


BMJ Open Tuberculosis care cascade in Zambia - identifying the gaps in order to improve outcomes: a population-based analysis

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ABSTRACT

Objective Tuberculosis (TB) remains a leading cause of morbidity and mortality in Zambia, especially for people living with HIV (PLHIV). We undertook a care cascade analysis to quantify gaps in care and align programme improvement measures with areas of need.

Design Retrospective, population-based analysis.

Setting We derived national-level estimates for each step of the TB care cascade in Zambia. Estimates were informed by WHO incidence estimates, nationally aggregated laboratory and notification registers, and individual-level programme data from four provinces.

Participants Participants included all individuals with active TB disease in Zambia in 2018. We characterised the overall TB cascade and disaggregated by drug susceptibility results and HIV status.

Results In 2018, the total burden of TB in Zambia was estimated to be 72 495 (range, 40 495–111 495) cases. Of these, 43 387 (59.8%) accessed TB testing, 40 176 (55.4%) were diagnosed with TB, 36 431 (50.3%) were started on treatment and 32 700 (45.1%) completed treatment. Among all persons with TB lost at any step along the care cascade (n=39 795), 29 108 (73.1%) were lost prior to accessing diagnostic services, 3211 (8.1%) prior to diagnosis, 3745 (9.4%) prior to initiating treatment and 3731 (9.4%) prior to treatment completion. PLHIV were less likely than HIV-negative individuals to successfully complete the care cascade (42.8% vs 50.2%, $p<0.001$). Among those with rifampicin-resistant TB, there was substantial attrition at each step of the cascade and only 22.8% were estimated to have successfully completed treatment.

Conclusions Losses throughout the care cascade resulted in a large proportion of individuals with TB not completing treatment. Ongoing health systems strengthening and patient-centred engagement strategies are needed at every step of the care cascade; however, scale-up of active case finding strategies is particularly critical to ensure individuals with TB in the population reach initial stages of care. Additionally, a renewed focus on PLHIV and individuals with drug-resistant TB is urgently needed to improve TB-related outcomes in Zambia.

BACKGROUND

The WHO End TB Strategy aims to reduce tuberculosis (TB) incidence by 90% and

Strengths and limitations of this study

- The national tuberculosis (TB) care cascade for Zambia in 2018 was characterised in order to identify gaps in care.
- The TB care cascade was constructed for all patients with TB as well as according to drug susceptibility results and HIV status.
- The analysis was informed by a published set of methodologies and used several data sources to derive estimates.
- Enhanced TB surveillance programmes, including the use of unique TB patient identifiers, would allow for real-time monitoring and improved estimates to inform programmatic strengthening.

TB-related deaths by 95% between 2015 and 2035.¹ While many high-burden countries in sub-Saharan Africa, including Zambia, have demonstrated large reductions in new TB cases and associated mortality, there remains significant need for improved TB care delivery.² TB remains a leading cause of morbidity and mortality in Zambia, especially among people living with HIV (PLHIV).^{2,3} In 2019, there were approximately 59 000 new individuals with active TB disease in Zambia (incidence rate of 333 per 100 000 per year), which resulted in 15 400 TB-related deaths, of which 62% were among PLHIV.² Despite substantial declines in TB incidence over the last decade, Zambia still has the seventh highest TB incidence in sub-Saharan Africa and remains one of 30 WHO high TB burden priority countries.²

The HIV ‘cascade of care’ is a public health model that outlines the key engagement steps required for PLHIV to ultimately achieve an undetectable viral load. This model has been widely applied by HIV programmes globally to inform and strengthen HIV care and delivery, and ultimately significantly increase the number of PLHIV who know their HIV

status, are started on antiretroviral therapy (ART) and have suppressed viral loads.⁴ Similarly, a national TB care cascade can provide key insights to identify and quantify gaps in the diagnosis and care of patients with TB that could then help guide programmatic and research priorities by aligning limited resources with the areas of greatest need.^{5 6} However, to date, only three high-burden TB countries—South Africa, India and Madagascar—have undertaken and published national-level TB care cascade analyses.^{7–9}

We sought to construct a national TB cascade of care for Zambia to evaluate care delivery for individuals with active TB disease through enumeration of gaps in the overall care cascade in 2018 as well as disaggregated by rifampicin susceptibility results and HIV status. Estimates were derived using multiple data sources, and the overall approach was informed by a recently published methodology for constructing TB care cascades.⁶

METHODS

Study design

We undertook a retrospective, population-based study to characterise the TB care cascade in Zambia in 2018. All Zambians estimated to be living with TB in 2018 were included in the analysis, regardless of age, HIV status, diagnosis status (ie, diagnosed or undiagnosed TB), TB drug susceptibility status or TB type (ie, new or retreatment).

Setting

Zambia has an estimated population of 18 400 000 people.¹⁰ It has a high prevalence of HIV (11.5% among adults aged 15–49 years old), and it is estimated that at least 1.2 million persons are living with HIV.¹¹ TB is a major public health problem in Zambia;³ during the last national TB prevalence survey conducted in 2013 and 2014, the prevalence of microbiologically confirmed TB was estimated to be 638 per 100 000 persons and was five times higher among HIV-positive individuals compared with HIV-negative individuals.¹²

Testing and treatment for TB are almost universally provided within Zambia's public health system. While exact estimates are not available, likely <1% of all individuals with TB are detected and managed within Zambia's private sector and the large majority are reported to Zambia's National TB Program (NTP)—this assumption is informed by a national data quality assessment conducted in 2019.¹³ Within the public health sector, the direct costs of all TB diagnostics and treatment are provided free of charge. In 2018, Xpert MTB/RIF was the recommended first-line diagnostic for all individuals undergoing evaluation for possible TB (pulmonary or extrapulmonary) in Zambia, as well as initial drug susceptibility testing (DST);¹⁴ however, it was not universally available at all facilities, in which case routine TB investigations included acid fast bacilli (AFB) fluorescence or Ziehl-Neelsen microscopy and chest radiography, where available. Among those with confirmed rifampicin-resistant (RR) or

multidrug-resistant (MDR) TB, it was recommended that either liquid culture or a molecular line probe assay should be used as follow-on tests for further DST.¹⁴ First-line TB treatment was provided to all patients without evidence of rifampicin resistance and consisted of isoniazid, rifampicin, ethambutol and pyrazinamide for 6–9 months in conformity with WHO recommendations.¹⁵ In 2018, Zambia began scaling up shorter treatment regimens that comprised new and repurposed TB drugs for 9–12 months for eligible patients with RR-TB and MDR-TB—this accounted for the majority of patients;^{16 17} however, some patients still received longer MDR-TB treatment regimens that comprised several TB drugs, including an injectable agent, for at least 20 months.

In Zambia, patients diagnosed with TB are notified in a paper-based register and initiated on TB therapy at the corresponding TB treatment facility, which is also responsible for documentation of the treatment outcome of the patient. Data on diagnostic outcomes (laboratory register), notifications and treatment outcomes (notification register) are aggregated from each facility through the district office to the provincial level and then to the national level on a monthly basis.

TB cascade data sources

Several data sources were used to inform estimates within each of the five steps of the care cascade (table 1, online supplemental appendix). To inform estimates of the overall burden of TB in Zambia in 2018 (step 1), WHO estimates of TB incidence from 2018 and 2017 were used.^{18–21} The proportion of total individuals with TB estimated to be RR was derived using estimates from the most recent national survey of TB drug resistance in Zambia;²² this source was chosen in order to ground estimates of RR-TB in empirical data. However, higher-end estimates from the latest Zambian national survey of TB drug resistance in 2008 were used to more closely align with WHO incidence estimates for RR-TB in 2018. Diagnostic outcomes (steps 2 and 3) were informed by a nationally aggregated database of TB diagnostics from 2018, which includes the number and type of investigations (Xpert or smear microscopy) and the number of patients with TB detected according to type of TB investigation and HIV status. All treatment outcomes (steps 4 and 5) were informed by a nationally aggregated TB treatment register from 2018.

Individual-level programmatic data from four Zambian provinces (Eastern, Lusaka, Southern, Western) regarding all patients investigated for TB and those started on treatment between 1 January and 31 December 2017 (n=43 896 and n=11 814, respectively) were used to determine (1) the proportion of patients who had both positive Xpert and smear microscopy results, as well as (2) the proportion of patients who were Xpert-negative or smear-negative but received empirical TB therapy. This helped to further refine estimates for steps 2 and 3 by accounting for and removing duplicate patients (online supplemental appendix). Patient-level data were

Table 1 Approach to and data sources for estimating each step of the tuberculosis care cascade in Zambia in 2018

	Step 1: TB burden	Step 2: accessed tests	Step 3: diagnosed	Step 4: notified and treated	Step 5: successfully treated
All TB cases	WHO estimates of TB incidence in 2018 plus 50% of the number of undetected cases from 2017. ^{19 21}	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based on TB test sensitivity by HIV status (informed by published reports ²⁵⁻²⁷), corrected for the number of patients with negative TB tests who were empirically treated (informed by unpublished individual-level data from 4 Zambian provinces in 2017).	Back-calculated from the number of cases notified (step 4) and the proportion of patients LTFU prior to initiation of TB therapy. Pretreatment LTFU estimated based on the difference between the number of microbiologically confirmed DS-PTB cases detected (informed by aggregated facility-level TB laboratory data from 2018 (unpublished)) and the number of microbiologically confirmed DS-PTB cases notified (informed by aggregated facility-level TB notification data from 2018 (unpublished)).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Add DS-TB and RR-TB cases successfully treated.
Rifampicin-resistant TB cases	Overall TB burden multiplied by estimated proportion of cases with rifampicin resistance (informed by most recent Zambia national TB drug resistance survey in 2008 ²²).	Back-calculated from RR-TB cases diagnosed (step 3) on the basis of cases bacteriologically diagnosed, by test type and test sensitivity (informed by published reports ^{25 28 29}).	Exact value from aggregated facility-level TB laboratory data from 2018 (unpublished).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (unpublished).
Drug-susceptible TB cases, all cases	Overall TB burden minus RR-TB cases.	Add the number of missed cases to the total number of DS-TB cases diagnosed (step 3). Missed cases estimated based on TB test sensitivity by HIV status (informed by published reports ²⁵⁻²⁷), corrected for the number of patients with negative TB tests who were empirically treated (informed by unpublished individual-level data from 4 Zambian provinces in 2017).	Back-calculated from the number of DS-TB cases notified (step 4) and the proportion of LTFU prior to initiation of TB therapy. Pretreatment LTFU estimated based on the difference between the number of microbiologically confirmed DS-PTB cases detected (informed by aggregated facility-level TB laboratory data from 2018 (unpublished)) and the number of microbiologically confirmed DS-PTB cases notified (informed by aggregated facility-level TB notification data from 2018 (unpublished)).	Exact value from aggregated facility-level TB notification data from 2018 (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (unpublished).

Continued

Table 1 Continued

	Step 1: TB burden	Step 2: accessed tests	Step 3: diagnosed	Step 4: notified and treated	Step 5: successfully treated
Drug-susceptible TB cases, HIV-positive individuals	WHO 2019 analysis of DS-TB incidence in 2017 plus 50% of the number of undetected cases from 2018. ^{19 21}	Add the number of missed cases of DS-TB among HIV-positive individuals to the total number of DS-TB cases diagnosed among HIV-positive individuals (step 3). Missed cases estimated based on TB test sensitivity in HIV-positive individuals, corrected for the number of patients with negative TB tests who were empirically treated. ^{25 26}	Back-calculated from the number of cases notified (step 4) and the proportion of patients LTFU prior to initiation of TB therapy (pretreatment LTFU assumed to be the same independent of HIV status).	Exact value from aggregated facility-level TB notification data from 2018 adjusted for the proportion of patients without an HIV test. (unpublished).	Exact value from aggregated facility-level TB treatment outcomes data from 2018 (number successfully treated) adjusted for proportion of patients without an HIV test (unpublished).
Drug-susceptible TB cases, HIV-negative individuals	Total number of DS-TB cases minus number of DS-TB cases among HIV-positive individuals.	Total number of DS-TB cases who accessed TB tests minus the number of DS-TB cases who accessed TB tests among HIV-positive individuals.	Total number of DS-TB cases diagnosed minus the number of DS-TB cases diagnosed among HIV-positive individuals.	Total number of DS-TB cases notified minus the number of DS-TB cases among HIV-positive individuals notified.	Total number of DS-TB cases successfully treated minus the number of DS-TB cases among HIV-positive individuals successfully treated.

DS-PTB, drug-susceptible pulmonary tuberculosis; DS-TB, drug-susceptible tuberculosis; LTFU, lost-to-follow-up; RR-TB, rifampicin-resistant tuberculosis; TB, tuberculosis.

only available from 4 out of 10 provinces; however, they account for nearly 60% of Zambia's national TB notifications, and the range of socioeconomic characteristics of individuals as well as their access to healthcare services are representative of the other six provinces.^{23 24} Unfortunately, robust data from 2018 to inform these estimates were unavailable; thus, we used 2017 data because they were well characterised and temporally close to the year for which we sought to characterise the TB care cascade.

Diagnostic sensitivity estimates of Xpert²⁵ and smear microscopy^{26 27} for detection of TB stratified according to HIV status, as well as Xpert,²⁵ molecular line probe assays²⁸ and liquid culture²⁹ for rifampicin resistance, were informed by previously published systematic reviews and meta-analyses.

TB cascade estimation methods

We calculated national-level estimates for each step of the TB care cascade in Zambia in 2018 (table 1, online supplemental appendix). This included the following: step 1: the total burden of active TB disease (individuals with prevalent TB in 2018); step 2: the total number of individuals with TB who accessed TB testing; step 3: the total number who were diagnosed with TB; step 4: the total number who were notified and started on TB treatment; and step 5: the total number who successfully completed

TB treatment. Each step of the cascade and the overall TB care cascade were calculated among all patients and disaggregated according to rifampicin resistance results (RR-TB and drug-susceptible TB (DS-TB)) and, among those with DS-TB, by HIV status. There were insufficient data available to characterise the RR-TB care cascade disaggregated according to HIV status. RR-TB was defined as the detection of rifampicin resistance on any clinical specimen using Xpert, molecular line probe assay or liquid culture; this definition therefore encompassed all patients with MDR-TB and extensively drug-resistant TB. DS-TB was defined as any TB case without known rifampicin resistance; thus, there is a possibility that patients with other forms of drug resistance, including isoniazid monoresistance, may have been included in this definition. However, unless rifampicin resistance is detected, TB DST is not routinely performed in Zambia—this reflects the clinical reality of many high-burden TB settings and conforms with WHO recommendations.

The approach to all estimates followed the recommendations outlined in a published set of methods for constructing national-level TB care cascades.⁶ An overview of the approach used to calculate each step of the TB care cascade is summarised in table 1 and is described in brief below. However, a highly detailed summary of all

assumptions, calculations, estimates and data sources is summarised in the online supplemental appendix.

We first started with step 4 (the total number of patients who were notified and started on TB treatment, including new, relapse, treatment after failure, treatment after loss-to-follow-up patients and other previously treated individuals³⁰) and step 5 (the total number who successfully completed TB treatment), which were both directly informed by exact values from aggregated facility-level notification data. Step 3 (the total number who were diagnosed with TB) was then back-calculated from the number of individuals notified (step 4) and the proportion of patients who were estimated to have been lost-to-follow-up (LTFU) prior to initiation of TB therapy (pretreatment LTFU), which was informed by aggregated facility-level laboratory data. Step 2 (the total number of individuals with TB who accessed TB testing) was calculated by adding the number of individuals with TB who would not have been microbiologically diagnosed due to the incomplete sensitivity of TB diagnostic tests (based on published reports), corrected for the number of test-negative patients with TB who were empirically diagnosed, to the number of total patients with TB diagnosed (step 3). The overall approach for steps 2–5 was similar for both DS-TB and RR-TB (table 1, online supplemental appendix). The overall TB burden (all forms) was estimated using the WHO TB incidence estimate for 2018, plus 50% of the number of all individuals with TB who remained undiagnosed in 2017; a 50% estimate has previously been used and assumed that the remaining 50% of undiagnosed individuals with TB in 2017 either self-cured or died.^{8,31} To determine the total number of individuals with rifampicin-resistant TB (step 1), we multiplied the overall TB burden by the proportion of all patients who had rifampicin resistance detected during the Zambian national drug resistance survey.²² The total number of individuals with DS-TB was calculated using the total TB burden minus the number of RR-TB cases.

All 'gaps' between each step were calculated by taking the difference in the total number of individuals with TB and the uncertainty estimate (either 95% CI or range) between the succeeding and preceding steps. All TB care cascades were depicted graphically using bar charts representing the absolute number of cases and the associated uncertainty measurement (if applicable). For each step of each cascade, proportions relative to the total TB burden (step 1) as well as relative to the prior step were calculated. It should be noted that several steps of the cascade used exact numbers from aggregated facility-level programmatic data (steps 3, 4 and 5). For the purposes of these analyses, data were assumed to be accurate and complete; however, such data may be incompletely recorded and a small proportion may be entered incorrectly—estimates of uncertainty around exact values from programmatic data were unavailable. Furthermore, unique patient identifiers are not available within Zambia's NTP and thus this analysis does not present a cohort of individuals who were tracked through each step of the TB care cascade.

While we assumed for the purposes of this analysis that the same patients were being characterised at each step of the cascade, one cannot exclude the possibility that different individuals are being captured at different steps of the care cascade.

Evaluating diagnostic and treatment outcomes

To understand any progress that may have underpinned the 2018 TB care cascade, we also evaluated TB diagnostic and treatment completion trends from 2015 to 2018. Using facility-level aggregated laboratory data, we plotted (1) the total number of sputum Xpert tests undertaken each year against the total number of pulmonary TB cases diagnosed each year, including the proportion that was microbiologically confirmed, as well as (2) the total number of Xpert tests undertaken (on any specimen) each year against the total number of RR-TB cases diagnosed and notified each year. We also plotted the proportion (and corresponding 95% CI) of patients with TB each year who started TB treatment who successfully completed it, disaggregated according to TB type: (1) new/relapse pulmonary TB—overall, (2) HIV-positive new/relapse pulmonary TB, (3) HIV-negative new/relapse pulmonary TB, (4) retreatment TB not including individuals who experienced relapse, and (5) extrapulmonary TB.

RESULTS

Overall national TB care cascade for 2018

In 2018, the overall burden of TB in Zambia was estimated to comprise 72 495 individuals with TB (range, 40 495–111 495; table 2, figure 1A). Of the total burden of individuals with TB, 43 387 (range, 42 390–44 710; 59.8%) were estimated to have sought care for their TB illness and undergone microbiological TB testing. Among these individuals, 40 176 (range, 40 128–40 212; proportion of total TB burden 55.4%) were diagnosed with TB, 36 431 (exact value; proportion of total TB burden 50.3%) were notified and initiated on TB therapy, and 32 700 (exact value; proportion of total TB burden 45.1%) completed TB therapy. Therefore, 39 795 (range, 8191–79 191; 54.9%) of the estimated individuals with TB in 2018 did not complete the care cascade (table 3). Individuals who did not seek care for their TB illness or who sought care but did not undergo microbiological TB testing accounted for 29 108 (range, 0–66 777; 73.1%) individuals with TB lost along the cascade in 2018 (table 3). Suboptimal empirical diagnosis of individuals with TB who had negative microbiological test results (due to incomplete diagnostic sensitivity of these tests) contributed to an additional 3211 (95% CI 2262 to 4506; 8.1%) missed TB cases; losses to follow-up prior to TB treatment initiation accounted for 3745 (95% CI 3697 to 3781; 9.4%) patients lost, and unfavourable outcomes (loss-to-follow-up, death and treatment failure) prior to TB treatment completion accounted for 3731 (exact value; 9.4%) patients lost.



Table 2 Overview of the tuberculosis (TB) care cascade in Zambia in 2018 according to type

	Step 1: TB burden			Step 2: accessed tests			Step 3: diagnosed			Step 4: notified and treated			Step 5: successfully treated		
	Cases, range*	% of total burden†	% relative to prior step‡	Cases, range*	% of total burden†	% relative to prior step‡	Cases, range*	% of total burden†	% relative to prior step‡	Cases, range*	% of total burden†	% relative to prior step‡	Cases, range*	% of total burden†	% relative to prior step‡
Overall TB Cascade	72 495 (40 495–111 495)	100	59.8	43 387 (95% CI 42 390 to 44 710)	59.8	59.8	40 176 (95% CI 40 128 to 40 212)	55.4	92.6	36 431	50.3	90.7	32 700	45.1	89.8
Rifampin-resistant TB	1740 (486–4014)	100	52.3	910 (95% CI 776 to 1093)	52.3	52.3	627	36.0	68.9	509	29.3	81.2	396	22.8	77.8
Drug-susceptible TB, all	70 755 (40 009–107 481)	100	60.0	42 477 (95% CI 41 614 to 43 625)	60.0	60.0	39 549 (95% CI 39 501 to 39 585)	55.9	93.1	35 922	50.8	90.8	32 304	45.7	89.9
HIV-positive, drug-susceptible TB	43 411 (23 911–65 911)	100	57.0	24 746 (95% CI 24 290 to 25 349)	57.0	57.0	23 133 (95% CI 23 106 to 23 154)	53.3	93.5	21 012 (95% CI 20 962 to 21 064)	48.4	90.8	18 579 (95% CI 18 535 to 18 625)	42.8	88.4
HIV-negative, drug-susceptible TB	27 344 (16 098–41 570)	100	64.8	17 731 (95% CI 17 324 to 18 276)	64.8	64.8	16 415 (95% CI 16 395 to 16 431)	60.0	92.6	14 910 (95% CI 14 858 to 14 960)	54.5	90.8	13 725 (95% CI 13 679 to 13 769)	50.2	92.1

*Values in parentheses represent ranges, unless explicitly specified as 95% CI.

†Value represents the proportion of TB cases relative to the total TB burden (step 1).

‡Value represents the proportion of TB cases relative to the prior step in the cascade.

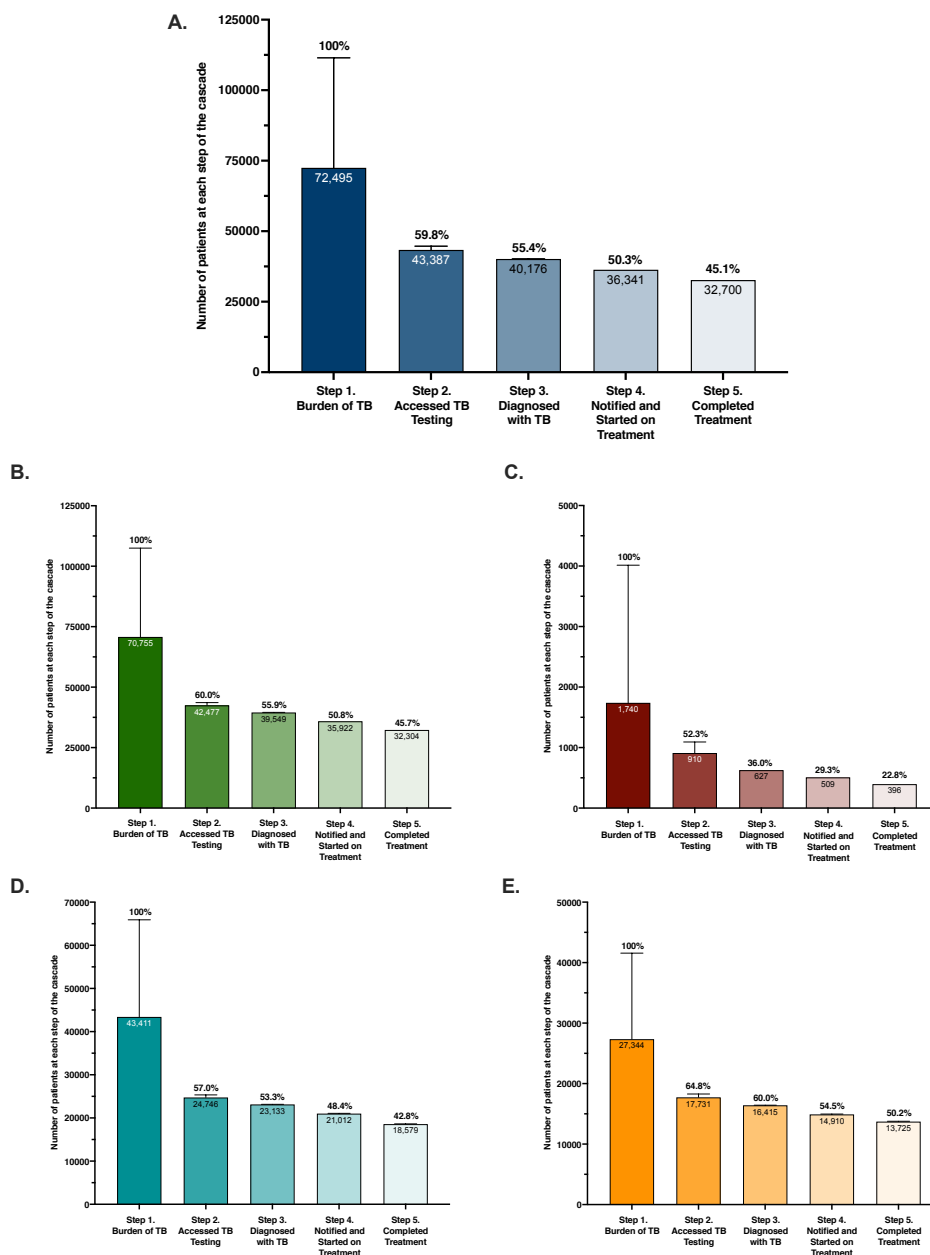


Figure 1 The tuberculosis (TB) care cascade in Zambia in 2018 among (A) all tuberculosis cases; (B) drug-susceptible cases; (C) rifampicin-resistant cases; (D) drug-susceptible cases among HIV-positive individuals; and (E) drug-susceptible cases among HIV-negative individuals.

TB care cascade by drug susceptibility results

We estimated the burden of individuals with DS-TB in 2018 to be 70 755 (range, 40 009–107 481), approximately 97.6% of the total TB burden. The DS-TB cascade was largely similar to the overall TB cascade, with 32 304 (exact value; 45.7%) of all individuals being diagnosed with TB, initiating on and completing TB treatment (table 2, figure 1B). The total number of RR-TB cases was estimated to be 1740 (range, 486–4014), or 2.4% of the total TB burden. Compared with individuals with DS-TB, individuals with RR-TB were substantially less likely to access microbiological TB testing (52.3% vs 60.0%, $p < 0.001$), have their TB diagnosed (68.9% vs 93.1%,

$p < 0.001$), be notified and initiated on TB treatment (81.2% vs 90.8%, $p < 0.001$) and to complete TB therapy (77.8% vs 89.9%, $p < 0.001$) (figure 1C). Thus, only 396 (exact value; 22.1%) individuals with RR-TB completed the TB care cascade. The majority of those with RR-TB along the pathways were due to individuals who did not seek care or who did not have access to TB and/or DST, accounting for 830 cases (range, 0–2961; 61.7%) (table 3); however, 283 (95% CI 149 to 466; 21.1%) of lost RR-TB cases were among those who accessed TB testing and had RR-TB missed, 118 (exact value; 8.8%) were among those who had RR-TB detected but were not notified and started on appropriate TB therapy, and 113 (exact value;

Table 3 Gap analysis of the tuberculosis (TB) care cascade in Zambia in 2018 according to type

	Overall TB cases lost throughout the care cascade		Gap 1: patient did not seek care at TB facility and/or have TB tests sent		Gap 2: TB tests sent but TB missed		Gap 3: TB diagnosed but patient not started on TB treatment and/or not notified		Gap 4: TB treatment started but not completed	
	Cases, range*	Proportion (%)†	Cases, range*	Proportion (%)†	Cases, range*	Proportion (%)†	Cases, range*	Proportion (%)†	Cases, range*	Proportion (%)†
Overall TB cascade	39 795 (8191–79 191)	100	29 108 (0–66 777)	73.1	3211 (95% CI 2262 to 4506)	8.1	3745 (95% CI 3697 to 3781)	9.4	3731	9.4
Rifampin-resistant TB	1344 (486–4014)	100	830 (0–2921)	61.7	283‡ (95% CI 149 to 466)	21.1	118	8.8	113	8.4
Drug-susceptible TB, all	38 451 (40 009–107 481)	100	28 278 (0–63 856)	73.5	2928 (95% CI 2112 to 4040)	7.6	3627 (95% CI 3579 to 3663)	9.4	3618	9.4
HIV-positive, drug-susceptible TB	24 832 (5376–47 286)	100	18 597 (0–40 495)	75.2	1613 (95% CI 1185 to 2194)	6.5	2121 (95% CI 2094 to 2142)	8.5	2379 (95% CI 2337 to 2529)	9.8
HIV-negative, drug-susceptible TB	13 619 (2419–27 801)	100	10 939 (98–24 620)	70.6	1315 (95% CI 927 to 1846)	9.7	1505 (95% CI 1486 to 1520)	11.1	1239 (95% CI 1089 to 1281)	8.7

*Values in parentheses represent ranges, unless explicitly specified as 95% CI.

†Proportions are relative to the total number of TB cases estimated to have been lost throughout the care cascade.

‡For rifampicin-resistant TB, either the TB diagnosis or the rifampicin resistance was missed.

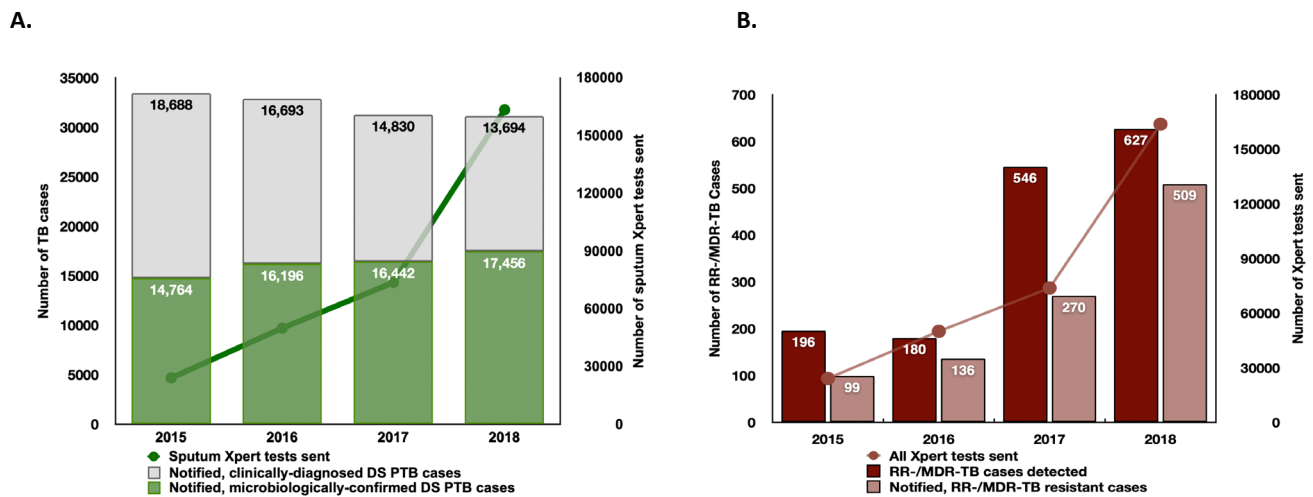


Figure 2 Diagnoses and notifications of (A) all forms of drug-susceptible pulmonary TB in Zambia between 2015 and 2018 and (B) drug-resistant TB in Zambia between 2015 and 2018. DS, drug susceptible MDR-TB, multidrug-resistant tuberculosis; PTB, pulmonary tuberculosis; RR-TB, rifampicin-resistant tuberculosis; TB, tuberculosis.

8.4%) were among those who did not complete RR-TB therapy (table 3).

DS-TB care cascade by HIV status

Of 70 755 individuals with DS-TB in 2018, 43 411 (range, 23 911–65 911; 61.4%) were estimated to be among PLHIV. Compared with patients with DS-TB who were HIV-negative, HIV-positive patients with DS-TB were less likely to access microbiological TB testing (57.0 vs 64.8%, $p < 0.001$) and were less likely to complete TB treatment (88.4% vs 92.1%, $p < 0.001$). This resulted in a lower overall proportion of HIV-positive patients compared with HIV-negative patients completing the TB care cascade (42.8% vs 50.2%, $p < 0.001$; table 2, figure 1D,E). For both HIV-positive and HIV-negative patients with DS-TB, the largest loss in the care cascade was due to patients not accessing microbiological TB testing, resulting in 18 597 (range, 0–40 495; 75.2%) and 10 939 (range, 98–24 620; 70.6%) missed patients, respectively (table 3).

TB diagnosis trends from 2015 to 2018

Between 2015 and 2018, Xpert MTB/RIF was increasingly used as the first-line TB diagnostic tool in Zambia, where 24 140 Xpert tests were sent for suspected pulmonary TB in 2015, which increased to 163 470 sent in 2018 (figure 2A). During this same period, the number of sputum AFB smear microscopy investigations decreased from 95 300 in 2015 to 25 323 in 2018. While there was a small decrease in the absolute number of pulmonary TB cases diagnosed and notified in 2018 compared with 2015

(31 272 vs 33 452), the proportion of microbiologically confirmed TB cases that were notified during that period substantially increased (56.0% (95% CI 55.5 to 56.6) vs 44.1% (95% CI 43.6 to 44.7); figure 2A). The scale-up of Xpert testing between 2015 and 2018 was also associated with a more than threefold increase in the annual number of RR cases detected (627 vs 196) and more than fivefold increase in the annual number of RR-TB cases that were notified and started on appropriate TB treatment (509 vs 99; figure 2B). During this period, there was a corresponding reduction in the proportion of RR-TB cases LTFU prior to the initiation of TB treatment, from 49.5% in 2015 to 18.8% in 2018 ($p < 0.001$).

TB treatment completion trends from 2015 to 2018

Finally, we examined trends in the proportion of patients with DS-TB who completed TB treatment once they were notified and initiated on therapy (figure 3). Among new/relapse pulmonary TB cases, treatment completion rates steadily increased between 2015 and 2018 (86.2 (95% CI 85.8 to 86.6) vs 90.3% (95% CI 90.0 to 90.7), $p < 0.001$). There was also a trend towards improved TB treatment completion rates from 2015 to 2018 among retreatment pulmonary TB cases (84.4% (95% CI 83.3 to 85.5) vs 87.2% (95% CI 84.5 to 89.6), $p = 0.06$); however, completion rates declined from 2017 to 2018 (95.0% (95% CI 93.4 to 96.3) vs 87.2% (95% CI 84.5 to 89.6), $p < 0.001$). From 2015 to 2018, the proportion of patients with extrapulmonary TB completing TB treatment also improved (80.3% (95% CI

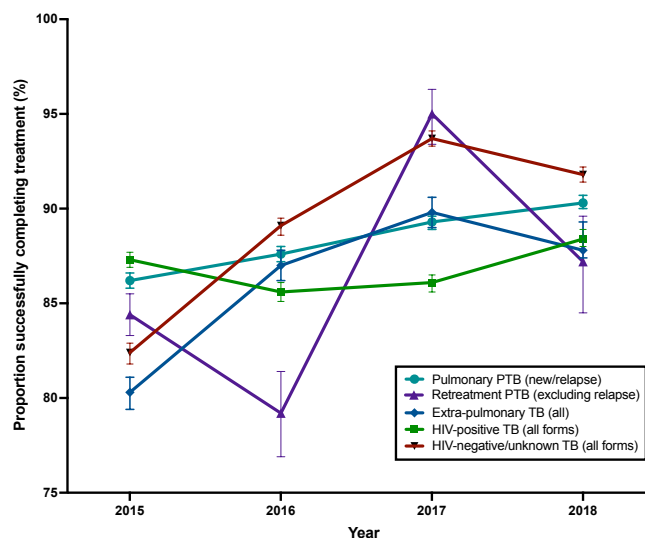


Figure 3 Overview of drug-susceptible tuberculosis (TB) treatment outcomes in Zambia between 2015 and 2018, disaggregated according to tuberculosis type. Shapes represent the proportion of patients completing tuberculosis treatment. PTB, pulmonary tuberculosis

79.4 to 81.1) vs 87.8% (95% CI 87.4 to 89.3), $p < 0.001$). The proportion of HIV-positive patients completing TB therapy did not meaningfully change from 2015 to 2018 (87.3% (95% CI 86.9 to 87.7) vs 88.4% (95% CI 88.0 to 88.9), $p = 0.001$). Improvements in treatment completion rates from 2015 to 2018 were seen among patients who had a negative or unknown HIV status (82.4% (95% CI 81.8 to 82.9) vs 91.8% (95% CI 91.4 to 92.2), $p < 0.001$), although there was a small decline between 2017 and 2018 (93.7% (95% CI 93.3 to 94.1) vs 91.8% (95% CI 91.4 to 92.2), $p < 0.001$; [figure 3](#)). In 2018, a lower proportion of HIV-positive TB patients completed therapy compared with HIV-negative patients (difference 3.4% (95% CI 2.8 to 4.0), $p < 0.001$). Differences in the proportion of patients completing TB therapy according to HIV status were driven by a higher absolute number and proportion of cases who died or were LTFU during treatment among HIV-positive individuals compared with HIV-negative individuals (online supplemental table 1).

DISCUSSION

In this study we found that less than half of all TB cases in Zambia in 2018 were diagnosed with TB, initiated on TB treatment and completed therapy. We identified important losses at each step of the TB care cascade; however, we estimate that more than 40% of all individuals with TB in Zambia are not accessing microbiological TB testing—this accounted for nearly three-quarters of the estimated number of cases lost throughout the cascade. These results highlight important research and programmatic priorities for improving TB care and TB-related outcomes in Zambia.

This represents the fourth national TB care cascade that has been characterised from a high-burden TB

country and builds on similar analyses from South Africa, India and Madagascar.^{7–9} Our overall TB care cascade results are similar to those from these countries, which each found that only about 50% of all patients with TB were progressing through all steps of the care cascade and completing TB treatment. In India the largest losses in the care cascade were among those who did not access TB testing (28% of all cases).⁷ In Madagascar the largest losses in the cascade were among those who were not diagnosed with TB despite seeking care and accessing a TB diagnostic facility (26% of all cases),⁹ while in South Africa steady losses were seen prior to TB diagnosis (12% of all cases), prior to starting TB treatment (13% of all cases) and prior to successful completion of TB therapy (17% of all cases).⁸ In Zambia, 40% were estimated to have not accessed TB testing, while 4%–5% of all TB cases were lost at each subsequent step of the care cascade. These differences highlight specific programmatic needs at different steps within the TB care cascade for each country and provides insight into the unique challenges that each faces.

Our results are consistent with several TB prevalence surveys suggesting that a large proportion of individuals with TB face barriers to healthcare-seeking, barriers to accessing microbiological TB testing or both.^{32 33} Unfortunately, we are not able to discern whether the estimated 40% gap in patients not accessing TB microbiological investigations is predominantly driven by (1) individuals who fundamentally lacked access to primary health and TB facilities, (2) individuals who either delayed or never presented to TB testing facilities for evaluation of their illness, or (3) individuals who sought care at health facilities but their illness was not suspected to be TB and thus they never had TB testing undertaken.³⁴ After onset of symptoms, individuals with undiagnosed TB may have long and complex journeys to TB care as they often face many barriers to care-seeking and accessing TB services (eg, lack of knowledge, lack of social support, lack of time/finances, TB/HIV-related stigma, cultural and gender norms).^{33 35 36} In the last Zambian national TB prevalence survey conducted in 2013 and 2014, only 60% of previously undiagnosed individuals with TB were symptomatic, of whom 50% had sought care for their illness at a health facility.¹² Furthermore, once patients do access healthcare services, their TB illness may be missed—this has been shown to be a common problem in recent standardised patient studies conducted in Kenya,³⁷ India³⁸ and China.³⁹

Collectively, this suggests that both community-based and facility-based active TB case finding strategies, as well as training of healthcare providers to improve recognition of and testing for TB, are likely to be important activities to increase detection of individuals with TB in Zambia. Community-based active TB case finding may help overcome individuals' barriers to health-seeking and accessing TB services, possibly resulting in a greater absolute number of patients with TB diagnosed and patients who are detected earlier.^{40–42} However, effective

and sustainable community-based active TB case finding strategies are not well described and represent an urgent TB research need.^{33 43} There is strong evidence demonstrating that facility-based, active TB case finding strategies are efficient and may yield a large number of cases that would otherwise have been missed, especially in high-burden settings.^{44–47} A recent study evaluating a multicomponent active TB case finding strategy in a high-burden primary healthcare facility in Lusaka, Zambia found that total TB notifications increased by 35% during the intervention period; of the total TB cases, 91.5% were from facility-based case finding interventions, while 8.5% were from community-based case finding interventions.⁴⁷ One important component of this strategy was the implementation of patient-friendly TB fast-track points at health facilities that improved access by allowing individuals with TB symptoms to skip the regular queue and undergo rapid screening and testing for TB. Further research is needed to understand what potential strategies to improve TB care engagement and diagnosis are most preferred by and acceptable to community members in high-burden settings.

We estimate that nearly 10% of individuals diagnosed with TB were LTFU prior to the initiation of TB treatment. Pretreatment LTFU is common in many high-burden settings, as demonstrated by a systematic review that found that 4%–38% (weighted proportion 18%) of patients with TB in sub-Saharan Africa were lost at this step in the cascade.⁴⁸ This may be accounted for by patients who died prior to initiation of therapy—a common finding among such patients—and patients who cannot be traced after diagnosis either due to missing/incorrect contact information or because they have moved away. A recent qualitative study among patients with TB and healthcare workers (HCW) in India provided further understanding of the factors that may contribute to LTFU prior to initiation of TB therapy.⁴⁹ The authors identified challenges and constraints related to organisational and administrative barriers resulting in patient disengagement from TB services over frustration, as well as negative HCW attitudes and behaviours resulting in patient distrust and feeling that their autonomy had been violated. There is an important need to design, evaluate and implement strategies that may address patient-level and health systems factors and reduce pretreatment LTFU.⁴⁸ It should be noted that pretreatment loss-to-follow-up estimates may be overestimated because they fail to account for individuals who were in fact started on TB therapy but were not officially registered and therefore never notified to the NTP (under-notification). Zambia's NTP has recently completed a study to estimate the proportion of patients who are diagnosed but not notified, as well as the proportion of those who are started on treatment but never reported. This study will yield improved estimates of pretreatment loss-to-follow-up, which will allow for improved evaluations of programmatic changes that aim to improve TB diagnosis and linkage to TB treatment and care.

We found that important progress has been made in Zambia with regard to microbiological TB diagnosis and TB treatment completion from 2015 to 2018. During this period there was a massive effort to scale up the availability of Xpert MTB/RIF as the first-line TB diagnostic for all forms of TB. This was associated with a 12% increase in the proportion of patients with TB who were microbiologically confirmed (2692 additional annual DS-TB patients identified). Importantly, because Xpert also provides rapid simultaneous detection of rifampicin resistance, its scale-up was also associated with a threefold increase in patients with RR-TB detected and a fivefold increase in the number of patients with RR-TB who were notified and started on TB treatment. Zambia is currently preparing to scale up Xpert Ultra cartridges, which when paired with continued efforts to decentralise Xpert testing should allow for further gains in the detection of HIV-associated TB, extrapulmonary TB and RR-TB.⁵⁰ There was also evidence of improved TB treatment completion rates for nearly all forms of TB between 2015 and 2018. While it is important to recognise progress that has been made, smaller but critically important gaps in the TB care cascade remain due to missed diagnoses and lack of treatment completion. Further efforts to expand access to microbiological TB testing and interventions to bolster TB treatment adherence that are grounded in person-centred care approaches, such as decentralisation of services coupled with improved education and communication as well as material and psychological support, are needed.^{51 52}

PLHIV accounted for 60% of DS-TB cases in Zambia and were more likely to be lost at several steps of the cascade compared with HIV-negative individuals. This finding emphasises the need to strengthen HIV-TB collaborative activities.^{33 53} Due to non-specific clinical presentations and radiographic findings, one of the most important challenges to improving HIV-associated TB outcomes remains TB diagnosis.⁵⁴ Non-specific symptoms may delay care-seeking among PLHIV, and without systematic TB screening among PLHIV presenting to and in care the diagnosis of many TB cases may be further delayed or missed. Systematic screening for TB at each clinical presentation⁵⁵ must be coupled with access to improved microbiological diagnostic tools such as Xpert Ultra⁵⁶ and urine lipoarabinomannan (LAM)^{56 57} testing to facilitate rapid TB detection and TB treatment initiation in order to minimise pretreatment LTFU and improve clinical outcomes. Compared with HIV-negative patients, HIV-positive patients were less likely to complete TB therapy, and TB treatment completion rates among PLHIV did not significantly change over a 4-year period from 2015 to 2018. Previously, a study among PLHIV in Zambia found that a large number of individuals LTFU from HIV services had died and that programmatic mortality rates were substantially under-reported;²³ this suggests that mortality among PLHIV LTFU from TB treatment services is high and that TB-related mortality among PLHIV in Zambia is likely underestimated. The implementation of tailored



interventions to improve adherence to TB treatment^{51 58} as well as⁵⁹ ART among this highly vulnerable population therapy is needed.

Notably, we found that less than a quarter of RR-TB cases in 2018 were detected, started on appropriate treatment and completed appropriate therapy. This was despite improved access to rapid drug susceptibility via the scale-up of Xpert MTB/RIF testing from 2015 to 2018 and shorter and simplified drug-resistant TB regimens being introduced in 2018.¹⁶ The high rate of attrition of patients with RR-TB throughout the care cascade argues for the need for specific investments in systems strengthening to improve drug-resistant TB diagnosis and treatment in Zambia, mirroring this dire need in most high TB burden countries.^{19 33 60 61} One important contributing factor to the large number of patients with RR-TB not accessing DST is the high proportion of patients who are being diagnosed clinically and/or on the basis of radiological findings only—this accounted for approximately 44% of pulmonary TB cases in Zambia in 2018. Notably, the scale-up of Xpert testing between 2015 and 2018 was associated with more than 30% reduction in the proportion of RR-TB/MDR-TB cases that were LTFU after diagnosis and prior to initiation of treatment. This is likely due to the substantially faster detection of rifampicin resistance compared with conventional culture-based methods. Collectively, this demonstrates the importance of continued efforts to expand access to Xpert testing in Zambia in order to facilitate confirmation of TB diagnoses coupled with rapid detection of rifampicin resistance. While the implementation of existing diagnostic tools as well as improved DR-TB treatment regimens must be optimised, there remains a continued need for the development of rapid low-cost DST that can be scaled up to provide decentralised access to first-line and second-line DST aligned with current treatment recommendations,⁶² as well as continued progress towards shorter, less toxic and more effective DR-TB treatment regimens.⁶³

This study used a validated analysis method⁶ incorporating a number of data sources to derive nationally representative estimates of the TB care cascade in Zambia; however, there were some limitations. As with other published TB cascades analyses, there is uncertainty around the estimates, especially the overall number of TB cases. The total burden of TB was calculated using indirect estimates from modelling that were based on case notification data and a prior national TB prevalence survey. We derived a conservative estimate of the total TB burden that accounted for missed cases from the prior year⁸ and that therefore may be a more appropriate estimate than measurements of TB incidence, which are rarely feasible to directly estimate.⁶⁴ Due to a lack of a unique national patient identifier, we were unable to link specific individuals with their outcomes as they progressed through the TB care cascade, and thus unique individuals in one step of the cascade may differ from those in the following step; where possible, we attempted to account for duplicate diagnostic and treatment data, which were uncommon.

Implementation of a unique TB patient identifier and an improved TB data surveillance programme with enhanced data integration would greatly improve future estimates and allow for real-time individual-level, facility-level and subnational-level data to inform programme strengthening.

Given the potential importance of gender to TB epidemiology^{32 65} and potential differential health-seeking behaviours and access to TB services,^{36 66 67} we sought to characterise the TB care cascade among men and women. For example, the prevalence of TB among men in Zambia's first national TB prevalence survey in 2013/2014 was almost twice as high as that among women (833 vs 487 cases per 100 000 persons),¹² and men with presumptive TB were less likely to have sought care for their symptoms than women (31.4% vs 38.4%).⁶⁸ Unfortunately, sex-disaggregated data sources were not available that would have allowed for each step of the cascade to be estimated. It is important that TB programmes collect sex-disaggregated diagnostic and treatment data to help ensure equity in access and treatment benefits. Additionally, because incidence, diagnosis, notification and treatment numbers are from 2018, we feel our analysis accurately represents the national TB care cascade in 2018; however, pretreatment LTFU estimates were informed by patient-level data from 2017 and the proportion of cases with rifampicin resistance was informed by higher-end estimates from the most recent national drug resistance survey conducted in 2008.²² An updated drug resistance survey is currently underway and will provide new estimates that will better guide programmatic priorities. Finally, to our knowledge, there are no locally or regionally representative estimates of TB relapse rates after documented TB treatment completion. This is an important quality metric of individuals' adherence to therapy as well as TB treatment programmes and should be assessed in future research studies.⁶

In conclusion, in 2018 only 45% of individuals with TB in Zambia completed the TB care cascade, and most losses were among patients who never accessed TB testing. Additionally, only 22% of all patients with RR-TB successfully completed appropriate TB treatment, and HIV-positive patients had substantially worse TB outcomes compared with HIV-negative patients. Our results suggest that continued systems strengthening coupled with patient-centred engagement strategies is required throughout the TB cascade of care; however, implementation of active TB case finding strategies, coupled with a renewed focus on those with rifampicin resistance and PLHIV, is urgently needed to improve TB-related outcomes and TB control in Zambia.

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Patient consent for publication Not required.

Ethics approval Because this was a retrospective, population-level analysis without the use of any patient identifiers, the University of Zambia Biomedical Research Ethics Committee determined that this study met the criteria for exempt status (REF 001-02-21).

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