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Mortality in South African Children and Adolescents Routinely Treated for Tuberculosis

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Abstract

BACKGROUND: In South Africa, tuberculosis (TB) is a leading cause of death among those <20 years of age. We describe changes in TB mortality among children and adolescents in South Africa over a 13-year period, identify risk factors for mortality, and estimate excess TB-related mortality.

METHODS: Retrospective analysis of all patients <20 years of age routinely recorded in the national electronic drug-susceptible TB treatment register (2004–2016). We developed a

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multivariable Cox regression model for predictors of mortality and used estimates of mortality among the general population to calculate standardized mortality ratios (SMRs).

RESULTS: Between 2004 and 2016, 729 463 children and adolescents were recorded on TB treatment; 84.0% had treatment outcomes and 2.5% (18 539) died during TB treatment. The case fatality ratio decreased from 3.3% in 2007 to 1.9% in 2016. In the multivariable Cox regression model, ages 0 to 4, 10 to 14, and 15 to 19 years (compared with ages 5 to 9 years) were associated with increased risk of mortality, as was HIV infection, previous TB treatment, and extrapulmonary involvement. The SMR of 15 to 19-year-old female patients was more than double that of male patients the same age (55.3 vs 26.2). Among 10 to 14-year-olds and those who were HIV-positive, SMRs increased over time.

CONCLUSIONS: Mortality in South African children and adolescents treated for TB is declining but remains considerable, with 2% dying during 2016. Adolescents (10 to 19 years) and those people living with HIV have the highest risk of mortality and the greatest SMRs. Interventions to reduce mortality during TB treatment, specifically targeting those at highest risk, are urgently needed.

The World Health Organization (WHO) estimated that 1.1 million children (<15 years) developed tuberculosis (TB) in 2018, with 31% in Africa.[1] Estimates for adolescent (10–19 years[2]) TB are not routinely reported by the WHO, but modeling suggests that 535 000 15- to 19-year-olds developed TB globally in 2012.[3] In South Africa, children (<15 years) accounted for 7% (~16 000) of notified patients with TB in 2018; no published data are available for 15- to 19-year-olds.[1]

In a review of all-cause mortality for 2013, developing countries accounted for 98% of all deaths in individuals <20 years old, with HIV and TB accounting for 11% of deaths.[4] Death due to TB may occur before the diagnosis of TB, before treatment initiation, during TB treatment, or after completion of TB treatment. However, TB programs routinely only report death during treatment. The WHO reports TB deaths as a proportion of all estimated incident patients with TB, combining deaths before and during TB treatment,[5] and estimated that children (<15 years) accounted for 14% (208 740) of all TB deaths in 2018.[1] Mortality is currently not sufficiently disaggregated by age to estimate the mortality in 15- to 19-year-olds in addition to children (<15 years). In South Africa, although general mortality rates vary by age, sex, and HIV status, TB was the leading cause of mortality among individuals 15 to 24 years old and a leading cause of mortality in children 1 to 4 years old in 2016.[6]

To achieve the global targets of a 95% reduction in TB deaths by 2035 compared to 2015[7] and prevent TB deaths, targeted strategies need to be developed and implemented. An improved understanding of the profile of patients who die and the risk factors for death during TB treatment will support this process. Given the lack of reporting of agespecific TB mortality data, we aimed to describe mortality during routine TB treatment in South Africa among all children and adolescents <20 years old, disaggregated into 4 age categories. Using the large national electronic recording system of routine individual patients with TB, we describe TB case fatality ratios (CFRs) over time; calculate standardized mortality ratios (SMRs), comparing TB mortality and population-based mortality estimates; and identify risk factors for death during TB treatment.

METHODS

Study Design

This was a retrospective cohort study of all individuals <20 years old routinely recorded in the South African drug-susceptible TB treatment register reporting cohort between 2004 and 2016. We used age categories of 0 to 4, 5 to 9, 10 to 14, and 15 to 19 years.

Electronic Tuberculosis Register

The South Africa National Department of Health's national TB program implemented the Electronic Tuberculosis Register (http://etrnet.info/) for routine reporting of all drug-susceptible TB treatment in 2004. Drug-resistant TB is recorded in a separate Web-based register[8] and is not included in this analysis. ETR. Net is an electronic system, with paper-based records as a source, that allows facility, district, provincial, and national reporting on case-finding, sputum conversion, and treatment outcome cohorts.[9,10] In the 2017 evaluation of the South African TB care cascade, it was estimated that 71.1% of those estimated to have TB and 86.5% of those diagnosed with TB in South Africa were notified and treated (recorded within ETR.Net).[11]

Definitions

Patients with drug-susceptible TB were defined as patients who had no documented resistance to anti-TB drugs. From 2011, testing with Xpert MTB/RIF (Xpert; Cepheid, Sunnyvale, CA) for all patients with presumptive TB was introduced in South Africa with rapid detection of *Mycobacterium tuberculosis* and mutations conferring rifampin resistance.[12] Retreatment refers to patients who had previously received <4 weeks of anti-TB treatment, regardless of the time since the previous treatment episode. Newly treated patients with TB were classified as having had no previously reported TB treatment or as having received <4 weeks of TB treatment at any stage. The site of TB disease was categorized as pulmonary TB when there was any pulmonary involvement or as extrapulmonary tuberculosis (EPTB) when patients had disease exclusively affecting any organ other than the lung parenchyma.[13] *International Classification of Diseases, 10th Revision* (ICD-10) codes referring to central nervous system TB, including TB meningitis, or miliary TB, were combined as disseminated disease; all other ICD-10 codes were defined as not disseminated disease. HIV status was determined by using several proxies, including documentation of co-trimoxazole preventive therapy or antiretroviral therapy (ART), HIV test results, and CD4 test results. HIV status was classified as HIV-negative; HIV-positive, on ART; HIV-positive, not on ART; and HIV status unknown. The timing of ART could not be determined.

TB Treatment Outcomes

In South Africa, treatment outcomes for patients with TB are assigned by treating clinicians and captured in ETR.Net, which includes preprogrammed algorithms to verify outcomes consistent with national and WHO definitions.[13,14] When a treatment outcome is not allocated or inconsistent with the definitions, a patient is reported in ETR.Net as not evaluated. For this analysis, "not evaluated" was combined with "lost to follow-up," and 2

outcomes were used: Outcome 1 included the outcomes cured or treatment completed, died, lost to follow-up, failed, or transferred out;[14] and outcome 2 defined vitality status (dead or alive; restricted to patients in whom the final vitality status was definitively recorded). Person-time was calculated as the difference between the start date of TB treatment and the treatment outcome date recorded in the register, representing person-years on TB treatment.

Mortality

Death included death due to any cause during the TB treatment episode. The CFR was calculated as the number of deaths as a proportion of the number of patients with TB for the specified group and period; 95% confidence intervals (CIs) were calculated around point estimates. To compute the CFR for each age band by sex, data for 2004–2016 were used as a single cohort. For SMRs, population estimates were used from the Thembisa model, an established publicly available mathematical model of South African HIV epidemiology and general demographic statistics.[15] Thembisa uses age- and sex-specific mortality rates on the basis of an analysis of South African cause-of-death statistics and the South African National Burden of Disease study and projects mortality rates from 2016 onward.[16] For HIV, estimates of mortality were available by sex but not age. The SMR was calculated as the ratio between the observed TB deaths and the expected deaths on the basis of mortality estimates of the general population. The expected deaths were the product of the mortality rates, determined from the Thembisa estimates, and the person-time from our cohort for each demographic category. Expected deaths were based on mortality due to any cause, including TB.

Statistical Analysis

Descriptive statistics of demographic and clinical variables were completed for the overall cohort, for patients with TB with a known vitality status, and for patients with TB who were documented to have died. HIV status was evaluated for completeness; analysis for predictors of mortality was restricted to the period of 2013–2016, the years during which <80% of patients with TB had a known HIV status in each age category. Missing data were excluded from analysis, except for HIV status, for which unknown HIV status was included as a predictor for mortality. A Cox proportional hazards regression model for hazard ratios (HRs) predicting death was developed. Univariate analyses were conducted, and collinearity in the final model was avoided. We added predictors incrementally, observing the change in significance of the likelihood ratio test of each model, to produce a final adjusted model. Survival analysis was completed by using Kaplan-Meier curves. SAS software (version 9.4; SAS Institute, Inc, Cary, NC) was used for the data analysis.

Ethical Considerations

Approval was received from the Stellenbosch University Health Research Ethics Committee (N16/07/088), and permission was obtained from the South African National Department of Health for the use of the national ETR.Net data set.

RESULTS

Between January 1, 2004, and December 31, 2016, the ETR.Net reporting cohort included 729 463 patients with TB <20 years of age who were treated for drug-susceptible TB. The vital status was recorded in 612 655 (84.0%) patients with TB, and of these, 18 539 (3.0%) died during TB treatment. Unknown treatment outcomes were more common among patients who were previously treated, those with EPTB, and those with disseminated TB, but they decreased over time, with 89.7% of patients having a known treatment outcome in 2016 (Supplemental Table 3).

There were 339 719 (46.6%) patients <5 years of age; 37 628 (5.2%) were previously treated for TB; 65 418 (9.0%) had only EPTB; and 12 245 (1.9%) had disseminated TB (Table 1). HIV testing changed over time, from 0.4% of children and adolescents with TB having a known HIV status in 2004 to 94.3% in 2016.

The overall CFR was 2.5%, which increased from 2004 to a peak in 2007, gradually declining thereafter (Fig 1). CFRs differed by age category and were higher among 10- to 19-year-olds, with no decline over time (Fig 1). When applied to the whole cohort, the CFR was highest in the first year of life and then declined steeply over the next 2 years, with no difference by sex. CFRs increased in later childhood and peaked for boys at 12 years of age (CFR = 4.3%) before declining through adolescence. Girls had a lower but earlier peak (CFR = 3.2% at 11 years) and a plateau during early adolescence, followed by a steep increase from 16 years of age to a CFR of 4.2% at the age of 19 years (Fig 2).

Risk Factors for Mortality on TB Treatment, Restricted to 2013–2016

Ages 0 to 4, 10 to 14, and 15 to 19 years (compared with ages 5–9 years); previous TB treatment; only having EPTB; having disseminated disease; and HIV infection (with and without current ART use) were all associated with an increased hazard of death (Table 2). The cumulative mortality at 2 and 6 months of anti-TB treatment, respectively, was 4.8% and 7.5% if the patient was HIV-positive and not on ART, 2.4% and 4.9% if the patient was HIV-positive and on ART, and 0.5% and 0.9% if the patient was HIV-negative (Fig 3).

SMRs

The SMRs for 0- to 4- and 5- to 9-year-olds did not differ by sex and remained between 3 and 5 for 0- to 4-year-olds and between 30 and 45 for 5- to 9-year-olds over time. For 10- to 14-year-olds, the SMR increased differentially by sex, from <60 in both boys and girls in 2004 to 77 in boys and 92 in girls in 2016. For 15- to 19-year-olds, the SMRs in male patients increased from 20 in 2004 to a peak of 35 in 2010 and decreased to 26 in 2016. In female patients, the SMR increased from 60 in 2004 to a peak of 76 in 2008 and decreased to 55 in 2016 (Fig 4, Supplemental Table 4). The SMRs for HIV-negative individuals remained constant, across sex, between 2013 and 2016. For HIV-positive individuals, SMRs increased from 9 to 12 in female patients and from 4 to 6.5 in male patients (Fig 5, Supplemental Table 5).

DISCUSSION

Between 2004 and 2016, 2.5% (18 539) of all children and adolescents in the routine national TB treatment register died, but with a decrease in mortality over time. CFRs and SMRs changed over time and differed by age, sex, HIV status, and ART use.

Most previous research on TB mortality in children and adolescents has been restricted to age <15 or ≥15 years old. Therefore, there are limited data across the age continuum. In a retrospective study from Kenya, 4.4% of children (<15 years) died during drug-susceptible TB treatment,[17] whereas in a systematic review, the pooled TB case fatality estimate for children (<15 years) in low–HIV prevalence settings was 0.9%.[18] We have shown an initial peak in the CFR in the first year of life, followed by a second peak in early adolescence. By age band, 10-to 14-year-olds had the highest CFR (3.2%); even when analyzed by continuous age and disaggregated by sex, the highest CFR was reported in 12-year-olds. In a systematic review, CFRs in 0- to 4 year-olds (pooled estimate 2.0%; 95% CI: 0.5–7.4) were consistently higher than those in 5- to 14-year-olds (pooled estimate 0.8%; 95% CI: 0.3–2.1).[18] The use of broad age bands for children between 5 and 14 years of age may have obscured a peak in early adolescent TB CFR. A limited case-series from South Africa has been used to describe adult-type pulmonary TB in 10- to 14-year-olds,[19] and challenges with adherence to TB medication and ART have been described in this group.[20,21] The higher CFR noted in this group may reflect a combination of poor adherence related to health system engagement and the type and severity of disease in this age group. We showed that both younger age and relative older age were associated with increased mortality, consistent with studies that have confirmed the increased risk of TB and death in infants,[22] children <2[18,23] or 5 years of age,[17,24,25] and 15- to 19-year- olds.[26] It is important that routine TB programs collect sufficient detail for routine monitoring and evaluation in more nuanced age categories.

Although children 0 to 4 years of age were at a higher risk of death, the SMRs revealed that in 2016, excess TB mortality among 0- to 4-year-olds was fourfold, whereas excess TB mortality among 5- to 9-year-olds, 10- to 14-year-olds, and 15 to 19-year-olds was 25 to 45 times, 77 to 90 times, and 26 to 55 times higher, respectively. In South Africa, TB is the leading cause of natural death among men, but it ranks fifth among women. When disaggregated by age, TB is not among the 10 leading causes of death for infants, but it is ranked fourth in children aged 1 to 14 years and first in those aged 15 to 64 years.[6] Under-5 mortality in South Africa has mostly been attributed to neonatal causes, associated with prematurity, diarrhea, and pneumonia, whereas the devastating effect of HIV had been largely reversed by 2011,[27] attributed to the successful implementation of the prevention of mother-to-child transmission (PMTCT) program and to the scale-up of ART access. We note that excess mortality in 0- to 4-year-olds is much lower than that in other pediatric groups because there are additional reasons for the youngest children to die. In South Africa, only 1.3% of all deaths are reported among 5- to 14-year-olds, and 10- to 14-year-olds had the lowest absolute numbers of death between 2010 and 2015.[6] This lower expected mortality, combined with the high CFR, in 10- to 14-year-olds may explain the highest SMRs being recorded in 10- to 14-year-olds, who have limited other reasons for death but a high TB CFR. Earlier work has revealed how age-standardized death rates for HIV and AIDS and

TB increased rapidly from 1997 to 2006 and then declined to 2012, whereas deaths due to other causes increased.[28] The difference in the SMR in 10- to 19-year-old male and female patients is notable. In 2016, 15- to 19-year-old female patients had an SMR more than double that of male patients because of the higher CFR and the lower expected mortality in female patients. During early adolescence and puberty, there may be more TB in girls compared with boys,[29] and differential access to health services by sex[30,31] makes girls more likely to access the health care system. This results in a higher chance of diagnosis and subsequent recording of death while on treatment, compared with boys who may die before diagnosis. In addition, the significant burden of TB among pregnant women[32] and the threefold increased risk of maternal mortality with TB in HIV-positive pregnant women[33] further contribute to the greater CFR. Among adolescents and young adults in South Africa, almost 50% of deaths are due to unnatural causes, and 84.6% of these unnatural deaths occur in male adolescents and young adults.[6] Specifically, the greater expected mortality among young boys in South Africa due to disproportionate exposure to interpersonal violence has been shown among 10- to 17-year-olds, with homicide as a leading cause of death, mainly affecting young boys.[34] Female patients between 15 and 19 years of age attending reproductive health services could be identified for TB education and opportunities for TB and HIV prevention.

The risk of mortality associated with severe forms of TB is well documented. The authors of a systematic review reported the risk of death for children treated for TB meningitis to be 19.3% (95% CI: 14.0–26.1).[35] We documented a CFR of 7.4% among children and adolescents with neurologic and miliary TB (which is lower than published estimates) for several potential reasons. First, we combined all neurologic TB and miliary TB as a single category of disseminated TB. Second, we did not restrict this analysis to children but included older adolescents. Third, we only included children recorded in the routine TB treatment register. In South Africa, it is estimated that at least 14.4% of all patients diagnosed with TB are not notified and treated,[11] and in a hospital-based study of 0- to 12-year-olds, in-hospital death and a diagnosis of TB meningitis were associated with lack of registration.[36] Future work combining reported TB deaths, vital registration data, and autopsy data will likely provide better estimates of TB mortality, including disseminated forms.

Consistent with earlier work,[18,37,38] we have shown that CFRs in HIV-positive children were higher than those in HIV-negative children, and the difference was reduced but persisted despite ART. This is similar to work from Kenya in which ART reduced the adjusted hazard ratio for death from 4.8 among HIV-positive children not on ART to 3.7 among children (≤15 years) on ART with TB.[17] Cumulative mortality in HIV-positive individuals halved at 2 and 6 months when we compared those on ART with those not on ART. The SMR among HIV-negative individuals has remained constant, whereas the SMR among HIV-positive individuals has increased. The SMR remains higher in HIV-positive female patients compared with male patients, likely reflecting the earlier and greater access to ART among female patients and the lower overall HIV mortality compared with TB mortality among female patients in ART programs.[39]

During the study period, South Africa scaled up PMTCT and HIV testing and expanded access to universal ART.[40,41] The reductions in vertical HIV transmission through PMTCT may contribute to the reduction in TB CFRs in the youngest age bands over time. The HIV profile of older children and adolescents includes vertical transmission among those born before the scale-up of PMTCT, children infected despite PMTCT, and horizontal transmission. Well-functioning PMTCT programs will reduce vertical transmission of HIV, but it remains critical that all HIV-positive children and adolescents have access to immediate ART. Regular screening for TB and TB preventive therapy will reduce TB incidence and may improve TB outcomes through early diagnosis.

Our study was associated with several strengths and limitations. We used a large individual-level national data set spanning 13 years to identify patient factors associated with mortality and the timing of death, but we were limited to those who started TB treatment. We quantified unknown vitality status and, for the purpose of estimating CFRs, assumed all those lost to follow-up to be alive. Because we were restricted to those patients registered and on treatment, we probably underreport on pediatric TB because children and adolescents with TB may be undiagnosed, untreated, or unreported. Additional work is required to estimate the losses of children and adolescents with TB across the care cascade. Although mortality during treatment occurs as a discrete event and is probably accurately noted, our CFRs are likely an underestimate of mortality, with additional unreported mortality expected among those undiagnosed or lost to follow-up. In addition, we do not have data on mortality in those who did not initiate TB treatment or who were not in the TB treatment register. Future work to reduce loss to follow-up and ascertain definitive outcomes among those lost to follow-up is required. Because of the reliance on treatment register data, we were not able to evaluate pretreatment mortality and the role of additional risk factors for mortality, including nutritional status, BCG vaccination status, pregnancy status, the degree of HIV-related immune suppression, HIV viral load, and the precise timing and duration of ART. More work is needed to explore the relationship between pregnancy and death during TB treatment, especially considering the high TB CFR in female individuals of reproductive age.

We report on TB mortality over a 13-year period, which overlaps with significant progress made in the management of HIV in South Africa and reveals that overall mortality during treatment has declined in children and adolescents. This reduction in the hazard of death is consistent with earlier work from South Africa.[23,42] We highlighted the high risk of TB mortality in the youngest age group, during early adolescence, and among female patients in later adolescence. The modulating effect of HIV and ART on TB mortality continues to be highly relevant. Early detection and treatment of HIV with TB remains essential, and tailored approaches to treatment support are required in infants and during adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ART
antiretroviral therapy

CFR
case fatality ratio

CI
confidence interval

EPTB
extrapulmonary tuberculosis

ETR.Net
Electronic Tuberculosis Register

HR
hazard ratio

ICD-10
International Classification of Diseases, 10th Revision

PMTCT
prevention of mother-to-child transmission

SMR
standardized mortality ratio

TB
tuberculosis

WHO
World Health Organization

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WHAT'S KNOWN ON THIS SUBJECT:

Modeling studies have highlighted the significant burden of tuberculosis (TB) mortality in children and adolescents, but adolescent reporting has been limited. The effect of HIV on TB mortality and the reversal with antiretroviral therapy has been well described.

WHAT THIS STUDY ADDS:

In this study, we provide child and adolescent TB mortality estimates in the context of the world's largest antiretroviral program. We provide the first quantification of standardized mortality ratios for children and adolescents with TB.

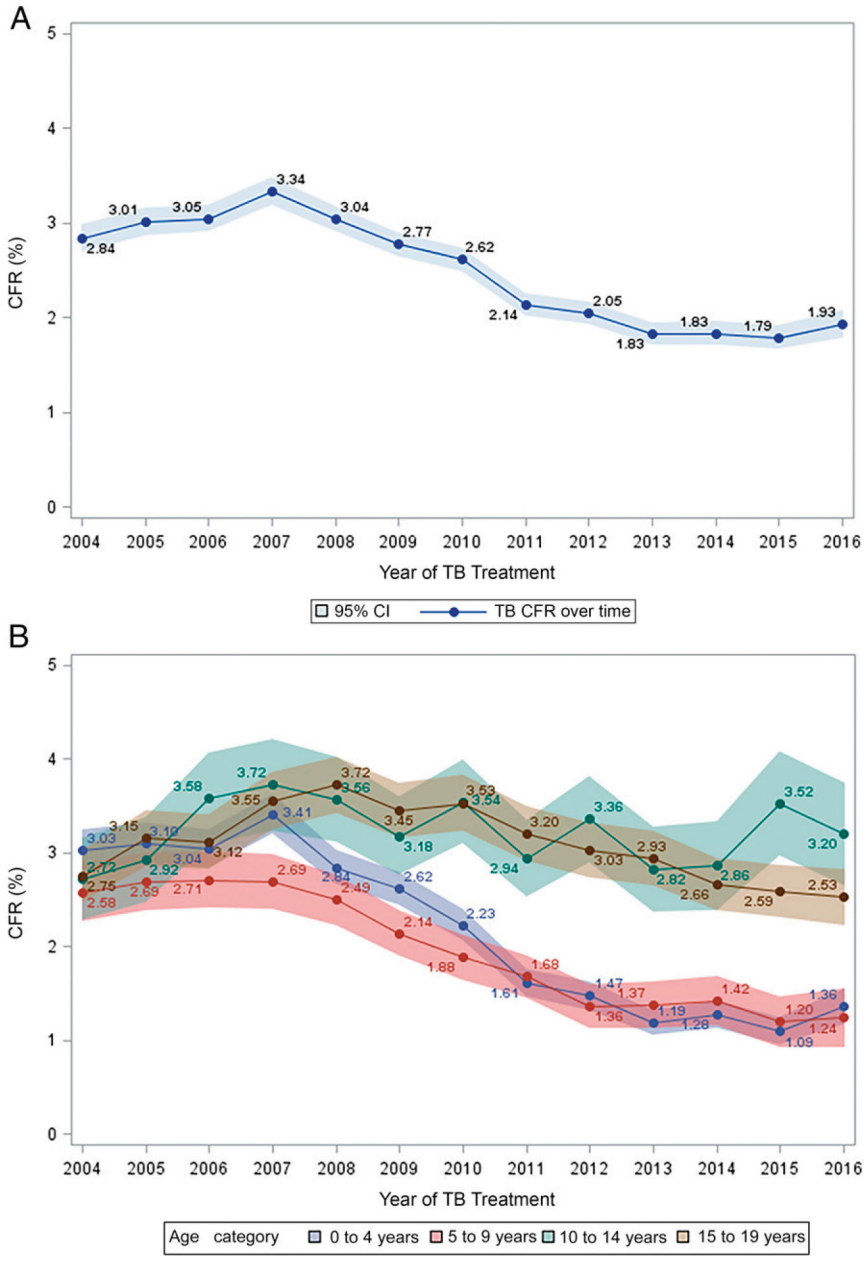

FIGURE 1.

Overall CFR and stratification by age category for children and adolescents treated for drug-susceptible TB, South Africa, 2004–2016. A, Overall CFR. B, Stratification by age category.

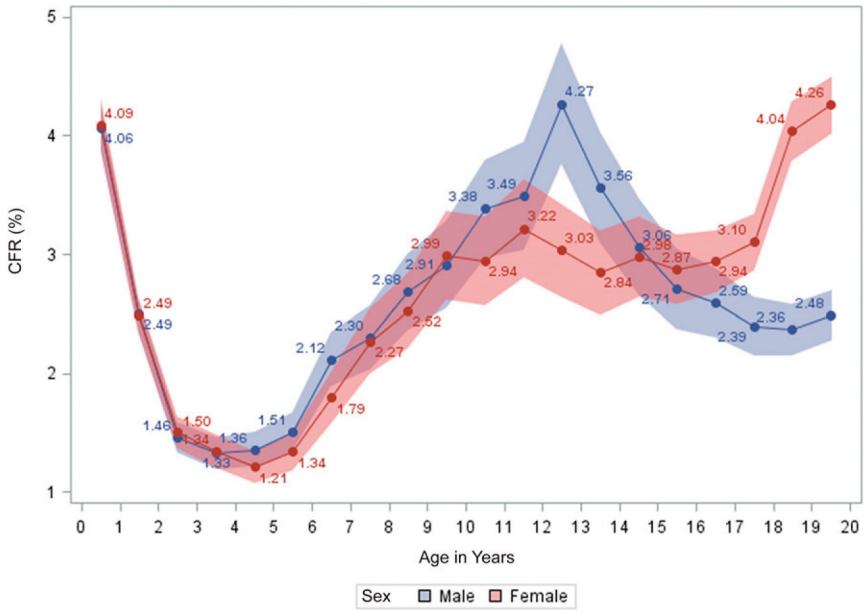

FIGURE 2.

CFR of all children and adolescents treated for drug-susceptible TB in South Africa between 2004 and 2016, stratified by age and sex.

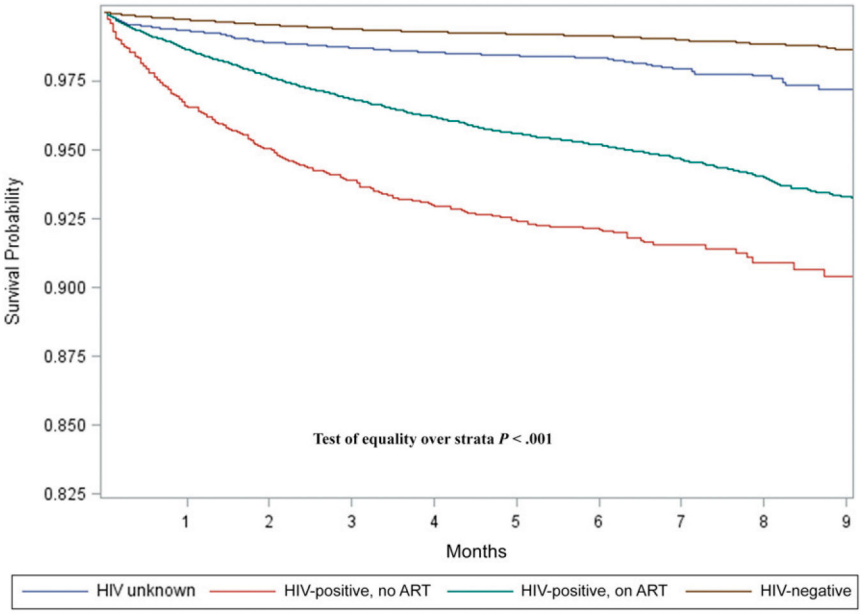

FIGURE 3.

Kaplan-Meier survival curve stratified by HIV and ART status of children and adolescents on drug-susceptible TB treatment between 2013 and 2016 in South Africa.

FIGURE 4.

SMRs of children and adolescents on drug-susceptible TB treatment in South Africa, 2004–2016. SMR is the ratio of observed TB deaths to the expected deaths and is based on the Thembisa estimates of mortality rates for the general population. Expected mortality is based on the product of the age- and sex-specific population estimates of mortality rates from Thembisa and the person-time in the TB cohort.

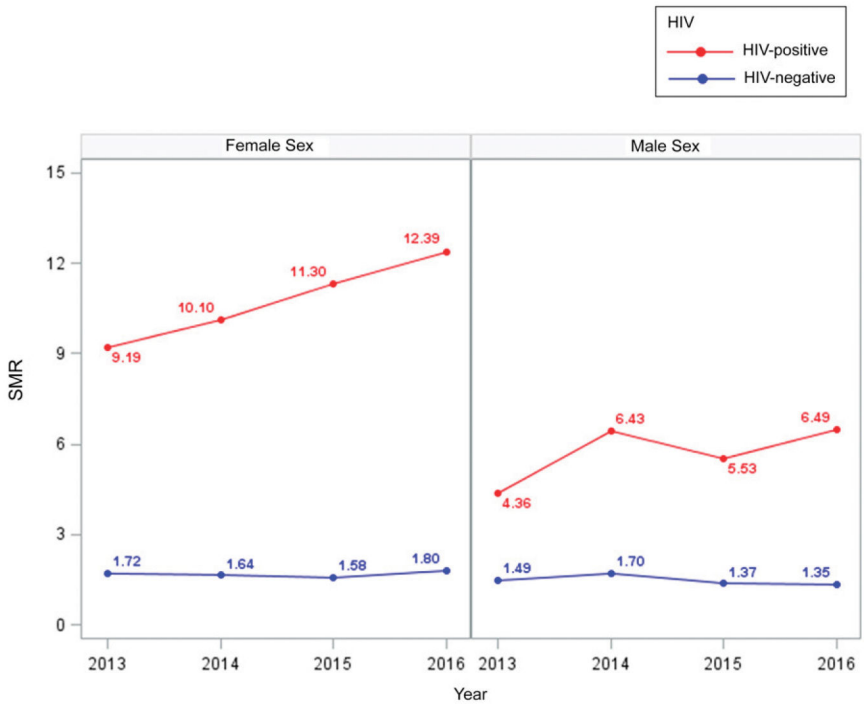

FIGURE 5.

SMRs by HIV status of children and adolescents on drug-susceptible TB treatment in South Africa, 2013–2016. SMR is the ratio of observed TB deaths to the expected deaths and is based on the Thembisa estimates of mortality rates for the general population. Expected mortality is based on products of the HIV-positive and HIV-negative population estimates of mortality rates (regardless of age) from the Thembisa model and the person-time in the TB cohort.

TABLE 1

Demographic and Clinical Characteristics of Children and Adolescents Treated for Drug-Susceptible TB in the South African Reporting Cohort, by Vitality Status and Mortality, 2004–2016

Variable	All Patients With TB in Reporting Cohort (*N* = 729 463), *n*	Patients With TB With Known Vitality Status (*n* = 612 655 [84.0%]), *n* (%)	Patients With TB Who Died (*n* = 18 539 [3.0%]), *n* (%)	CFR[a] (Patients With TB Who Died: 2.5%), %
Age, y				
0–4	339 719	287 085 (84.51)	7709 (2.69)	2.26
5–9	134 616	115 156 (85.54)	2776 (2.41)	2.06
10–14	74 674	63 615 (85.19)	2417 (3.80)	3.23
15–19	180 454	146 799 (81.35)	5637 (3.84)	3.12
Sex				
Male	355 560	298 020 (83.82)	8614 (2.89)	2.42
Female	373 897	314 634 (84.15)	9925 (3.15)	2.65
HIV status				
HIV-negative	245 787	216 753 (88.19)	2387 (1.10)	0.97
HIV-positive, on ART	56 068	48 493 (86.49)	2680 (5.53)	4.77
HIV-positive, no ART	46 575	37 418 (80.34)	2917 (7.80)	6.26
HIV status unknown	381 033	309 991 (81.36)	10 555 (3.40)	2.77
Previous TB history				
New	691 834	584 350 (84.46)	16 610 (2.84)	2.40
Retreatment	37 628	28 305 (75.22)	1929 (6.82)	5.13
Site of TB disease[b]				
Pulmonary TB	664 041	561 255 (84.52)	15 760 (2.81)	2.37
EPTB	65 418	51 400 (78.57)	2779 (5.41)	4.25
Disseminated disease[c]				
Not disseminated	640 136	541 006 (84.51)	15 189 (2.81)	2.37
Disseminated	12 245	9389 (76.68)	882 (9.39)	7.20
Year				
2004	53 081	40 389 (76.09)	1505 (3.73)	2.83
2005	55 426	44 096 (79.56)	1670 (3.79)	3.01

Variable	All Patients With TB in Reporting Cohort (*N* = 729 463), *n*	Patients With TB With Known Vitality Status (*n* = 612 655 [84.0%]), *n* (%)	Patients With TB Who Died (*n* = 18 539 [3.0%]), *n* (%)	CFR[a] (Patients With TB Who Died: 2.5%), %
2006	60 482	49 638 (82.07)	1842 (3.71)	3.04
2007	62 981	52 069 (82.67)	2101 (4.04)	3.34
2008	68 106	56 206 (82.53)	2072 (3.69)	3.04
2009	69 559	58 800 (84.53)	1930 (3.28)	2.77
2010	64 003	53 342 (83.34)	1674 (3.14)	2.62
2011	63 887	55 268 (86.51)	1364 (2.47)	2.14
2012	55 002	48 037 (87.34)	1127 (2.35)	2.05
2013	51 572	45 454 (88.14)	942 (2.07)	1.82
2014	47 904	39 784 (83.05)	878 (2.21)	1.83
2015	42 986	38 635 (89.88)	769 (1.99)	1.79
2016	34 474	30 937 (89.74)	665 (2.15)	1.93
Outcome 1				
Cured or completed	591 640	591 640 (100.00)	—	—
Died	18 539	18 539 (100.00)	18 539 (100.00)	—
Loss to follow-up	116 808	0 (0.00)	—	—
Failed or drug resistant	2476	2476 (100.00)	—	—

—, not applicable.

[a]CFR was calculated as a percentage by using the number of deaths over the total number of patients with TB.

[b]The binary classification of site of disease included pulmonary TB, which was based on the presence of any pulmonary TB, and EPTB, which was restricted to exclusive EPTB.

[c]Disseminated disease was based on ICD-10 coding, with neurologic TB and miliary TB recorded as disseminated disease and all other ICD-10 codes recorded as not disseminated.

TABLE 2

Crude and Adjusted Cox Proportional Regression Model Predicting HRs of Death for Children and Adolescents Treated for Drug-Susceptible TB in South Africa Between 2013 and 2016 (Data Set = 175 530 and 154 135 Included in Final Model, Respectively)

Variable	HR (95% CI)	*P*	aHR (95% CI)	*P*
Age, y				
0–4	0.94 (0.83–1.06)	.29	1.33 (1.18–1.51)	<.001
5–9	Reference	—	Reference	—
10–14	2.27 (1.99–2.60)	<.001	1.75 (1.53–2.00)	<.001
15–19	2.09 (1.86–2.35)	<.001	2.12 (1.89–2.39)	<.001
Sex				
Male	Reference	—	Reference	—
Female	1.08 (1.01–1.16)	.03	0.96 (0.90–1.04)	.32
HIV status				
HIV-negative	Reference	—	Reference	—
HIV status unknown	2.01 (1.74–2.31)	<.001	2.1 1 (1.83–2.43)	<.001
HIV-positive, no ART	8.48 (7.47–9.61)	<.001	7.99 (7.02–9.09)	<.001
HIV-positive, on ART	5.66 (5.22–6.12)	<.001	5.11 (4.71–5.55)	<.001
Previous TB history				
New	Reference	—	Reference	—
Retreatment	2.11 (1.83–2.44)	<.001	1.37 (1.18–1.58)	<.001
Site of TB disease[a]				
Pulmonary TB	Reference	—	Reference	—
EPTB	2.17 (1.98–2.39)	<.001	1.68 (1.53–1.85)	<.001
Disseminated disease[b]				
Not disseminated	Reference	—	—	—
Disseminated	3.23 (2.75–3.78)	<.001	—	—
Year				
Continuous, for 1-y increase	1.00 (0.97–1.04)	.82	0.99 (0.96–1.03)	.70

HIV status was evaluated for completeness, and analysis for predictors of mortality was restricted to the period of 2013–2016, the years during which >80% of patients with TB had a known HIV status in each age category. aHR, adjusted hazard ratio; —, not applicable.

[a]The binary classification of site of disease included pulmonary TB, which was based on the presence of any pulmonary TB, and EPTB, which was restricted to exclusive EPTB.

[b] Disseminated disease was based on ICD-10 coding, with neurologic TB and miliary TB recorded as disseminated disease and all other ICD-10 codes recorded as not disseminated. Because of collinearity with site of disease, disseminated disease was not included in the final model.