EXCELLENT TREATMENT OUTCOMES IN CHILDREN TREATED FOR TUBERCULOSIS UNDER ROUTINE OPERATIONAL CONDITIONS IN CAPE TOWN

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Running header: Paediatric TB treatment outcomes

Summary: While recognised that HIV infection increases the risk of developing TB, our understanding of the impact of HIV on risk of mortality for children treated for TB is limited. We aimed to identify predictors of mortality in children treated for drug-susceptible TB.

ABSTRACT

Background

Tuberculosis (TB) remains a leading cause of death in children globally. While recognised that HIV infection increases the risk of developing TB, our understanding of the impact of HIV on risk of mortality for children treated for TB is limited. We aimed to identify predictors of mortality in children treated for drug-susceptible TB.

Methods

A retrospective analysis of all children (<15 years) routinely treated between 2005 and 2012 for drug-susceptible TB in Cape Town was conducted using the programmatic electronic TB treatment database. Survival analysis using cox regression was used to estimate hazard ratios for death. Logistic regression was used to estimate the odds of unfavourable outcomes.

Results

Of 29,519 children treated for and notified with TB over the study period, <1% died during TB treatment and 89.5% were cured or completed treatment. The proportion of children with known HIV status increased from 13% in 2005 to 95% in 2012. Children under 2 years had an increased hazard of death (aHR: 3.13; 95%CI:1.78-5.52) and greater odds of unfavourable outcome (aOR: 1.44; 95%CI:1.24-1.66) compared to children 10-15 years. HIV-positive children had increased mortality compared to HIV-negative children (aHR: 6.85; 95%CI:4.60-10.19) and increased odds of unfavourable outcome (aOR: 2.01; 95%CI:1.81-2.23). Later year of TB treatment was a protective predictor for both mortality and unfavourable outcome.

Conclusion

We demonstrate a dramatic improvement in HIV testing in children with TB over time and excellent overall treatment outcomes. HIV infection and young age were associated with increased risk of death and unfavourable outcome.

Keywords: Tuberculosis, Childhood, Mortality, Outcomes

BACKGROUND

The World Health Organization (WHO) estimated that one million children (<15 years) developed tuberculosis (TB) in 2015 with a mortality of 210,000 (1). This makes TB one of the most significant global causes of death in children. As only a third of the children estimated to have TB are identified, diagnosed and notified(2), it is likely that a large proportion of the mortality is due to untreated TB. Whilst far more can be done to improve case detection, many children do not survive even when started on appropriate TB treatment. Understanding risk factors for death in children treated for TB would allow more focussed interventions to support these children once diagnosed.

In high TB burden settings, the majority of children demonstrate evidence of *M.tb* infection before reaching adulthood (3). However, once infected with *M.tb*, children under two years of age are at the highest risk of progressing to TB disease, with severe and disseminated forms of disease, including TB meningitis, also more frequently seen in this age group (4). These forms of disease are associated with high rates of mortality, even if diagnosed and appropriately treated (5).

The WHO estimates that nearly 100,000 children die from TB in Africa each year, and that about a third are HIV-positive. It is well established that HIV increases the risk of a child developing TB (6, 7) but our understanding of the impact of HIV on the risk of mortality for children who are treated for TB disease is incomplete. There are few studies documenting outcomes for children with drug-susceptible TB, and age-disaggregated mortality data are not easily available. Operational studies in Africa and Asia have identified HIV infection and young age as risk factors for mortality in children (8, 9) but these are limited by small

numbers and short study durations. This study aimed to review TB treatment outcomes and identify predictors of mortality amongst all children routinely treated for drug-susceptible TB at the community level, in Cape Town, South Africa between 2005 and 2012.

METHODS

Setting

This retrospective cohort study was conducted in the City of Cape Town, Western Cape, South Africa. According to a 2011 population estimate, 25% of the total population of 3.7 million people in Cape Town were under 15 years of age (10). In 2012 South Africa reported the highest notification rate of TB in the world at 993/100,000 population and Cape Town reported a TB incidence of 741/100,000 and an overall HIV prevalence of 19.8% (estimated using antenatal survey) (11). Children (<15 years) accounted for 13.3% of notified TB cases in Cape Town between 2009 and 2012 (12). TB care in Cape Town is decentralized, with 103 primary health care facilities offering outpatient TB treatment. Clinical history taking, examination, tuberculin skin test (TST), and chest x-rays are implemented according to national guidelines for the diagnosis of TB in children (13). Sputum testing, including smear microscopy and MGIT culture techniques were available but not routinely conducted for children and the use of the Xpert MTB/RIF test (Cepheid, Sunnyvale, CA, USA) was not available during the study period (13).

Study Population and Data sources

An electronic TB register (ETR.net) is routinely completed at a sub-district level from collated facility-based paper TB treatment registers. Fields captured include patient-specific details (age, gender, address), disease-specific details (site of disease, sputum smear results, treatment regimen, HIV status and CD4 count), and TB treatment outcome (treatment completed, cured, loss to follow up, died, failed). All patients treated for TB should be recorded in the facility-based register even if the diagnosis and treatment initiation took

place at a hospital; hospitals generally do not function as TB reporting units in this setting. A separate register is maintained for drug-resistant TB reporting (EDRWeb). All children (<15 years) who started treatment for presumed or confirmed drug-susceptible TB between 1 January 2005 and 30 June 2012 and who were recorded in ETR.net for the City of Cape Town District, were included. The cut-off of 15 years was used to be consistent with the age category used for notification data nationally and by WHO.

Definitions

New vs. retreatment cases: Retreatment cases were defined as children having previously received more than four weeks of TB treatment, regardless of the time since their previous episode or outcome. *Smear positivity:* Patients were recorded as sputum smear-positive if a sputum specimen, taken prior to TB treatment, was noted as 1+, 2+ or 3+ for acid fast bacilli on microscopy. *Site of disease:* Children were classified as having either pulmonary TB (PTB) alone or having any extra-pulmonary TB (EPTB), which may have included isolated EPTB or a combination of PTB and EPTB. *Disease type:* Primary TB referred to first infection with *M.tb*, as typically seen in children with non-severe disease, classified by treating clinician. This usually included children with documented exposure and minimal disease seen on chest x-ray. *HIV status:* Children were considered HIV-positive if they had any of the following recorded: a positive HIV result, a CD4 result, or were receiving either antiretroviral medication or co-trimoxazole prophylaxis. *TB treatment outcome:* These included cured, completed, died, loss to follow up, failed, moved or transferred out (Outcome 1). Death referred to mortality due to any cause before the end of TB treatment. Two additional outcome classifications were created for analysis. A binary mortality indicator (Outcome 2) classified all non-surviving children as “died”, while children who were cured, completed or

failed treatment but were alive at the end of treatment were classified as “alive”. This definition excluded children with unknown outcomes or those who moved, transferred or were lost to follow up. A binary classification (Outcome 3) was created defining children who were cured or completed treatment as “favourable” and all other outcomes as “unfavourable”.

Data Collection

Data were exported from ETR.net per sub-district and combined into a single database. Personal identifiers were included for matching and exclusion of duplicate entries, and subsequently removed. The data was analysed using SAS software (SAS Institute Inc., Cary, NC). Ethical approval and a waiver of individual informed consent were received from the Stellenbosch University Health Research Ethics Committee (S12/01/018) and permission was obtained from the City of Cape Town Health Directorate.

Statistical analysis

Descriptive statistics for demographic and clinical variables were calculated and analysed by HIV status. Missing data were excluded from analysis except for HIV, where unknown HIV status was included as a separate category. All variables were analysed categorically using frequencies and percentages. Age was stratified into the following bands: <2 years, 2 to <5 years, 5 to <10 years and 10 to <15 years. Time to death was calculated as the time in days between TB treatment initiation and documented date of death. Patients were censored from analysis at 273 days after TB treatment initiation (9 months) or at the time of their death, whichever occurred first. Kaplan Meier survival curves were generated for time to death by HIV status and age category. Graphical testing of the proportional hazards

assumption was conducted using the log likelihood of survival and person years, across the strata of HIV categories (positive, negative and unknown). A Cox proportional hazards model was used to determine the unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for epidemiological and clinical predictors of death. Odds ratios (OR) and 95% CIs for predicting unfavourable outcomes were estimated using generalised estimating equations with logit link. Predictors were added incrementally with attention to the change in significance of each model to produce a final multivariable model, which allowed the reporting of adjusted HRs and ORs.

RESULTS

Between 1 January 2005 and 30 June 2012, 29,519 children <15 years were recorded in the ETR.net (Figure 1). Gender proportions were approximately equal; 70% of children were below 5 years (Table 1). Less than 14% of children had sputum smear results but, of those who did, almost 60% were sputum smear-positive (Table 1). The majority of children treated (92.5%) did not have any EPTB and almost 80% had primary TB (Table 1). Overall, only 55% of children had known HIV status (Table 1). However, when disaggregated by year of treatment, more than 90% of children had a recorded HIV status after 2010, with 95.1% having known HIV status in 2012 (Table 2 and Figure 2). Treatment outcomes were recorded in 95.9% of children, although this included children who were lost to follow up, moved, transferred, or failed TB treatment in which the survival outcome was unknown (Figure 1). Less than 1% of children with recorded treatment outcomes died during TB treatment and 89.5% were cured or completed TB treatment (Table 1).

In multivariable analysis for predictors of death, age, HIV status, the presence of disseminated TB, type of TB disease and year of treatment were included. Children under 2 years had a higher rate of death (aHR: 3.1; 95%CI: 1.8-5.5) than children 10 to <15 years (Table 3). HIV-positive children had an increase death rate compared to HIV-negative children (aHR: 6.9; 95%CI: 4.6-10.2) and treatment from 2007 onwards was associated with a lower rate of death, regardless of HIV status (Table 3). Figure 3 demonstrates the rapid reduction in the probability of survival in HIV-positive children, with HIV-unknown children also showing a more rapid decline in survival compared to the HIV-negative children after the first month of treatment. Figure 4 demonstrates the more rapid decline in survival

probability in children under the age of 2 years throughout the 6-month period of treatment.

In analysis for predictors of unfavourable treatment outcome, age, HIV status, the presence of disseminated TB, type of disease and year of treatment were included. Children under 2 years had an increased odds of unfavourable outcome (aOR: 1.4; 95%CI: 1.2-1.7) compared to children aged 10 to <15 years (Table 4). The presence of any EPTB (aOR: 1.4; 95%CI: 1.2-1.6), treatment for non-primary TB (aOR: 1.2; 95%CI: 1.0-1.3) and HIV-positive status (aOR: 2.0; 95%CI: 1.8-2.2) were also associated unfavourable outcome (Table 4). Later year of treatment was associated with lower odds of unfavourable outcome (Table 4).

DISCUSSION

The evaluation and interpretation of routine data was identified in 2009 as a priority for South Africa's public health response to TB and HIV (14). This analysis represents by far the largest single reported cohort of children treated for TB, with almost thirty thousand children included over a period of more than seven years. Completeness of documentation was excellent.

In low TB incidence settings, 30-40% of childhood TB has been reported to occur in children less than five years (15-17). In this study, approximately 70% of children with TB were under five. While it is possible that this may reflect some degree of over-treatment (18), it is likely that this high proportion reflects the vulnerability of this age-group to TB disease progression. The proportion of children with any EPTB was 7.6%, much lower than is seen in other cohorts (19). A previous study from Cape Town showed at least 40% under-reporting of culture-confirmed TB in children. This included many children with severe forms of disease, such as TB meningitis, that are commonly referred to hospitals for investigations and treatment (20). Another explanation for the low proportion of EPTB in this cohort includes the classification of intra-thoracic lymph node TB as PTB rather than EPTB. It may also reflect healthcare workers diagnosing and treating TB at an earlier stage in the disease pathogenesis, prior to more severe (and extrapulmonary) forms of disease developing.

Overall, excellent treatment outcomes were demonstrated; 85.9% of children had a favourable outcome, a high proportion considering that all unknown outcomes (including those who moved or transferred) were classified as unfavourable. We found a mortality rate in children treated for TB of less than 1% (0.32% amongst HIV-negative children and 2.7% amongst HIV-positive children). This is similar to death rates reported in low TB incidence settings (15, 17) as well as a pooled estimate from a recent meta-analysis from low HIV prevalence settings (21). In regions of high TB and HIV prevalence, mortality for children on TB treatment has varied from 3.3% to 17% (8, 9, 16, 19, 21-23).

This wide range is reflective of differences in setting (inpatient and outpatient care) as well as date of study, with some taking place prior to widespread HIV treatment. Loss to follow up during TB treatment was 6.1% in our study. This is consistent with previous reports of children with TB in other countries in Africa (9, 22).

In our cohort, HIV positivity and age less than two years were independent risk factors for death. This finding is similar to previous studies where HIV positivity (21, 24, 25) and age under 5 years (3, 23) were associated with an increased likelihood of death. Unknown HIV status, TB meningitis, and sputum smear-positive PTB have been reported in previous studies as risk factors for death in children on TB treatment (8, 9). Although the presence of EPTB and unknown HIV status were associated with an increased risk of death in univariate analysis, they did not remain significant in multivariable analysis. For predictors of unfavourable outcomes, age under two years, HIV positivity, the presence of EPTB and non-primary TB were associated with unfavourable outcome.

The proportion of children tested for HIV increased over the study period. By 2012, more than 95% of children treated for TB had an HIV test result recorded (Figure 2). Although the overall proportion of children with HIV has remained relatively unchanged, the proportion of positive tests amongst children with known HIV status has fallen. This is likely to be a function of a decrease in HIV prevalence amongst children in the Western Cape as a result of effective prevention of mother to child transmission (PMTCT) as well as only high-risk children being tested for HIV in the earlier years of the study period. Later year of treatment was found to be protective for death and unfavourable outcome while on TB treatment. This is likely to be due in large part to the change in government response to the interlinked HIV and TB epidemics. Over the study period funding significantly increased for the expansion of antiretroviral therapy (ART), scaling up of PMTCT, the promotion of HIV and TB treatment integration, and increased investments in HIV prevention (26). This scale up specifically improved access for children with TB and HIV coinfection by expanding the CD4 count threshold at which children could receive ART and by making ART available to all those with TB as

well as all children under one year (27). The improved TB outcomes seen with each incremental year in our study are most likely attributable to the impact of these changes, as during this period the TB management of children had remained unchanged, including diagnostic strategies and treatment regimens (13).

Data completion was excellent for most fields with missing data in some. This included TST usage, chest radiograph results, or the basis for a clinical diagnosis. Details of HIV treatment or the provision of co-trimoxazole prophylaxis was not available in the electronic TB register, highlighting an opportunity for further improvement in the integration of TB-HIV services. Pilot programs have been initiated in the Western Cape to implement a three-tier monitoring system at country level for pre-antiretroviral wellness, ART, TB, and mother and child health services to ensure harmonization and accurate monitoring of services (28). It is expected that integrated monitoring systems will mitigate the limitations we have seen in this study. The overall number of children with unknown HIV status was high, and as exclusion may have led to bias, these children were included in all analyses as a separate group. We used the date of death in the register for analysis; linkage to a vital statistics or mortality register was not done to verify these dates. Additional variables such as nutritional status, vaccination records or opportunistic infections are not recorded in ETR.net. While the protective effect of Bacille Calmette Guerin (BCG) vaccination against disseminated disease is well-documented (29-31) we had no information on BCG vaccination status. However, BCG vaccination is routinely given at birth to all infants and coverage was estimated to be 84% across South Africa in 2012 (32). Our study defined death as a child who died before the end of TB therapy and did not differentiate death due to TB from other causes. Record reviews and/or post mortem studies to more accurately document the causes of death would be required. This study only included outcomes for children recorded in TB treatment registers, and might underestimate mortality. Children with severe and disseminated forms of TB admitted to hospital may die before diagnosis or after diagnosis but prior to recording in ETR.net. Further research linking multiple data

sources is therefore needed to estimate overall mortality for paediatric TB. Children who moved, transferred, or were lost-to-follow-up during treatment represented a large proportion of children with unfavourable outcomes. Classifying these children as having unfavourable outcomes will mean that favourable outcomes were underestimated. Finally, this study was restricted to one city in South Africa; it may not be possible to generalise findings to other settings.

Our study reports a large cohort of children treated for TB over a seven-year period in a setting with a high burden of TB and HIV. It has demonstrated significant improvement in HIV testing over time and excellent TB treatment outcomes among those reported to the TB program. The predominance of children treated for primary TB highlights the early diagnosis currently taking place in a high burden setting. Specific higher risk groups for mortality and unfavourable outcomes have been identified for further study and interventions.

AUTHOR CONTRIBUTIONS

MO, KL, ACH and JAS contributed to conception and design of the study. MO and RD undertook data extraction and matching. MO carried out statistical analysis. KDP contributed towards data interpretation and setting-specific contextualisation. MO and JAS wrote a first draft of the article with subsequent critical input from all authors. ACH and JAS were co-senior authors. All authors approved the final version.

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DISCLAIMER

The contents are the responsibility of the author(s) and do not necessarily reflect the views of USAID.

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CONFLICTS OF INTEREST

None declared

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Table 1. Demographic characteristics of children treated for TB between 1 January 2005 and 30 June 2012 in Cape Town, South Africa; n = 29,519

		Total (%)
Age (n = 29,519)	0 to <2	10,100 (34.2)
	2 to <5	10,575 (35.8)
	5 to <10	5,477 (18.6)
	10 to <15	3,367 (11.4)
Gender (n = 29,519)	Male	14,885 (50.4)
	Female	14,634 (49.6)
Type treatment (n = 29,519)	New	28,701 (97.2)
	Re-treatment	818 (2.8)
Smear status (n = 3,839)	Positive	2,243 (58.4)
	Negative	1,596 (41.6)
Site of TB disease (n = 29,518)	PTB alone	27,229 (92.3)
	Any EPTB	2,289 (7.8)
Disease type (n = 29,487)	Primary	23,437 (79.5)
	Non-primary	6,050 (20.5)
HIV status (n = 29,519)	Positive	3,143 (10.7)
	Negative	13,162 (44.6)
	Unknown*	13,214 (44.8)
Year of TB treatment (n = 29,519)	2005	3,519 (11.9)
	2006	3,825 (13)
	2007	3,784 (12.8)
	2008	4,132 (14)
	2009	4,110 (13.9)
	2010	4,319 (14.6)
	2011	3,928 (13.3)
	2012**	1,902 (6.4)
Treatment outcome 1 (n = 28,318)	Cured/completed	25,353 (89.5)
	Died	203 (0.7)
	Moved/Transferred	932 (3.3)
	Loss to follow up	1,712 (6.1)
	Failed	118 (0.4)
Treatment outcome 2[א] (n = 25,674)	Alive [†]	25,471 (99.2)
	Died	203 (0.8)
Treatment outcome 3 (n = 29,519)	Unfavourable [ϱ]	4,166 (14.1)
	Favourable [ϰ]	25,353 (85.9)

*Missing data were recorded as unknown and excluded from analysis except for HIV, where HIV unknown is included as a separate category

**Year of treatment includes only 6 months of data for 2012

ϰ Excludes children with unknown outcomes or those who moved, transferred or were lost to follow up during the course of treatment where survival status was unknown

† Alive includes all children who were cured, completed or failed treatment

ϱ All children who failed, died, moved, transferred, were lost to follow up or not evaluated

ϰ All children who were cured or completed treatment

Table 2. Demographic characteristics of children treated for TB between 1 January 2005 and 30 June 2012 in Cape Town, South Africa stratified by HIV status; n = 29,519

		HIV positive (%)	HIV negative (%)	HIV unknown* (%)
Total		3,143 (10.7)	13,162 (44.6)	13,214 (44.8)
Age (n = 29,519)	0 to <2	983 (31.3)	4,414 (33.5)	4,703 (35.6)
	2 to <5	846 (26.9)	5,018 (38.1)	4,711 (35.7)
	5 to <10	839 (26.7)	2,134 (16.2)	2,504 (19)
	10 to <15	475 (15.1)	1,596 (12.1)	1,296 (9.8)
Gender (n = 29,519)	Male	1,529 (48.7)	6,626 (50.3)	6,730 (50.9)
	Female	1,614 (51.4)	6,536 (49.7)	6,484 (49.1)
Type of TB treatment (n = 29,519)	New	2,892 (92)	12,880 (97.9)	12,929 (97.8)
	Re-treatment	251 (8)	282 (2.1)	285 (2.2)
Smear status (n = 3,839)	Positive	193 (27.8)	855 (44.7)	548 (44.5)
	Negative	502 (72.2)	1,058 (55.3)	683 (55.5)
Site of TB disease (n= 29,518)	PTB alone	2,838 (90.3)	12,273 (93.3)	12,118 (91.7)
	Any EPTB	305 (9.7)	888 (6.8)	1,096 (8.3)
TB disease type (n = 29,487)	Primary	2,265 (72.1)	10,550 (80.3)	10,622 (80.5)
	Non-primary	876 (27.9)	2,596 (19.8)	2,578 (19.5)
Outcome 1 (n = 28,318)	Cured/ completed	2,454 (83.4)	11,699 (92.1)	11,200 (88.4)
	Died	78 (2.7)	41 (0.3)	84 (0.7)
	Moved/Transferred	123 (4.2)	342 (2.7)	467 (3.7)
	Loss to follow up	269 (9.1)	577 (4.5)	866 (6.8)
	Failed	19 (0.7)	51 (0.4)	48 (0.4)
Outcome 2[ϰ] (n = 25,674)	Alive [†]	2,865 (97.4)	12,669 (99.7)	12,581 (99.3)
	Died	78 (2.7)	41 (0.3)	84 (0.7)
Outcome 3 (n = 29,519)	Unfavourable [ϱ]	689 (21.9)	1,463 (11.1)	2,014 (15.2)
	Favourable [ϰ]	2,454 (78.1)	11,699 (88.9)	11,200 (84.8)
Year ** (n = 29,519)	2005	262 (7.4)	202 (5.7)	3,055 (86.8)
	2006	317 (8.3)	356 (9.3)	3,152 (82.4)
	2007	300 (7.9)	455 (12.0)	3,029 (80.0)
	2008	465 (11.3)	1,343 (32.5)	2,324 (56.2)
	2009	552 (13.4)	2,661 (64.7)	897 (21.8)

	2010	586 (13.6)	3,344 (77.4)	389 (9.0)
	2011	451 (11.5)	3,203 (81.5)	274 (7.0)
	2012	210 (11.0)	1,598 (84.0)	94 (4.9)

*Missing data were recorded as unknown and excluded from analysis except for HIV, where HIV unknown is included as a separate category

**For year of treatment the percentages are calculated and shown per year to demonstrate the change in the status of HIV over time

ᵡ Excludes children with unknown outcomes or those who moved, transferred or were lost to follow up during the course of treatment where survival status was unknown
ϯ Alive includes all children who were cured, completed or failed treatment
ϱ All children who failed, died, moved, transferred, were lost to follow up or not evaluated
ϰ All children who were cured or completed treatment

Table 3. Crude and adjusted model for predicting hazard ratio of death for children treated for TB between 1 January 2005 and 30 June 2012 in Cape Town, South Africa using cox regression

		HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value
*Age			<0.001		<0.001
	0 to <2	1.80 (1.14 - 2.85)	0.01	3.13 (1.78 - 5.52)	<0.001
	2 to <5	0.51 (0.30 - 0.86)	0.01	0.94 (0.50 - 1.76)	0.84
	5 to <10	0.99 (0.58 - 1.68)	0.96	1.25 (0.71 - 2.22)	0.44
	10 to <15	Ref			
Gender	Male	Ref			
	Female	1.07 (0.81 - 1.41)	0.64		
Type of TB treatment [a]	New	Ref			
	Re-treatment	2.49 (1.44 - 4.33)	<0.01		
*HIV status			<0.001		<0.001
	Unknown	2.09 (1.44 - 3.03)	<0.001	1.43 (0.91 - 2.24)	0.12
	Positive	8.31 (5.69 - 12.15)	<0.001	6.85 (4.60 - 10.19)	<0.001
	Negative	Ref			
Smear status [b]	Positive	Ref			
	Negative	2.45 (1.11 - 5.39)	0.03		
*Site of TB disease [b]	PTB alone	Ref			
	Any EPTB	1.96 (1.32 - 2.91)	<0.001	1.39 (0.82 - 2.35)	0.22

*TB disease type [a]	Primary	Ref			
	Non-primary	1.52 (1.12 - 2.06)	<0.01	1.63 (1.00 - 2.66)	0.05
*Year			<0.001		<0.01
	2005	Ref			
	2006	0.87 (0.56 - 1.35)	0.53	0.86 (0.56 - 1.33)	0.50
	2007	0.45 (0.26 - 0.77)	<0.01	0.47 (0.27 - 0.80)	<0.01
	2008	0.51 (0.31 - 0.84)	<0.01	0.49 (0.30 - 0.81)	<0.01
	2009	0.55 (0.34 - 0.89)	0.02	0.52 (0.31 - 0.88)	0.01
	2010	0.57 (0.35 - 0.92)	0.02	0.59 (0.35 - 0.99)	0.05
	2011	0.34 (0.19 - 0.61)	<0.001	0.39 (0.21 - 0.72)	<0.01
	2012	0.22 (0.09 - 0.56)	<0.01	0.25 (0.10 - 0.66)	<0.01

*Variable used in final/adjusted multi variable cox regression model

a, b - due to the likelihood of collinearity only 1 of each of these variables was included in the final model

Table 4. Crude and adjusted model of unfavourable outcomes for children treated for TB between 1 January 2005 and 30 June 2012 in Cape Town, South Africa using logistic regression

		OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
*Age			<0.001		<0.001
	0 to <2	1.14 (1.03 - 1.28)	0.02	1.44 (1.24 - 1.66)	<0.001
	2 to <5	0.83 (0.74 - 0.93)	<0.01	1.06 (0.92 - 1.23)	0.43
	5 to <10	0.88 (0.78 - 1.00)	0.04	0.99 (0.86 - 1.14)	0.88
	10 to <15	Ref			
Gender	Male	Ref			
	Female	1.00 (0.93 - 1.07)	0.94		
Type of TB treatment [a]	New	Ref			
	Re-treatment	2.40 (2.05 - 2.81)	<0.001		
*HIV status			<0.001		<0.001
	Unknown	1.44 (1.34 - 1.55)	<0.001	1.06 (0.97 - 1.17)	0.22
	Positive	2.25 (2.03 - 2.48)	<0.001	2.01 (1.81 - 2.23)	<0.001
	Negative	Ref			
Smear status [b]	+	Ref			
	-	1.14 (0.94 - 1.37)	0.18		
*Site of TB disease [b]	PTB alone	Ref			
	Any EPTB	1.54 (1.38 - 1.71)	<0.001	1.38 (1.20 - 1.59)	<0.001
*TB disease type [a]	Primary	Ref			
	Non-primary	1.21 (1.12 - 1.31)	<0.001	1.15 (1.01 - 1.31)	0.03

*Year			<0.001		<0.001
	2005	Ref			
	2006	0.83 (0.74 - 0.94)	<0.01	0.83 (0.74 - 0.94)	<0.01
	2007	0.78 (0.69 - 0.88)	<0.001	0.78 (0.69 - 0.88)	<0.001
	2008	0.74 (0.66 - 0.83)	<0.001	0.74 (0.65 - 0.83)	<0.001
	2009	0.60 (0.53 - 0.68)	<0.001	0.59 (0.52 - 0.68)	<0.001
	2010	0.58 (0.51 - 0.66)	<0.001	0.58 (0.51 - 0.67)	<0.001
	2011	0.52 (0.46 - 0.59)	<0.001	0.53 (0.46 - 0.62)	<0.001
	2012	0.52 (0.44 - 0.61)	<0.001	0.54 (0.45 - 0.64)	<0.001

*Variable used in final/adjusted multi variable cox regression model

a, b - due to the likelihood of collinearity only 1 of each of these variables was included in the final model

Figure 1. Overview of treatment outcomes of children 0- 15 years of age routinely treated for TB between 1 January 2005 and 30 June 2012 in Cape Town, South Africa

Figure 2. Changes in HIV testing and recording of children routinely treated for TB between 1 January 2005 and 30 June 2012 in Cape Town, South Africa

Figure 3. Kaplan-Meier curve of survival on TB treatment stratified by HIV status of children routinely treated for TB between 1 January 2005 and 30 June 2012 in Cape Town, South Africa

Figure 4. Kaplan-Meier curve of survival on TB treatment stratified by age category of children routinely treated for TB between 1 January 2005 and 30 June 2012 in Cape Town, South Africa

Figure 1

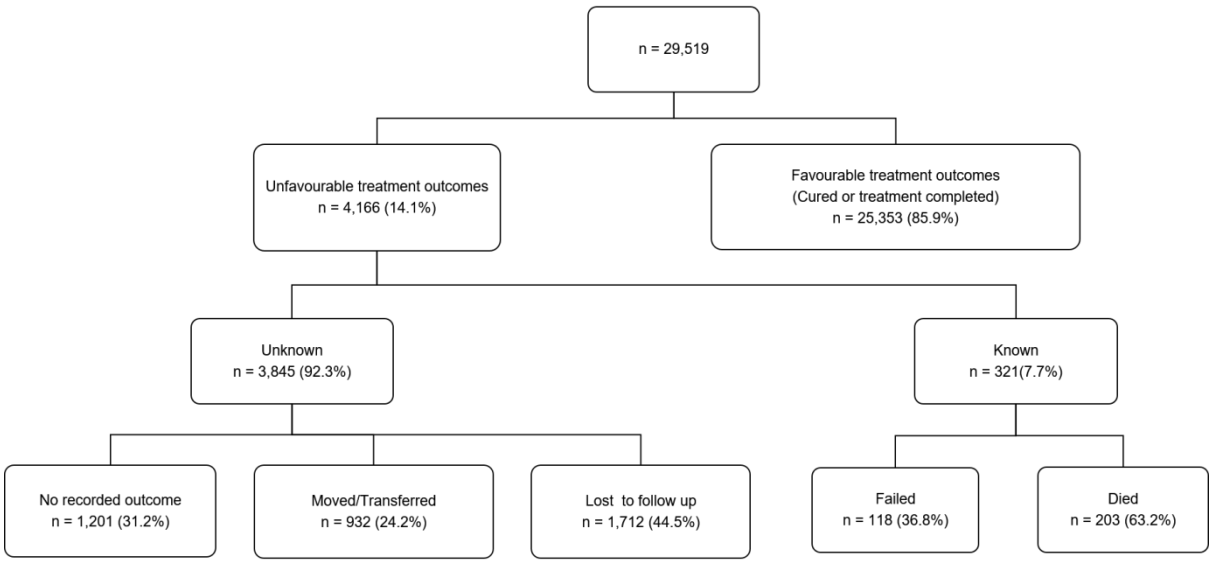

n = 29,519
Unfavourable treatment outcomes
n = 4,166 (14.1%)
Favourable treatment outcomes
(Cured or treatment completed)
n = 25,353 (85.9%)
Unknown
n = 3,845 (92.3%)
Known
n = 321(7.7%)
No recorded outcome
n = 1,201 (31.2%)
Moved/Transferred
n = 932 (24.2%)
Lost to follow up
n = 1,712 (44.5%)
Failed
n = 118 (36.8%)
Died
n = 203 (63.2%)

Figure 2

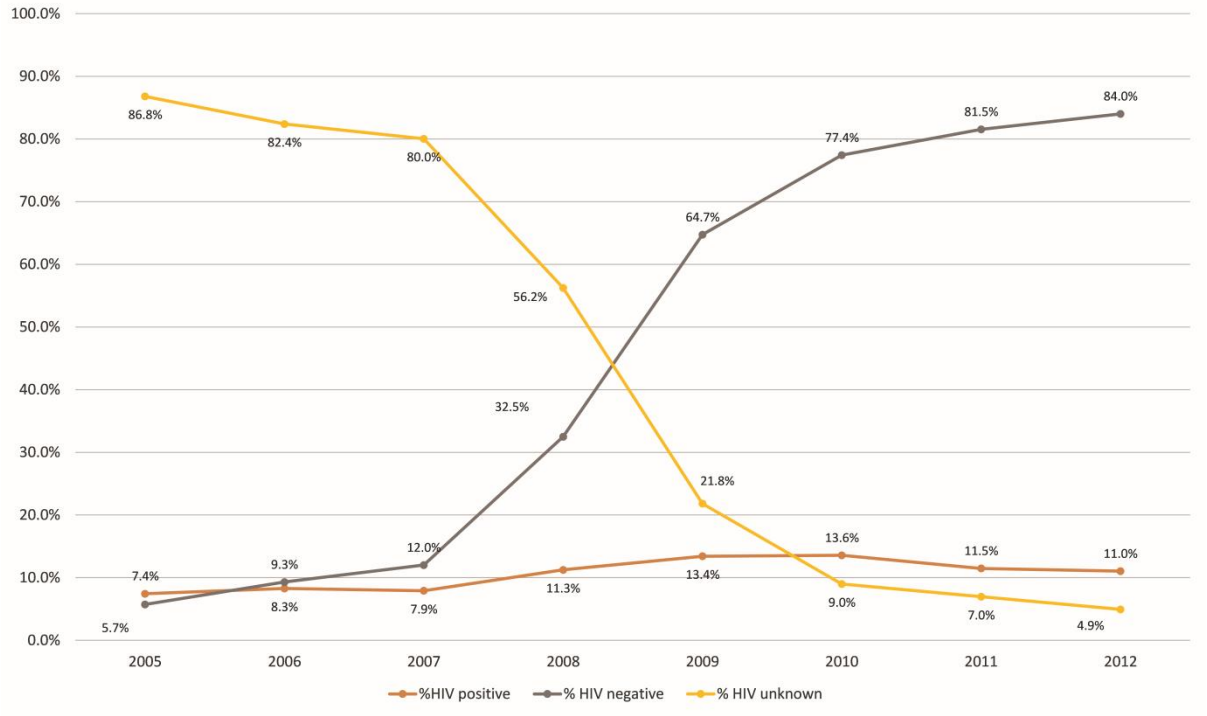

100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
2005
2006
2007
2008
2009
2010
2011
2012
86.8%
82.4%
80.0%
56.2%
21.8%
9.0%
7.0%
4.9%
5.7%
9.3%
12.0%
32.5%
64.7%
77.4%
81.5%
84.0%
7.4%
8.3%
7.9%
11.3%
13.4%
13.6%
11.5%
11.0%
%HIV positive
% HIV negative
% HIV unknown

Figure 3

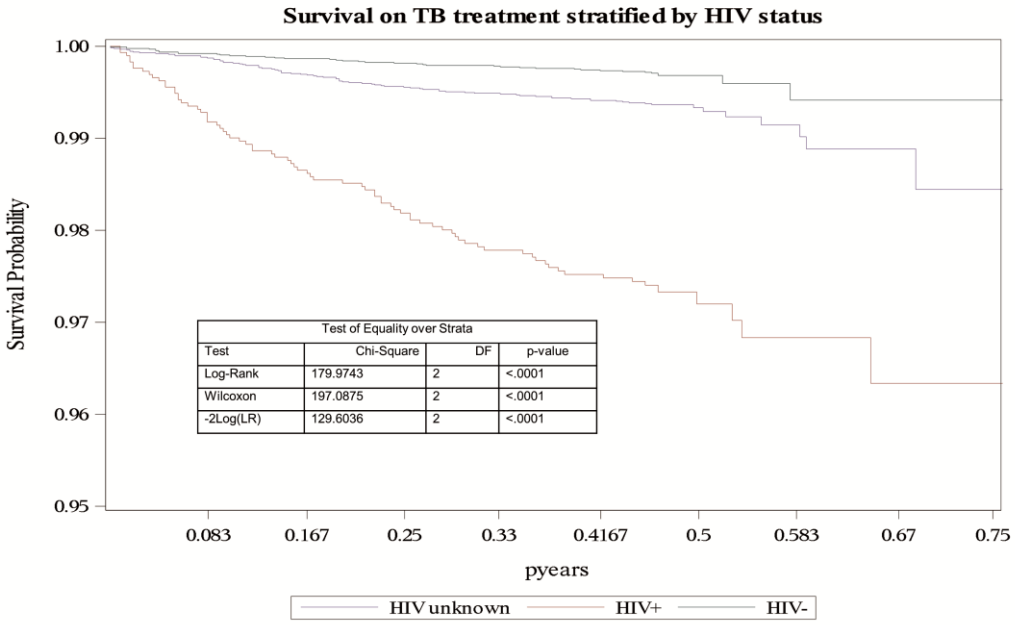
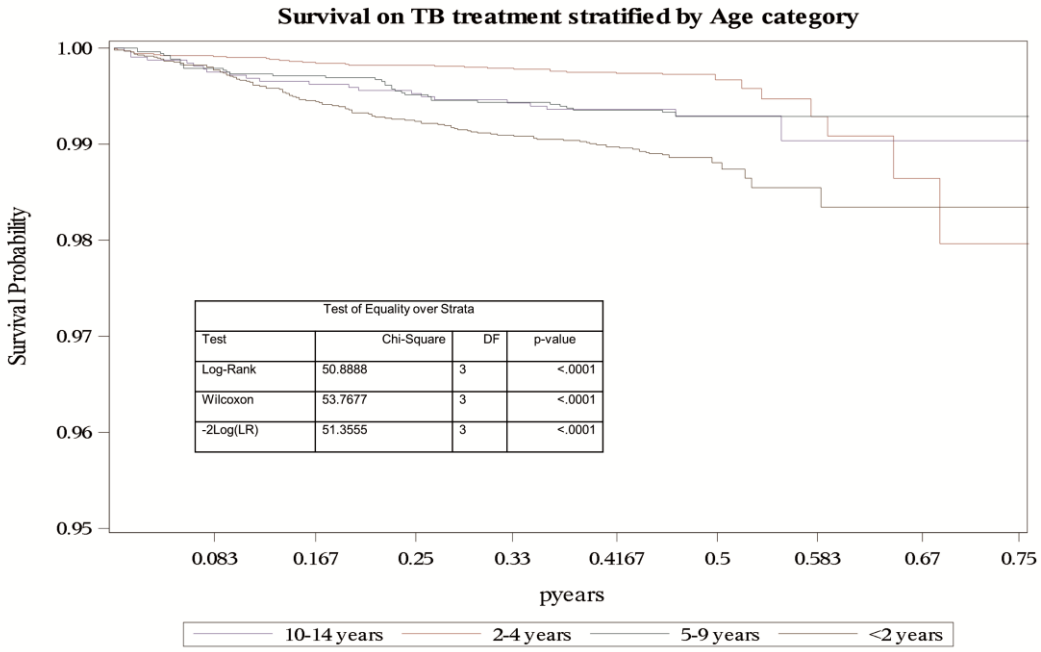

Survival on TB treatment stratified by HIV status
Survival Probability
1.00
0.99
0.98
0.97
0.96
0.95
0.083
0.167
0.25
0.33
0.4167
0.5
0.583
0.67
0.75
pyears
HIV unknown
HIV+
HIV-
Test of Equality over Strata
Test | Chi-Square | DF | p-value
Log-Rank | 179.9743 | 2 | <.0001
Wilcoxon | 197.0875 | 2 | <.0001
-2Log(LR) | 129.6036 | 2 | <.0001

Figure 4


Survival on TB treatment stratified by Age category
Survival Probability
1.00
0.99
0.98
0.97
0.96
0.95
Test of Equality over Strata
Test | Chi-Square | DF | p-value
Log-Rank | 50.8888 | 3 | <.0001
Wilcoxon | 53.7677 | 3 | <.0001
-2Log(LR) | 51.3555 | 3 | <.0001
0.083
0.167
0.25
0.33
0.4167
0.5
0.583
0.67
0.75
pyears
10-14 years
2-4 years
5-9 years
<2 years