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

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Abstract

The cascade of care is a model for evaluating patient retention across sequential stages of care required to achieve a successful treatment outcome. This approach was first used to evaluate HIV care and has since been applied to other diseases. The tuberculosis (TB) community has only recently started using care cascade analyses to quantify gaps in quality of care. In this article, we describe methods for estimating gaps (patient losses) and steps (patients retained) in the care cascade for active TB disease. We highlight approaches for overcoming challenges in constructing the TB care cascade, which include difficulties in estimating the population-level burden of disease and the diagnostic gap due to the limited sensitivity of TB diagnostic tests. We also describe potential uses of this model for evaluating the impact of interventions to improve case finding, diagnosis, linkage to care, retention in care, and post-treatment monitoring of TB patients.

Introduction

Tuberculosis (TB) is the leading infectious cause of death globally [1]. The World Health Organization (WHO) has highlighted "patient-centered care for all people with TB" as a central pillar of its post-2015 End TB strategy [2]. The cascade of care (also called the continuum of care) is a useful model for evaluating patient retention across sequential stages of care required to achieve a successful outcome. The cascade helps to quantify gaps in care delivery, pointing to areas in which quality of care could be improved. Over the last decade, the HIV community

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Abbreviations: COPD, chronic obstructive pulmonary disease; DST, drug susceptibility testing; IHME, Institute for Health Metrics and Evaluation; LPA, line probe assay; MDR TB, multidrug-resistant tuberculosis; PCR, polymerase chain reaction; PTLFU, pretreatment loss to follow-up; TB, tuberculosis; UNAIDS, Joint United Nations Programme on HIV/AIDS; WHO, World Health Organization.

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has pioneered use of the cascade to evaluate care delivery in diverse populations [3–5]. This model has subsequently been applied to other diseases [6,7]. The care cascade is instrumental in tracking progress in the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 global strategy for HIV [8,9].

Care cascades have only recently been used to evaluate TB care [10,11], although TB programs have a tradition of conducting cohort analyses and, more recently, of using patient pathways analyses to understand dropouts in care [12]. In addition, WHO has outlined an onion model in which patient losses across different steps in care are visualized as a series of concentric circles [13], and this conceptual model informs our approach to the care cascade.

The United Nations Secretary General's Special Envoy on TB has called for more widespread use of care cascade analyses to help achieve the End TB strategy [14]. In addition, National Strategic Plans for India and South Africa refer to closing gaps in the care cascade as a key component of their TB elimination strategies [15,16]. We discuss approaches for estimating care cascade stages for individuals with active TB, describe uses of this model for targeting interventions to address gaps in care, and suggest areas for future research. We argue that the care cascade has two potential benefits: as an approach for quantifying TB outcomes and as a conceptual framework for examining the quality of health services across various stages of care.

TB has a range of states, ranging from latent infection (in which bacilli lie dormant, controlled by the immune system) to subclinical disease (in which the patient has no symptoms but has microbiological or radiographic evidence of disease) to active disease (in which the patient has symptoms in addition to microbiological or radiographic findings) [17]. The current manuscript describes an approach for estimating the care cascade for active disease. We do not cover treatment of latent infection, which affects around one-quarter of the world's population [18]. Other articles provide guidance on constructing care cascades for TB subpopulations, including individuals with latent infection [19], children with active disease [20], individuals with HIV/TB coinfection [21], and household contacts of TB patients [22].

A model for the TB care cascade, with examples from India and South Africa

In Fig 1 (panel A), we present a model for the TB care cascade, integrating the WHO onion model with elements of the HIV care cascade [10,13]. Each cascade stage contains a step (i.e., the absolute number of individuals achieving a point in care) and a gap (i.e., the difference between steps, representing individuals with suboptimal outcomes). Recent studies in India and South Africa used this general approach to estimate national-level TB outcomes. These countries differ with regard to HIV prevalence, initial diagnostic tests used, and healthcare landscape (Table 1) [10,11]. The studies presented outcomes for 2013 despite being published in 2016 and 2017, respectively, because multidrug-resistant tuberculosis (MDR TB) outcomes take 3 years to be reported, given the long treatment duration.

Outcomes and major gaps in each country cascade vary, highlighting different deficiencies in care (Figs 1 and 2 and Table 1). The South African program performed better in terms of individuals with TB in the population accessing a TB test (Gap 1) but achieved poorer treatment outcomes than India's public sector. About 37% of all patient losses in the South African cascade consisted of individuals who experienced poor outcomes during therapy (Gap 4). In contrast, India's TB program did a poorer job of case finding: 50% of all patient losses consisted of individuals with incident TB who did not access a TB test (Gap 1). For both countries, Gap 2 is the second largest contributor to patient losses. MDR TB cascade outcomes in both countries are very poor, with deficiencies at every stage [10,11].

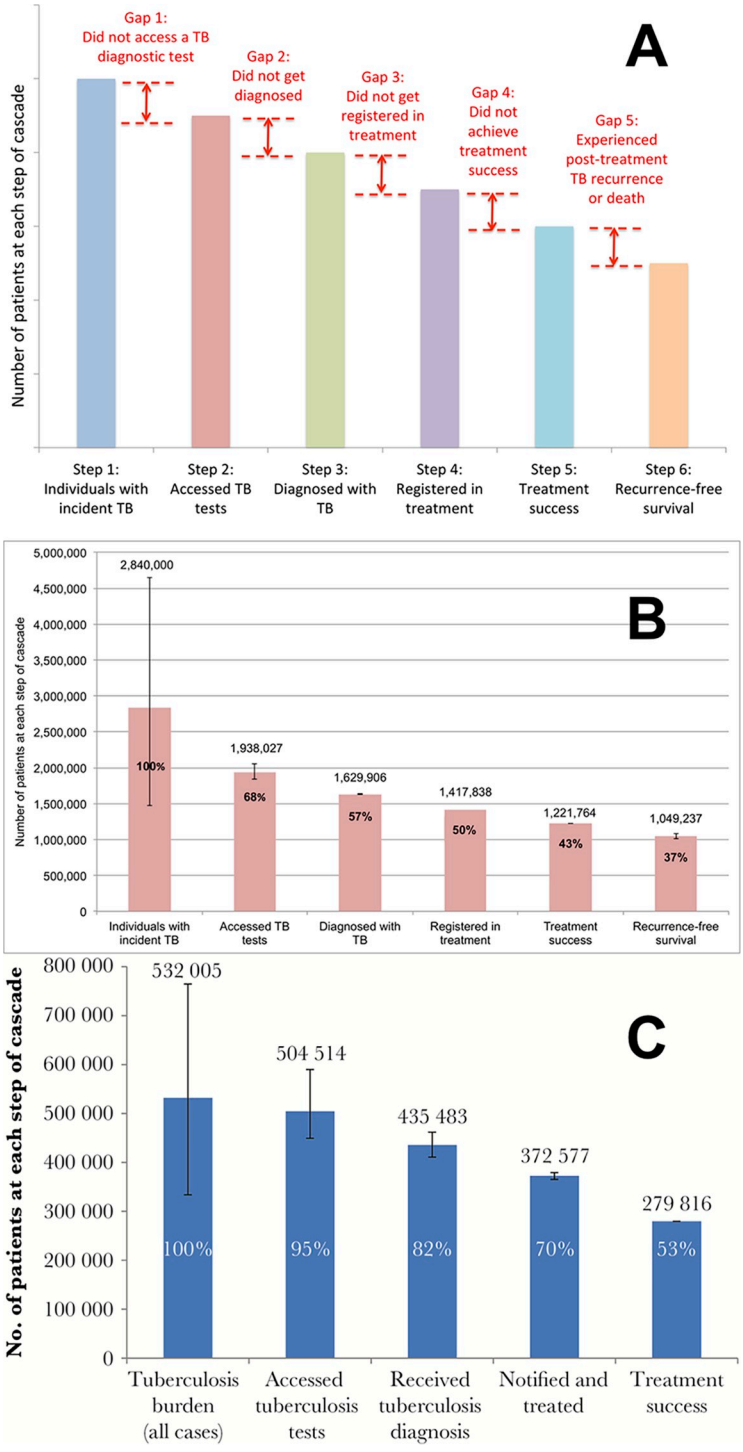

Fig 1. Examples of TB care cascades, including a generic model. (A) A generic model for a care cascade for active TB; (B) the care cascade for individuals with any form of active TB in India in 2013, modified from [10] based on updated WHO TB incidence estimates [23]; and (C) the care cascade for patients with any form of active TB in South Africa in 2013 [11]. The Indian care cascade has 1-year recurrence-free survival as the final step, while the South African care cascade stops at treatment success. Individuals with latent TB are not included in these models. Whiskers represent 95% confidence intervals. TB, tuberculosis; WHO, World Health Organization.

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Table 1. Comparison of the Indian and South African TB care cascades for 2013.

	Indian TB care cascade (modified from [10])[a]	South African TB care cascade (from [11])
Country context		
Epidemiology	Low HIV prevalence	High HIV prevalence
Healthcare landscape	Similar proportions of TB patients are treated in the private and public sector	Public sector treats the vast majority of TB patients
Most common tests used to diagnose TB	Sputum microscopy as the most common frontline test	Xpert MTB/RIF and sputum microscopy as the frontline tests
Methodological approach for constructing the cascade		
Data sources	Number of treated patients from country TB reports; meta-analyses of local studies to estimate key gaps	Number of diagnosed and treated patients from a national electronic TB register; meta-analysis of local studies to estimate PTLFU
Total number of individuals with TB at the population level	Estimated number of prevalent TB cases in 2013 (modified Fig 1 uses revised WHO TB incidence estimates for India [23])	Estimated number of incident TB cases in 2013 plus half of the estimated number of patients with undetected TB in 2012
Choice of end outcome for the cascade	1-year recurrence-free survival	Treatment success[b]
Study findings		
Care cascade completion rate for all forms of TB[c]	43%[a,c]	53%
Care cascade completion rate for MDR TB[c]	7%[a,c]	22%

[a]These estimates are adjusted from the original publication based on revised TB incidence estimates for India in 2015. Overall TB incidence in India was revised substantially upward by WHO, and estimates of MDR TB incidence in India were not available in prior WHO reports.

[b]Treatment success is defined as patients who either achieved cure or treatment completion.

[c]Cascade completion here is defined as the outcome of treatment success, rather than recurrence-free survival to allow comparison between the Indian and South African cascades.

Abbreviations: MDR TB, multidrug-resistant TB; PTLFU, pretreatment loss to follow-up; TB, tuberculosis.

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These two studies may provide insights into the situation in other countries with similar epidemiological contexts. In addition to focusing on other high–TB-burden countries, future cascade analyses should address high-risk populations in countries with a lower TB burden (e.g., immigrants in Europe) and countries with high MDR TB rates (e.g., former Soviet Bloc countries) [24,25], which are epidemiological contexts not represented in the current literature.

Methods for designing this guidance document

Members of our team contributed to the recent Indian care cascade analysis [10]. We studied methods used in the South African cascade for further insights [11]. Our prior research is relevant for estimating different cascade stages, including the number of individuals with TB in the population (NA, VC) [26,27], the diagnostic gap (MP, RN) [28–30], pretreatment loss to follow-up (PTLFU; RS, SS, VC, MP) [31–35], and post-treatment disease recurrence (VC) [36]. Our team also includes an expert in the HIV care cascade (KM) [37–40]. Input was incorporated from members of our team by email and in-person discussions. Limitations of the analytical approach are described in the main manuscript and S1 Appendix.

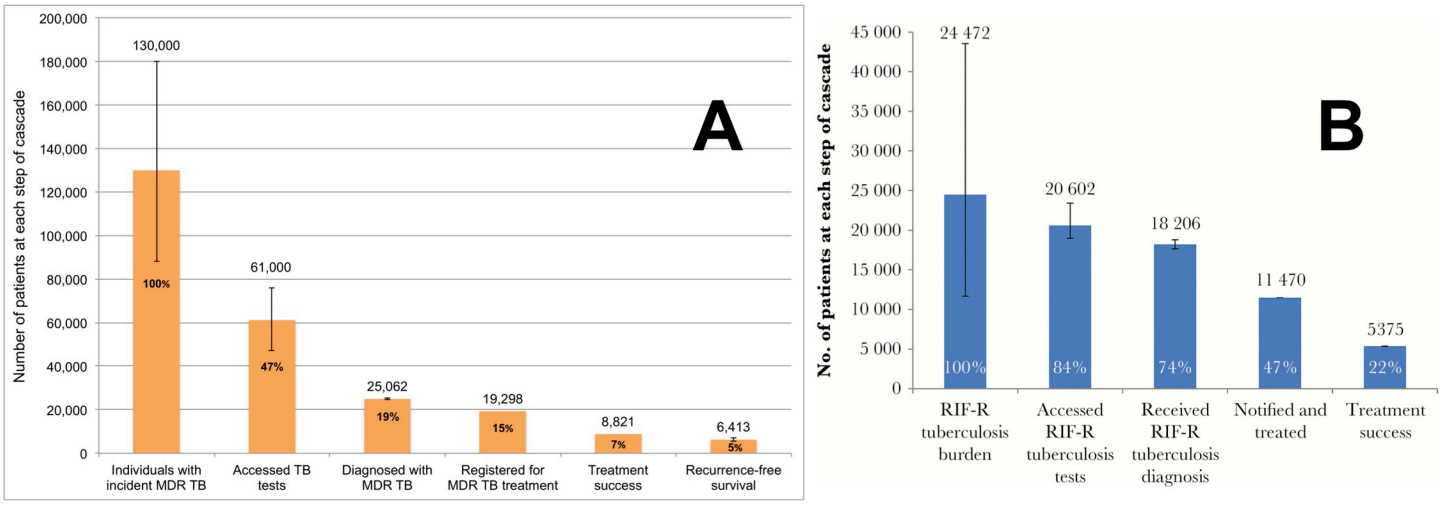

Fig 2. Examples of MDR TB care cascades. (A) The care cascade for individuals with MDR TB in India in 2013, modified from [10] based on updated WHO MDR TB incidence estimates [23], and (B) the care cascade for individuals with rifampin-resistant TB in South Africa in 2013 [11]. Rifampin resistance is considered to be a surrogate marker for multidrug resistance. The Indian care cascade has 1-year recurrence-free survival as the final step, while the care cascade for South Africa stops at treatment success. Whiskers represent 95% confidence intervals. MDR, multidrug-resistant TB; TB, tuberculosis; WHO, World Health Organization.

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General principles for constructing a cascade

The approach for constructing a care cascade depends on the assessment's primary goal, which may include the following: (1) large-scale evaluations for monitoring patient outcomes in national programs or (2) smaller-scale evaluations for identifying gaps in quality of care at the clinic, city, or district levels. Large evaluations may aim to achieve nationally representative estimates of patient outcomes, while smaller-scale evaluations may additionally collect data on process indicators (indicators of quality of care) to enable intervention development.

Different approaches for estimating a care cascade have varied risks of bias [41]. Recently published TB care cascades used data from different patient cohorts to estimate each stage—what we refer to as a routine data approach (S1 Appendix) [10,11,19]. This approach does not account for the patient population's changing composition at each stage, introducing biases that may carry forward to subsequent stages [41]. In a cohort-based approach, the same individuals are followed through each cascade stage, minimizing risk of bias and achieving higher internal consistency (S1 Appendix) [41]. This approach allows estimation of the transition time of patients across stages, which has implications for disease transmission [5,42]. We encourage use of cohort-based approaches whenever possible, although this approach is more resource intensive. If representative sampling of health facilities is used, it may be feasible to estimate cascade outcomes with reasonable precision using moderate samples even for large countries such as India or China. For example, the Population-based HIV Impact Assessment Project uses primary data collection with representative sampling to estimate the HIV care cascade in several African countries [43].

Another challenge in estimating a TB care cascade is that common diagnostic tests for active TB have relatively low (e.g., sputum microscopy) or higher but imperfect (e.g., Xpert MTB/RIF) sensitivity [44,45]. Xpert MTB/RIF, a polymerase chain reaction (PCR)-based test, has 85% to 92% sensitivity for diagnosing pulmonary TB, including rifampin resistance, compared to 40% to 60% sensitivity for sputum microscopy [44], but most high-burden countries are still reliant on microscopy for detecting active TB. A considerable proportion of TB patients are diagnosed empirically, especially when sputum microscopy is the only test used.

In contrast, HIV tests have very high sensitivity and specificity, allowing for accurate identification of HIV-infected individuals who should be followed through subsequent cascade stages. HIV viral load also provides a reliable biological marker of effective treatment. In contrast, the diverse forms of TB (e.g., pulmonary, extrapulmonary, drug resistant) and potential for disease recurrence pose unique challenges for estimating TB care cascades. We therefore recommend approaches for estimating each stage based on the primary diagnostic test used in a given setting and the specific form of TB.

Strategies for inclusion of private sector TB patients

A challenge for estimating care cascades in many countries (e.g., India [26,46], Indonesia [47], and Pakistan [48]) is that a large proportion of TB patients are managed in the private sector. Notification rates for these patients are low [26,46,49,50]. They are often treated empirically, without undergoing bacteriological testing [51,52], and the quality of private sector care is poor in standardized patient studies [53].

Given low private sector notification rates, representative sampling of private laboratories with TB testing capabilities could allow cohort-based tracking of patients starting from Step 2 (accessed a TB test). Audits of lab registers would identify bacteriologically diagnosed private sector patients who may not be notified to national programs. From Step 2, approaches for estimating cascade stages would be similar to those for the public sector; however, this approach does not account for private sector patients who are diagnosed empirically, without a TB test. As such, representative sampling of private clinics that deliver a high volume of TB care (e.g., qualified physicians participating in public–private mix projects) may also be necessary in settings with high rates of empirical treatment. Chart audits could identify patients at these clinics who are treated empirically, who could be followed for treatment outcomes and disease recurrence rates.

Estimating each stage of the TB care cascade

We describe approaches for estimating the TB care cascade below and in S1 Appendix. In Table 2, we summarize approaches for measuring care cascade outcomes and suggest process indicators for each cascade gap that may reveal deficiencies in quality of care. Data for process

Table 2. Recommended outcome and process indicators for a care cascade for active TB.

Cascade stage	Outcome indicators for cascade steps (useful for monitoring program outcomes)	Methods or required data for outcome indicators	Process indicators for cascade gaps[a] (useful for understanding quality of care)	Methods or required data for process indicators
Stage 1: Reaching health facilities and accessing a TB test	**Step 1: Number of individuals with incident or prevalent TB in the population**		**Gap 1: Number of individuals with TB who did not reach health facilities and access a TB diagnostic test[b]**	
	Number of individuals with prevalent active TB in a population for each form of TB	Population-based TB prevalence survey, including drug-susceptibility testing and prior TB treatment history for diagnosed patients	Distance to nearest TB health facility as a surrogate measure of the proportion of individuals without access to TB services[c]	Questions asked to TB patients diagnosed in population-based prevalence surveys
	Annual number of individuals with incident active TB in a population for each form of TB	Modeling methods may facilitate estimation of incidence from active TB prevalence, surveys of the annual risk of TB infection, government case notifications, TB drug sales, or other data	Proportion who have not sought medical care	Questions asked to TB patients diagnosed in population-based prevalence surveys

(*Continued*)

Table 2. (Continued)

Cascade stage	Outcome indicators for cascade steps (useful for monitoring program outcomes)	Methods or required data for outcome indicators	Process indicators for cascade gaps[a] (useful for understanding quality of care)	Methods or required data for process indicators
			Time delays in care seeking[d]	In-depth interviews with individuals starting TB treatment at health facilities[d]
			Number of individuals who died of TB without having received TB care	Population-based verbal autopsy surveys, including in-depth interviews with families of individuals who died of probable TB
Stage 2: Diagnosis	**Step 2: Number of individuals with TB who reached health facilities and accessed a TB diagnostic test[b]**		**Gap 2: Number of individuals with TB who accessed a TB diagnostic test[b] but did not get successfully diagnosed**	
	Number of individuals with smear-positive TB who accessed TB tests	Extrapolation from the proportion of patients who did not submit a second sputum sample (S1 Appendix)	Proportion of individuals with suspected TB who did not undergo any sputum testing	Audit of patient records at TB diagnostic facilities
	Number of individuals with Xpert-positive TB who accessed TB tests	Number evaluated equals the number diagnosed		
	Number of individuals with smear- or Xpert-negative TB who accessed TB tests or who had initiation of appropriate workup	Estimation based on the sensitivity of sputum microscopy or Xpert MTB/RIF in a given setting (S1 Appendix)	Proportion of individuals with suspected TB with negative sputum microscopy or Xpert test results who do not receive a medical diagnosis	Audit of patient records at TB diagnostic facilities
	Number of individuals with extrapulmonary TB who had initiation of appropriate workup	Estimation based on the anticipated rate of underdiagnosis of extrapulmonary TB in a given setting (S1 Appendix)		
	Number of individuals with MDR or RR TB who accessed TB tests	Extrapolation from culture-based studies estimating the proportion of MDR/RR TB among new and previously treated patients in a given setting (S1 Appendix)		
			Health system–related delays in diagnosis[d]	In-depth interviews with patients starting TB treatment[d]
Stage 3: Linkage to treatment	**Step 3: Number of individuals diagnosed with TB[e]**		**Gap 3: Number of individuals diagnosed with TB who did not get registered in treatment**	
	Number of individuals with smear- or Xpert-positive (i.e., bacteriologically diagnosed) TB who were successfully diagnosed	Data on bacteriologically diagnosed pulmonary TB patients is usually efficiently captured in patient registers at diagnostic facilities	Proportion of patients lost prior to referral from a TB diagnostic facility to a treatment facility	Audit of diagnostic and referral registers at TB diagnostic facilities
	Number of individuals with smear-negative, Xpert-negative, or extrapulmonary TB who were successfully diagnosed	These patients have more prolonged diagnostic workups and may be listed in separate registers from bacteriologically diagnosed pulmonary TB patients, such as registers used to refer patients to treatment sites	Proportion of patients lost after referral from the TB diagnostic facility to a treatment facility	Audit of referral registers at TB diagnostic facilities and registers at treatment facilities
	Number of individuals with MDR TB or RR TB who were successfully diagnosed as having drug-resistant TB	These patients can be identified through lab registers recording drug-susceptibility test results. Otherwise, they may be misclassified as drug-susceptible TB patients	Delays in treatment initiation[d]	In-depth interviews with patients starting TB treatment[d]
Stage 4: Retention in treatment	**Step 4: Number of individuals registered in TB treatment[e]**		**Gap 4: Number of individuals who did not complete TB treatment (due to treatment failure, loss to follow-up, or death)**	

(*Continued*)

Table 2. (Continued)

Cascade stage	Outcome indicators for cascade steps (useful for monitoring program outcomes)	Methods or required data for outcome indicators	Process indicators for cascade gaps[a] (useful for understanding quality of care)	Methods or required data for process indicators
	Number of individuals registered (or notified) in TB treatment	TB treatment records or electronic registers	Proportion of patients who experience treatment failure, die, or are lost to follow-up in the intensive phase of therapy	TB treatment records
			Proportion of patients who experience treatment failure, die, or are lost to follow-up in the continuation phase of therapy	TB treatment records
			Proportion of expected doses of TB medication actually taken during the treatment course (measure of the quality of medication adherence) [54]	TB treatment records
Stage 5: Post-treatment survival	**Step 5: Number of individuals who completed TB treatment[e]**		**Gap 5: Number of individuals who experienced post-treatment TB recurrence or death**	
	Number of patients who complete TB therapy	TB treatment records or electronic registers	Proportion of patients who experience TB recurrence or death within 1 year of treatment completion	Cohort studies involving close follow-up of patients every few months after treatment, with careful workup of new pulmonary symptoms, ideally with mycobacterial culture
			Proportion of patients with post-TB lung disease, including obstructive disease, restrictive/fibrotic disease, and pulmonary hypertension	Routine post-treatment follow-up of patients with spirometry and other measures of pulmonary function
Stage 6: Achieving durable cure	**Step 6: Number of individuals who achieve 1-year recurrence-free survival[e]**			
	Number of patients who survive for 1 year after completing TB treatment without disease recurrence	Cohort studies involving close follow-up of patients every few months after treatment up to 12 months, with careful workup of any new pulmonary symptoms, ideally with mycobacterial culture		

[a] Gaps can be estimated as the difference between two steps (i.e., Gap 1 = Step 1 − Step 2). The process indicators described in the table will further inform reasons for each gap.

[b] "Accessed a TB diagnostic test" refers to individuals with TB who either accessed an appropriate bacteriological test for TB or who had initiation of appropriate workup (for extrapulmonary or pulmonary TB patients who might be diagnosed empirically).

[c] Distance of a patient's home from the nearest health facility is only one aspect of access to care; other factors include economic and social barriers, though these may be harder to measure routinely.

[d] Single in-depth interviews with TB patients at the time of treatment initiation can be used to capture information on delays in care seeking, diagnosis, and treatment initiation.

[e] Steps 3, 4, 5, and 6 are best estimated by following a single patient cohort, starting with diagnosed TB patients identified in Step 3 (i.e., a cohort-based or denominator–denominator linked approach).

Abbreviations: MDR, multidrug-resistant; RR, rifampin-resistant; TB, tuberculosis.

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indicators could be collected concurrently with cohort-based studies aiming to measure care cascade outcomes.

Stage 1: Reaching health facilities and accessing a TB test. Estimating the number of individuals with active TB in a population (Step 1) is valuable for national-level cascades

because the number of individuals with TB who do not access a TB test (Gap 1) may be a large gap and may contribute considerably to TB transmission [10]. The annual number of individuals with incident TB is the ideal metric for Step 1 because most programs report subsequent outcomes, such as the number of individuals who complete treatment, on a yearly basis.

For most countries, incidence and prevalence estimates are routinely reported by WHO and are informed by country experts [24]. Alternative estimates are available from the Institute for Health Metrics and Evaluation (IHME) [55,56]. However, WHO and IHME incidence estimates are partly extrapolated from notification data, which may have inaccuracies, especially where the private sector delivers a large proportion of TB care [26,57]. When possible, we suggest validating WHO or IHME estimates against independent sources of information on TB burden, such as private sector TB drug sales [26]. Mathematical models, incorporating data from population-based surveys of active or latent TB prevalence and mortality [27], may also be informative. Moreover, population-based prevalence surveys provide objective data on the number of individuals with active TB in the population, which can be used for longitudinal monitoring [58]. Prevalence surveys may also provide information on Gap 1 process indicators (Tables 2 and 3), which can be used to monitor the population's care-seeking behavior and the impact of TB public education programs on modifying this behavior.

For Gap 1, individuals who die without accessing TB care are particularly concerning. Achieving accurate estimates of these individuals is challenging, given limitations in the accuracy of vital registration systems and medical certification of causes of death in many countries. Verbal autopsy may help refine TB mortality estimates in such settings [59].

Stage 2: Diagnosis. We define Stage 2 starting from when individuals with pulmonary TB reach a health facility and access TB tests (e.g., sputum microscopy, Xpert MTB/RIF) or when appropriate workup is initiated by a healthcare provider for individuals with extrapulmonary or pulmonary TB who might be diagnosed empirically. While estimating Stage 2 requires different methods for each form of TB, it provides valuable insights on gaps in care. For example, in the Indian and South African TB care cascades, about 310,000 (16% of those tested) and 69,000 (14% of those tested), respectively, were not successfully diagnosed or never received their diagnosis [10,11]. Estimating Gap 2 is especially valuable for smear-negative, Xpert-negative, and drug-resistant TB, which are more difficult to diagnose. This gap may reveal patient losses from use of suboptimal diagnostic tests (e.g., sputum microscopy) or from poor adherence to algorithms for empirical diagnosis.

Individuals with smear-positive TB evaluated with sputum microscopy are, by definition, likely to be diagnosed [60]. A small proportion may be missed if they do not submit a second sputum sample (S1 Appendix), especially in locations where same-day microscopy has not

Table 3. Survey data that can be collected during active TB prevalence surveys, in addition to standard diagnostic tests, to facilitate estimation of care cascade outcome and process indicators.

Survey questions for individuals diagnosed with active TB in a prevalence survey	Benefit for understanding care cascade outcomes and process indicators
History of prior TB treatment	Estimation of the proportion of individuals with active TB who have a prior TB treatment history in the population
Nearest government facility with TB services	Estimation of proportion of individuals with active TB who may not have adequate access to TB services
Whether the patient has sought care for TB symptoms	Indirect evidence of the proportion of incident cases seeking care and of the delay before doing so
If care was sought, whether the patient was screened with a sputum test or chest X-ray	Indirect evidence of the proportion of incident cases with access to TB diagnostic tests and a measure of quality of care
Duration of TB symptoms	May help to model annual incidence from point prevalence; indirect evidence of delays in seeking care

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been implemented [61]. In settings using Xpert, because a single sputum sample is usually submitted, the number of individuals with Xpert-positive TB who access the test (Step 2) can be assumed to be the same as the number who get diagnosed with Xpert-positive TB (Step 3).

In settings without more advanced diagnostic tests, individuals with smear-negative TB are diagnosed empirically. Most individuals who have negative sputum smears have conditions other than TB (e.g., bacterial pneumonia), making it challenging to estimate the number of true smear-negative TB patients evaluated at diagnostic facilities. Because the number of individuals with smear-positive TB in Step 2 can be more reliably estimated, the estimated ratio of individuals with smear-negative to smear-positive TB in a setting (a reflection of the sensitivity of sputum microscopy compared to a gold standard of culture) can be used to roughly estimate the number of true smear-negative TB patients who get evaluated at diagnostic facilities (S1 Appendix). Estimates of this ratio may be more relevant if based on high-quality local studies of the sensitivity of sputum microscopy in programmatic conditions [10]. In settings using Xpert MTB/RIF as the primary test, a similar ratio method based on estimates of Xpert's sensitivity can be used to estimate Step 2 for individuals with Xpert-negative TB (S1 Appendix).

Estimating the number of true extrapulmonary TB patients who access appropriate workup is also challenging because clinical presentation and sensitivity of diagnostic tests vary depending on the site of disease. Studies that identify individuals with possible extrapulmonary TB who present to diagnostic facilities and follow them to determine the number who complete appropriate workup and get diagnosed may inform Step 2 and Gap 2 estimates. The number of MDR (or rifampin-resistant) TB patients reaching health facilities and accessing a TB test (Step 2) can be estimated using MDR TB rates in new and previously treated patients, which are available for most countries from WHO [23] or national MDR TB prevalence surveys [62] (S1 Appendix). Finally, estimating Stage 2 for children can be particularly challenging because of the low sensitivity of diagnostic tests in this population [63,64] (S1 Appendix).

Stage 3: Linkage to treatment. PTLFU—loss of diagnosed patients prior to treatment registration—is a major point of attrition in TB programs [10,11,65]. Most studies have examined this gap for smear-positive [10,65] or drug-resistant TB patients [66–70]. Few have examined this gap for smear-negative [71,72], Xpert-negative, or extrapulmonary TB patients. Future care cascade analyses should estimate this gap for all forms of TB.

To measure PTLFU, many studies identify newly diagnosed TB patients in registers at diagnostic facilities and prospectively track them to see if they get registered at treatment centers, an approach which can also facilitate cohort-based estimates for remaining cascade stages (Table 2). While we agree with this approach, it can be challenging for a few reasons. First, in some settings, TB treatment initiation and official registration (or notification) do not happen concurrently. Patients may be lost to follow-up after starting therapy but before official treatment registration [32]. Second, patients may get diagnosed in one location (e.g., a city) but start treatment elsewhere (e.g., a rural area), making follow-up difficult, especially since unique identification numbers are uncommon in many countries [31,32,73]. Third, missing or illegible contact information often makes patient tracking difficult, especially in settings using paper records [31–33,73,74].

Capturing patient information in electronic registration systems at diagnosis and treatment initiation may improve estimation of PTLFU [66]. South Africa has introduced unique patient identification numbers along with a national electronic notification system to ensure patients attending different facilities are not counted multiple times. India is rolling out a similar system. Such systems may facilitate patient tracking across large geographic areas. Officially registering (i.e., notifying) patients at the time of diagnosis, as India is trying to do, may also improve estimation of PTLFU.

Finally, interviewing patients at the time of treatment registration allows assessment of delays in care seeking, diagnosis, and treatment initiation, which are helpful process indicators

(Table 2) [42,75]. Some interventions may impact PTLFU and time delays differently. For example, a South African study found that use of Xpert reduced treatment delays for rifampin-resistant TB patients without reducing PTLFU [66].

Stage 4: Retention in treatment. Most national TB programs routinely report data on patients registered in treatment (Step 4) and who do not complete therapy (Gap 4), based on the WHO guidelines [76]. Suboptimal Gap 4 outcomes consist of patients who are lost to follow-up, experience treatment failure (i.e., positive sputum smear or culture despite therapy), or die while on treatment [76].

While estimating Stage 4 using aggregate numbers from TB programs may be helpful, we recommend using prospective patient-tracking approaches that allow for rigorous cohort-based care cascade estimates. For this approach, patients diagnosed with TB in Step 3 can be followed through Step 4 (treatment registration) and Step 5 (treatment completion) using clinical records (Table 2). This approach also allows elucidation of the time during treatment when most poor outcomes occur (e.g., intensive or continuation phase). Digital adherence technologies—including digital pillboxes and cell phone–based strategies—may also facilitate more accurate estimation of Stage 4 and timing of patient losses [54,77].

Stages 5 and 6: Post-treatment survival and achieving durable cure. Step 5 (treatment completion) can be assessed using treatment cards or registers in most national TB programs [76]. However, estimating Step 6 (1-year recurrence-free survival) requires following patients after treatment completion. Post-treatment follow-up is not routine in most programs, though some national guidelines recommend such monitoring [15,78,79]. Studies show high rates of post-treatment disease recurrence and death under programmatic conditions, highlighting the importance of evaluating these longer-term outcomes [25,80–83].

Post-treatment disease recurrence is an indicator of quality of care, since recurrence may result from poor medication adherence during therapy [80,84] or undiagnosed drug resistance [25,85]. In settings where HIV coinfection is common, disease recurrence is often due to exogenous reinfection with a new TB strain [86,87]. One-year TB recurrence-free survival may be a less useful outcome for the cascade in such settings, although high recurrence rates in these settings may indicate need for transmission control interventions. We recommend 12 months of post-treatment follow-up because most cases of TB relapse (91%) occur in this time period, based on a meta-analysis of clinical trials [88].

To achieve accurate Gap 5 and Step 6 estimates, we recommend a cohort-based approach with prospective follow-up of patients who complete treatment because retrospective follow-up of patients who finish treatment may be compromised by higher loss to follow-up. In addition, Gap 5 can most accurately be estimated by collecting sputum samples for mycobacterial culture from symptomatic patients (for those who had pulmonary TB) or repeated clinical evaluation (for those who had extrapulmonary TB), which is not possible to do retrospectively. Patients who complete TB treatment should ideally be regularly reevaluated (e.g., every 3 months), for at least 1 year [36,80].

Discussion

The care cascade represents a valuable and feasible approach for monitoring TB programs [10]. Unique challenges involved in constructing a TB care cascade include difficulties in estimating the number of individuals with active TB in the population, challenges in estimating the diagnostic gap (Gap 2) due to the suboptimal sensitivity of common diagnostic tests, and heterogeneity in approaches for estimating cascade stages for different forms of TB. In addition, the case-finding gap (Gap 1) includes individuals with TB who do not access TB tests for various reasons, including not having access to health facilities, not seeking care, and not being

referred for TB testing after reaching a healthcare provider. Understanding which barrier contributes most to Gap 1 is an important undertaking that we have not covered in this manuscript. Some challenges involved in estimating the care cascade are not unique to TB—for example, use of written records and lack of unique identification numbers, which makes tracking patients across stages more difficult. Additionally, it is not easy to account for patients managed in the private sector in some countries, without conducting primary data collection.

Despite these challenges, key cascade stages can be evaluated in most settings. While robust estimates of the number of individuals with active TB in the population may not always be available, cohort studies can be implemented in most settings starting from Stage 2 or 3 to estimate subsequent stages. Even without estimates of the number of individuals with active TB in the population, these research approaches can provide valuable insights for strengthening health systems by identifying gaps with the largest patient losses.

There are limitations in the scope of what the care cascade model measures. For example, delays in care seeking, diagnosis, and treatment initiation may not be adequately captured; however, as described above, the care cascade also provides a framework for understanding how patients traverse stages in care, into which other process indicators can be embedded. If cohort-based approaches are used to measure the care cascade, data on some of these process indicators can be collected concurrently to gain additional insights into quality of care.

Ideally, care cascade estimates would rely on robust survey data and longitudinal monitoring by health systems, including nationally representative TB prevalence and mortality data, electronic medical records for capturing notification and outcomes of private sector TB patients, and routine post-treatment follow-up to estimate TB recurrence. Countries currently have variable availability of these data and infrastructure.

Patient outcomes may be improved by implementing interventions addressing the most concerning gaps, which may be related to case finding, diagnostic workup, linkage to treatment, retention in care, or medication adherence (to reduce TB recurrence) (Fig 3). Patient mobility (e.g., urban–rural travel) is a barrier for ensuring linkage to, and retention in, care in many settings [31]. Written records often require healthcare workers to track patients through different paper registers for diagnosis, drug susceptibility testing, treatment initiation, and treatment monitoring, which may contribute to diagnostic and treatment delays.

Robust electronic systems with unique identification numbers for tracking patients, linking them to care, and monitoring medication adherence in real time have the potential to improve gaps in the care cascade [54,90]. Once patients are started on treatment, a holistic management approach, including provision of economic incentives and enablers, nutritional support, and care for comorbidities (e.g., substance use, depression), may also improve outcomes [91].

Although important information can be obtained from routine programmatic data, dedicated cohort studies will yield the most accurate care cascade estimates, especially for stages such as recurrence-free survival, for which programs may not routinely collect data. If representative sampling is used, multisite cohort studies can produce accurate national-level care cascade estimates that could be used for longitudinal monitoring of outcomes.

Conclusion

The care cascade has the potential to improve program monitoring and to inform targeting of interventions to improve case finding, diagnosis, linkage to treatment, retention in care, and recurrence-free survival for TB patients. Combined with other approaches, such as patient pathways analyses, the care cascade can provide critical information on quality of care to national TB programs [12]. The model may refine estimates for the STOP TB

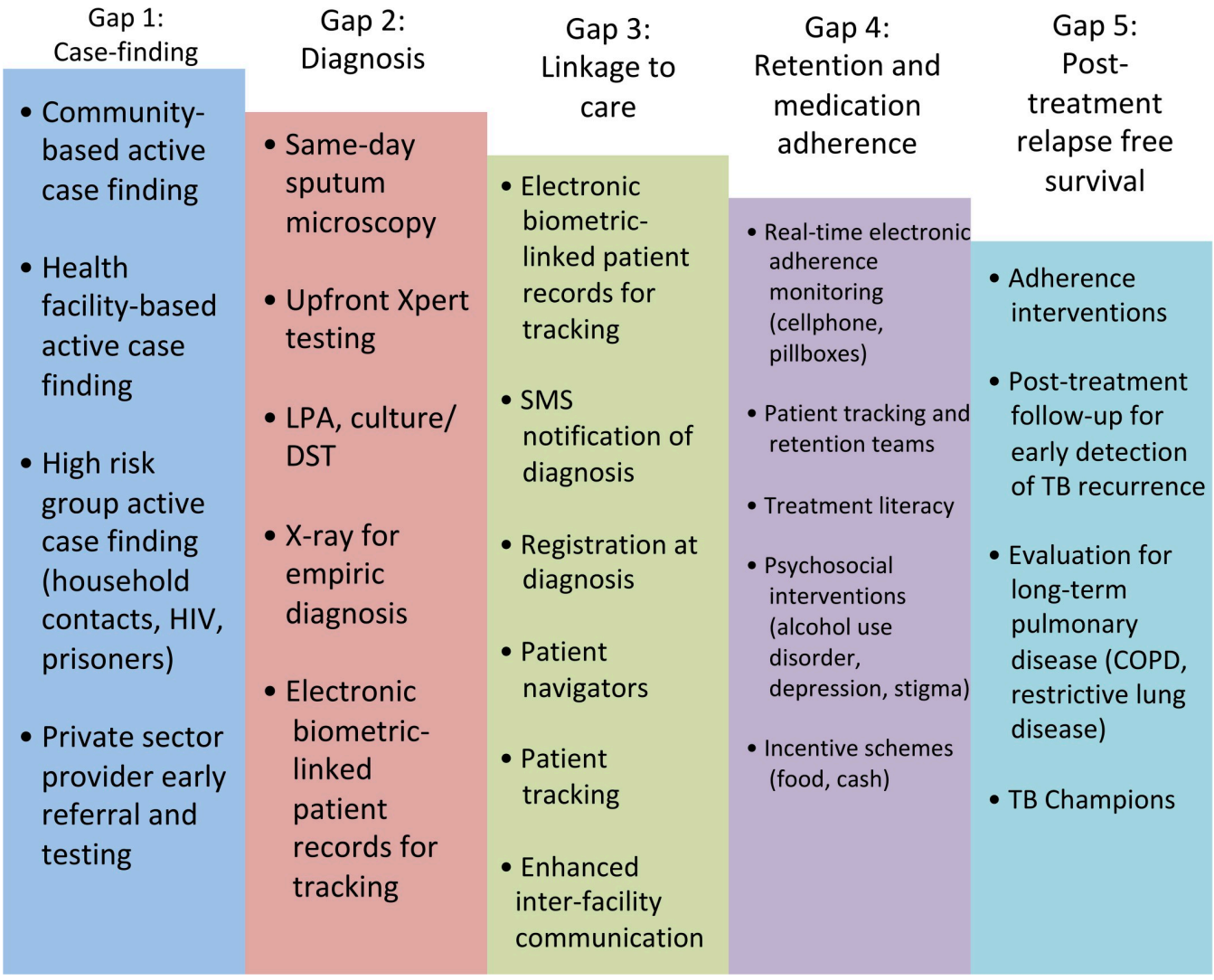

Fig 3. An example of how potential interventions can be mapped onto different gaps to address patient losses in the TB care cascade. Different interventions might be chosen based on the setting. We do not cover the evidence basis for these interventions here. TB Champions refers to individuals who have survived TB who serve as advocates to increase awareness and support for patients with active TB who are in treatment or who have completed treatment [89]. COPD, chronic obstructive pulmonary disease; DST, drug susceptibility testing; LPA, line probe assay; SMS, short messaging service; TB, tuberculosis.

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Partnership's 90-(90)-90 global targets, which include getting 90% of people with active TB on appropriate therapy, reaching at least 90% of key high-risk or underserved populations as part of this approach, and ensuring that 90% of those patients achieve treatment success by 2025 at the latest. By providing a systematic approach to evaluating care delivery, followed by corrective interventions, the care cascade may serve as an important tool for achieving the ambitious goal of reducing TB incidence by 90% by 2035, as envisioned by the End TB strategy [92].

Supporting information

S1 Appendix. Constructing a tuberculosis cascade of care: a "how to" guide.
(PDF)

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Supplementary Appendix: Constructing a tuberculosis cascade of care: a "how to" guide

Supplement to:

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

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Constructing a tuberculosis cascade of care: a "how to" guide

This document is a practical guide to assist tuberculosis (TB) program managers and researchers in constructing TB care cascades that are relevant and appropriate to their local settings. As a result, this document provides relatively simplified approaches for achieving cascade estimates. We describe two different approaches below. The methodological strengths and limitations of each approach are discussed in the section of the main manuscript titled "General principles for constructing a cascade." We encourage modification of these approaches as needed for each setting.

The first approach, which we will refer to as the *routine data approach*, is a denominator-numerator unlinked methodology [1], in which the estimates for each stage are gathered or extrapolated from readily available programmatic data or previously conducted local studies. The routine data approach depends on the availability of robust data collection by TB programs and of previously conducted studies to estimate specific gaps in the cascade. If such information is available, the primary data collection and data analysis requirements for the routine data approach are substantially less demanding than for the cohort-based approach. This general approach has been used most recently to estimate TB care cascades at a national level for India and South Africa [2,3]. However, this approach may introduce bias into cascade estimates, because it fails to account for the changing composition of the patient population at each stage of the cascade. Additionally since this approach involves the retrospective use of data, it does not enable evaluation of reasons for gaps in the care cascade.

The second approach, which we will refer to as the *cohort-based approach*, uses a denominator-denominator linked method, in which the same group of individuals is followed across multiple stages of the cascade. In practice, this approach requires prospective or retrospective cohort studies that can be conducted in TB programs with high-quality patient records. The cohort-based approach is more resource intensive, because it requires primary data collection; however, this approach may minimize bias in cascade estimates.

We recommend that estimates be calculated independently for different forms of TB, depending on the primary diagnostic modality used in a given setting. For example, sputum smear microscopy is still the initial diagnostic test used in India, which is a relatively low HIV prevalence country. A recent evaluation of the TB care cascade in India provided separate estimates for new smear-positive, new smear-negative, extrapulmonary, retreatment smear-positive, retreatment smear-negative, and multidrug-resistant (MDR) TB patients—following definitions of these patient categories used by India's Revised National TB Control Programme [2].

In contrast, South Africa is a country with high HIV prevalence, and Xpert MTB/Rif is a commonly used diagnostic test, in addition to smear microscopy and (to a lesser extent) mycobacterial culture. A recent evaluation of the TB care cascade in South Africa provided separate estimates for drug-susceptible TB patients, HIV-infected drug-susceptible TB patients, and rifampin-resistant TB patients (i.e., patients presumed to have MDR TB) [3]. These groups included combined estimates for patients with a positive bacteriological test (i.e, Xpert- or smear-positive) and patients with negative bacteriological tests (i.e., Xpert- or smear-negative).

Approach 1: the routine data approach

Step A: Number of individuals registered in TB treatment

The first step is to obtain data on the number of individuals who are *registered in TB treatment* (cascade Step 4) for different types of TB, over a one-year time period (Figure 1).

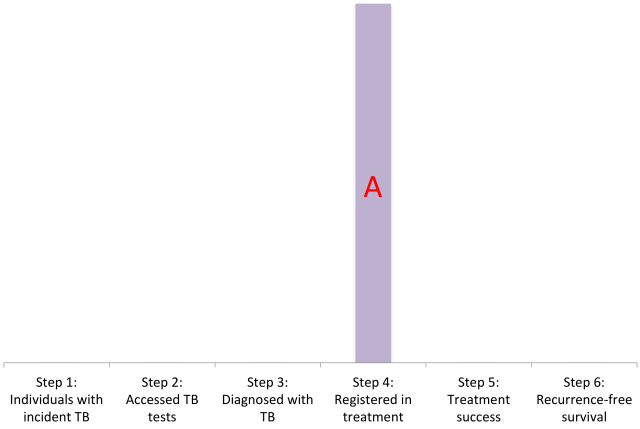

Figure 1: Step A in the routine data approach to constructing a TB care cascade

These statistics can be obtained from a variety of sources, including hospital or clinic records or city- or district-level TB reports to construct local-level cascades. For country-level cascades, these statistics can be obtained from national reports (e.g., *TB India* reports for India) [4,5] or from national electronic databases with individual-level data (e.g., South Africa's electronic TB and drug-resistant TB registers) [3]. In addition, the World Health Organization (WHO) reports this information for several countries in its case notifications database (http://www.who.int/tb/country/data/download/en/) (Table 1).

Table A. Variables in the WHO TB case notifications database that provide estimates of the number of individuals registered in TB treatment at a country level

Variable	Types of patients included
new_labconf	New pulmonary bacteriologically confirmed TB cases (e.g., smear-, Xpert-, or culture-positive)
new_clindx	New pulmonary clinically diagnosed TB cases (not bacteriologically confirmed)
new_ep	New extrapulmonary cases (bacteriologically confirmed or clinically diagnosed)
ret_rel_labconf	Relapse pulmonary bacteriologically confirmed TB cases (e.g., smear-, Xpert-, or culture-positive)
ret_rel_clindx	Relapse pulmonary clinically diagnosed TB cases (not bacteriologically confirmed)
ret_rel_ep	Relapse extrapulmonary cases (bacteriologically confirmed or clinically diagnosed)
ret_nrel	Previously treated patients, excluding relapse cases (pulmonary or extrapulmonary, bacteriologically confirmed or clinically diagnosed)
conf_rrmdr_tx	Rifampin-resistant (RR) or MDR TB patients who were laboratory confirmed and started on treatment
conf_xdr_tx	Extensively drug-resistant (XDR) TB patients who were laboratory confirmed and started on treatment

To start with, we suggest separately extracting treatment registration numbers for each of the following forms of TB, at minimum: (1) laboratory confirmed new pulmonary TB patients (i.e., smear-, Xpert-, or culture-positive cases); (2) empirically diagnosed new pulmonary TB patients (i.e., smear-, Xpert-, or culture-negative cases); (3) new extrapulmonary TB patients; (4) laboratory confirmed retreatment pulmonary TB patients; (5) empirically diagnosed retreatment pulmonary TB patients and retreatment extrapulmonary TB patients (sometimes referred to collectively as "retreatment other" patients); and (6) drug-resistant TB patients (including MDR and extensively drug-resistant, or XDR, TB patients). Individual cascades can then be constructed for each of these different types of TB. These individual cascades can later be easily combined to construct a cascade that includes all forms of TB.

Step B: Number of individuals who achieve treatment success

The second step is to obtain data on the number of patients who achieve *treatment success* (cascade Step 5) for different types of TB, over the same one-year time period (Figure 2).

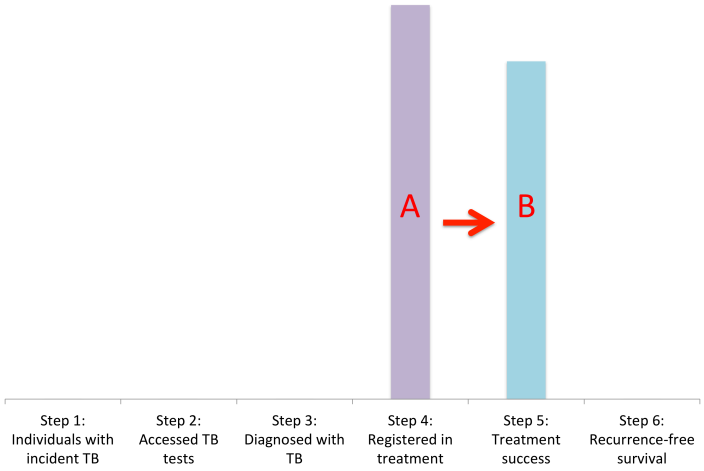

Figure 2: Step B in the routine data approach to constructing a TB care cascade

These statistics can be obtained from similar sources as listed for Step A, including clinic records or city- and district-level TB reports to construct local-level cascades. For country-level cascades, these statistics can be obtained from national reports (e.g., the *TB India* reports for India) [4,5] or from national electronic TB databases with individual-level data (e.g., South Africa's electronic TB and drug-resistant TB registers) [3]. The World Health Organization (WHO) aggregates and reports this information for several countries in its "treatment outcomes" database (http://www.who.int/tb/country/data/download/en/), though the categorization of types of TB and the variables under which treatment success data are captured in the WHO database have varied over time.

We recommend extracting treatment success data that correspond to the categories described above: (1) laboratory confirmed new pulmonary TB patients; (2) empirically diagnosed new pulmonary TB patients; (3) new extrapulmonary TB patients; (4) laboratory confirmed retreatment pulmonary TB patients; (5) empirically diagnosed retreatment pulmonary and retreatment extrapulmonary TB patients

(sometimes referred to collectively as “retreatment other” patients); and (6) drug-resistant TB patients (including MDR and XDR patients).

Step C: Number of individuals who achieve one-year recurrence-free survival

The third step is to estimate the number of individuals who *achieve TB recurrence-free survival for at least one-year* (cascade Step 6) after the completion of TB therapy (Figure 3). Most TB programs do not routinely engage in long-term follow-up of patients after the completion of TB treatment; however, studies that estimate post-treatment TB disease recurrence and mortality rates in your specific country or region may be available in the published literature (Table B).

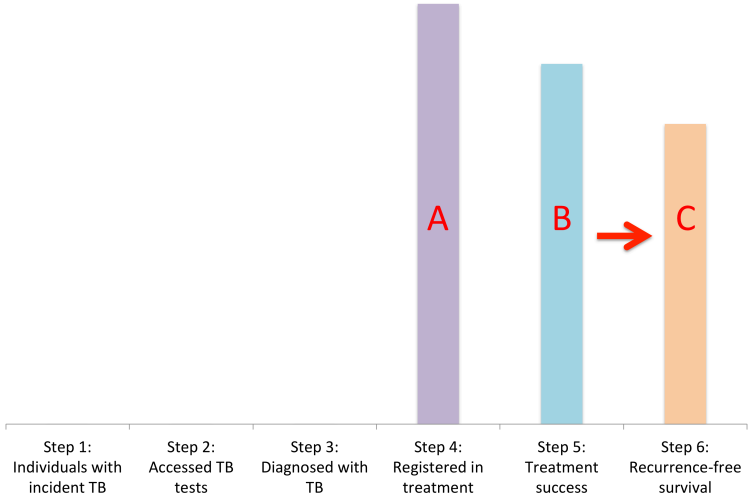

Figure 3: Step C in the routine data approach to constructing a TB care cascade

Table B: Examples of studies estimating post-treatment tuberculosis recurrence rates under routine programmatic conditions

Author	Country	Year of cohort	Post-treatment recurrence and death rates
Becerra et al. [6]	Peru	1999—2002	5% for MDR TB patients
Cox et al. [7]	Uzbekistan	2001—2002	7% for drug-susceptible TB patients; 44% for MDR TB patients
Gelmanova et al. [8]	Russia	2000—2004	7% for MDR TB patients
Marx et al. [9]	South Africa	1996—2008	16.5% of smear-positive TB patients
Sadacharam et al. [10]	India	2002—2003	18% of new smear-positive TB patients; 27% of previously treated TB patients
Thomas et al. [11]	India	2000—2001	15% of new smear-positive TB patients
Velayutham et al. [12]	India	2015—2016	11% of new smear-positive TB patients experienced TB recurrence within 12 months; ~2% died

It is important that estimates of post-treatment recurrence and death be extracted from observational studies conducted under programmatic conditions (i.e., routine care provide by TB programs), rather than from rigorous clinical trials, since clinical trials may reflect a higher standard of care than is normally delivered under programmatic conditions. For example, a systematic review of studies of post-treatment TB recurrence for patients taking the DOTS regimen found considerably higher TB recurrence rates for patients treated under routine programmatic conditions [7].

Using your local estimate of post-treatment TB recurrence and death, you can then estimate Step 6 of the cascade as follows:

Step 6 cascade value = (Step 5 cascade value) – (estimated post-treatment TB recurrence and death rate)(Step 5 cascade value)*

In settings where estimates of post-treatment TB recurrence and death are not available, there are two options. First, you can conduct a study using representative sampling of patients or health centers to estimate the local rate of post-treatment TB recurrence and death, which can be retrospective [6,8-10,13] or prospective [11,12]. If a prospective approach is used, we recommend following the rigorous methodology used by Velayutham et al. [12]. In that study, a cohort of Indian patients who completed TB therapy under programmatic conditions were followed prospectively with follow-up visits by researchers every 3 months. During these visits, patients were screened for symptoms of TB and sputum samples were collected for sputum microscopy and mycobacterial culture to help diagnose recurrent TB. This methodology minimized post-treatment loss to follow-up of patients, screened systematically for TB recurrence, and also carefully captured information on mortality. Post-treatment mortality should be included as a suboptimal outcome in Gap 5, because studies suggest that the increased risk for mortality in TB patients extends for several months after the completion of TB treatment, potentially due to disease relapse, undiagnosed drug-resistant, or pulmonary complications (e.g., fibrosis and bronchiectasis) of TB [14,15]. As such, death in the year after completing TB treatment may also reflect the quality of care delivered during TB therapy.

If it is not possible to conduct a local study of TB recurrence, then Step 6 of the TB cascade can be omitted, which results in treatment success (Step 5) being the final step of the cascade.

Step D: Number of individuals diagnosed with TB

Next, we move “backwards” from the number of individuals who are registered in TB treatment (cascade Step 4) to estimate the preceding steps of the cascade, starting with estimation of the number of individuals *diagnosed with TB* (cascade Step 3) (Figure 4).

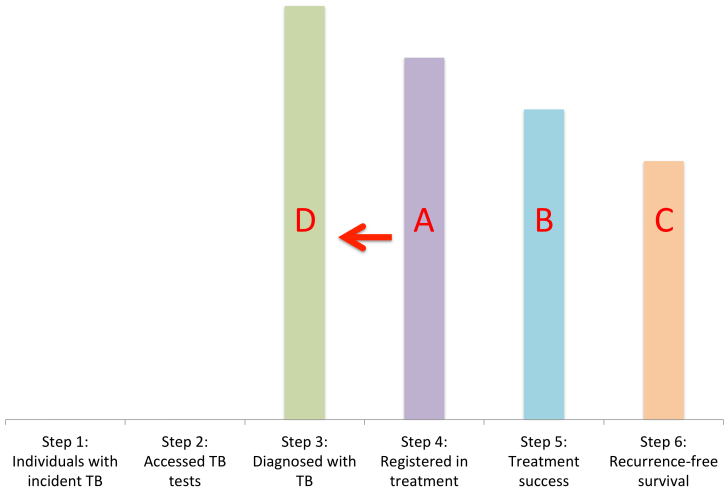

Figure 4: Step D in the routine data approach to constructing a TB care cascade

The number of individuals diagnosed with TB can be estimated using a few approaches. In some countries, diagnosed TB patients are immediately "notified" to TB programs. These TB programs typically have electronic records of all diagnosed TB patients. South Africa uses an electronic system with unique patient identifier numbers enabling patients to be followed through multiple stages of the cascade [13]. Other TB programs report the number of diagnosed patients in aggregate for some forms of TB; however, they do not capture individual records of diagnosed patients. For example, India reports the aggregate "number of smear-positive patients diagnosed" every year at the district and national levels (notably, these values are only reported for smear-positive patients and not for other forms of TB) [4]. Unlike electronic databases containing individual-level data, this information does not allow tracking of individual patients through each subsequent step of the cascade.

In situations where individual-level or aggregate data on the number of diagnosed TB patients are not available, we recommend estimating the number of diagnosed TB patients (cascade Step 3) by back-calculation from the number of patient registered for TB therapy (cascade Step 4) using estimates of pretreatment loss to follow-up (i.e., the number of diagnosed TB patients who fail to get registered for TB therapy).

In addition to targeted searches of the medical literature, a few resources are available to help identify studies of pretreatment loss to follow-up that may be relevant for your country, region, district, or city. First, a systematic review published in 2014 summarized findings from 23 studies of pretreatment loss to follow-up conducted throughout countries in Africa, Asia, and the Western Pacific region (Table C) [16]. Second, the recently published Indian and South African TB care cascades both estimated pretreatment loss to follow-up through systematic reviews of local studies in those two countries [2,3]. Individual local studies contained in these systematic reviews may be helpful for estimating subnational cascades in these two countries. In some situations, studies that estimate pretreatment loss to follow-up at the national level may be available, as is the case for MDR TB patients in South Africa [13].

Table C: Examples of studies estimating TB pretreatment loss to follow-up rates in different settings

Author	Country	Scope of study	Year of data collection	Pretreatment loss to follow-up rate
Subbaraman et al. [2]	India	Systematic review of 16 local Indian studies	2000—2015	16% for new patients; 23% for MDR TB patients
Naidoo et al. [3]	South Africa	Systematic review of 15 local South African studies, including drug-susceptible TB	2006—2016	19% for bacteriologically confirmed patients
Cox et al. [13]	South Africa	Nationally-representative study of rifampin-resistant (presumed MDR TB) patients in South Africa	2011, 2013	37% for MDR TB patients after widespread introduction of Xpert testing
Uchenna et al. [17]	Nigeria	Five states in southern Nigeria	2009	17% for smear-positive patients
Razia et al. [18]	Pakistan	Five tertiary centers and 16 peripheral centers in one district	2009	6% for smear-positive patients
Buu et al. [19]	Vietnam	Several district tuberculosis units	2000	8% for smear-positive patients
Korobitsyn et al. [20]	Tajikistan	Four districts	2008-2009	8% for smear-positive patients

In some cases, studies of pretreatment loss to follow-up that are relevant to your country, region, district, or city may not be available. In those situations, new studies can be designed and conducted to estimate pretreatment loss to follow at the clinic, city, district, regional, or national level. For countries interested in estimating pretreatment loss to follow-up at the national level, we recommend using rigorous representative sampling approaches (e.g., probability proportionate to size) to select clinics or districts throughout the country where these studies can be conducted. In addition, rigorous prospective studies with careful patient tracking strategies are most likely to achieve accurate estimates of pretreatment loss to follow-up.

Once estimates of pretreatment loss to follow-up are determined for each form of TB, you can then estimate Step 3 of the cascade as follows:

Step 3 cascade value = (Step 4 cascade value) / (1 – estimated pretreatment loss to follow-up rate)

Step E: Number of individuals with TB who reached health facilities and accessed a TB diagnostic test

Next, we move "backwards" from the number of patients who are *diagnosed with TB* (cascade Step 3) to estimate the *number of TB patients who accessed a TB diagnostic test (or who had an appropriate diagnostic workup initiated for extrapulmonary TB)* (cascade Step 2) (Figure 5).

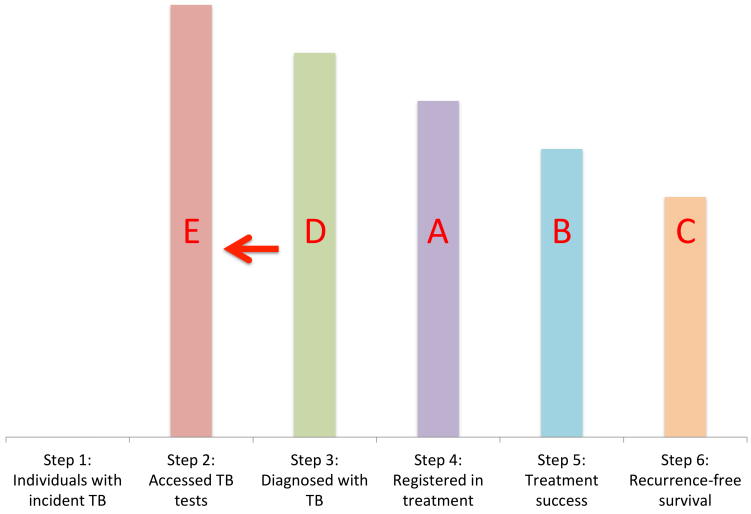

Figure 5: Step E in the routine data approach to constructing a TB care cascade

Estimation of this step requires different approaches for every form of TB, and we describe approaches to estimating Step 2 separately for each form of TB.

Estimating Step 2 for pulmonary TB patients who would have a positive bacteriological test

For pulmonary TB patients who would have a positive bacteriological test (i.e., smear- or Xpert-positive) if they completed an evaluation for TB, an estimation of the proportion of patients who are drop out between Step 2 and Step 3, that incorporates a measure of the accuracy of the diagnostic test used, can facilitate back-calculation of the value for Step 2 from the value for Step 3.

For example, India primarily uses sputum microscopy for upfront diagnosis of most pulmonary TB patients. Two sputum samples are collected and tested on separate days—a "spot" sample at the time of initial evaluation and a second "morning" sample the next day. In the Indian context, one of the ways in which a smear-positive patient could reach a TB diagnostic facility and access a TB test (Step 2) but remain undiagnosed would be if she had a false negative "spot" sample and did not return to the clinic the next day to submit a second "morning" sample that would have resulted in a diagnosis. In the recently published Indian cascade of care, the authors estimated that approximately 11% of patients visiting TB microscopy centers do not submit a second sputum sample for evaluation, based on a systematic review and meta-analysis of studies [2]. A recent meta-analysis found that the incremental yield of a second sputum sample for diagnosing smear-positive TB is 11.9% [21]. Using these two values, the authors first estimated the proportion of smear-positive patients who go undiagnosed as follows:

Proportion of smear-positive patients who go undiagnosed = (Proportion of all patients screened who submit one sputum sample but do not submit a second sputum sample)(Incremental yield of a second sputum sample for diagnosing smear-positive TB)*

Using this value for the proportion of smear-positive patients who go undiagnosed, it is then possible to estimate the value for cascade Step 2 for smear-positive patients as follows:

Step 2 cascade value for smear-positive patients = (Step 3 cascade value for smear-positive patients) / (1 – proportion of smear positive patients who go undiagnosed)

To estimate the proportion of Xpert-positive TB patients who go undiagnosed, a similar approach may be used to estimate Step 2 in settings that primarily use Xpert for upfront testing, since a small percentage of patients may initially have Xpert test results that return as "error," "invalid," or "no result." Some of these patients may have a positive test result if Xpert testing is repeated, which may be standard practice in some settings. However, it is worth noting that, in general, a fairly small percentage of all sputum samples (~1%) [22] return with an error or invalid result, so it may be reasonable to skip these calculations and to simply assume that there are no Xpert-positive TB patients who go undiagnosed. Under this assumption, the Step 2 estimate is equal to the Step 3 estimate for Xpert-positive patients.

Estimating Step 2 for pulmonary TB patients who have a negative bacteriological test (i.e. diagnosed empirically)

Estimating the number of patients who have a negative bacteriological test (i.e., negative sputum microscopy or negative Xpert result) but who would truly have pulmonary TB (if tested with a more sensitive test such as mycobacterial culture or if diagnosed empirically after a rigorous workup) is very challenging. Admittedly any estimates produced may have considerable uncertainty. However, estimation of Step 2 for patients who have a negative bacteriological test can provide some of the most useful information in the entire TB cascade, since these estimates help to evaluate the efficiency of protocols for empiric diagnosis of patients in a TB program.

For example, in the Indian TB cascade, the authors estimated that about 514,161 patients who truly had smear-negative TB likely reached government TB facilities and accessed a TB test in India; however, only 320,982 smear-negative patients were estimated to have been successfully diagnosed at government TB facilities. This suggested that 193,179 smear-negative patients, or about 38% of all smear-negative TB patients reaching government TB diagnostic facilities and accessing TB tests, were not being successfully diagnosed—highlighting considerable inefficiency in processes for empiric diagnosis of TB patients [2].

One approach is to estimate the number of true smear- or Xpert-negative patients who reached TB diagnostic facilities and accessed a TB test by extrapolation from the number of smear- or Xpert-positive patients who accessed a TB test—since the number of patients with positive tests is generally a more reliable estimate. This extrapolation can be calculated using estimates of the sensitivity of sputum smear microscopy or Xpert (Table D).

Table D: Estimates of the sensitivity of diagnostic tests for pulmonary TB

Author	Scope of study	Year of data collection	Estimated sensitivity for culture-positive TB
Sputum smear microscopy			
Davis et al. [23]	Systematic review of 8 studies comparing sputum microscopy with samples collected over multiple days with same-day microscopy	Studies published from 2005—2012	64% for multi-day sputum microscopy vs. 63% for same-day microscopy
Steingart et al. [24]	Systematic review of 45 studies comparing conventional Ziehl-Neelsen or Kinyoun sputum microscopy with fluorescent microscopy	Studies published from 1950—2004	32% to 94% for conventional microscopy vs. 52% to 97% with fluorescent microscopy
Subbaraman et al. [2]	Smear sensitivity estimate extrapolated from study of Xpert MTB/Rif implementation across 18 geographically diverse sites in India[25]	2012—2013	59% (95%CI:56% to 61%) for smear microscopy as used throughout the public sector in India
Xpert MTB/Rif			
Steingart et al. [22]	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			
Dorman et al. [26]	10 sites across 8 high burden countries	2016	91% in HIV-negative patients; 90% in HIV-positive patients

Since the sensitivity of these tests may vary by country, region, or health facility—especially for sputum smear microscopy [24]—ideally, relevant local studies should be used. For example, the Indian TB cascade estimated the sensitivity of sputum smear microscopy based on a recent nationally representative study of the rollout of Xpert, which allowed the authors to estimate that sputum smear microscopy has approximately 59% sensitivity in India [2]. In cases where robust local studies are not available, estimates of the sensitivity of these tests from multi-national studies [26] or from systematic reviews and meta-analyses can be used (Table D) [22-24,27].

Using the example of sputum microscopy, once the correct sensitivity estimate is determined, the number of smear-negative TB patients in Step 2 can be estimated as follows:

Step 2 cascade value for smear-negative patients = (Step 2 cascade value for smear-positive patients)(1 – sensitivity) / (sensitivity)*

Similarly, the number of Xpert-negative TB patients in Step 2 can be estimated as follows:

Step 2 cascade value for Xpert-negative patients = (Step 2 cascade value for Xpert-positive patients)(1 – sensitivity) / (sensitivity)*

An alternative (or potentially complementary) approach to inform estimates of Step 2 and Gap 2 for smear-negative or Xpert-negative patients could be to quantify the number of patients evaluated at TB

diagnostic facilities who ultimately receive a medical diagnosis. While there may be uncertainty about the true number of smear- or Xpert-negative patients undergoing evaluation, ideally, if the medical care is of high quality, all patients who are evaluated for suspected TB should receive a TB- or non-TB-related medical diagnosis (e.g., community-acquired pneumonia, upper respiratory infection, chronic obstructive pulmonary disease) and appropriate follow-up plan. If most patients with negative sputum smears or Xpert results do not get evaluated further and do not receive a medical diagnosis, this may suggest poor quality of medical care more generally. There are substantial limitations to this approach, however, given the considerable challenges in diagnosing smear- or Xpert-negative TB in settings without access to mycobacterial culture. In addition, encouraging designation of a medical diagnosis for all patients may provide healthcare workers with an incentive to label patients as having common non-TB pulmonary conditions without completing the careful diagnostic workup required to rule out smear- or Xpert-negative TB.

Estimating Step 2 for extrapulmonary TB patients

Estimating Step 2 for extrapulmonary TB patients is very challenging. Ideally, this value would be informed by robust studies that estimate the proportion of extrapulmonary TB patients who get evaluated at TB diagnostic facilities but who fail to get appropriately diagnosed. Such estimates are very challenging to obtain in most low- and middle-income countries, where extrapulmonary TB is frequently diagnosed clinically without collection of diagnostic samples for mycobacterial stain, culture, polymerase chain reaction-based testing, or histopathology.

In addition, the ease of diagnosing extrapulmonary TB based on clinical grounds varies substantially based on the sites of disease. For example, TB lymphadenitis, especially involving neck lymph nodes, is generally visible and easy to diagnose. TB meningitis is usually serious enough to warrant hospitalization, which may facilitate its diagnosis. In contrast, TB pleuritis, miliary TB, and TB at other body sites generally require a chest X-ray or more advanced imaging to facilitate diagnosis, and these imaging modalities may not be widely accessible in many low- and middle-income countries.

In light of these challenges, we suggest two potential approaches to estimating Step 2 for extrapulmonary TB patients. The first approach would be to conduct robust studies at TB facilities in which patients with suspected extrapulmonary TB are followed prospectively through the entire workup, with the goal of estimating the proportion who do not complete the clinical workup to achieve a diagnosis. These studies could be conducted at a single clinic or hospital (to construct a local cascade) or at a representative sample of health facilities (to construct regional or national cascades).

A second approach, used in the Indian TB care cascade [2], is to assume that extrapulmonary TB is more challenging to diagnose than smear-positive pulmonary TB but easier to diagnose than smear-negative TB, since some common forms of extrapulmonary TB are more clinically evident. Under these assumptions, the proportion of extrapulmonary TB patients who remain undiagnosed despite reaching a TB diagnostic facility and having an appropriate workup initiated by a health provider can be estimated by taking the average of the proportion of undiagnosed smear-positive TB patients and the proportion of undiagnosed smear-negative TB patients. This approach will likely yield a conservative estimate for the proportion of extrapulmonary TB patients who remain undiagnosed in most low- and middle-income countries.

Whenever possible, we recommend using the first approach (conducting prospective cohort studies) to estimate the proportion of extrapulmonary TB patients who may remain undiagnosed, because these prospective cohort studies provide real-world data to help estimate this gap.

Once an estimate is achieve for the proportion of extrapulmonary TB patients who had an appropriate workup initiated by a healthcare provider but who remain undiagnosed, then the Step 2 value for extrapulmonary TB patients can be estimated as follows:

Step 2 cascade value for extrapulmonary TB patients = (Step 3 cascade value for extrapulmonary TB patients) / (1 – proportion of extrapulmonary TB patients who go undiagnosed)

Estimating Step 2 for MDR TB patients

Step 2 for MDR (or rifampin-resistant, RR) TB patients can be arrived at using estimates of the number of MDR TB patients among notified pulmonary TB patients. These data are routinely reported by the WHO based either upon surveillance data from the National TB Programs in these countries or upon modeling estimates. The surveillance data estimates are generally derived from studies that screen all patients with suspected TB using mycobacterial culture at TB diagnostic facilities linked to national TB programs [28]. These surveillance data provide estimates of the proportion of MDR TB among new and retreatment pulmonary TB patients. Extrapolating from these proportions, the WHO is then able to estimate the probable number of MDR TB patients among all pulmonary TB patients who get diagnosed in the national TB programs in these different countries. These values are reported in online WHO datasets under variable names such as *e_rr_in_notified_pulm* (estimated number of rifampin-resistant TB cases among notified pulmonary TB cases).

Note that the estimated number of MDR TB patients among all pulmonary TB patients diagnosed is not the same as the number of MDR TB patients who are actually diagnosed by national TB programs. Because many national TB programs still primarily use sputum microscopy and many clinicians in the private sector diagnose TB empirically, many patients are not diagnosed (or even screened for) MDR TB and are instead misclassified as drug-susceptible TB patients, resulting in the need to use surveillance data to estimate the number of MDR-TB patients who reach TB diagnostic facilities and access a TB test (Step 2).

Estimating Step 2 for children with TB

A recent analysis of the care cascade for children in Uganda and Kenya estimated the number of children with active TB in the population using the TB case detection rate for children in Africa [29]. This approach does not account for variability in the quality of clinical workup and differences in case detection across African countries, and it does not allow for estimation of the proportion of patients who might be missed because of suboptimal adherence to clinical algorithms for empirical diagnosis. We therefore recommend estimating Stage 2 for children using similar methods as those described for adult TB patients, but with substitution of high-quality estimates of the sensitivity of different diagnostic tests in children [30,31], especially high-quality local estimates where available. This would allow for estimation of the number of smear-, Xpert-, or culture-negative children with TB who reach TB diagnostic facilities and accessed a test based on the number of bacteriologically-confirmed child TB patients. Comparing these estimates to the number of patients who are actually diagnosed empirically

would provide information on the number of children with sputum- or Xpert-negative active TB who may be missed during the diagnostic workup (Gap 2).

Step F: Number of individuals with incident or prevalent TB in the population

Step 1 in the TB cascade—estimating the overall number of individuals with incident or prevalent TB in the population—is arguably the most important step in cascade model (Figure 6). Having an estimate for Step 1 allows estimation of the number of TB patients who do not reach health facilities and access a TB test (Gap 1), which may be the largest gap in the TB cascade in some low- and middle-income countries [2].

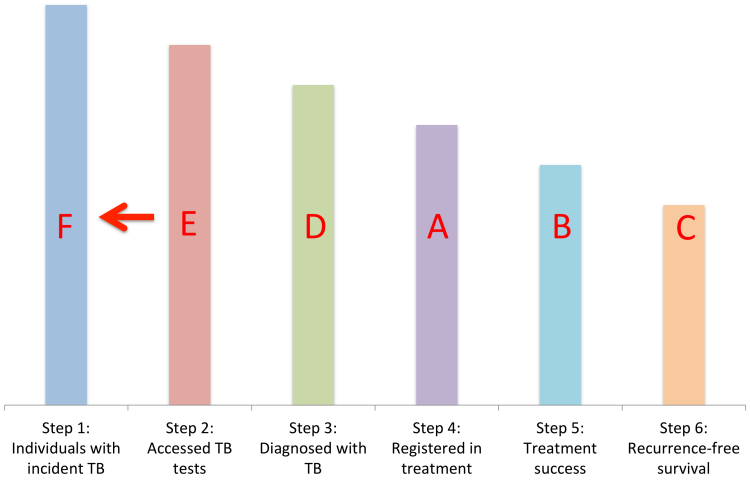

Figure 6: Step F in the routine data approach to constructing a TB care cascade

The ideal estimate of TB burden to use for constructing national- or regional-level cascade is the number of individuals with incident TB in a population. Incidence estimates are extremely challenging to arrive at, however, and these estimates often have considerable uncertainty. As such, we suggest two alternative approaches:

(1) Using estimates of TB burden from population-based point prevalence surveys of active TB as the value for Step 1. A point prevalence estimate for India was used in the initial estimation of the Indian TB cascade of care [2], and nationally-representative point prevalence survey data are available for some countries [32] and even some cities [33].

(2) In the South African TB cascade, the authors use the WHO time series analysis of TB incidence (which is usually estimated using data on changes in notification rates over time) to estimate the TB burden for all TB patients. The authors added the incident cases for a single year plus 50% of the undetected cases from the prior year, under the assumption that about half of undetected cases from the prior year would have died or achieved self-cure [3].

Other approaches for estimating TB incidence or collecting data on TB prevalence are mentioned in the main manuscript.

Approach 2: the cohort-based approach

Use of a cohort-based approach to constructing a TB care cascade has the potential to provide rigorous denominator-denominator linked estimates of patient losses across multiple cascade stages, though it may also be relatively resource-intensive, as it required primary data collection [1]. This approach can be used to evaluate local care cascades at a clinic, hospital, or city level.

This approach could also be used to achieve care cascade estimates at a regional or national level, if rigorous representative sampling (e.g., probability proportionate to size) is used to select clinics or districts throughout a country where prospective or retrospective data could be collected for patient cohorts at each site [34]. While Approach 2 (the cohort-based approach) is more time- and labor-intensive, it is likely to produce more accurate cascade estimates for national-level cascades than Approach 1 (the routine data approach). Serial cohort-based studies would allow use of the care cascade for assessment of changes in a national TB program's outcomes over time. Finally, cohort-based studies may be the only practical approach to estimating TB cascades in settings where pre-existing data on key gaps in care are limited.

We recommend that individuals with TB be tracked prospectively if possible, rather than tracking them retrospectively using health records. The benefits of tracking patients prospectively are as follows:

(1) Medical records (particularly paper records) often contain incomplete patient information. Researchers may be able to obtain more complete information when following patients prospectively, because healthcare providers are more likely to remember specific patient details.

(2) Tracking patients who have similar names through medical records can be very challenging if a study is conducted retrospectively.

(3) Determining the true outcomes for patients listed as having been "lost to follow-up" can be very challenging or impossible if patients are tracked retrospectively months or years after these outcomes have occurred. For example, pretreatment loss to follow-up patients (i.e., patients diagnosed with TB who do not start TB treatment) may have actually started on TB treatment at another facility. Patients on treatment who are reported as being lost to follow-up may have actually transferred care to another TB facility. If researchers are trying to determine post-treatment TB recurrence rates, contacting patients months or years after TB treatment has been completed may be impossible, since they may have moved to other locations or changed their contact information. If patients are followed prospectively, researchers are more likely to be able to track patients and contact them directly to determine their true outcomes.

Steps A, B, C, and D: tracking a single cohort of patients from TB diagnosis to post-treatment recurrence-free survival

Step A in the cohort-based approach is to identify all patients diagnosed with TB (cascade Step 3) at the selected TB diagnostic facilities (Figure 7). Ideally, this initial cohort should include patients diagnosed with all forms of TB—bacteriologically-diagnosed pulmonary TB, empirically-diagnosed pulmonary TB (i.e., those diagnosed with TB without a positive bacteriological test), extrapulmonary TB, and MDR TB. As noted above, these diagnosed patients should ideally be identified in a prospective fashion to facilitate tracking and determination of their outcomes throughout the subsequent stages of the cascade.

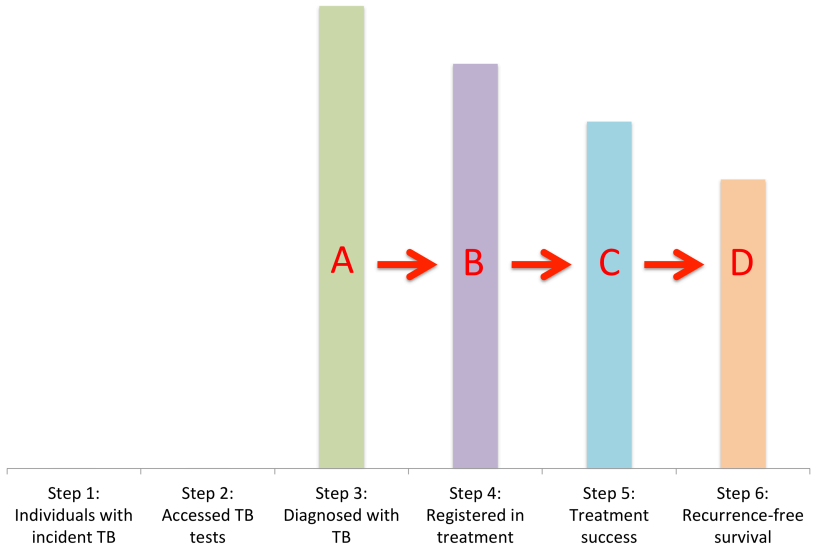

Figure 7: Steps A, B, C, and D in the cohort-based approach to constructing a TB care cascade

For Step B, these patients diagnosed with TB can then be tracked to determine who got successfully registered for and started on TB treatment (cascade Step 4). One challenge that arises in Step B is defining the length of time that can elapse between a patient's diagnosis and treatment registration before she is classified as a pretreatment loss to follow-up case. For example, in a meta-analysis of 14 studies of pretreatment loss to follow-up conducted in India, the different studies variably defined pretreatment loss to follow-up as consisting of patients who did not get registered for treatment between 2 weeks to as long as 3 months after the date of diagnosis [2]. A retrospective study in South Africa defined pretreatment loss to follow-up as consisting of patients who did not get registered for treatment within 6 months of diagnosis [13].

This decision regarding the "elapse time" required to define pretreatment loss to follow-up will depend on the study methodology used. For example, for studies in which patients are tracked prospectively to determine outcomes, research teams are often ethically obliged to intervene to retrieve patients who have not successfully registered to get them started on TB treatment, so a shorter elapse time (e.g., two to four weeks) may be reasonable. For retrospective studies that happen months to years after patients are diagnosed, longer elapse times (e.g., three to six months) may provide a more accurate estimate of how many patients do not get registered in TB treatment even with a relatively long duration of follow-up. In rare situations where rigorous longitudinal patient databases are available, it may be possible to estimate this step using rigorous survival methodologies, which can estimate time delays and

pretreatment loss to follow-up rates, as was done for a HIV care cascade study conducted in KwaZulu-Natal, South Africa [34].

For Step C, the patients in the original cohort who successfully get registered in TB treatment can then be followed to determine the proportion who achieve treatment success (cascade Step 5). This step may be relatively easy to estimate in most settings, because most national TB programs carefully document treatment outcomes for individual TB patients. In addition, with careful retrospective audits of individual treatment cards, survival methodologies can be also be used to present these findings, which may allow visualization of the relative time points during the treatment course when most patients experience unfavorable outcomes (i.e., loss to follow-up, treatment failure, or death). In settings where a large proportion of TB patients are treated in the private sector, TB drug sales data or the use of vouchers for patient medication refills at private pharmacies in public-private interface initiatives may facilitate estimation of this cascade stage [35].

For Step D, the patients in the original cohort who successfully complete TB therapy can then be followed after treatment for 12 months to determine the proportion who experience disease relapse or death. As discussed above, we recommend following the rigorous prospective cohort methodology used by Velayutham et al. to determine post-treatment relapse rates [12]. Routine follow-up home visits of patients who have completed therapy every few months, to screen for symptoms and collect sputum samples for microscopy and mycobacterial culture on symptomatic patients, will minimized post-treatment loss to follow-up of patients, screen systematically for TB recurrence, and also carefully captured information on mortality [11].

Step E: Number of individuals with TB who reached health facilities and accessed a TB diagnostic test

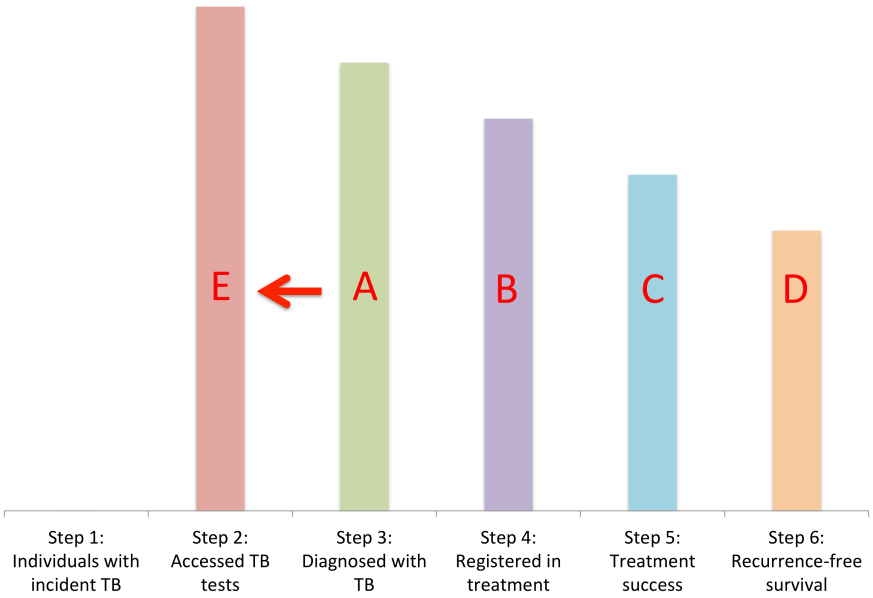

Figure 8: Step E in the cohort-based approach to constructing a TB care cascade

To estimate Step E for the cohort based approach (Figure 8), similar methodologies can be used as are described above for estimating Step E for the routine data approach. As described in detail above, different estimation approaches would be required for each form of TB.

Step F: Number of individuals with incident or prevalent TB in the population

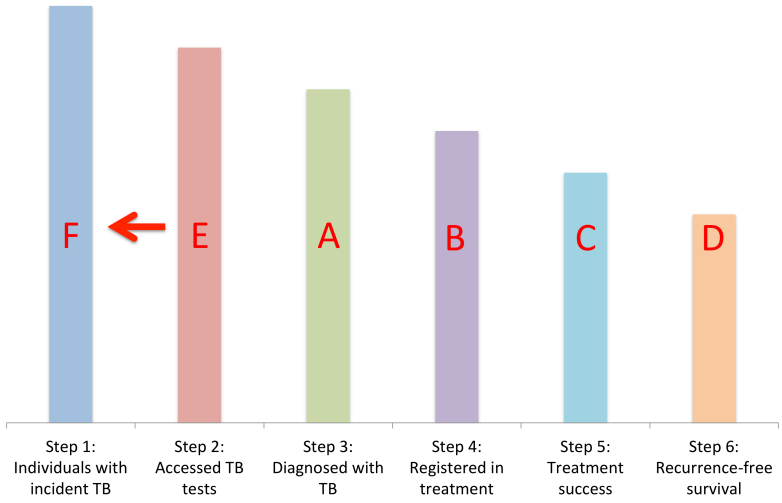

Figure 9: Step F in the cohort-based approach to constructing a TB care cascade

To estimate Step F for the cohort based approach (Figure 9), similar methodologies can be used as are described above for estimating Step F for the routine data approach.

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