1 **Mortality in South African children and adolescents routinely treated for tuberculosis**

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17 **Short title**: Mortality in South African Children and Teens with TB

42 **Abbreviations:**

43 aHR: adjusted hazard ratio; ART: anti-retroviral therapy; CFR: case fatality ratio; EPTB:
44 extrapulmonary TB; ETR.Net: Electronic tuberculosis register; HIV: human
45 immunodeficiency virus; HR: hazard ratio; ICD: international classification of disease;

46 PMTCT: prevention of mother-to-child transmission; SMR: standardized mortality ratio; TB:
47 tuberculosis; WHO: World Health Organization

Table of Contents Summary

49 Tuberculosis causes significant mortality in children and adolescents with the highest risk
50 seen in youngest children, during early adolescence and among females in later adolescence.

What's Known on This Subject

52 Modelling studies have highlighted the significant burden of TB mortality in children and
53 adolescents, but adolescent reporting has been limited. The effect of HIV on TB mortality
54 and the reversal with ART has been well described.

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

What This Study Adds

60 This study provides child and adolescent TB mortality estimates in the context of the world's
61 largest antiretroviral program. It provides the first quantification of standardized mortality
62 ratios for children and adolescents with TB.

Contributors' Statement

Dr Muhammad Osman conceptualised the study, design, developed the analytical methods, interpreted the study results, completed the first draft of the manuscript, facilitated revisions, and produced the final manuscript.

Drs Karen Du Preez, James Seddon, and Pren Naidoo, worked on the study conceptualisation, design, interpretation of the study results, review of the initial drafts and revision of the manuscript.

Mr Sicelo Dlamini contributed to data extraction, interpretation of the study results, review of the initial drafts and revision of the manuscript.

Dr Rory Dunbar contributed to data management (including cleaning and preparation), interpretation of the study results, review, and revision of the manuscript.

Dr Mareli Claassens worked on the analytical methods, interpretation of the study results, and revised the final manuscript.

Prof Alex Welte worked on the study conceptualisation, design, analytical methods, interpretation of the study results, reviewed the initial drafts and revised the manuscript.

Prof Anneke Hesseling worked on the study conceptualisation, design, interpretation of the study results, reviewed the initial drafts and critically revised the manuscript for all content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

82 **Abstract**
83 **Background**
84 In South Africa, tuberculosis (TB) is a leading cause of death among those <20 years. We
85 describe changes in TB mortality amongst children and adolescents in South Africa over a
86 13-year period, identify risk factors for mortality, and estimate excess TB-related mortality.
87 **Methods**
88 Retrospective analysis of all patients <20 years routinely recorded in the national electronic
89 drug-susceptible TB treatment register (2004-2016). We developed a multivariable Cox
90 regression model for predictors of mortality and used estimates of mortality among the
91 general population to calculate standardized mortality ratios (SMR).
92 **Results**
93 Between 2004-16, 729,463 children and adolescents were recorded on TB treatment; 84.0%
94 had treatment outcomes and 2.5% (18,539) died during TB treatment. The case fatality ratio
95 (CFR) decreased from 3.3% in 2007, to 1.9% in 2016. In the multivariable Cox regression
96 model, age 0-4, 10-14 and 15-19 years (compared to age 5-9 years) was associated with
97 increased risk of mortality, as was HIV infection, previous TB treatment and extrapulmonary
98 involvement. The SMR of 15-19-year-old females was more than double that of males the
99 same age (55.3 vs 26.2). Among 10-14-year-olds and those HIV-positive, SMRs increased
100 over time.
101 **Conclusions**
102 Mortality in South African children and adolescents treated for TB is declining but remains
103 considerable, with 2% dying during 2016. Adolescents (10-19 years) and those people living
104 with HIV have the highest risk of mortality and greatest SMRs. Interventions to reduce
105 mortality during TB treatment, specifically targeting those at highest risk, are urgently
106 needed.

Introduction

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

In a review of all-cause mortality for 2013, developing countries accounted for 98% of all deaths in <20 year-olds, with HIV and TB accounting for 11% of deaths.[4] Death due to TB may occur prior to the diagnosis of TB, before treatment initiation, during TB treatment, or after completion of TB treatment. However, TB programmes routinely only report death during treatment. The WHO reports TB deaths as a proportion of all estimated incident TB patients, 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 15-19-year-olds in addition to children (<15 years). In South Africa, while general mortality rates vary by age, sex and HIV status, TB was the leading cause of mortality amongst individuals 15-24 years and a leading cause of mortality in children 1-4 years 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 risk factors for death during TB treatment will support this process. Given the lack of reporting of age-specific TB mortality data, we aimed to describe mortality during routine TB treatment in South Africa among all children and adolescents below 20 years, disaggregated into four age categories. Using the large national routine individual TB patient electronic recording system, we describe TB case fatality ratios (CFRs) over time, calculate standardized mortality ratios

132   (SMRs) comparing TB mortality and population-based mortality estimates, and identify risk

133   factors for death during TB treatment.

Methods

Study design

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

Electronic TB register (ETR.Net)

The South Africa National Department of Health's National TB program implemented the Electronic TB register (ETR.Net) for routine reporting of all drug-susceptible TB treatment in 2004. Drug-resistant TB is recorded in a separate web-based register[8] and 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 the estimated TB incidence and 86.5% of those diagnosed with TB in South Africa were notified and treated (recorded within ETR.Net). [11]

Definitions

Drug-susceptible TB was defined as patients who had no documented resistance to anti-tuberculosis drugs. From 2011, testing with Xpert MTB/RIF (Xpert; Cepheid, Sunnyvale, CA) for all presumptive TB patients was introduced in South Africa with rapid detection of *M. tuberculosis* and mutations conferring rifampin resistance.[12] Retreatment refers to patients who had previously received more than 4 weeks of anti-tuberculosis treatment, regardless of the time since the previous treatment episode. Newly treated TB patients were classified as having had no previously reported TB treatment or who have received less than four weeks of TB treatment at any stage. The site of TB disease was categorised as

158 pulmonary TB (PTB) when there was any pulmonary involvement, or as extrapulmonary TB

159 (EPTB) when patients had disease exclusively affecting any organ other than the lung

160 parenchyma.[13] International classification of disease (ICD) 10 codes referring to central

161 nervous system TB, including TB meningitis, or miliary TB, were combined as disseminated

162 disease; all other ICD10 codes were defined as not disseminated disease. HIV status was

163 determined using several proxies including documentation of co-trimoxazole preventive

164 therapy or antiretroviral therapy (ART), HIV test results, and CD4 results. HIV status was

165 classified as HIV-negative, HIV-positive on ART, HIV-positive not on ART, and HIV status

166 unknown. The timing of ART could not be determined.

167 *TB treatment outcomes*

168 In South Africa, TB patient treatment outcomes are assigned by treating clinicians and

169 captured in ETR.Net, which includes pre-programmed algorithms to verify outcomes

170 consistent with national and WHO definitions[13, 14]. Where a treatment outcome is not

171 allocated or inconsistent with the definitions, ETR.Net reports a patient as 'not evaluated'.

172 For this analysis, 'not evaluated' was combined with lost-to-follow-up and two outcomes

173 were used: 'Outcome 1' included cured or treatment completed, died, lost-to-follow-up,

174 failed, or transferred out [14] and 'Outcome 2' defined vitality status (dead or alive; restricted

175 to patients where the final vitality status was definitively recorded). Person-time was

176 calculated as the difference between the start date of TB treatment and treatment outcome

177 date recorded in the register, representing person-years on TB treatment.

178 *Mortality*

179 Death included death due to any cause during the TB treatment episode. CFR was calculated

180 as the number of deaths as a proportion of the number of TB patients for the specified group

181 and period; 95% confidence intervals (CI) were calculated around point estimates. To

8

182   compute the CFR for each age band by sex, data for 2004-2016 were used as a single cohort.

183   For SMRs, population estimates were used from the Thembisa model, an established publicly

184   available mathematical model of South African HIV epidemiology and general demographic

185   statistics.[15] Thembisa uses age and sex-specific mortality rates based on an analysis of

186   South African cause-of-death statistics and the South African National Burden of Disease

187   study and projects mortality rates from 2016 onwards.[16] For HIV, estimates of mortality

188   were available by sex but not age. SMRs were calculated as the ratio between the observed

189   TB deaths and the expected deaths based on mortality estimates of the general population.

190   The expected deaths were the product of the mortality rates, determined from the Thembisa

191   estimates, and the person time from our cohort for each demographic category. Expected

192   deaths were based on mortality due to any cause, including TB.

193   *Statistical analysis*

194   Descriptive statistics of demographic and clinical variables were completed for the overall

195   cohort; TB patients with known vitality status; and TB patients who were documented to

196   have died. HIV status was evaluated for completeness; analysis for predictors of mortality

197   was restricted to the period 2013-2016, the years during which more than 80% of TB patients

198   had known HIV status in each age category. Missing data were excluded from analysis

199   except for HIV status, where unknown HIV status was included as a predictor for mortality.

200   A Cox proportional hazards regression model for hazard ratios (HR) predicting death was

201   developed. Univariate analyses were conducted and colinearity in the final model was

202   avoided. Predictors were added incrementally, observing the change in significance of the

203   likelihood ratio test of each model, to produce a final adjusted model. Survival analysis was

204   completed using Kaplan Meier curves. SAS software, Version 9.4. Copyright © 2002-2012

205   SAS Institute Inc., Cary, North Carolina, USA was used for data analysis.

206 *Ethical considerations*

207 Approval was received from the Stellenbosch University Health Research Ethics Committee

208 (N16/07/088), and permission was obtained from the South African National Department of

209 Health for the use of the national ETR.Net dataset.

Results

Between 1 January 2004 and 31 December 2016, the ETR.Net reporting cohort included

729,463 TB patients <20 years treated for drug-susceptible TB. Vital status was recorded in

612,655 (84.0%) TB patients, and of these, 18,539 (3.0%) died during TB treatment.

Unknown treatment outcomes were more common amongst retreatment patients, those with

EPTB or disseminated TB, but decreased over time, with 89.7% of patients having a known

treatment outcome in 2016 (Supplementary table 1).

There were 339,719 (46.6%) patients <5 years; 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 (Figure 1). CFRs differed by age category and were higher among 10-19-

year-olds, with no decline over time (Figure 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. Females 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. (Figure 2).

Risk factors for mortality on TB treatment, restricted to 2013-2016

Age 0-4, 10-14 and 15-19 years (compared to age 5-9 years), previous TB treatment, having

only 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' antituberculosis treatment was 4.8% and 7.5% if HIV-positive

234   and not on ART; 2.4% and 4.9% if HIV-positive on ART; and 0.5% and 0.9% if HIV-

235   negative (Figure 3).

236   *Standardized mortality ratios*

237   The SMRs for 0-4-year-olds and 5-9-year-olds did not differ by sex and remained between 3

238   and 5 for 0-4-year-olds and between 30 to 45 for 5-9-year-olds over time. For 10-14-year-

239   olds, the SMR increased differentially by sex, from under 60 in both males and females in

240   2004, to 77 in males and 92 in females in 2016. For 15-19-year-olds, the SMRs in males

241   increased from 20 in 2004, to a peak of 35 in 2010 and decreased to 26 in 2016. In females,

242   the SMR increased from 60 in 2004 to a peak of 76 in 2008 and decreased to 55 in 2016

243   (Figure 4 and Supplementary table 2). The SMRs for HIV-negative individuals remained

244   constant, across sex, between 2013 and 2016. For HIV-positive individuals, SMRs increased

245   from 9 to 12 in females and from 4 to 6.5 in males (Figure 5 and Supplementary table 3).

246

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 <15 years or ≥15 years old. There are therefore 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] while 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 CFR in the first year of life, followed by a second peak in early adolescence. By age band, 10-14-year-olds had the highest CFR (3.2%); even when analysed by continuous age and disaggregated by sex, the highest CFR was reported in 12-year-olds. In a systematic review, CFRs in 0–4 year-olds (pooled estimate 2.0%; 95%CI: 0.5-7.4) were consistently higher than 5–14-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 may have obscured a peak in early adolescent TB CFR. A limited case-series from South Africa has described adult-type pulmonary TB in 10-14-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 below 2,[18, 23] or 5 years [17, 24, 25], and 15-19-year-olds.[26] It is important that routine TB programs collect sufficient detail for routine monitoring and evaluation in more nuanced age categories.

271 While children 0-4 years were at higher risk of death, the SMRs demonstrated that in 2016,

272 excess TB mortality amongst 0-4 year-olds was four fold, while excess TB mortality amongst

273 5-9-year-olds was 25-45 times, amongst 10-14-year-olds 77-90 times, and amongst 15-19-

274 year-olds 26-55 times. In South Africa, TB is the leading cause of natural death among men

275 but ranks fifth among women. When disaggregated by age, TB is not among the ten leading

276 causes of death for infants, but is ranked fourth in children 1-14 years, and first for those 15-

277 64 years.[6] Under-5 mortality in South Africa has mostly been attributed to neonatal causes,

278 associated with prematurity, diarrhoea and pneumonia, while the devastating effect of HIV

279 had been largely reversed by 2011,[27] attributed to the successful implementation of the

280 prevention of mother-to-child transmission (PMTCT) program and scale-up of ART access.

281 We note that excess mortality in 0-4-year-olds is much lower than in other pediatric groups as

282 there are additional reasons for the youngest children to die. In South Africa, only 1.3% of all

283 deaths are reported among 5-14-year-olds and 10-14-year-olds had the lowest absolute

284 numbers of death between 2010 and 2015 [6]. This lower expected mortality combined with

285 the high CFR in 10-14-year-olds may explain the highest SMRs being recorded in 10-14-

286 year-olds who have limited other reasons for death but high TB CFR. Earlier work has shown

287 how age-standardized death rates for HIV/AIDS and TB increased rapidly from 1997 to

288 2006, and then declined to 2012, while deaths due to other causes increased.[28] The

289 difference in SMR in 10-19-year-old males and females is notable. In 2016, 15-19-year-old

290 females had a SMR more than double males due to the higher CFR and the lower expected

291 mortality in females. During early adolescence and puberty there may be more TB in females

292 compared to males [29] and differential access to health services by sex [30, 31] makes

293 females more likely to access the health care system. This results in a higher chance of

294 diagnosis and subsequent recording of death whilst on treatment, compared to males who

295 may die before diagnosis. In addition, the significant burden of TB among pregnant women

296   [32] and the three fold increased risk of maternal mortality with TB in HIV-positive pregnant

297   women[33] further contributes to the greater CFR. Among adolescents and young adults in

298   South Africa, almost 50% of deaths are due to unnatural causes and 84.6% of these unnatural

299   deaths occur in males. [6] Specifically the greater expected mortality among young males in

300   South Africa due to disproportionate exposure to interpersonal violence has been shown

301   among 10-17-year-olds, with homicide as a leading cause of death, mainly affecting young

302   men.[34] Females between 15-19 years attending reproductive health services could be

303   identified for TB education and opportunities for TB and HIV prevention.

304   The risk of mortality associated with severe forms of TB is well documented. A systematic

305   review reported the risk of death for children treated for TB meningitis to be 19.3% (95%CI:

306   14.0-26.1).[35] We documented a CFR of 7.4% among children and adolescents with

307   neurological and miliary TB, lower than published estimates, for several potential reasons.

308   First, we combined all neurological TB and miliary TB as a single category of disseminated

309   TB. Second, we did not restrict this analysis to children but also included older adolescents.

310   Third, we only included children recorded in the routine TB treatment register. In South

311   Africa it is estimated that at least 14.4% of all diagnosed TB cases are not notified and

312   treated[11] and in a hospital-based study of 0-12 year-olds, in-hospital death and a diagnosis

313   of TB meningitis were associated with lack of registration.[36] Future work combining

314   reported TB deaths, vital registration data and autopsy data, will likely provide better

315   estimates of TB mortality, including disseminated forms.

316   Consistent with earlier work [18], we have shown CFRs in HIV-positive children were higher

317   than HIV-negative children and the difference was reduced but persisted despite ART. This is

318   similar to work from Kenya where ART reduced the aHR for death from 4.8 among HIV-

319   positive not on ART to 3.7 among children (≤15 years) on ART with TB.[17] Cumulative

320   mortality in HIV-positive individuals, halved at 2 and 6 months comparing those on and not

321 on ART. SMR among HIV-negative has remained constant, while among HIV-positive it has

322 increased. SMR remains higher in HIV-positive females than males, likely reflecting the

323 earlier and greater access to ART among females with lower overall mortality compared to

324 TB mortality among females in ART programs.[39]

325 During the study period, South Africa scaled up PMTCT, HIV testing and expanded access to

326 universal ART.[40, 41] The reductions in vertical HIV transmission through PMTCT may

327 contribute to the reduction in TB CFR in the youngest age bands over time. The HIV profile

328 of older children and adolescents includes vertical transmission among those born prior to the

329 scale up of PMTCT, children infected despite PMTCT, and horizontal transmission. Well-

330 functioning PMTCT programs will reduce vertical transmission of HIV, but it remains

331 critical that all HIV-positive children and adolescents have access to immediate ART.

332 Regular screening for TB and TB preventive therapy will reduce TB incidence, and may

333 improve TB outcomes through early diagnosis.

334 Our study was associated with several strengths and limitations. We used a large individual

335 level national dataset spanning 13 years to identify patient factors associated with mortality

336 and the timing of death but were limited to those who started TB treatment. We quantified

337 unknown vitality status and for the purpose of estimating CFRs, assumed all those lost-to-

338 follow-up to be alive. As we were restricted to those patients registered and on treatment, this

339 study probably underreports on pediatric TB, as children and adolescents with TB may be

340 undiagnosed, untreated or unreported. Additional work is required to estimate the losses of

341 children and adolescents with TB across the care cascade. While mortality during treatment

342 occurs as a discrete event and is probably accurately noted, our CFRs are likely an

343 underestimate of mortality with additional unreported mortality expected among those

344 undiagnosed or lost-to-follow-up. In addition, we do not have data on mortality in those who

345 did not initiate TB treatment or who were not in the TB treatment register. Future work to

346   reduce loss to follow-up and ascertain definitive outcomes among those lost to follow up is

347   required. Due to the reliance on treatment register data, we were not able to evaluate pre-

348   treatment mortality, and the role of additional risk factors for mortality including nutritional

349   status, BCG vaccination status, pregnancy status, the degree of HIV-related immune

350   suppression, HIV viral load, or the precise timing and duration of ART. More work is needed

351   to explore the relationship between pregnancy and death during TB treatment especially

352   considering the high TB CFR in females of reproductive age.

353   We report on TB mortality over a 13-year period, which overlaps with significant progress

354   made in the management of HIV in South Africa and have shown that overall mortality on

355   treatment has declined in children and adolescents. This reduction in the hazard of death is

356   consistent with earlier work from South Africa.[23, 43] We highlighted the high risk of TB

357   mortality in the youngest age group, during early adolescence and among females in later

358   adolescence. The modulating effect of HIV and ART on TB mortality continues to be highly

359   relevant. Early detection and treatment of HIV with TB remains essential and tailored

360   approaches to treatment support are required in infants and during adolescence.

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363   program and the Research, Information, Monitoring, Evaluation and Surveillance (RIMES)
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496

497 **Table 1. Demographic and clinical characteristics of children and adolescents treated**
498 **for drug-susceptible tuberculosis in the South African reporting cohort by vitality status**
499 **and mortality, 2004-2016**

Variable		All TB patient in reporting cohort n N=729,463	TB patients with known vitality status n (row %) n=612,655 (84.0%)	Deceased TB patients n (row %) n = 18,539 (3.0%)	CFR %*** Deceased TB patients % 2.5%
Age	0-4 years	339,719	287,085 (84.51)	7,709 (2.69)	2.26%
	5-9 years	134,616	115,156 (85.54)	2,776 (2.41)	2.06%
	10-14 years	74,674	63,615 (85.19)	2,417 (3.80)	3.23%
	15-19 years	180,454	146,799 (81.35)	5,637 (3.84)	3.12%
Sex	Male	355,560	298,020 (83.82)	8,614 (2.89)	2.42%
	Female	373,897	314,634 (84.15)	9,925 (3.15)	2.65%
HIV	HIV-negative	245,787	216,753 (88.19)	2,387 (1.10)	0.97%
	HIV-positive, on ART	56,068	48,493 (86.49)	2,680 (5.53)	4.77%
	HIV-positive, no ART	46,575	37,418 (80.34)	2,917 (7.80)	6.26%
	HIV 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)	1,929 (6.82)	5.13%
Site of TB disease*	Pulmonary TB	664,041	561,255 (84.52)	15,760 (2.81)	2.37%
	Extra pulmonary TB	65,418	51,400 (78.57)	2,779 (5.41)	4.25%
Disseminated disease**	Not disseminated	640,136	541,006 (84.51)	15,189 (2.81)	2.37%
	Disseminated	12,245	9,389 (76.68)	882 (9.39)	7.20%
Year	2004	53,081	40,389 (76.09)	1,505 (3.73)	2.83%
	2005	55,426	44,096 (79.56)	1,670 (3.79)	3.01%
	2006	60,482	49,638 (82.07)	1,842 (3.71)	3.04%
	2007	62,981	52,069 (82.67)	2,101 (4.04)	3.34%
	2008	68,106	56,206 (82.53)	2,072 (3.69)	3.04%
	2009	69,559	58,800 (84.53)	1,930 (3.28)	2.77%
	2010	64,003	53,342 (83.34)	1,674 (3.14)	2.62%
	2011	63,887	55,268 (86.51)	1,364 (2.47)	2.14%
	2012	55,002	48,037 (87.34)	1,127 (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/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	2,476	2,476 (100.00)		

500 ART: anti-retroviral therapy, CFR: case fatality ratio, TB: tuberculosis
501 *The binary classification of site of disease included pulmonary TB based on the
502 presence of any pulmonary TB while extra pulmonary TB was restricted to exclusive
503 extra pulmonary TB

504   **Disseminated disease was based on ICD10 coding with Neurological TB and
505   Miliary TB recorded as disseminated disease and all other ICD10 codes recorded as
506   not disseminated.
507   ***CFR: Case fatality ratio was calculated as a percentage using the number of
508   deaths over the total number of TB patients

509 **Table 2. Crude and adjusted Cox proportional regression model predicting hazard ratio**
510 **of death for children and adolescents treated for drug-susceptible tuberculosis in South**
511 **Africa between 2013 and 2016* (dataset = 175,530 and 154,135 included in final model)**

| Variable		HR (95%CI)	p-value	aHR (95%CI)	p-value
Age	0-4 years	0.94 (0.83-1.06)	0.29	1.33 (1.18-1.51)	<0.001
	5-9 years	Ref		Ref	
	10-14 years	2.27 (1.99-2.60)	<0.001	1.75 (1.53-2.00)	<0.001
	15-19 years	2.09 (1.86-2.35)	<0.001	2.12 (1.89-2.39)	<0.001
Sex	Male	Ref		Ref	
	Female	1.08 (1.01-1.16)	0.03	0.96 (0.90-1.04)	0.32
HIV	HIV-	Ref		Ref	
	HIV unknown	2.01 (1.74-2.31)	<0.001	2.11 (1.83-2.43)	<0.001
	HIV+ no ART	8.48 (7.47-9.61)	<0.001	7.99 (7.02-9.09)	<0.001
	HIV+ on ART	5.66 (5.22-6.12)	<0.001	5.11 (4.71-5.55)	<0.001
Previous TB history	New	Ref		Ref	
	Retreatment	2.11 (1.83-2.44)	<0.001	1.37 (1.18-1.58)	<0.001
Site of TB disease**	Pulmonary TB	Ref		Ref	
	Extrapulmonary TB	2.17 (1.98-2.39)	<0.001	1.68 (1.53-1.85)	<0.001
Disseminated disease***	Not disseminated	Ref			
	Disseminated	3.23 (2.75-3.78)	<0.001		
Year	Continuous – for 1 year increase	1.00 (0.97-1.04)	0.82	0.99 (0.96-1.03)	0.70

512
513 aHR: adjusted hazard ratio, ART: anti-retroviral therapy, HR: hazard ratio, ICD: international
514 classification of disease, TB: tuberculosis
515 * HIV status was evaluated for completeness and analysis for predictors of mortality was
516 restricted to the period 2013-2016, the years during which more than 80% of TB patients had
517 known HIV status in each age category
518 **The binary classification of site of disease included pulmonary TB based on the presence
519 of any pulmonary TB while extra pulmonary TB was restricted to exclusive extra pulmonary
520 TB
521 ***Disseminated disease was based on ICD10 coding with Neurological TB and Miliary TB
522 recorded as disseminated disease and all other ICD10 codes recorded as not disseminated.
523 Due to collinearity with site of disease, disseminated disease was not included in the final
524 model

525 **Figure 1. Overall case fatality ratio and stratification by age category for children and**
526 **adolescents treated for drug-susceptible tuberculosis, South Africa, 2004-2016**
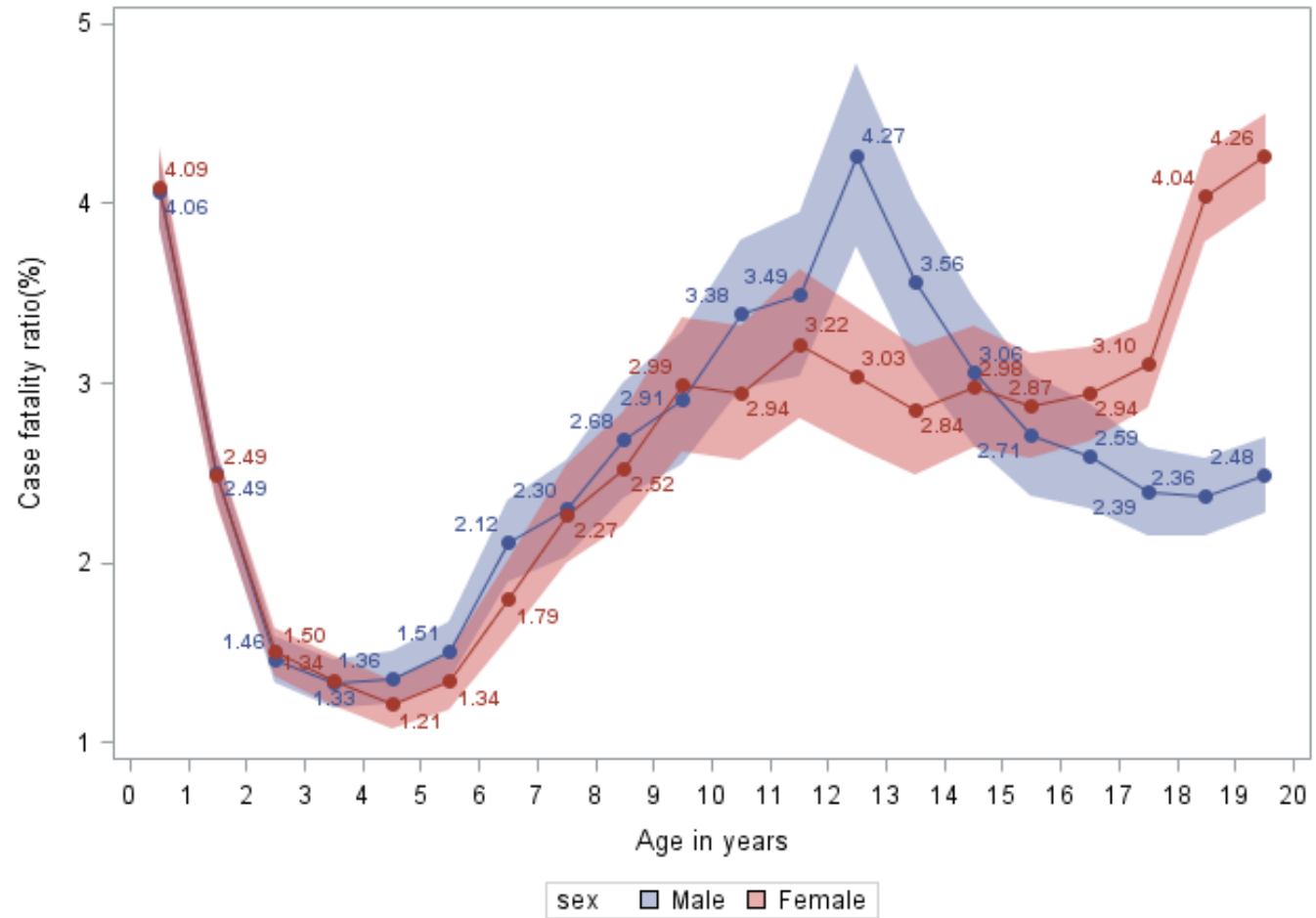
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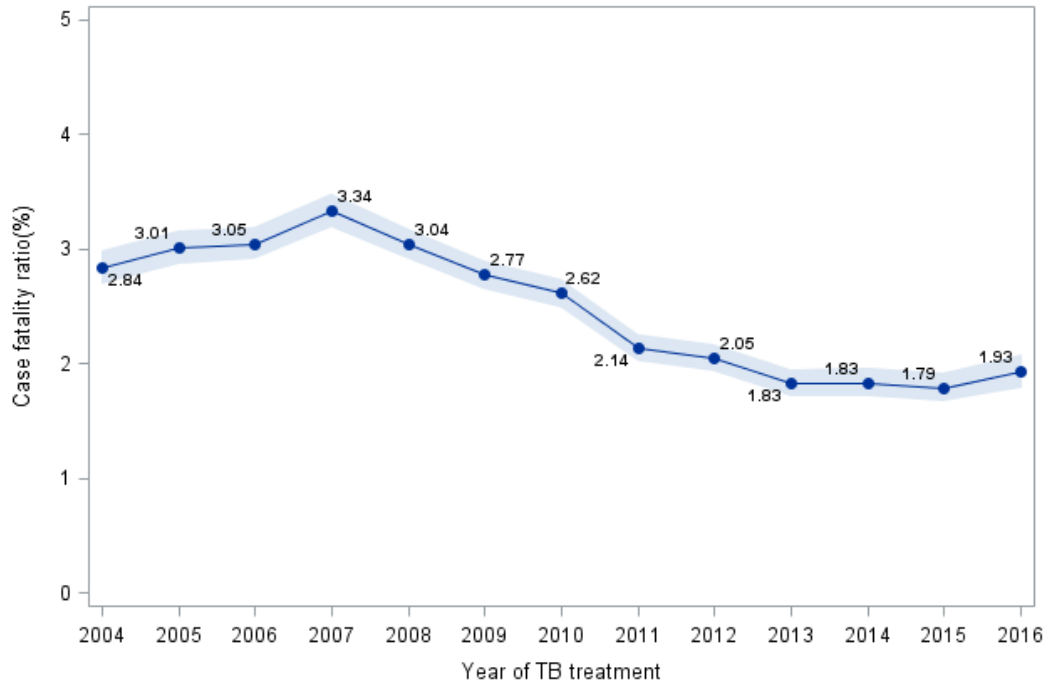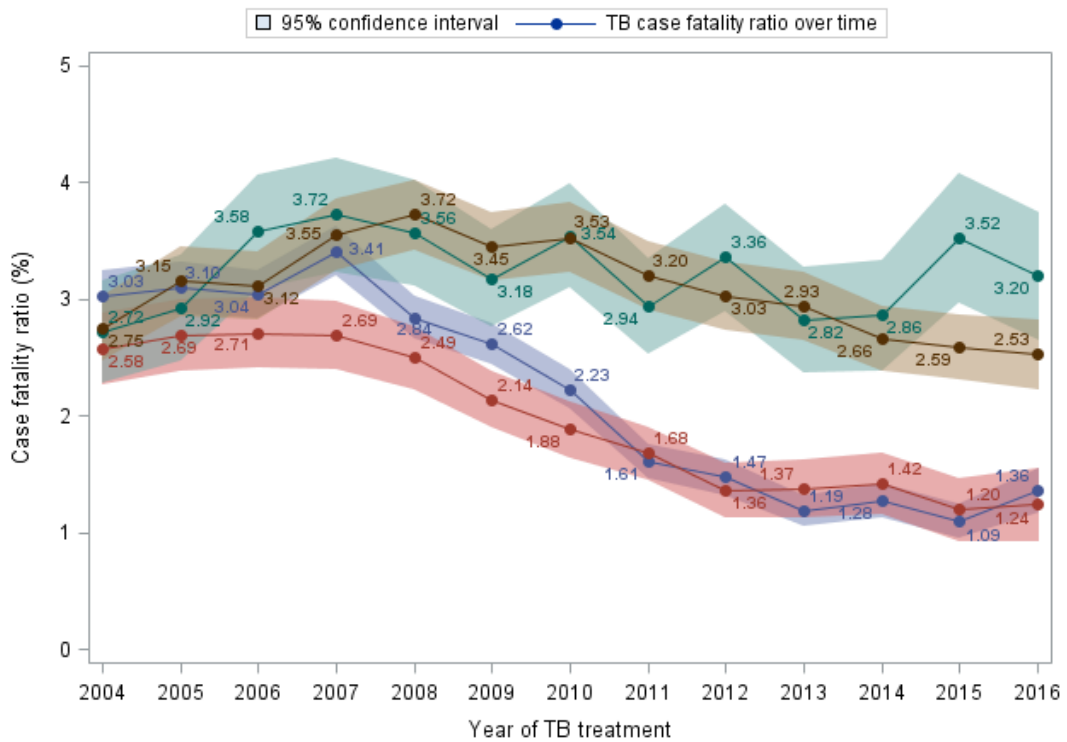
529 **Figure 2. Case fatality ratio of all children and adolescents treated for drug-susceptible tuberculosis in South Africa between 2004 and**
530 **2016 stratified by age and sex**

531
532

533   **Figure 3. Kaplan Meier survival curve stratified by HIV and ART status of children and adolescents on drug-susceptible tuberculosis**
534   **treatment between 2013 and 2016 in South Africa**
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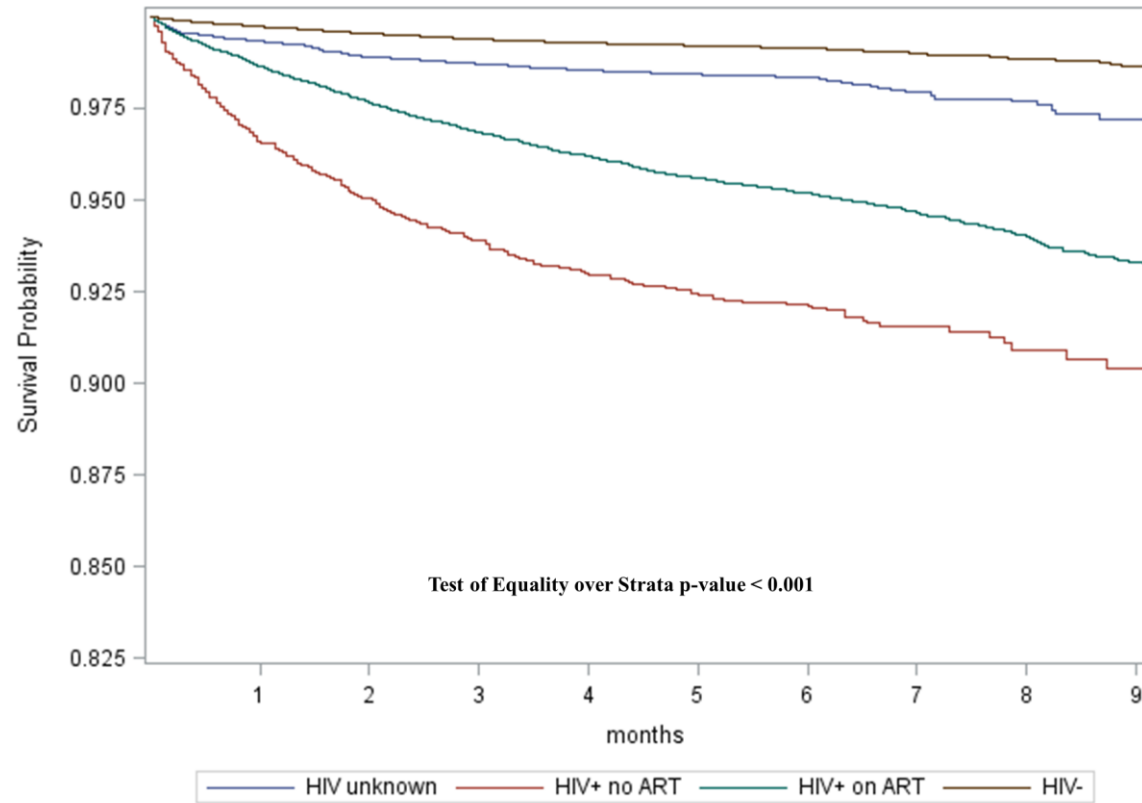
Figure 4. Standardized mortality ratios of children and adolescents on drug-susceptible tuberculosis treatment in South Africa, 2004-2016
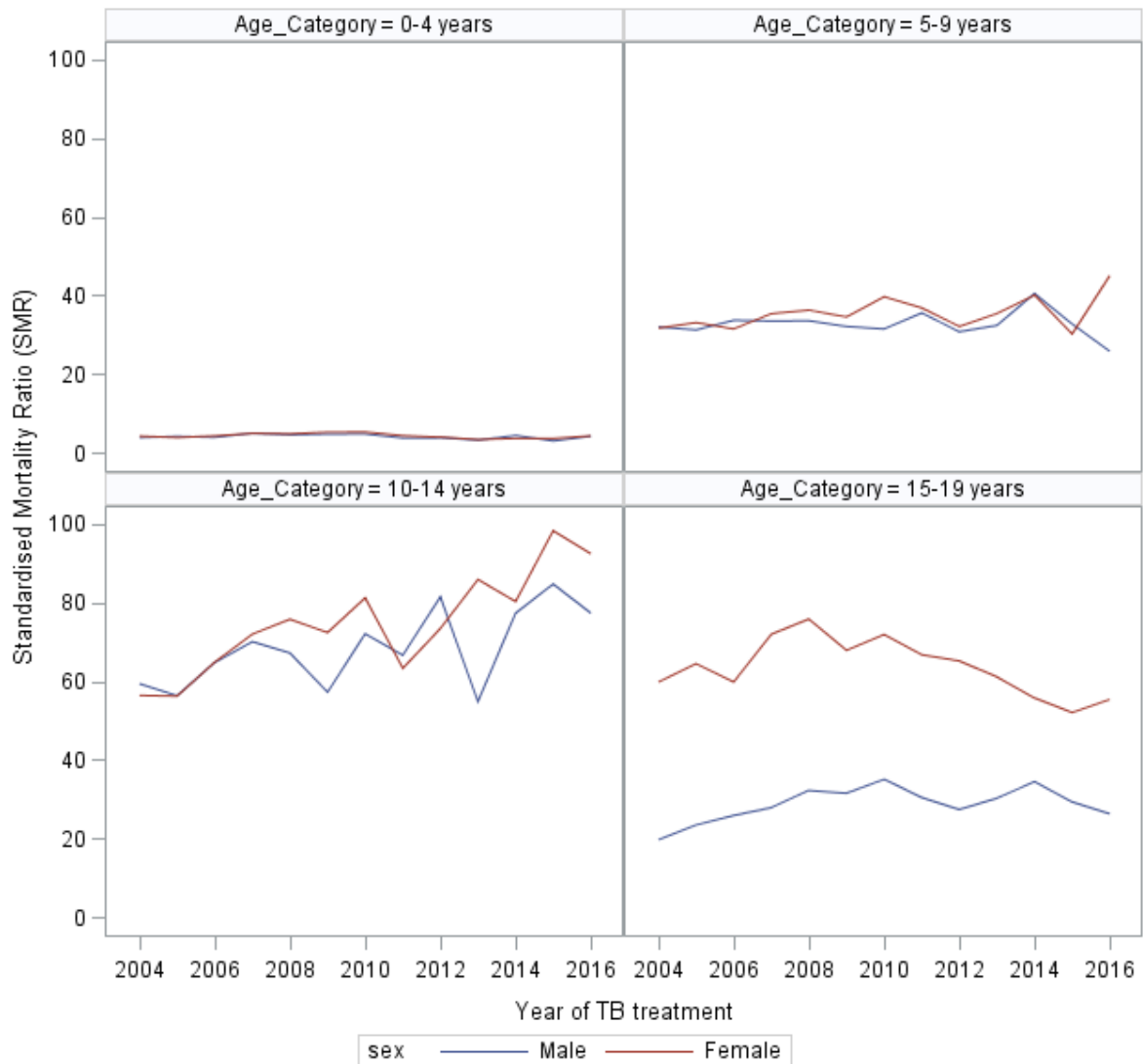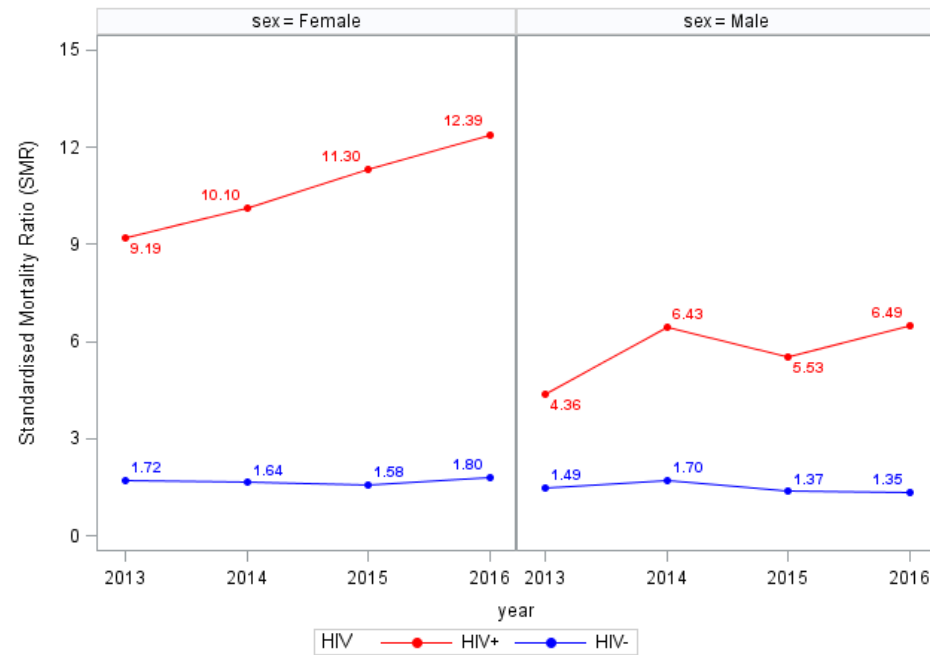

SMR: Standardized mortality ratio

Standardized mortality ratio is the ratio of observed TB deaths to the expected deaths 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.

547   **Figure 5. Standardized mortality ratios by HIV status of children and adolescents on drug-susceptible tuberculosis treatment in South**
548   **Africa, 2013-2016**

549

550   SMR: Standardized mortality ratio
551   Standardized mortality ratio is the ratio of observed TB deaths to the expected deaths based on the Thembisa estimates of mortality rates for the
552   general population. Expected mortality is based on products of the HIV-positive and HIV-negative population estimates of mortality rates
553   (regardless of age) from the Thembisa model and the person time in the TB cohort.

Supplementary table 1. Demographic and clinical characteristics of children and
555 **adolescents treated for drug-susceptible tuberculosis in the South African reporting**
556 **cohort comparing those with known and unknown treatment outcomes, 2004-2016**

Variable		Unknown outcomes n=116,808	Unknown outcomes Col %	Known outcomes n=612,655	Known outcomes Col %
Age	0-4 years	52,634	45%	287,085	47%
	5-9 years	19,460	17%	115,156	19%
	10-14 years	11,059	9%	63,615	10%
	15-19 years	33,655	29%	146,799	24%
Sex	Male	57,540	49%	298,020	49%
	Female	59,263	51%	314,634	51%
HIV	HIV uninfected	29,034	25%	216,753	35%
	HIV infected, on ART	7,575	6%	48,493	8%
	HIV infected, no ART	9,157	8%	37,418	6%
	HIV unknown	71,042	61%	309,991	51%
Previous TB history	New	107,484	92%	584,350	95%
	Retreatment	9,323	8%	28,305	5%
Site of TB disease*	Pulmonary TB	102,786	88%	561,255	92%
	Extra pulmonary TB	14,018	12%	51,400	8%
Disseminated disease**	Not disseminated	99,130	85%	541,006	88%
	Disseminated	2,856	2%	9,389	2%
Year	2004	12,692	11%	40,389	7%
	2005	11,330	10%	44,096	7%
	2006	10,844	9%	49,638	8%
	2007	10,912	9%	52,069	8%
	2008	11,900	10%	56,206	9%
	2009	10,759	9%	58,800	10%
	2010	10,661	9%	53,342	9%
	2011	8,619	7%	55,268	9%
	2012	6,965	6%	48,037	8%
	2013	6,118	5%	45,454	7%
	2014	8,120	7%	39,784	6%
	2015	4,351	4%	38,635	6%
	2016	3,537	3%	30,937	5%

557 Tests of significance not displayed as due to sample size all categories were significantly
558 different
559 *The binary classification of site of disease included pulmonary TB based on the presence of
560 any pulmonary TB while extra pulmonary TB was restricted to exclusive extra pulmonary TB
561 **Disseminated disease was based on ICD10 coding with Neurological TB and Miliary TB
562 recorded as disseminated disease and all other ICD10 codes recorded as not disseminated.

Supplementary table 2. Standardized mortality ratio of children and adolescents treated for drug-susceptible tuberculosis in the South

African reporting cohort using observed deaths and expected deaths by age and sex, 2004-2016

Year	Age category	Population		TB patients			Observed TB deaths		Expected deaths		TB mortality rate*		Population mortality rate*		Standardized mortality ratio**	
		Males	Females	Males	Females	M:F	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2004	0-4 years	2334879	2308638	12 358	10 996	1.1	366	341	96.05	81.34	6.64	6.90	1.74	1.65	3.81	4.19
2005	0-4 years	2379474	2352523	13 388	11 562	1.2	440	333	106.61	87.56	7.17	6.26	1.74	1.65	4.13	3.80
2006	0-4 years	2444741	2416644	15 139	13 636	1.1	452	423	117.30	99.65	6.46	6.70	1.68	1.58	3.85	4.24
2007	0-4 years	2526335	2497730	15 950	14 747	1.1	564	484	115.16	99.03	7.70	7.16	1.57	1.47	4.90	4.89
2008	0-4 years	2621407	2592124	17 107	15 910	1.1	493	446	109.14	94.29	6.37	6.25	1.41	1.32	4.52	4.73
2009	0-4 years	2706219	2675879	17 282	15 726	1.1	448	418	95.89	80.56	5.71	5.84	1.22	1.13	4.67	5.19
2010	0-4 years	2750868	2720376	15 150	14 096	1.1	337	315	71.01	60.29	4.93	4.93	1.04	0.94	4.75	5.22
2011	0-4 years	2785268	2754828	15 426	14 331	1.1	243	237	65.54	55.57	3.36	3.53	0.90	0.83	3.71	4.26
2012	0-4 years	2810947	2779685	13 112	12 200	1.1	198	175	53.06	44.76	3.19	3.04	0.85	0.78	3.73	3.91
2013	0-4 years	2827303	2795166	12 728	11 699	1.1	155	135	48.95	40.88	2.59	2.45	0.82	0.74	3.17	3.30
2014	0-4 years	2842809	2809913	11 903	10 676	1.1	172	116	39.78	32.23	3.39	2.55	0.79	0.71	4.32	3.60
2015	0-4 years	2863925	2830051	10 363	9 400	1.1	108	108	36.68	30.02	2.20	2.42	0.75	0.67	2.94	3.60
2016	0-4 years	2878225	2843684	7 854	6 974	1.1	112	90	26.84	21.41	3.01	2.73	0.72	0.65	4.17	4.20
2004	5-9 years	2343438	2317207	5 253	5 032	1.0	142	123	4.44	3.88	5.95	5.28	0.19	0.17	31.96	31.69
2005	5-9 years	2317283	2288393	5 683	5 417	1.0	156	143	5.00	4.32	5.84	5.64	0.19	0.17	31.22	33.08
2006	5-9 years	2288215	2259006	6 163	5 785	1.1	180	144	5.35	4.58	6.12	5.20	0.18	0.17	33.64	31.46
2007	5-9 years	2256597	2226708	6 048	5 977	1.0	166	157	4.96	4.45	5.80	5.54	0.17	0.16	33.46	35.31
2008	5-9 years	2246285	2216381	6 636	6 557	1.0	167	162	4.98	4.47	5.45	5.29	0.16	0.15	33.53	36.25
2009	5-9 years	2260739	2230755	6 836	6 745	1.0	149	142	4.64	4.12	4.68	4.48	0.15	0.13	32.09	34.50
2010	5-9 years	2308417	2277341	6 324	6 162	1.0	113	122	3.59	3.08	3.89	4.28	0.12	0.11	31.46	39.65
2011	5-9 years	2379139	2346792	6 332	6 223	1.0	114	97	3.21	2.64	3.74	3.24	0.11	0.09	35.53	36.80
2012	5-9 years	2462771	2430403	4 987	4 919	1.0	73	62	2.38	1.93	2.99	2.56	0.10	0.08	30.72	32.09
2013	5-9 years	2560976	2528238	4 384	4 494	1.0	64	58	1.98	1.64	3.02	2.67	0.09	0.08	32.35	35.38
2014	5-9 years	2649994	2616655	3 756	3 780	1.0	59	48	1.46	1.20	3.66	2.91	0.09	0.07	40.45	40.06

2015	5-9 years	2698355	2665124	3 274	3 165	1.0	45	32	1.38	1.06	2.83	2.07	0.09	0.07	32.70	30.16
2016	5-9 years	2734098	2700903	2 382	2 302	1.0	25	33	0.97	0.73	2.14	2.92	0.08	0.06	25.76	45.01
2004	10-14 years	2439044	2430155	2 336	3 108	0.8	72	76	1.21	1.35	6.91	5.29	0.12	0.09	59.36	56.37
2005	10-14 years	2415199	2409781	2 374	3 138	0.8	78	83	1.39	1.48	7.06	5.67	0.13	0.10	56.29	56.17
2006	10-14 years	2389810	2390728	2 619	3 254	0.8	105	105	1.62	1.62	8.49	6.68	0.13	0.10	64.77	64.82
2007	10-14 years	2377163	2385103	2 655	3 365	0.8	111	113	1.59	1.57	9.00	7.06	0.13	0.10	70.05	71.95
2008	10-14 years	2348607	2363315	3 045	3 638	0.8	116	122	1.73	1.61	8.19	7.14	0.12	0.09	67.15	75.75
2009	10-14 years	2314783	2335263	3 181	3 964	0.8	102	125	1.78	1.73	6.70	6.56	0.12	0.09	57.20	72.35
2010	10-14 years	2287884	2311838	3 031	3 768	0.8	115	126	1.60	1.55	8.12	7.15	0.11	0.09	72.07	81.20
2011	10-14 years	2260492	2285639	3 025	3 712	0.8	103	95	1.55	1.50	6.97	5.24	0.10	0.08	66.60	63.26
2012	10-14 years	2228208	2254137	2 769	3 160	0.9	111	88	1.36	1.20	8.10	5.71	0.10	0.08	81.46	73.40
2013	10-14 years	2218085	2243984	2 368	2 843	0.8	60	87	1.10	1.01	5.28	6.38	0.10	0.07	54.81	85.86
2014	10-14 years	2232793	2258547	2 210	2 648	0.8	71	68	0.92	0.85	7.30	5.78	0.09	0.07	77.30	80.30
2015	10-14 years	2279598	2306056	2 004	2 453	0.8	76	81	0.90	0.82	7.78	6.82	0.09	0.07	84.70	98.28
2016	10-14 years	2349029	2376279	1 828	2 178	0.8	62	66	0.80	0.71	6.90	6.17	0.09	0.07	77.30	92.40
2004	15-19 years	2565581	2544764	6 029	7 969	0.8	105	280	5.34	4.69	3.95	7.95	0.20	0.13	19.66	59.76
2005	15-19 years	2561058	2541232	5 724	8 139	0.7	123	314	5.26	4.87	4.66	8.49	0.20	0.13	23.40	64.45
2006	15-19 years	2542912	2522595	5 786	8 099	0.7	139	294	5.38	4.92	5.16	7.82	0.20	0.13	25.83	59.80
2007	15-19 years	2533098	2516378	5 827	8 409	0.7	148	358	5.32	4.98	5.56	9.19	0.20	0.13	27.84	71.91
2008	15-19 years	2520257	2505402	6 116	9 096	0.7	181	385	5.62	5.08	6.46	9.37	0.20	0.12	32.22	75.81
2009	15-19 years	2503993	2490819	6 362	9 463	0.7	181	365	5.75	5.38	6.12	8.31	0.19	0.12	31.48	67.85
2010	15-19 years	2484356	2474879	6 272	9 200	0.7	185	361	5.28	5.02	6.42	8.73	0.18	0.12	35.04	71.86
2011	15-19 years	2462125	2459166	6 098	8 740	0.7	154	321	5.07	4.81	5.37	7.87	0.18	0.12	30.38	66.71
2012	15-19 years	2444530	2447381	5 877	7 978	0.7	134	286	4.90	4.39	4.82	7.56	0.18	0.12	27.34	65.13
2013	15-19 years	2412192	2421212	5 713	7 343	0.8	143	240	4.73	3.93	5.33	6.99	0.18	0.11	30.22	61.08
2014	15-19 years	2375702	2390197	5 802	7 129	0.8	152	192	4.41	3.45	6.08	6.28	0.18	0.11	34.44	55.72
2015	15-19 years	2347061	2364970	5 568	6 759	0.8	135	184	4.61	3.54	5.16	5.80	0.18	0.11	29.27	52.02
2016	15-19 years	2318627	2337758	5 123	5 833	0.9	111	166	4.23	3.00	4.61	6.10	0.18	0.11	26.24	55.33

565   *mortality rates expressed per 100 person years

566   M:F: Male to Female ratio, TB: Tuberculosis, SMR: Standardized mortality ratio

567   **Standardized mortality ratio is the ratio of observed TB deaths to the expected deaths based on the Thembisa estimates of mortality rates for

568   the general population. Expected mortality is based on the age and sex specific population estimates of mortality rates

569 **Supplementary table 3. Standardized mortality ratio of children and adolescents treated for drug-susceptible tuberculosis in the South**
570 **African reporting cohort using observed deaths and expected deaths by HIV status, 2004-2016**
571

Year	HIV Status	TB patients		Observed TB deaths		Expected deaths		TB mortality rate*		Population mortality rate*		Standardized mortality ratio**	
		Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
2013	HIV-	16 614	16 656	142	144	95.38	83.81	1.80	1.81	1.21	1.05	1.49	1.72
2014	HIV-	16 450	16 072	148	122	87.06	74.62	2.06	1.74	1.21	1.06	1.70	1.64
2015	HIV-	15 210	14 944	121	121	88.21	76.69	1.67	1.69	1.22	1.07	1.37	1.58
2016	HIV-	12 314	11 836	97	110	72.07	61.03	1.65	1.95	1.23	1.08	1.35	1.80
2013	HIV+	4 927	6 182	217	324	49.76	35.25	9.27	11.20	2.13	1.22	4.36	9.19
2014	HIV+	5 078	6 087	265	261	41.23	25.84	12.27	10.09	1.91	1.00	6.43	10.10
2015	HIV+	4 664	5 536	222	273	40.14	24.16	9.84	10.42	1.78	0.92	5.53	11.30
2016	HIV+	3 863	4 509	200	231	30.82	18.65	10.74	10.81	1.66	0.87	6.49	12.39

572

573 TB: Tuberculosis; SMR: Standardized mortality ratio
574 *mortality rates expressed per 100 person years
575 **Standardized mortality ratio is the ratio of observed TB deaths to the expected deaths based on the Thembisa estimates of mortality rates for
576 the general population. Expected mortality is based on the HIV-positive and HIV-negative population estimates of mortality rates regardless of
577 age