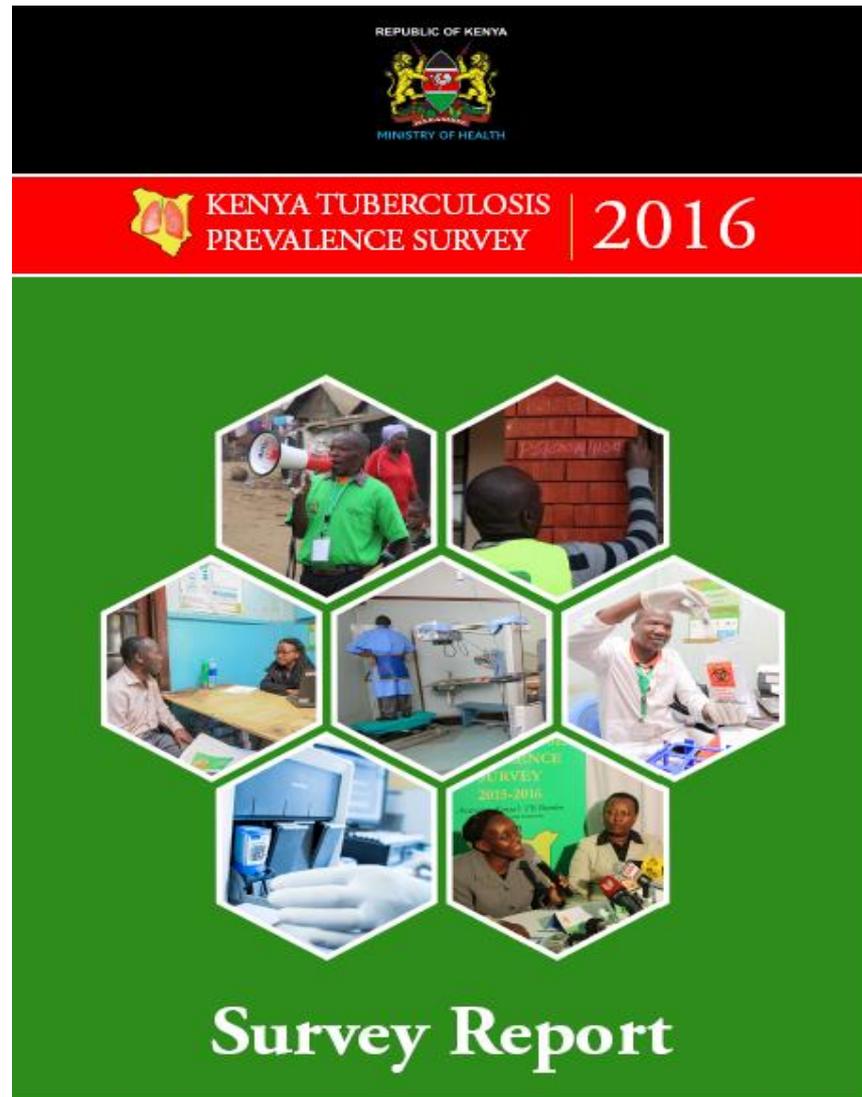
Directorate General of Disease Control and Environmental Health

June 2015

Supported by :



Prevalence survey, Kenya, 2016



22 Global Focus Countries



Africa: Ethiopia, Ghana, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Sierra Leone, South Africa, Tanzania, Uganda, Zambia

Asia: Bangladesh, Cambodia, China, Indonesia, Myanmar, Pakistan, Philippines, Thailand, Viet Nam

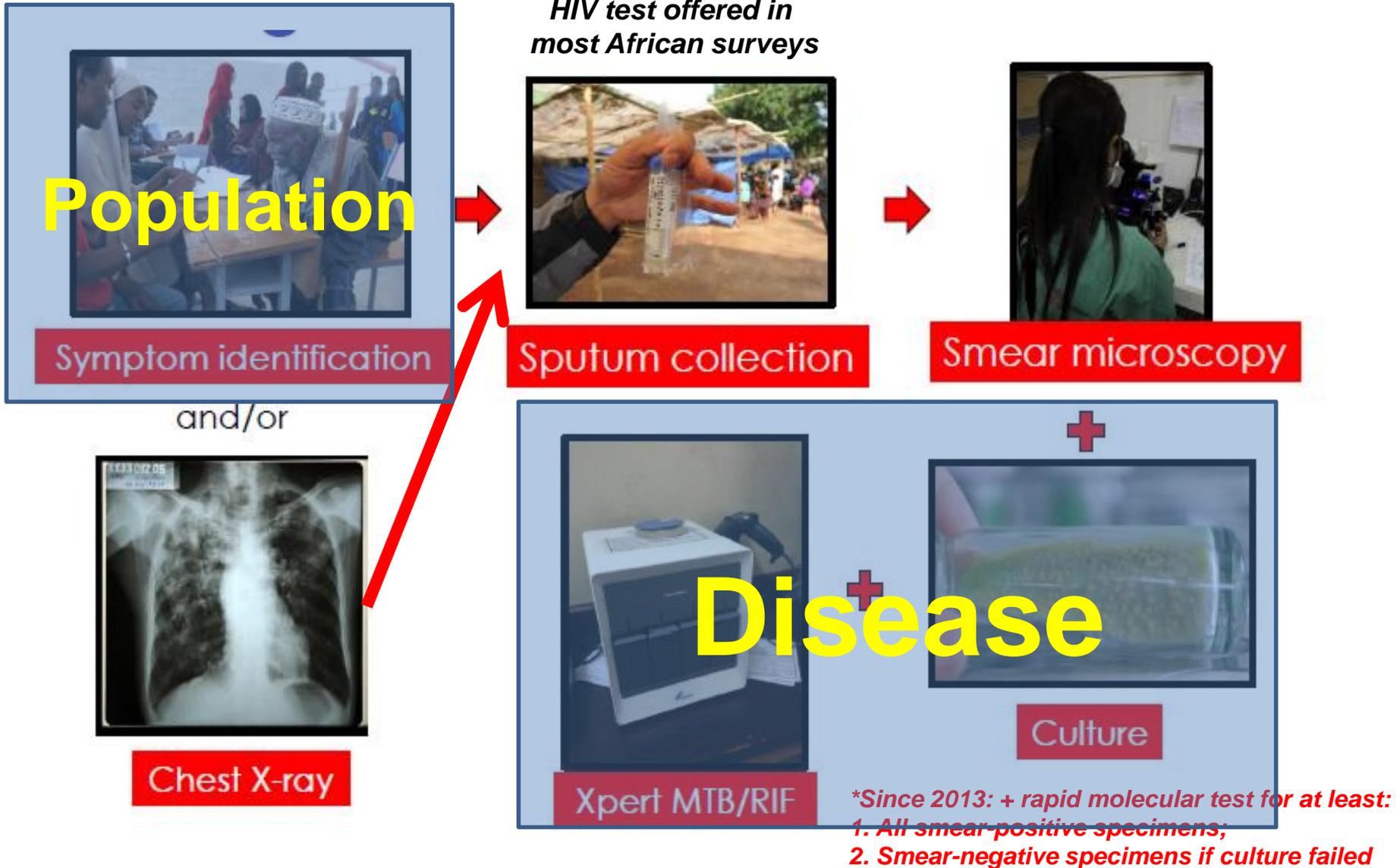
Prevalence

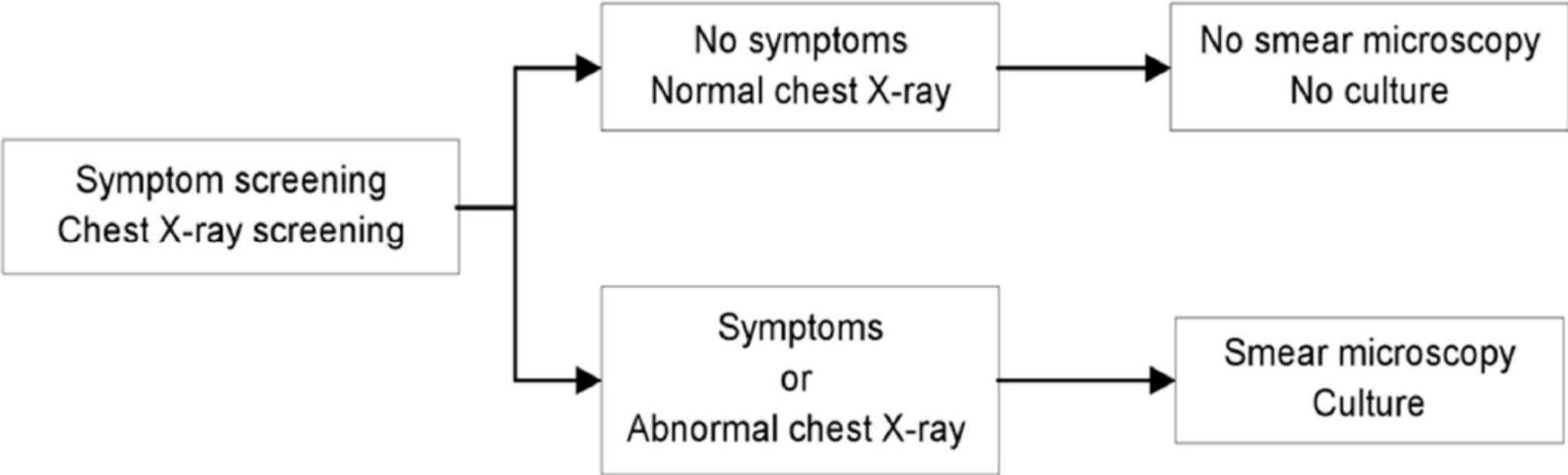
Number of persons in a population with a **disease or condition at a specified time**

Number of persons in the **population of interest at the specified time**

- A proportion of a population with the disease or condition at a specific point in time.
- Describes disease burden at the specified time. Presents a “snapshot” or “slice-in-time” similar to a census. It does not describe events.
- Knowing the prevalence is useful for public health program planning

Consistent methods since 2009







TB Prevalence of population aged 15 years old and above

Category	Number of patients detected during the survey	Prevalence 1/100,000 (95% CI)	Estimated number of TB patients over 15 yrs old Million (95% CI)
All type of TB	1,310	459 (433, 484)	5.0 (4.7, 5.3)
Smear positive TB	188	66 (53, 79)	0.7 (0.6, 0.9)
Bacteriologically confirmed TB	347	119 (103, 135)	1.2 (1.1, 1.5)

- Around 14.4% of detected TB patients during the survey were smear positive and 26.5% were bacteriologically confirmed TB



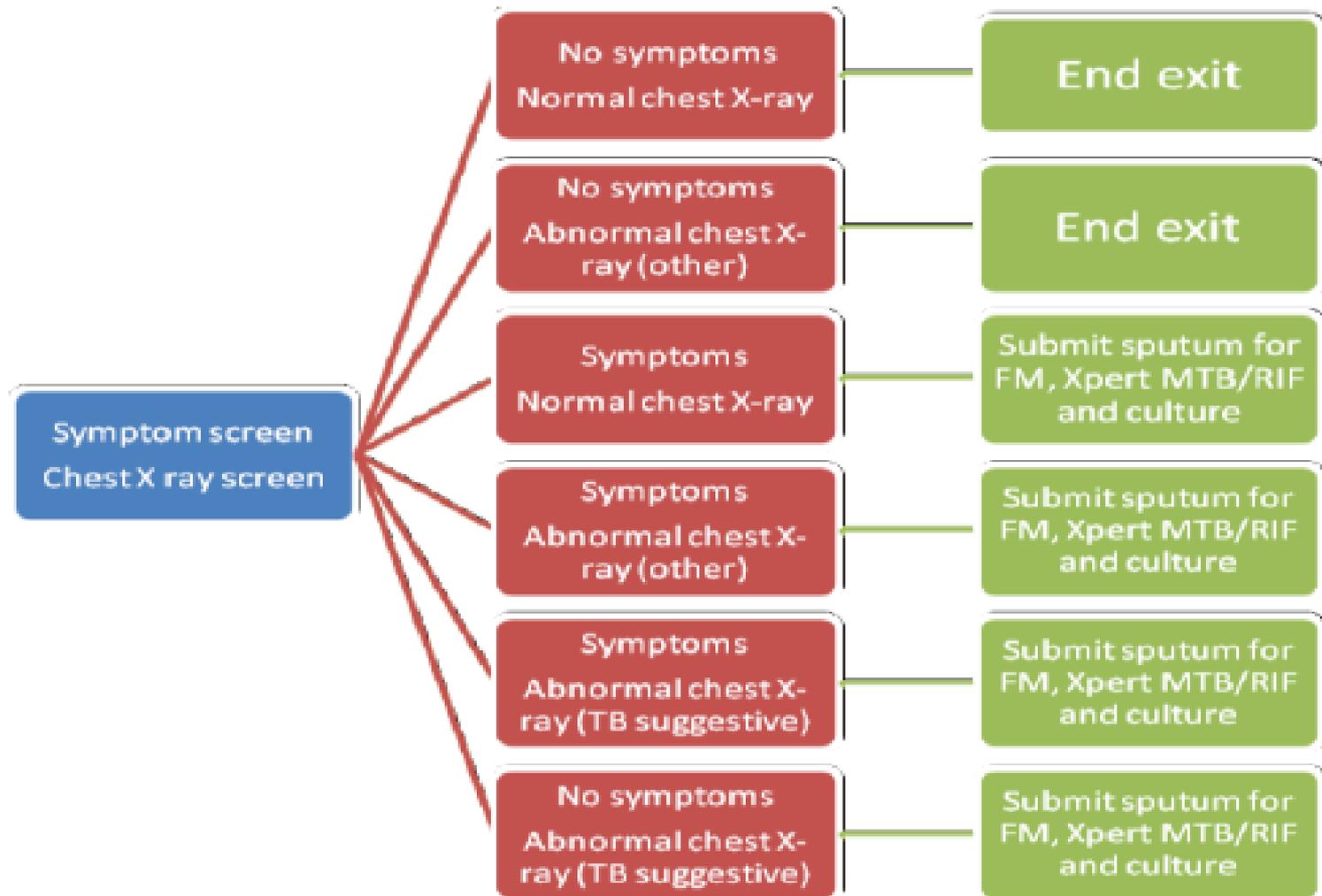
TB Symptoms

- Among 1,301 TB cases detected during the survey, 740 cases (56.9%) had symptoms and the remaining 561 cases (43.1%) had no symptoms
- The proportion of patients who had TB symptoms was higher among the elder people aged 60 years old and above (60.2%)

Age (years)	Without symptom		With symptom		Total	
	No.	%	No.	%	No.	%
15~59	308	46.2	358	53.8	666	100.0
≥60	253	39.8	382	60.2	635	100.0
Total	561	43.1	740	56.9	1301	100.0

- Focus on newly identified population groups or geographic areas at higher risk
- Increase in emphasis on and activities related to active case finding and case detection
- Increased focus on the private sector and its role in TB case detection and treatment
- Modifications to screening criteria and algorithms (especially in response to identification of cases who were symptom-screen negative, as well as smear negative, culture positive cases)
 - Implementation of GeneXpert (Xpert® MTB/RIF)
 - Increased use of digital X-rays

Screening sequence, Kenya



Screening

- Who to screen:
 - Known risk groups
 - HIV
 - Diabetics
 - Others based on local epidemiology
- How to screen
 - Sputum
 - Smear
 - Xpert
 - Radiography

Prevalence surveys: STAG, 2015

1. Make the following additions/modifications to the list of policy, programmatic and funding implications of prevalence surveys:

a. Add emphasis on the need to strengthen surveillance in general (beyond mandatory notification/correcting under-reporting);

b. Highlight the need for further research to understand detection and reporting gaps identified during surveys as a separate recommendation, and explicitly refer to “research” (as opposed to including this within point 1, without using the word “research”);