Who is falling through the cracks?

Using the TB care cascade for program monitoring and intervention development

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Objectives

- Describe findings of the Indian and South African TB care cascades[1,2]
- Describe approaches for constructing TB cascades at local and national levels[26]
- Discuss how cascades can be used to guide interventions

Funding and Disclosures

- Harvard Catalyst KL2/CMERIT Award (KL2 TR001100)
- Bill & Melinda Gates Foundation via the Arcady group (OPP1154665)
- Harvard Center for AIDS Research (5P30AI060354-13)

- I have no disclosures or conflicts of interest.

Recommended reading: “How to” guide

Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care

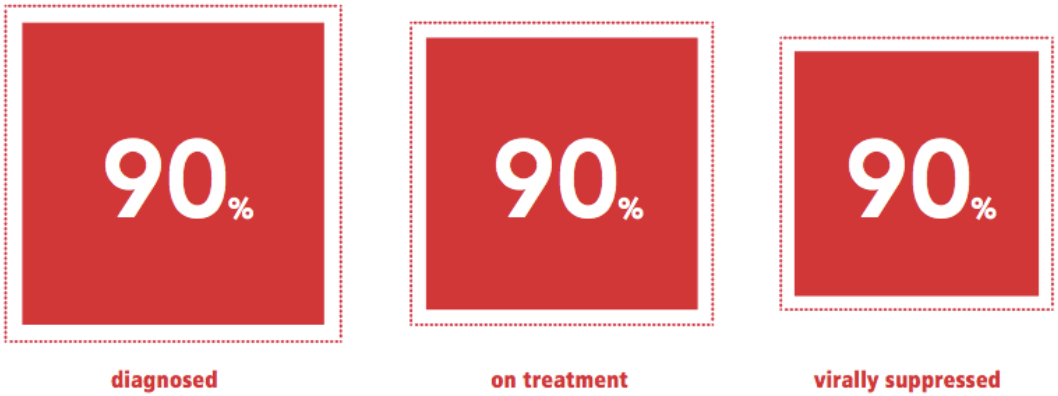
Ramnath Subbaraman[1,2]*, Ruvandhi R. Nathavitharana[3], Kenneth H. Mayer[3,4], Srinath Satyanarayana[5], Vineet K. Chadha[6], Nimalan Arinaminpathy[7], Madhukar Pai[8]

Source: Subbaraman R, et al. PLOS Medicine 2019; 16(2):e100254[26]

Mentors and Collaborators

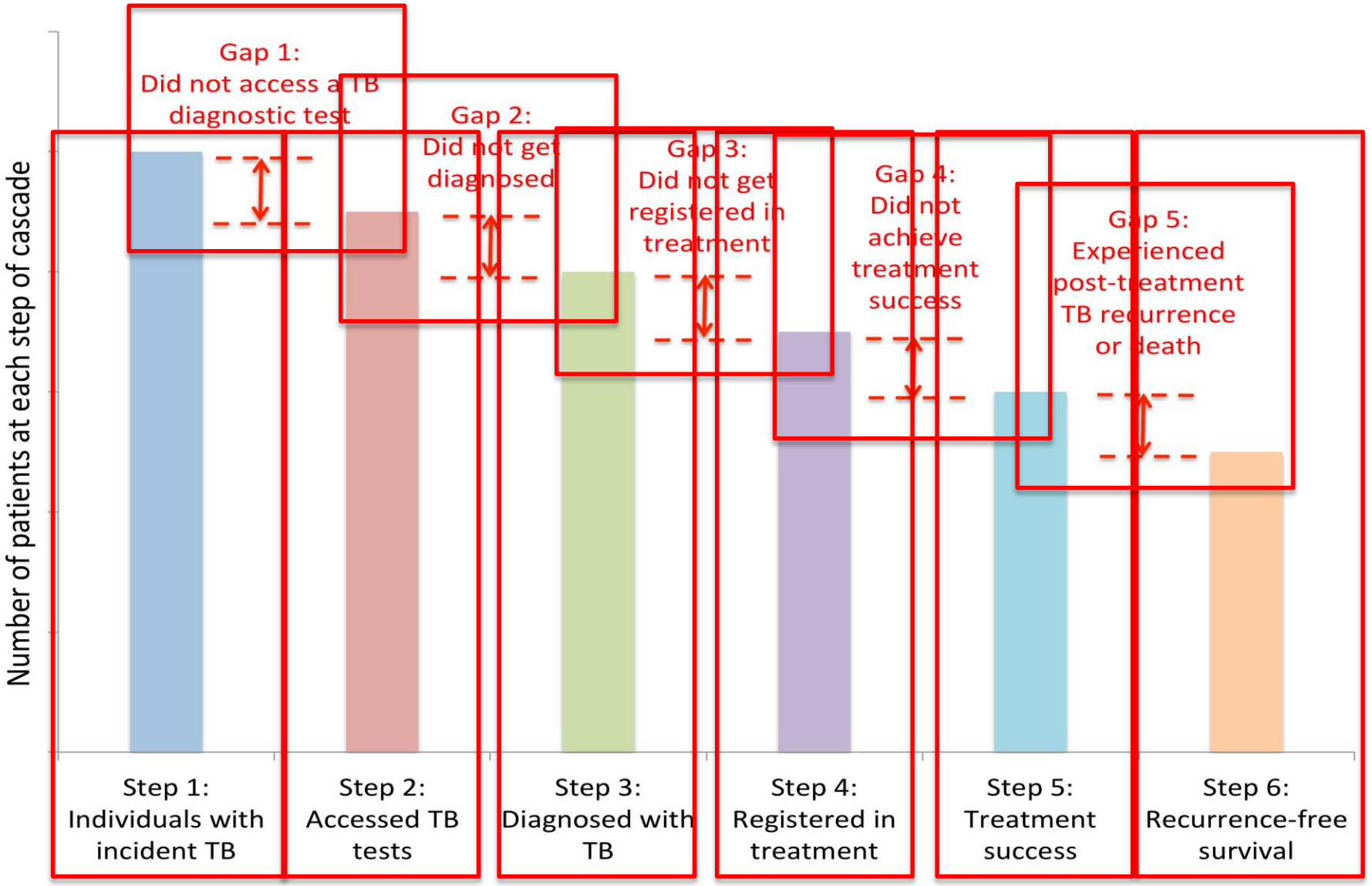
Cascade of Care Model

- Helps visualize “gaps” in care delivery for patients at a <u>population level</u> or a <u>facility level</u>
- Guides UNAIDS’ “90-90-90” global HIV targets[3]
- Not previously used for TB before the Indian and South African analyses[1,2]
- Our cascade integrates the HIV cascade model with a WHO “onion peel” model for TB[1,4]



Source: UNAIDS[3]

A Generic Model for a Tuberculosis Care Cascade[26]

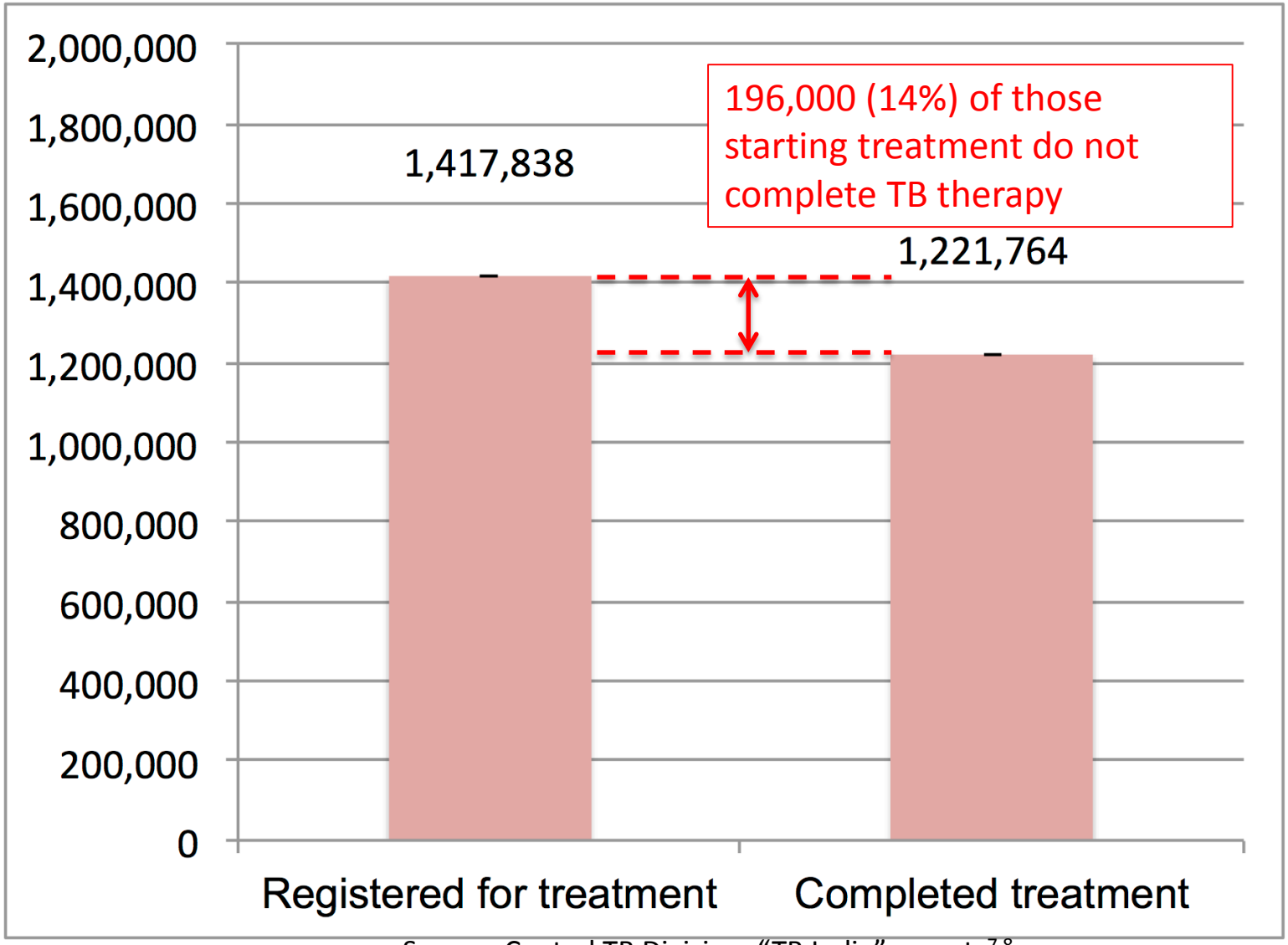


Why has the cascade not widely been used for TB?[26]

- Estimating burden of disease at the population level (especially incidence) is challenging
- No “perfect” diagnostic test for TB (unlike HIV)
- Heterogeneity in diagnosis and care for different forms of TB (smear +/-, Xpert +/-, extrapulmonary, drug-resistant)
- Limited ability to determine if patients achieved durable cure
- These are also reasons why the TB cascade may provide meaningful insights into deficiencies in care

EXAMPLE 1:
THE TUBERCULOSIS CASCADE OF CARE IN INDIA'S PUBLIC SECTOR

What we knew about India's public TB program before the cascade

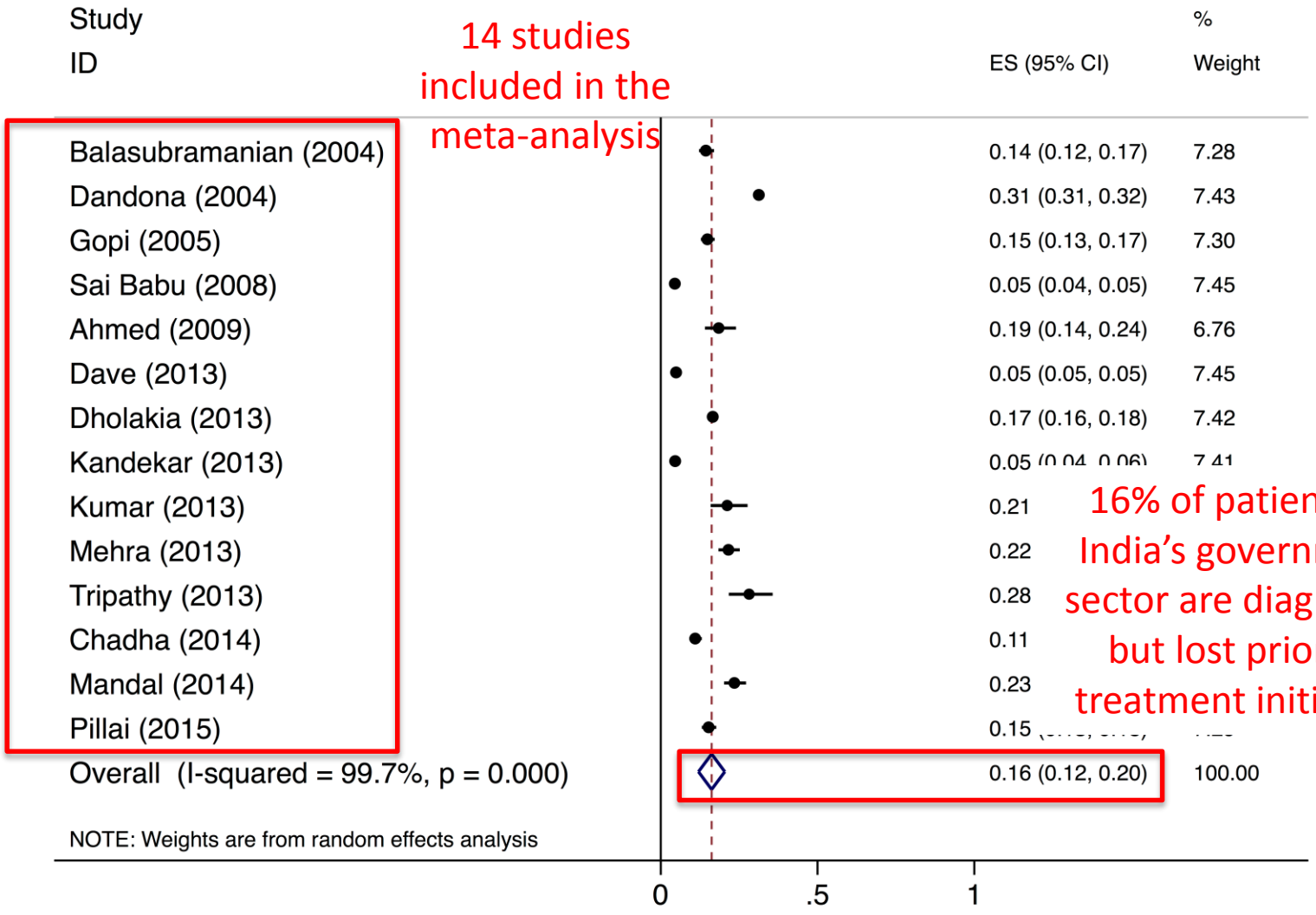


Source: Central TB Division. "TB India" reports[7,8]

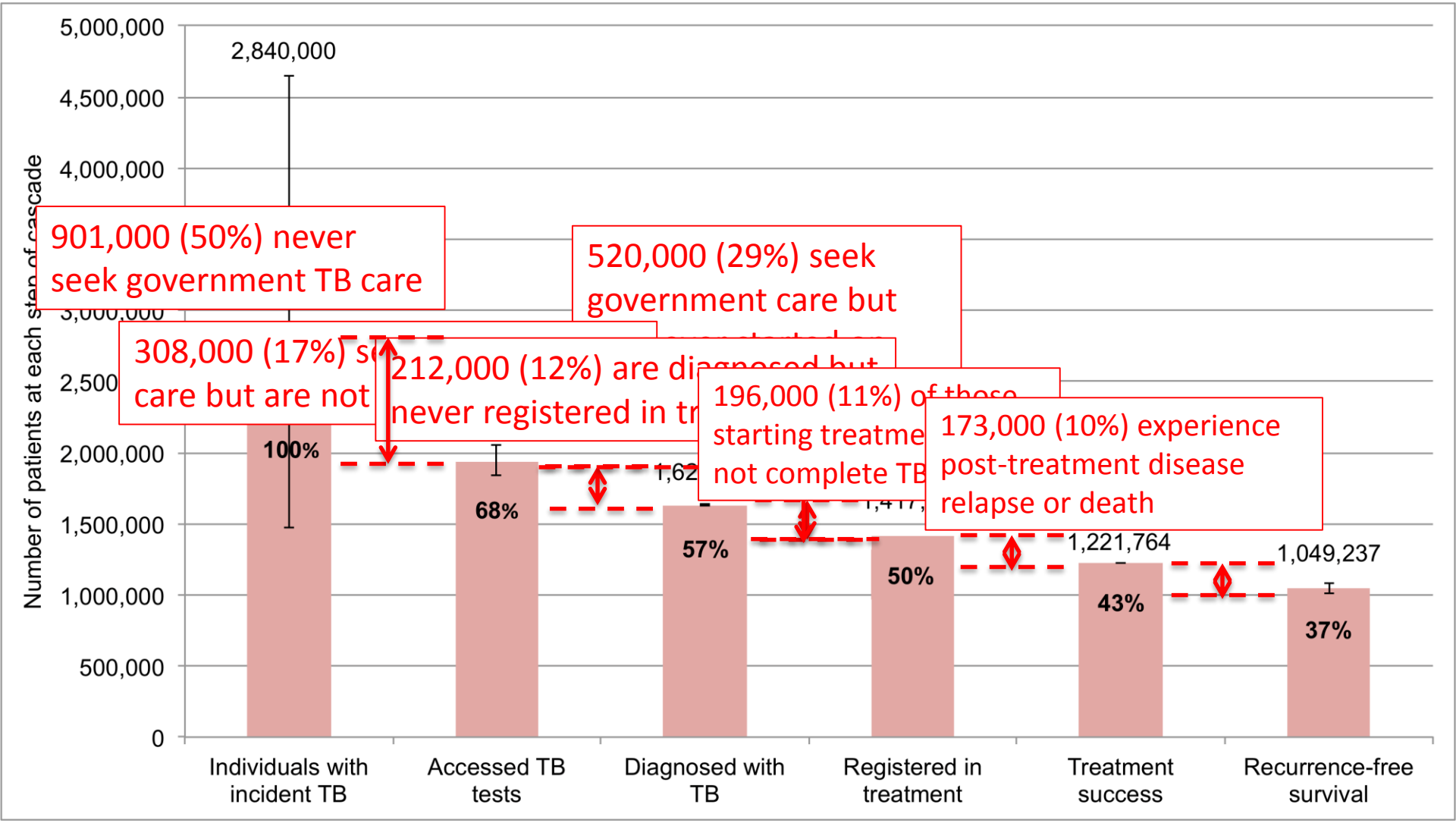
Methods

- TB prevalence and MDR TB burden extracted from the 2015 *WHO Global TB Report*[5]
- Notification and treatment completion data extracted from Indian government official reports[6-8]
- Five gaps estimated by systematic reviews + meta-analyses of 39 Indian studies from 2000-2015[1]

Pretreatment loss to follow-up meta-analysis (Gap 3)[9]

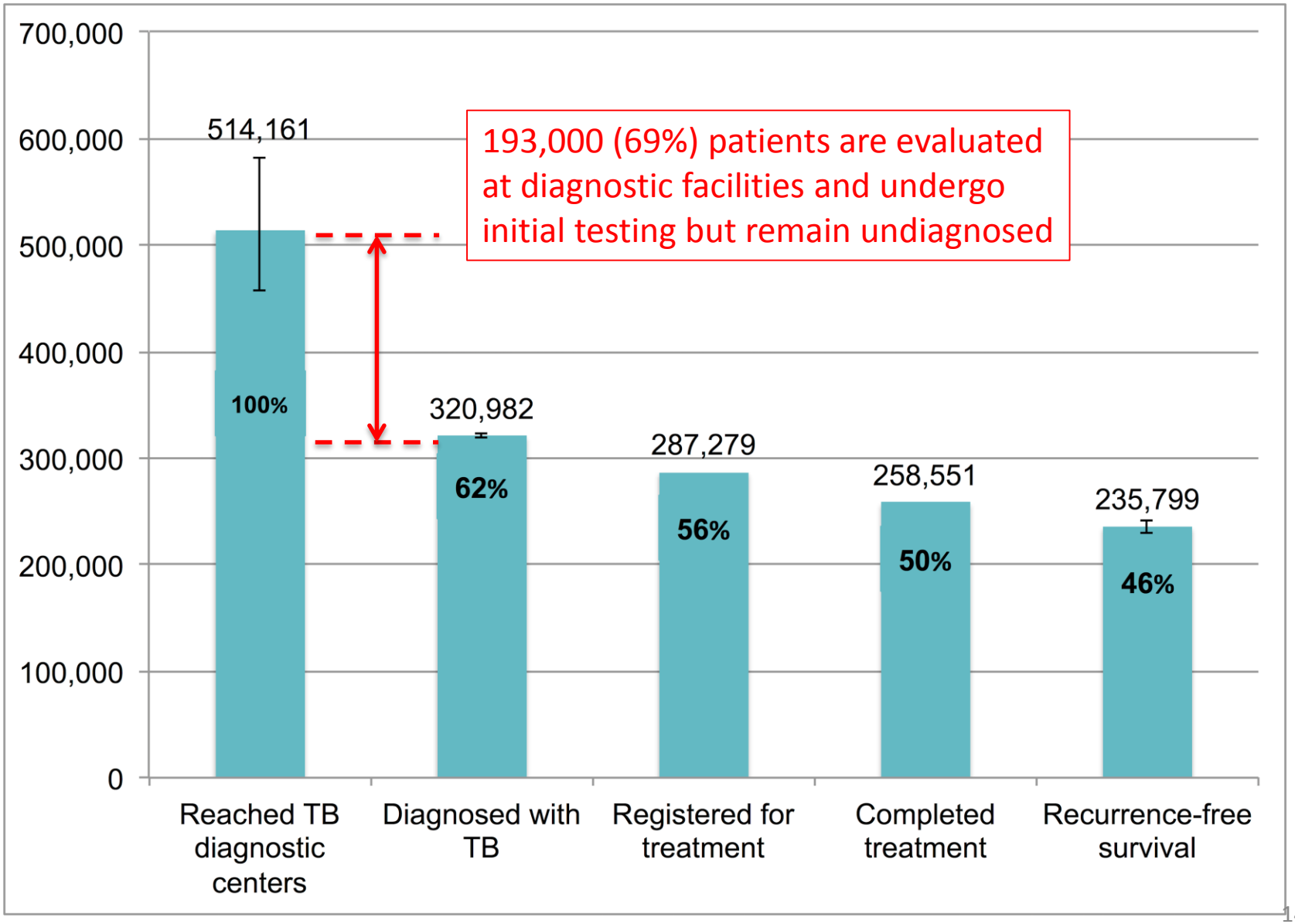


Cascade for all forms of TB in India, 2013[1]



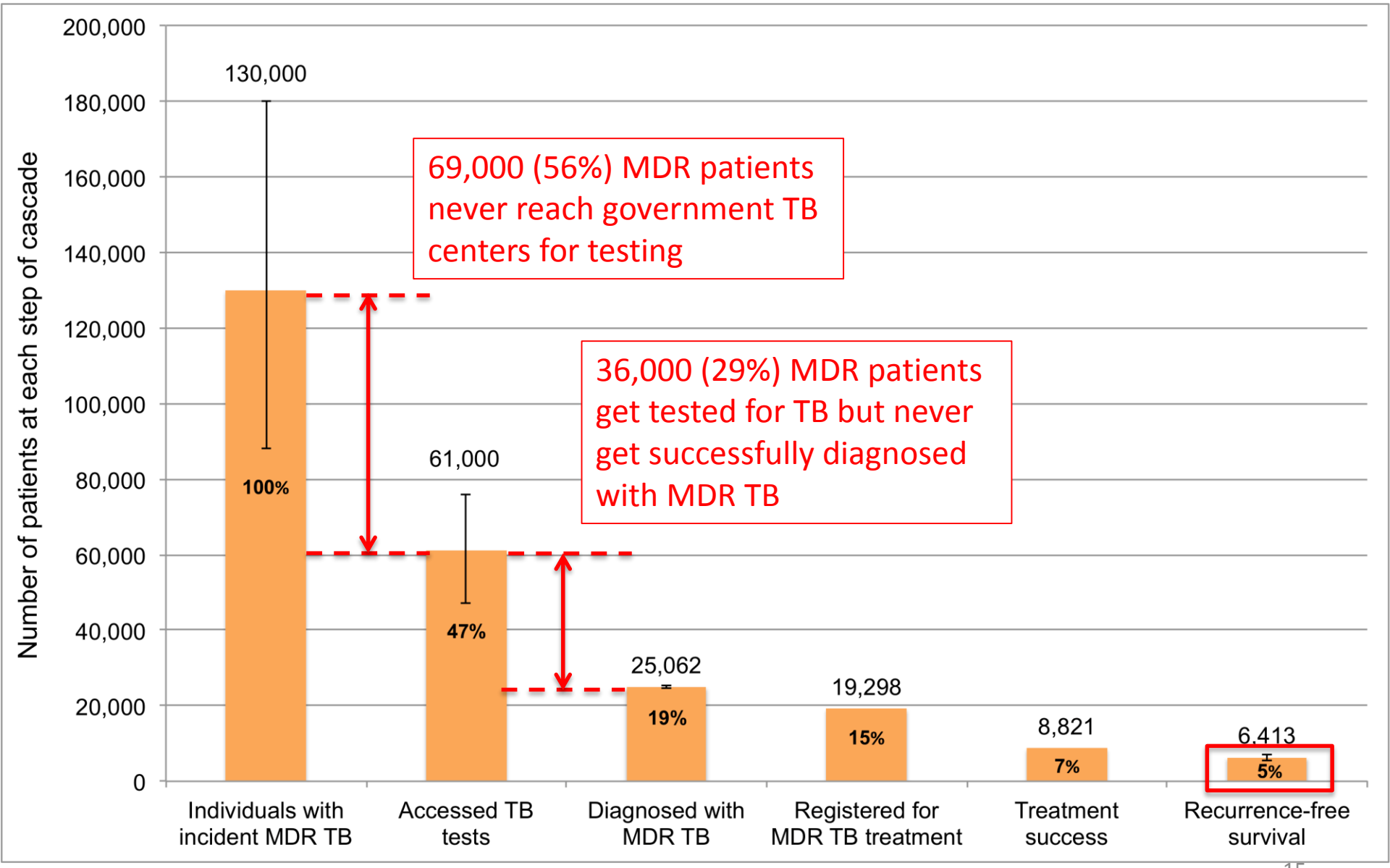
Subbaraman R, et al. *PLOS Medicine* 2016; 13(10):e1002149.[1] **(modified)**

New smear-negative cascade in India, 2013[1]



Subbaraman R, et al. *PLOS Medicine* 2016; 13(10):e1002149.[1]

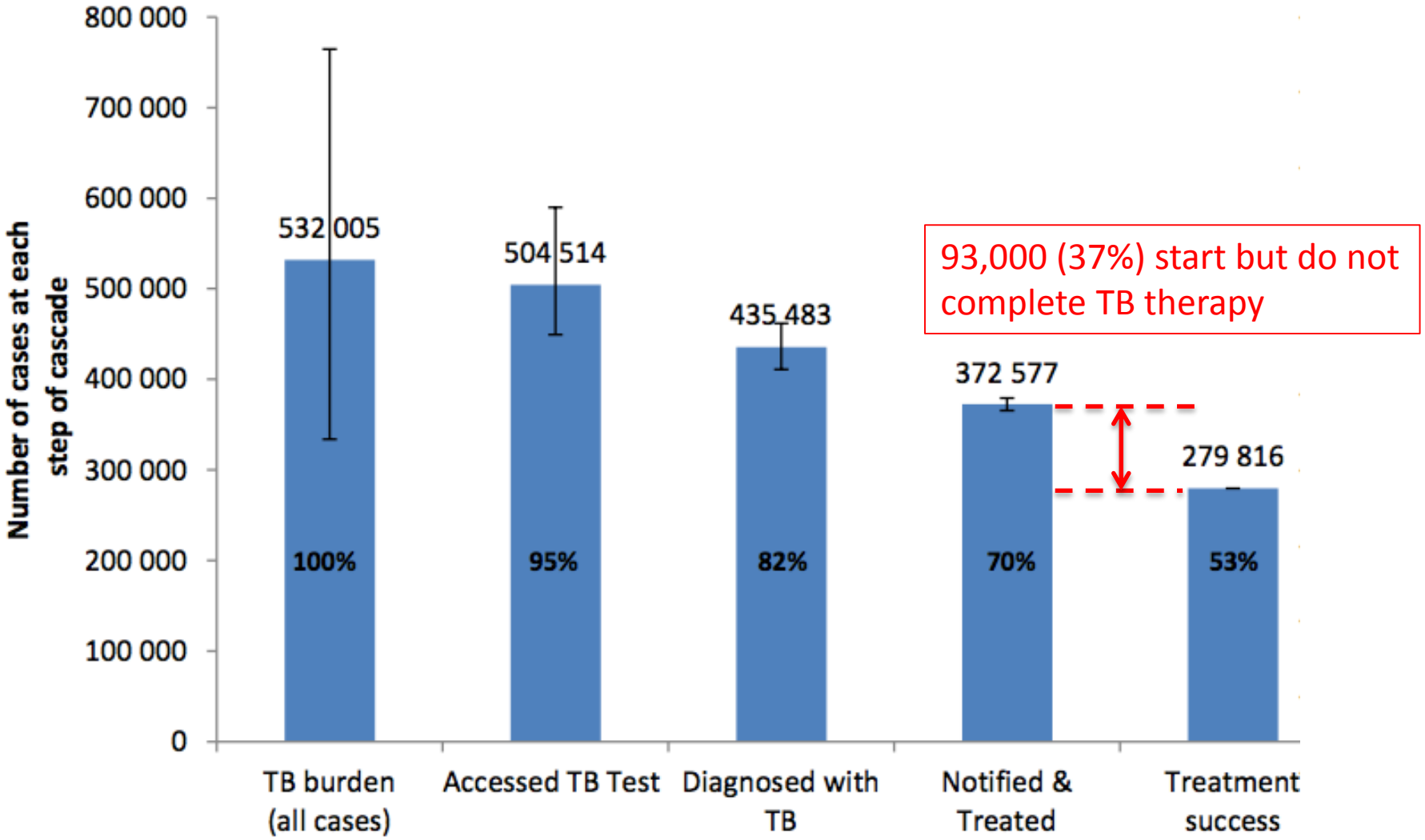
MDR TB cascade in India, 2013[1]



Subbaraman R, et al. *PLOS Medicine* 2016; 13(10):e1002149.[1]

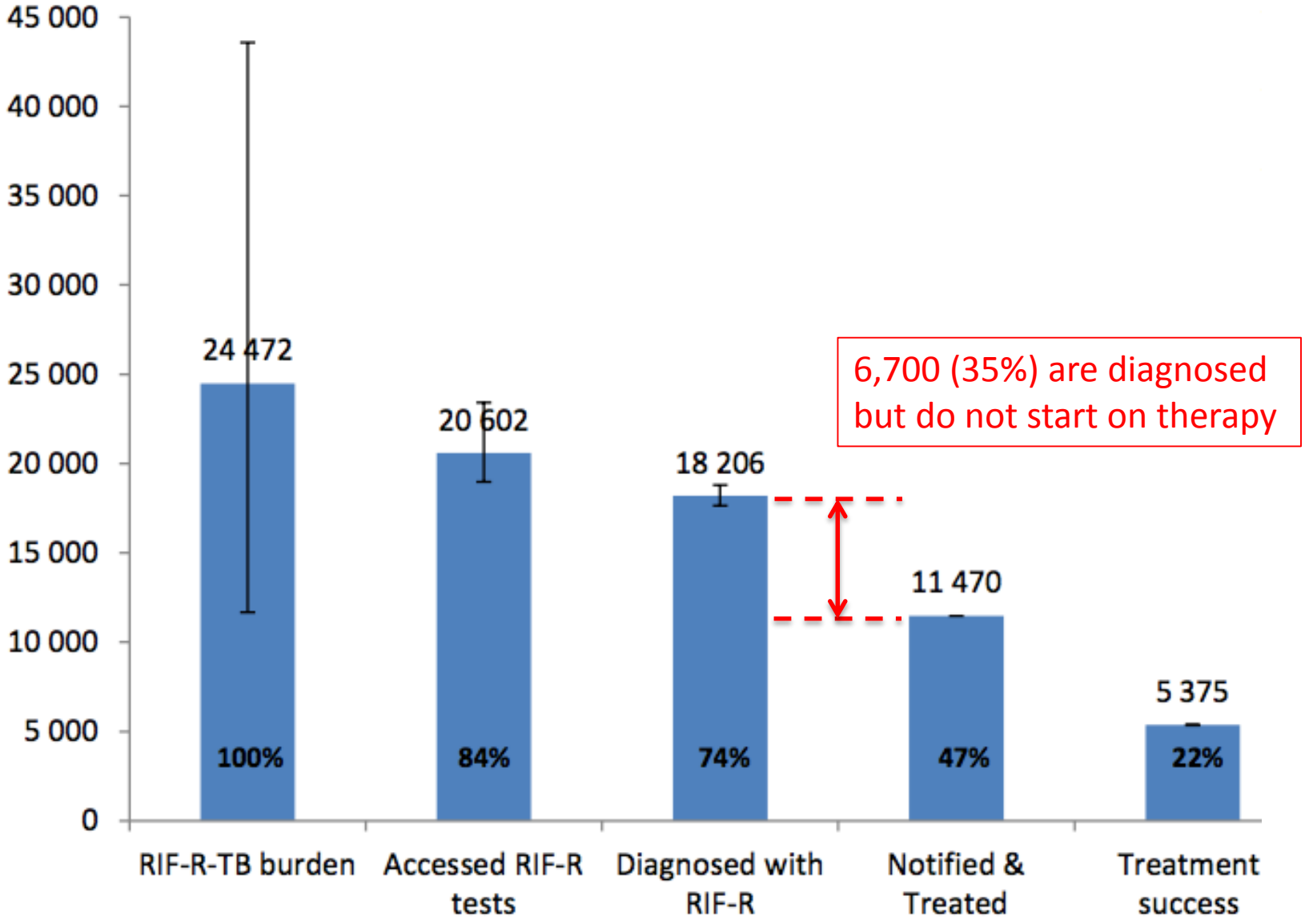
EXAMPLE 2:
THE SOUTH AFRICAN TB CARE CASCADE

Cascade for all forms of TB in South Africa, 2013[2]



Naidoo P, et al. *Journal of Infectious Diseases* 2017[2]

Cascade for MDR TB in South Africa, 2013[2]



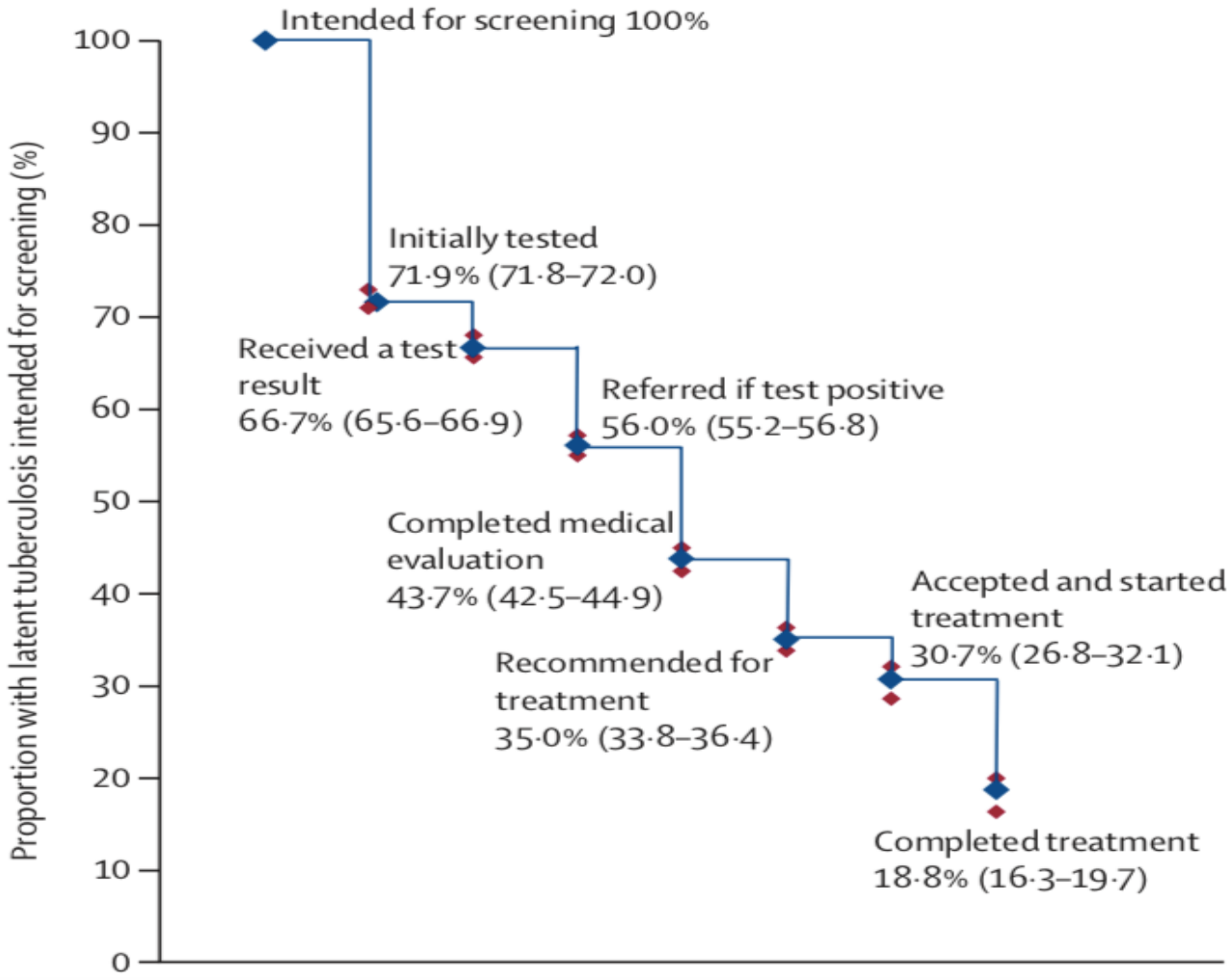
Naidoo P, et al. *Journal of Infectious Diseases* 2017[2]

Comparison: Indian and South African cascades

	India[1]	South Africa[2]
HIV prevalence	Relatively low	High
Healthcare landscape	Half of patients in private sector	Vast majority in public sector
Main diagnostic test	Sputum microscopy	Xpert, Sputum microscopy
Outcome metric used	Relapse-free survival	Treatment success
Cascade completion for all TB	45%	53%
Cascade completion for MDR	7%	22%
Major cascade gaps	**Gap 1** (not reaching government facilities) **Gap 2** (not getting diagnosed)	**Gap 3** (not starting treatment) **Gap 4** (not completing treatment)

EXAMPLE 3:
LATENT TB TREATMENT CARE CASCADE

The care cascade for latent TB treatment (More on this later)



Alsdurf, et al. *Lancet Infectious Diseases* 2016;16(11):1269-1278.

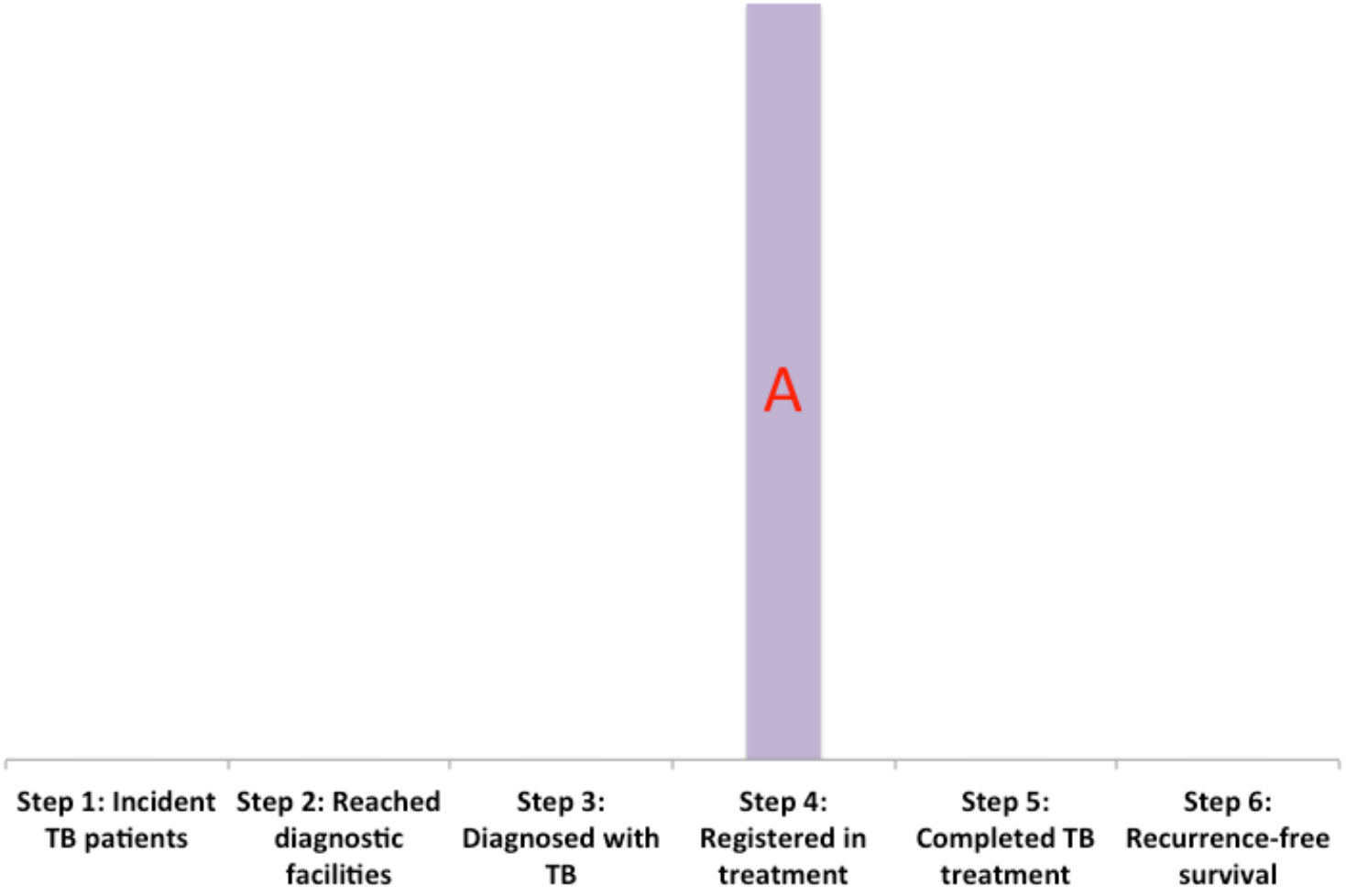
How can you build your own TB cascade?

General Principles

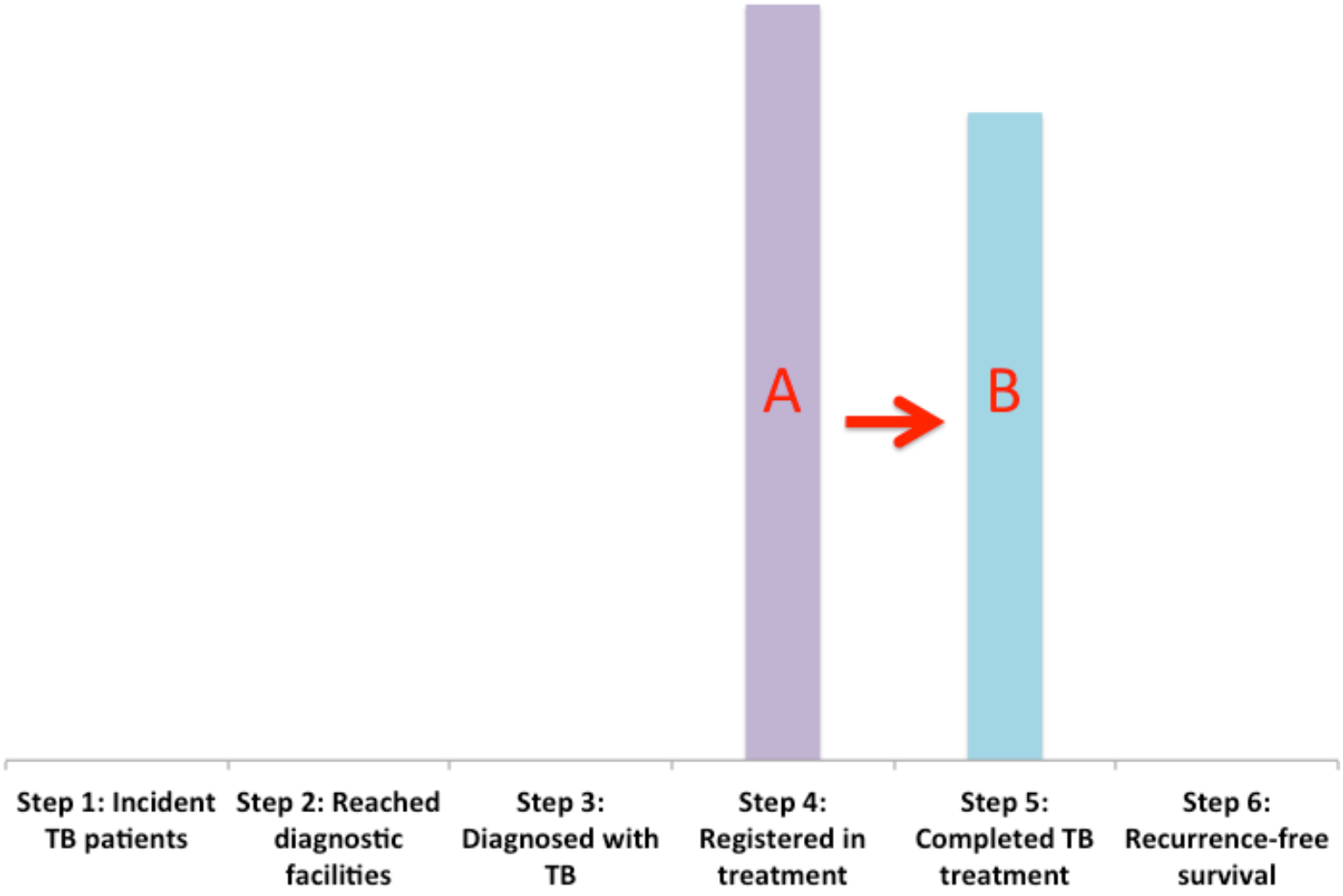
- What is the goal of the cascade analysis?
  - Large-scale evaluations at a national level → longitudinal monitoring of quality of care
  - Small-scale evaluations at a clinic or city level → identify gaps and develop interventions

- Different methods for early vs. later cascade stages:
  - Early stages: modeling or estimation approaches
  - Later stages: following a patient cohort across multiple stages ("denominator-denominator" linkage[10])

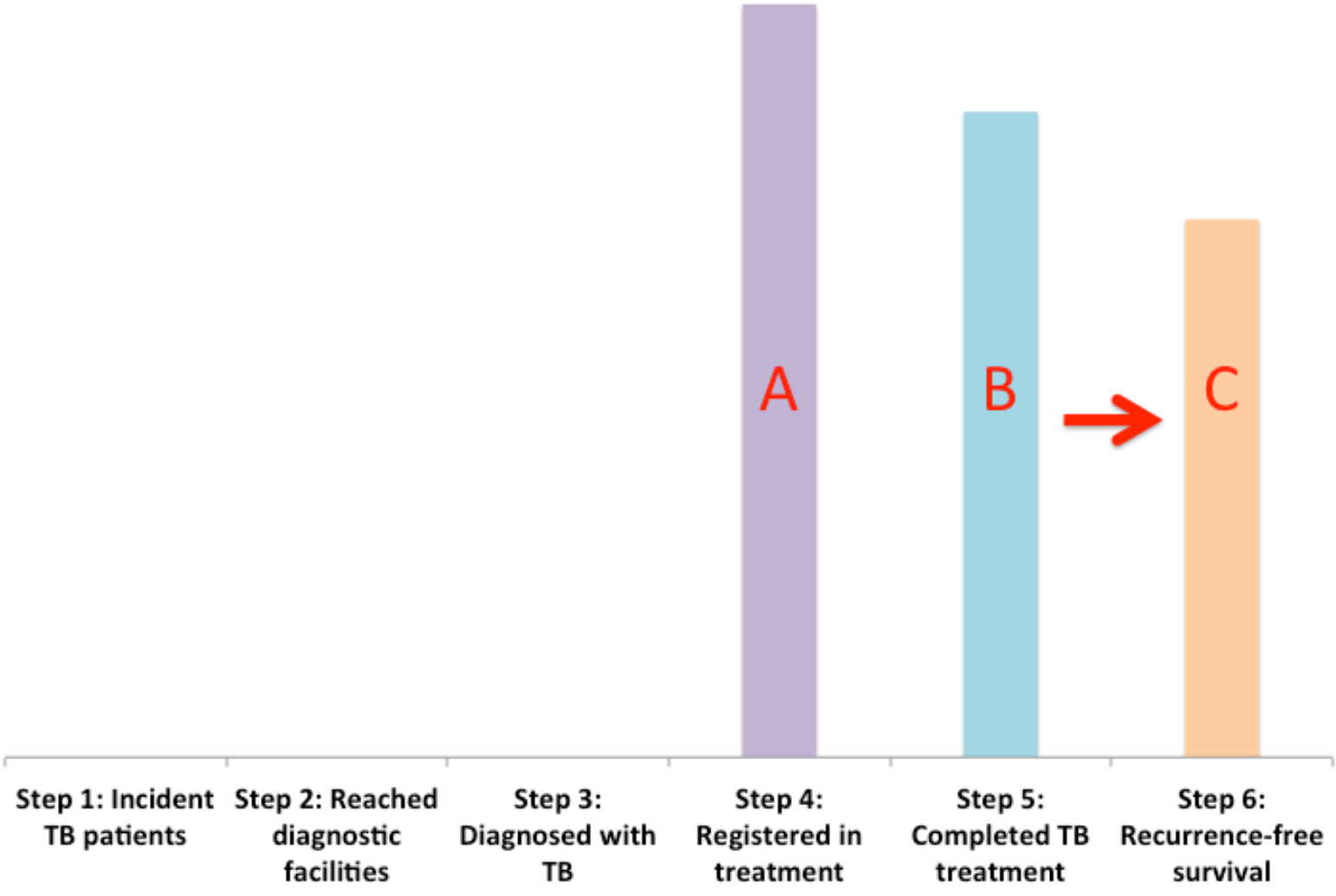
Step A: Patients Starting TB therapy



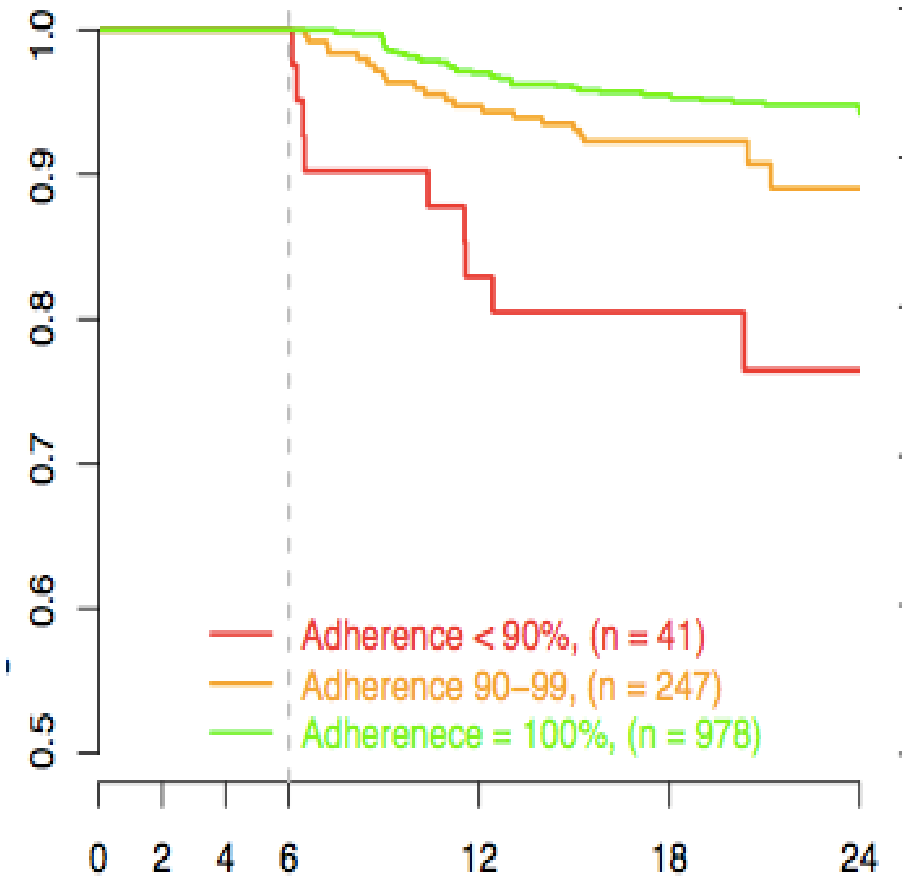
Step B: Patients completing TB therapy



Step C: Patients who achieve one-year



Why not just stop the cascade at treatment completion?



Source: TB ReFLECT Consortium[11]

TB patients taking HRZE with <90% adherence had 5.9 times increased risk of TB recurrence in a meta-analysis of the OFLOTUB, REMox, and Rifaquin trials.

Imperial et al. Nature Medicine 2018; 24:1708-1715.[28]

TB relapse in routine programmatic conditions

Severity of non-adherence	TB recurrence rate, 18 months after completing treatment
"Regular" adherence	9%
"Irregular" adherence	15%
"Very irregular" adherence	25%

Study of 534 smear + patients in India found a strong relationship between adherence and post-treatment TB recurrence.

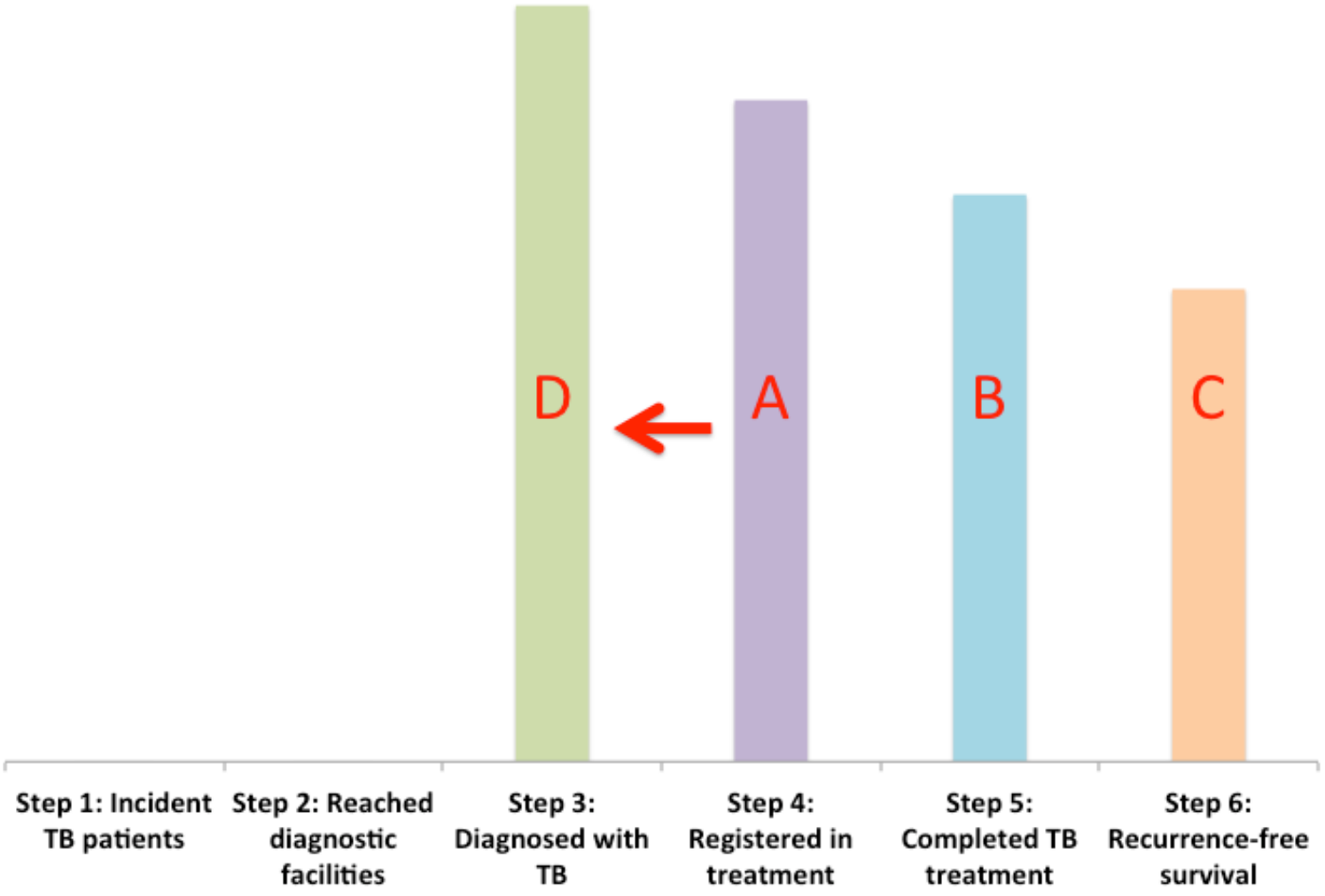
Thomas et al. Int J TB Lung Dis 2005; 9(5): 556-61[12]

Relapse rates are high in TB programs in South Africa (17%),[13] India (15-18%),[12,14] and for MDR TB patients in Uzbekistan (44%)[15]

How can I evaluate relapse in my TB program?

- In Indian cohort studies by Thomas et al.[12] and Velayutham et al.,[29] researchers did the following:
  - Followed a cohort of smear-positive patients who achieved cure under routine programmatic care
  - Visited patients' homes every 3 or 6 months after treatment completion
  - Collected sputum samples for microscopy and culture at every visit to identify relapse cases
- Follow-up for 12 months total would be reasonable (captures 91% of relapse in low HIV prevalence settings)
- Patients in a nationally-representative sample of TB clinics could be studied for country-wide estimates

Step D: Patients diagnosed with TB



Getting data on pretreatment loss to follow-up ("initial default")

Author	Country	Scope of study	PTLFU rate
Subbaraman et al.[1]	India	Systematic review of 16 studies	16% (new); 23% (MDR)
Naidoo et al.[2]	South Africa	Systematic review of 15 studies	19% (drug-susceptible)
Cox et al.[16]	South Africa	Nationally-representative study of rifampin-resistant (presumed MDR TB) patients	37% (MDR/RR-TB)
Uchenna et al.[17]	Nigeria	Five states in southern Nigeria	17% (smear-positive)
Razia et al.[17]	Pakistan	Five tertiary centers and 16 peripheral centers	6% (smear-positive)
Buu et al.[17]	Vietnam	Several district tuberculosis units	8% (smear-positive)
Korobitsyn et al.[17]	Tajikistan	Four districts	8% (smear-positive)

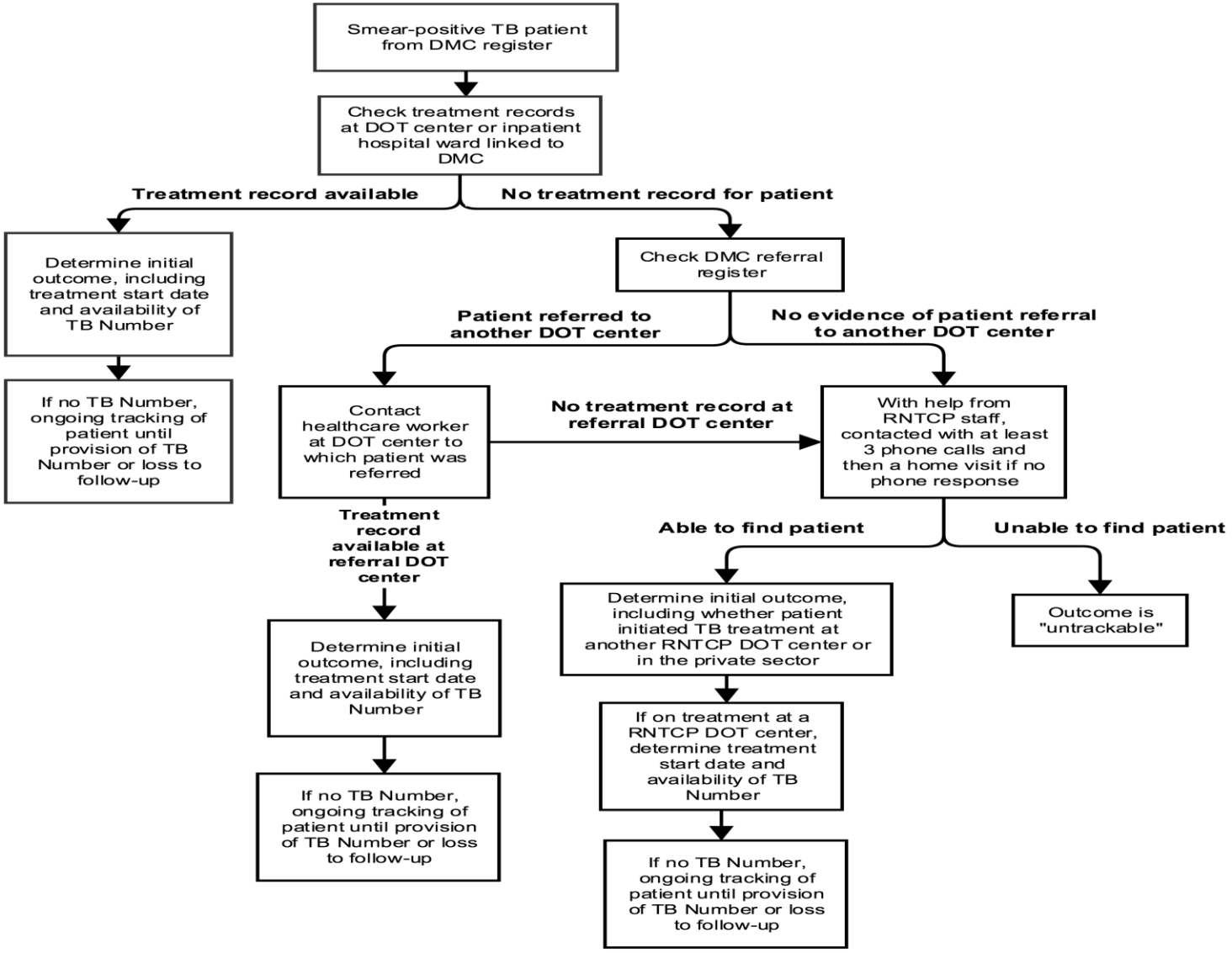
Tips for tracking newly diagnosed patients to determine PTLFU

- Determining PTLFU rigorously is easiest in settings with
  - electronic records using
  - unique patient IDs with
  - real-time availability of data and
  - broad geographic coverage

- In the absence of such system, patients need to be tracked using paper records, often across broad geographic catchment areas

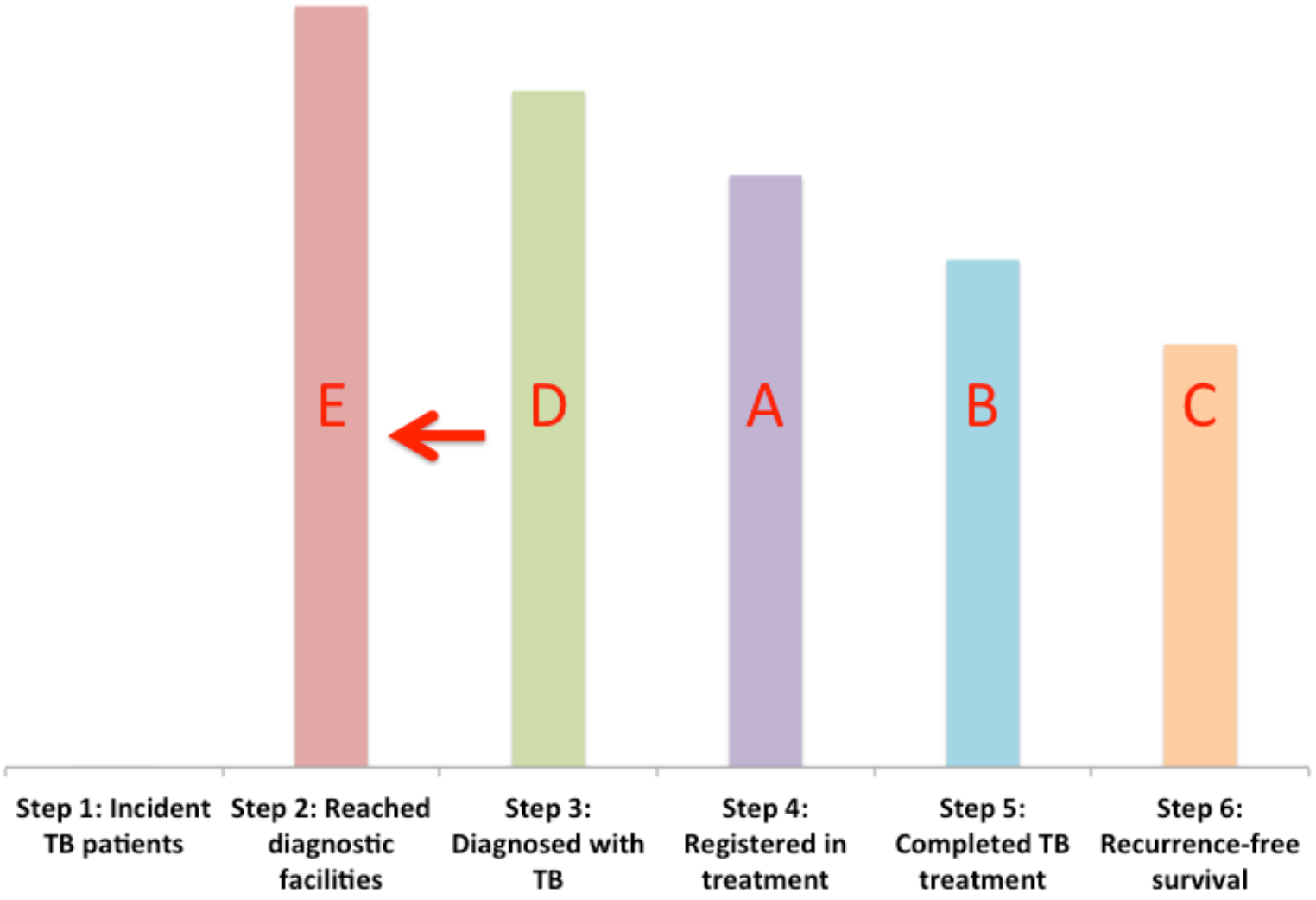
- Major question: when to you start tracking patients?
  - *Late tracking*: i.e., follow-up of patients months after diagnosis → more likely to represent "true" PTLFU, but could over-estimate losses, as patients are harder to find but may have started treatment elsewhere
  - *Early tracking*: i.e., follow-up of patients a few weeks after diagnosis → may partly represent treatment delay rather than PTLFU, but more likely to identify patients who started treatment elsewhere

Example of a patient tracking protocol



Thomas B, Subbaraman R, et al. BMC Infect Dis 2018; 18:142.

Step E: Patients who reached TB diagnostic facilities



Step E: Number who get evaluated at diagnostic centers and those not diagnosed

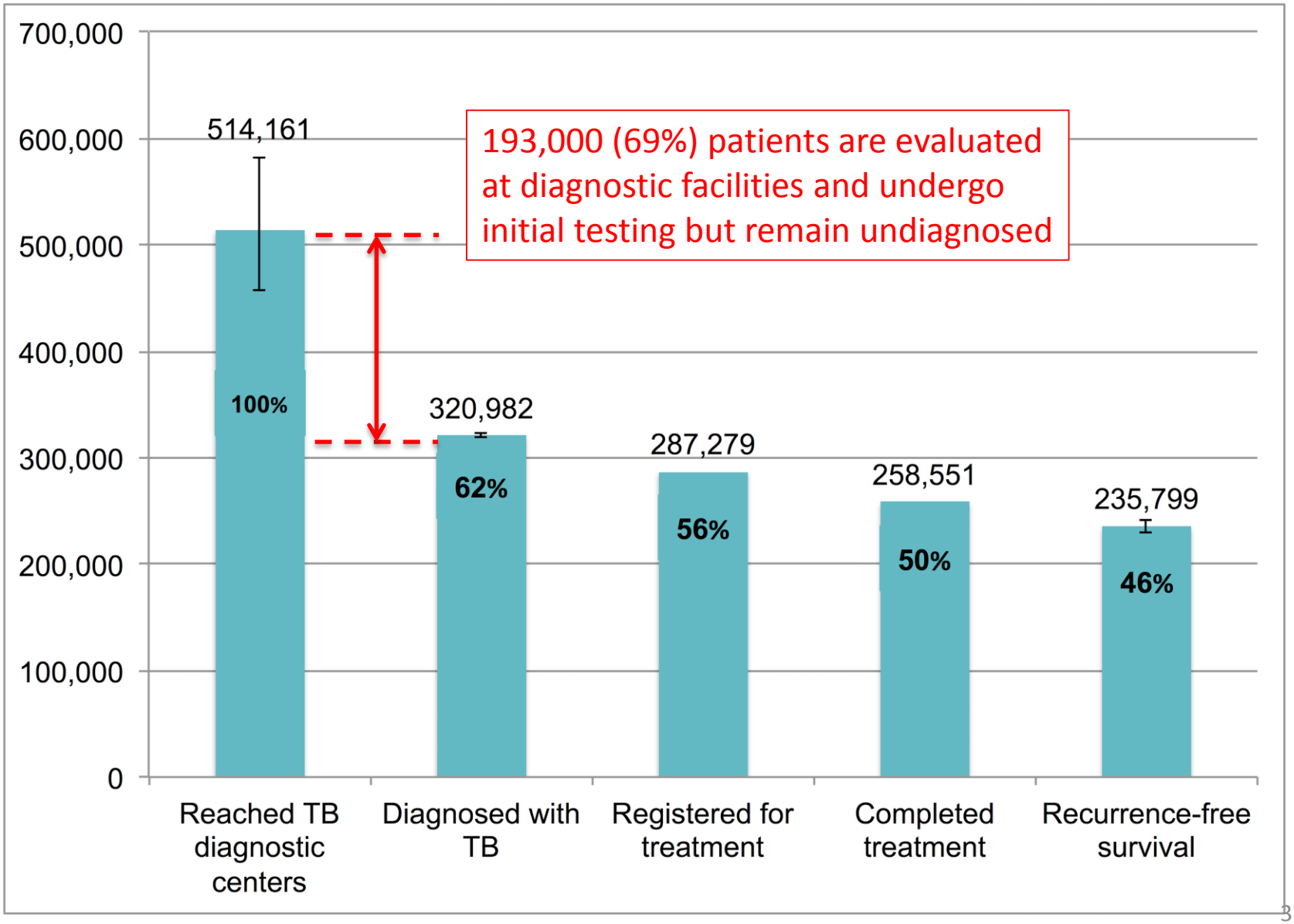
- Different methods for every form of TB!

Form of TB	Methods and Examples
Smear/Xpert-positive	Estimated from proportion who do not submit second sputum sample or who have an initial indeterminate Xpert[1]
Smear/Xpert-negative	• Estimated from the sensitivity of the diagnostic test[1] • Prospective studies of attrition during diagnostic workup[18-20]
Extrapulmonary	Prospective studies of attrition during the diagnostic workup
Drug-resistant	Estimates of the number of MDR/RR-TB patients among all pulmonary TB patients (reported routinely by the WHO)

Standard test sensitivities for estimating Step E for test-negative patients

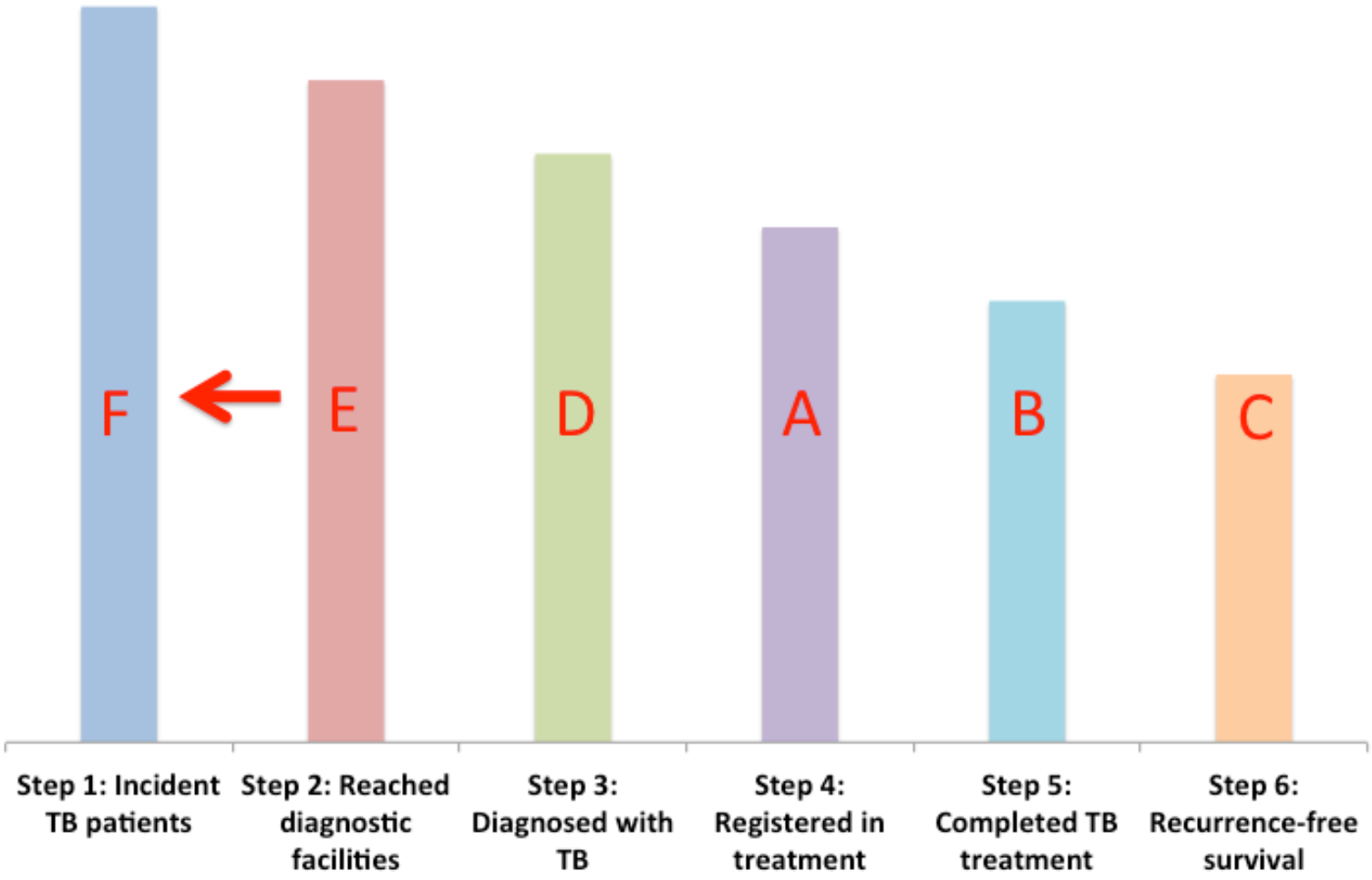
Author	Scope of study	Year of data collection	Estimated sensitivity for culture-positive TB
Sputum smear microscopy			
Davis et al.[21]	Systematic review of 8 studies	Studies published from 2005—2012	64% for multi-day sputum microscopy vs. 63% for same-day microscopy
Steingart et al.[22]	Systematic review of 45 studies	Studies published from 1950—2004	32% to 94% for conventional microscopy vs. 52% to 97% with fluorescent microscopy
Xpert MTB/Rif			
Steingart et al.[23]	Systematic review and meta-analysis of 27 studies	Studies published up to 2013	86% in HIV-negative patients; 79% in HIV-positive patients
Xpert Ultra			
Schumacher et al.[24]	10 sites across 8 high countries	2014—2016	91% in HIV-negative patients; 90% in HIV-positive patients

New smear-negative cascade in India, 2013[1]



Subbaraman R, et al. *PLOS Medicine* 2016; 13(10):e1002149.[1]

Step F: Overall TB burden



What is the best burden of disease metric?

- Incident TB patients: theoretically the ideal metric

  (Ask your favorite TB modeler for help or use WHO data, but honestly, it's all guesswork)

- Point prevalence survey data: grounded in reality but studies may not be available for your country

- *You will be criticized no matter what metric you use!*

- And yet, this is a very important step to identify the case detection gap and to monitor over time

Using the cascade to inform intervention development

Ok, many patients are falling through the cracks….so what do we do next?

- Questions we need to answer next:
  - *Who* is disproportionately falling out of the care cascade?
  - *Why* are patients falling out of the care cascade?

- First two questions inform the third question:
  - *What interventions* are needed to reduce these gaps?

The "***WHO***" question: Example of "missing men" from TB programs

Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis

Katherine C. Horton[1,2]*, Peter MacPherson[3,4], Rein M. G. J. Houben[2,5], Richard G. White[2,5], Elizabeth L. Corbett[1,6]

- 88 TB prevalence surveys from 28 countries were analyzed to determine male:female rations of TB prevalence:notification rates
- P:N ratio is 1.6 times higher for men than for women, suggesting *men are more likely to face delay in TB diagnosis or not to get diagnosed at all* (Gap 1)
- Suggests that men are a high-risk group in Gap 1

Horton K, et al. *PLOS Medicine* 2016; 13(9):e1002119.[1]

The "***WHY***" question

- Reasons patients fall out of the care cascade could be related to factors related to the patient, their family, society (structural), or the health system

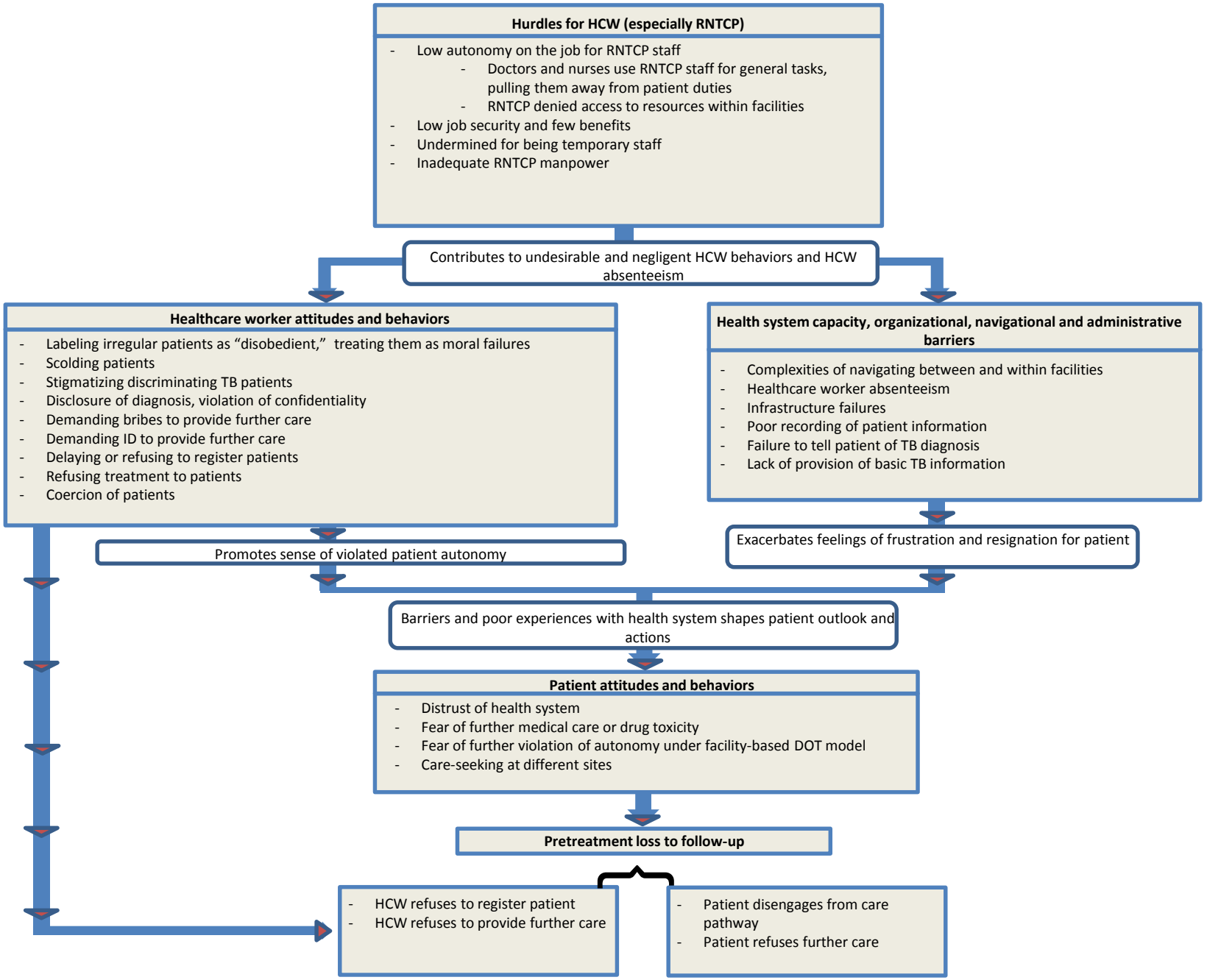
- Regression analyses in cohort studies can help to identify predictors of poor outcomes at each care cascade stage

- Qualitative studies can help to identify reasons and develop explanatory models for poor outcomes that can inform intervention development

Example: Understanding Pretreatment Loss to Follow-up in Chennai, India

- Tracked 344 newly diagnosed-TB patients from 22 microscopy centers

Factor	Odds ratio (95%CI)
Age >50	2.9 (1.4—6.5)
Prior history of TB	3.9 (2.2—7.1)
"Untrackable" DMC register information	4.5 (1.3—15.1)
Diagnosed at high-volume DMC	3.2 (1.7—6.3)
Address located outside of Chennai	3.0 (1.4—6.5)*


Hurdles for HCW (especially RNTCP)
- Low autonomy on the job for RNTCP staff
- Doctors and nurses use RNTCP staff for general tasks, pulling them away from patient duties
- RNTCP denied access to resources within facilities
- Low job security and few benefits
- Undermined for being temporary staff
- Inadequate RNTCP manpower
Contributes to undesirable and negligent HCW behaviors and HCW absenteeism
Healthcare worker attitudes and behaviors
- Labeling irregular patients as "disobedient," treating them as moral failures
- Scolding patients
- Stigmatizing discriminating TB patients
- Disclosure of diagnosis, violation of confidentiality
- Demanding bribes to provide further care
- Demanding ID to provide further care
- Delaying or refusing to register patients
- Refusing treatment to patients
- Coercion of patients
Health system capacity, organizational, navigational and administrative barriers
- Complexities of navigating between and within facilities
- Healthcare worker absenteeism
- Infrastructure failures
- Poor recording of patient information
- Failure to tell patient of TB diagnosis
- Lack of provision of basic TB information
Promotes sense of violated patient autonomy
Exacerbates feelings of frustration and resignation for patient
Barriers and poor experiences with health system shapes patient outlook and actions
Patient attitudes and behaviors
- Distrust of health system
- Fear of further medical care or drug toxicity
- Fear of further violation of autonomy under facility-based DOT model
- Care-seeking at different sites
Pretreatment loss to follow-up
- HCW refuses to register patient
- HCW refuses to provide further care
- Patient disengages from care pathway
- Patient refuses further care

FIND	DIAGNOSE	LINK	RETAIN & ADHERE	CURE & SURVIVE
• Community-based active case finding	• Same-day sputum microscopy	• Electronic biometric-linked patient records for tracking	• Real-time electronic adherence monitoring (cellphone, pillboxes)	• Adherence interventions
• Health facility-based active case finding	• Upfront Xpert testing	• SMS notification of diagnosis	• Patient tracking and retention teams	• Post-treatment follow-up for early detection of TB recurrence
• High risk group active case finding (household contacts, HIV, prisoners)	• LPA, culture/DST	• Registration at diagnosis	• Treatment literacy	• Evaluation for long-term pulmonary disease (COPD, restrictive lung disease)
• Private sector provider early referral and testing	• X-ray for empiric diagnosis	• Patient navigators	• Psychosocial interventions (alcohol use disorder, depression, stigma)	• TB Champions
	• Electronic biometric-linked patient records for tracking	• Enhanced inter-facility communication	• Incentive schemes (food, cash)	

Lessons learned from the HIV care cascade can help End TB

Michael J. A. Reid, MD, MPH*
Eric Goosby, MD†

"To effectively employ a care cascade approach will require integrated strategic information systems that incorporate geospatial data on diagnostic capacity and linkage systems across all tiers of the health system."[32]

"The care cascade approach . . . can provide a framework to help identify the 4 million missing TB patients, many of whom are not accessing life-saving TB treatment . . . It is an approach that has worked for HIV. We must believe it can also work for TB."[32]

QUESTIONS?

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