Title

The impact of the evolving HIV response on the epidemiology of tuberculosis in South African children and adolescents

Authors:

Karen du Preez (MSc)[1], Muhammad Osman (MSc)[1], James A. Seddon (PhD)[1,2], Pren Naidoo (PhD)[1], H. Simon Schaaf (PhD)[1], Zahn Munch (PhD)[3], Rory Dunbar (PhD)[1], Lindiwe Mvusi (MBChB)[4], Sicelo S. Dlamini (MPH)[5], Anneke C. Hesseling (PhD)[1]

Affiliations:

1. Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
2. Department of Infectious Diseases, Imperial College London, United Kingdom
3. Department of Geography and Environmental Studies, Stellenbosch University, Stellenbosch, South Africa
4. National TB Control & Management Cluster, National Department of Health, South Africa
5. Research Information Monitoring, Evaluation & Surveillance (RIMES), National TB Control & Management Cluster, National Department of Health, South Africa

Running head: Child and adolescent TB in South Africa

Abstract word count: 254 **Full text word count:** 3325/3000

Number of Figures: 3

Number of Tables: 3

Number of Supplemental Tables: 2

Number of references: 31

Keywords: Tuberculosis; HIV; Children; Adolescents; South Africa

Corresponding author email and full address:

Dr Karen du Preez, MBChB, MSc (Epi)

E-mail: karen_dupreez@sun.ac.za; Telephone: +27219389173; +27845811785

Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Parow, 7505, South Africa.

Alternative contact author:

Dr Muhammad Osman

Email: mosman@sun.ac.za; Telephone: +27 83 556 9838

Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Parow, 7505, South Africa.

Summary: (38/40 words)

We studied trends in tuberculosis case notification rates (2004-2016) in South African children and adolescents and explored associations between tuberculosis, age, HIV and sex. Age- and HIV-stratified analyses identified adolescents and young HIV-positive children as particularly vulnerable groups.

Abstract

Background

Few studies have evaluated tuberculosis control in children and adolescents. We used routine tuberculosis surveillance data to quantify age- and HIV-stratified trends over time and investigate the relationship between tuberculosis, HIV, age and sex.

Methods

All children and adolescents (0-19 years) routinely treated for drug-susceptible tuberculosis in South Africa and recorded in a de-duplicated national electronic tuberculosis treatment register (2004-2016) were included. Age- and HIV-stratified tuberculosis case notification rates (CNRs) were calculated in four age bands: 0-4, 5-9, 10-14 and 15-19 years. The association between HIV infection, age and sex in children and adolescents with TB was evaluated using multivariable logistic regression.

Results

Of 719,400 children and adolescents included, 339,112 (47%) were 0-4-year-olds. The overall tuberculosis CNR for 0-19-year-olds declined by 54% between 2009 and 2016 (incidence rate ratio [IRR]=0.46, 95% confidence interval [CI] 0.45-0.47). Trends varied by age and HIV, with the smallest reductions (2013-2016) in HIV-positive 0-4-year-olds (IRR=0.90, 95%CI 0.85-0.95) and both HIV-positive (IRR=0.84, 95%CI 0.80-0.88) and HIV-negative (IRR=0.89, 95%CI 0.86-0.92) 15-19-year-olds. Compared to 0-4-year-old males, odds of HIV co-infection among 15-19-year-olds were nearly twice as high in females (adjusted odd's ratio [aOR]=2.49, 95%CI 2.38-2.60) than in males (aOR=1.35, 95%CI 1.29-1.42).

Conclusions

South Africa's national response to the HIV epidemic has made a substantial contribution to the observed declining trends in tuberculosis CNRs in children and adolescents. The slow decline of tuberculosis CNRs in adolescents and young HIV-positive children is concerning. Understanding how tuberculosis affects children and adolescents beyond conventional age bands and by sex, can inform targeted tuberculosis control strategies.

Background

Modelling studies suggest that 1.5 million children and adolescents develop tuberculosis (TB) each year.[1, 2] Despite TB being preventable and treatable, the World Health Organization (WHO) estimates that 233,000 children (<15 years), died from TB in 2017.[3] South Africa, one of the high TB burden countries, had an estimated TB incidence rate of 520/100,000 population in 2018[1] and an national HIV prevalence of 14.0% in 2017.[4] Despite an initial slow response to the HIV epidemic in South Africa, substantial efforts were made from 2009 to reduce HIV transmission, including to children, with sequential changes to national guidelines leading to progressive roll-out of antiretroviral therapy (ART).[5] All HIV-positive infants became eligible for ART in 2010, and all young children (<5 years) in 2012.[6, 7] Since 2016, all HIV-positive individuals in South Africa have been eligible for ART under the universal-test-and-treat policy.[8]

The risk of developing TB varies substantially with age and HIV status. The risk of progression from *Mycobacterium tuberculosis* infection to disease is the highest in young children, falls to a nadir in pre-pubertal children, and then rises again through adolescence.[9] HIV infection increases this risk of developing TB by approximately 8-fold, with ART reducing the risk by approximately 70%.[10] Adolescents (10-19-year-olds) have also been identified as a vulnerable population, especially if HIV-positive.[2, 11, 12] In addition, there is some evidence that the age-related risk of TB in children and adolescents varies by gender.[13]

The prevalence of HIV and the risk of HIV acquisition also changes with age. For young children, the risk of acquiring HIV is primarily through vertical transmission, either perinatally or during infancy (breastfeeding). During adolescence, the risk of HIV infection due to horizontal transmission rises into young adulthood, with adolescent females being at higher risk of becoming HIV-positive than their male counterparts.[14] With the widespread roll-out of ART to HIV-positive children, an increasing number of perinatally-infected individuals, born during the early stages of the HIV epidemic, have survived into adolescence.[15] HIV-positive adolescents are at high risk of attrition in routine HIV-care services,[16] which may further increase their risk of developing TB if not on ART.[10]

Given the intimate relationship between HIV and TB, it would be expected that the progressive roll-out of ART in South Africa would have produced a substantial decrease in TB case notification

rates (CNRs) in children and adolescents, correlating with the decline in TB incidence in adults. However, it is important to evaluate the interaction between TB, HIV and age since both the risk of TB and HIV is influenced by age. One of the strengths of South Africa's National TB Programme was the implementation of an individual case-based, electronic TB register (ETR.Net) for surveillance of all treated drug-susceptible TB cases since 2004, allowing in-depth age-disaggregated analyses over time. This source of surveillance data provides a unique opportunity to evaluate the relationship between TB, HIV, sex and age and to review trends in TB notification rates over time. In this study, we investigated TB trends in South African children and adolescents by four 5-year age bands in the context of routine programmatic changes in the HIV programme over more than a decade. We further investigated the relationship between HIV infection, age and sex in children and adolescents with TB.

Methods

Study design

This was a retrospective cohort study of all newly registered children and adolescents (0-19 years) routinely recorded in the South African national ETR.Net as the drug-susceptible case-finding cohort from 2004 to 2016.

Setting

South Africa had an estimated population of 58 million people in 2018 and is divided into 9 provinces. In 2017, the estimated national HIV prevalence among pregnant women attending routine ante-natal services was 30.7%[17], and amongst infants 2.7%.[4] Several changes to the national HIV programme have been made since 2010, sequentially increasing access of ART to wider groups of children and adolescents.[5]

Electronic TB treatment register

Since 2004, routine data for drug-susceptible TB have been captured electronically in the ETR.Net from paper-based TB treatment registers at all designated TB reporting units, allowing facility, district, provincial and national reporting on case-finding, sputum conversion and

129 treatment outcome cohorts.[18, 19] These data are also used for annual reporting of national TB
130 surveillance data to WHO.

131 During the study period, TB data were collected and managed by the National Department of
132 Health through the Research, Information, Monitoring, Evaluation and Surveillance (RIMES) unit.
133 Back-end data from ETR.Net were extracted for the period 2004 to 2016 and underwent a
134 systematic data cleaning and de-duplication process.

135 *Definitions*

136 Children and adolescents were divided into four 5-year age-bands (0-4, 5-9, 10-14 and 15-19),
137 to determine the burden of TB and HIV amongst children and adolescents across the age
138 spectrum. HIV status was classified as HIV-negative, HIV-positive, and HIV-unknown,
139 constructed using documented HIV testing results, CD4 results, and cotrimoxazole or ART use
140 from the ETR.Net. The term 'newly treated' refers to TB patients who had not been previously
141 treated, or who had previously received <4 weeks of TB treatment. The site of disease was
142 categorised by treating clinicians as per national guidelines and distinguished only between any
143 pulmonary TB (PTB; with or without extra-pulmonary TB [EPTB]), or EPTB exclusively. Intra-
144 thoracic lymphadenopathy, common in children, is considered PTB in the national
145 programme.[20] International classification of disease (ICD)-10 codes referring to miliary TB and
146 central nervous system TB, including TB meningitis, were combined and classified as
147 'disseminated TB'. A bacteriologically confirmed TB diagnosis included any positive
148 smear/culture/Xpert MTB/RIF (Xpert; Cepheid, Sunnyvale, CA) result on at least one specimen
149 prior to treatment initiation.

150 *Statistical Analyses*

151 Age-stratified TB CNRs were calculated as the number of drug-susceptible TB cases per 100,000
152 population per year in each age category. The Thembisa model, a mathematical model of the
153 South African HIV epidemic and a publicly available data source containing both age-
154 disaggregate HIV and general population statistics,[21] provides population estimates per 1-year
155 age band by sex for each year. These were summed to produce a population estimate per age
156 category for each year of the study, which were used to calculate 1) age-disaggregated TB CNRs

overall and by HIV status, and 2) national age-specific HIV prevalence estimates. To minimize potential bias introduced due to the large proportion of missing HIV data in the earlier years of the study, all HIV analyses were restricted to years where >80% of patients had a known HIV status in all age groups. These criteria were met from 2013, and HIV analyses were therefore only completed using data from the last four years of the study (2013-2016). HIV-stratified TB CNR calculations excluded TB cases with an unknown HIV status, and were expressed as per 100,000 population using the HIV-positive and HIV-negative Thembisa model population estimates.[21] Overall and HIV-stratified incidence rate ratios (IRR) and 95% confidence intervals (CIs) were calculated for each age group.

Univariable and multivariable logistic regression were used to calculate odds ratios (ORs), adjusted ORs (aORs) and 95% CIs of the relationship between clinical characteristics and HIV infection, excluding patients with HIV-unknown status and restricted to data from 2013-2016. We completed age- and sex-stratified analyses of the prevalence of HIV co-infection, and included an interaction term in the multivariable model to account for the observed effect modification of sex and age on the risk of HIV infection. We decided *a priori* that all variables with an independent association (two-sided p-value <0.05) in univariable analyses would be included in the multivariable model. Due to the collinearity between 1) EPTB (site of disease) and disseminated disease, and 2) bacteriological investigation and bacteriological confirmation status, the variable with the strongest association of each was included in the multivariable model. Analyses were completed using STATA SE version 14 (StataCorp, College Station, TX, USA).

Ethics

Stellenbosch University Health Research Ethics Committee provided ethics approval (N16/07/088); permission for the use of ETR.Net data was provided by the National Department of Health of South Africa.

Results

Clinical characteristics stratified by age

A total of 719,400 children and adolescents with drug-susceptible TB were treated and reported in South Africa during 2004-2016 (Table 1). Overall, differences by sex were not observed, with 368,885 (51.3%) of TB cases occurring amongst females. However, the proportion of females increased with age. HIV status was only recorded for 339,177 (47.1%) cases and few had been previously treated for TB (35,566; 4.9%). Most had PTB (654,533; 91.0%) while 2.0% (13,057) had disseminated TB. Bacteriological investigation was recorded in 221,771 (30.8%) of whom 154,255 (69.6%) had a confirmed diagnosis. The proportion who had bacteriological investigations performed and who had bacteriologically confirmed TB increased with age.

Burden and trends of TB and HIV co-infection over time

Both the total number of TB cases and the overall national TB CNR in those <20 years, peaked in 2009 with a steady decline thereafter (IRR 2016 vs 2009: 0.46, 95% CI 0.45-0.47). The 0-4-year age group consistently contributed the most cases each year, followed by the 15-19-year-olds (Figure 1). TB CNRs were highest in the 0-4-year-olds (peak 2008: 635/100,000 population) and peaked in all age groups between 2008 and 2009 (Figure 2).

The uptake of HIV testing improved in all age groups over time, with HIV status reported for >80% of children and adolescents with TB in each age group from 2013. The HIV prevalence amongst children and adolescents with TB varied substantially between the 4 age groups, with the overall percentage HIV co-infected in 2016 being 15% in 0-4-year-olds, 27% in 5-9-year-olds, 43% in 10-14-year-olds and 30% in 15-19-year-olds (Figure 3).

Between 2009 and 2016, TB CNRs declined the most in 5-9-year-olds (72%; IRR 0.28 [95%CI 0.27-0.29]) and the least in 15-19-year-olds (27%; IRR 0.73 [0.71-0.74]) (Supplemental Table 1). The biggest decline in HIV-stratified TB CNRs between 2013 and 2016 was again observed amongst 5-9-year-olds (HIV-negative: 44%, IRR 0.56 [95%CI 0.53-0.58]; HIV-positive: 43%, IRR 0.57 [0.53-0.61]). Both HIV-negative and HIV-positive 15-19-year-olds experienced small reductions in TB CNRs (IRR 0.89 [95%CI 0.86-0.92] and IRR 0.84 [0.80-0.88] respectively). The reduction in TB CNRs amongst HIV-negative 0-4-year-olds was more than three times the

reduction of TB CNRs in HIV-positive 0-4-year-olds (34% [IRR 0.66, 95%CI 0.64-0.67] vs. 10% [IRR 0.90, 95%CI 0.85-0.95]).

The association between HIV infection, age and sex

Between 2013 and 2016, 173,909 children and adolescents were treated for TB: 40,422 (23.2%) HIV-positive and only 17,511 (10.1%) with an unknown HIV status (Table 2).

There was a strong association between age and HIV co-infection (Supplemental Table 2, restricted to 2013-2016). Sex was also associated with HIV status, but in age-stratified analyses the association disappeared in children aged 0-9 years and became more pronounced in the adolescent groups (10-19-year-olds). Previous TB treatment, EPTB only, disseminated TB, bacteriological investigation completed, and bacteriological confirmation were all associated with HIV co-infection.

In multivariable analysis restricted to 2013-2016 (Table 3), the association between age and HIV co-infection was the strongest in 10-14-year-olds, irrespective of sex (males: aOR=4.66 [95%CI: 4.39-4.94]; females: aOR=3.47 [95%CI: 3.28-3.67]; reference: 0-4-year-old males). Variation by sex was the most pronounced amongst 15-19-year-olds, with the odds in females nearly double that of males the same age (aOR (females)=2.49 [95%CI: 2.38-2.60] and aOR (males)=1.35 [95%CI: 1.29-1.42]). The association between HIV co-infection and previous TB treatment, having disseminated TB and bacteriological investigation remained in the multivariable model, with all aORs being slightly lower than in the univariable model.

Discussion

We evaluated age-stratified trends in TB CNRs in the context of HIV in a cohort of nearly 720,000 children and adolescents routinely treated for drug-susceptible TB in South Africa over a 13-year period. Overall, TB CNRs among children and adolescents declined by 54% from 2009 to 2016. This decline was largely driven by young children 0-4 years of age, who accounted for 47% of the total burden and experienced the highest CNRs throughout the study period. This is consistent with what is expected in a high TB incidence setting with a broad-based population pyramid.[9, 22] However, we found important differences in TB CNRs over time when dis-aggregating data by age and HIV status. Adolescents aged 15-19 years experienced the slowest

decline in TB CNRs, irrespective of HIV infection status. In this age group, females with TB had a considerably higher risk of HIV co-infection than males.

When evaluating disease trends over time in different age groups and in the context of the changes in health policies, it is important to consider the birth cohort effect. In South Africa, prevention-of-mother-to-child-transmission of HIV (PMTCT) options were initially limited with slow implementation and uptake prior to 2008.[23] HIV-positive children would have been at high risk of both TB and of early mortality.[10, 24] As the roll-out and uptake of PMTCT increased, children born from 2008 onwards would have a reduced risk of perinatal HIV infection. This effect is evident in the stark reduction in national HIV prevalence amongst 0-4-year-olds during the study period (figure 2). HIV-positive children born before 2008 and who survived then had increased access to ART and subsequently moved into the 5-9 and 10-14-year-old age groups. This explains the transitioning peak in the national HIV prevalence curves through the age groups as children aged and started surviving. Early sexual debut could further contribute to the increasing HIV prevalence amongst 15-19-year-olds, especially amongst females.[25]

Amongst children 0-9 years old, the reduction in HIV prevalence was mirrored by a stark reduction in TB CNRs (59% in 0-4-year-olds [IRR 0.41, 95%CI 0.40-0.42] and 72% in 5-9-year-olds [IRR 0.28, 95%CI 0.27-0.29]) between 2009 and 2016. This is likely due to a reduction in vertical transmission resulting in lower HIV prevalence and subsequent reduced risk of developing TB, as well as early diagnosis and access to ART for those HIV-positive. The change also reflects the high susceptibility of children to TB and the indirect effect of a reduced risk of TB transmission as the adult TB epidemic followed the same downward trajectory since 2009, primarily driven by ART roll-out and uptake.[5] However, HIV prevalence has been increasing amongst 10-19-year-olds during the study period (figure 2).[21] In 10-14-year-olds, this was likely still the result of the higher vertical transmission rates prior to and during the earlier years of the PMTCT programme in these HIV survivors. These perinatally-infected children may have accessed ART before, or as they transitioned into adolescence and experienced the protective effect of ART. In 15-19-year-olds, horizontal HIV transmission drives new HIV infections. A recent study showed that only 66% of 140,028 15-19-year-olds seeking HIV care in South Africa before or during 2016, started

ART.[26] Nearly a third of this vulnerable population therefore remains at high risk of developing TB.

The relatively small reduction in TB CNRs of only 27% amongst 15-19-year-olds between 2009 and 2016 is concerning and remained in the HIV-stratified TB CNRs between 2013 and 2016 (16% drop in HIV-positive and 11% drop in HIV-negative). Adolescents are an important and challenging group to engage in TB and HIV services, and are at high risk of unfavourable TB and HIV treatment outcomes.[12, 16, 27, 28] The success of HIV prevention strategies relies on how well health services accommodate the needs of adolescents. As the population of HIV-positive adolescents infected perinatally is also growing, these individuals are at high risk of being lost in the transition between pediatric and adult care, especially in high-burden settings.[29] TB prevention strategies and treatment should not only consider young children, but also adolescents.

During 2013-2016, TB CNRs for HIV-positive 0-4-year-olds declined much less than for their HIV-negative peers (10% vs 34%, respectively). Young children acquiring HIV infection despite a well-functioning and widely implemented national PMTCT programme likely represent an extremely vulnerable at-risk sub-set of children. These may be children who had undiagnosed perinatal HIV infection or whose mothers did not access PMTCT services, and TB may have been the event that led to the diagnosis of HIV.[30] Unfortunately, we did not have good data on the timing of HIV diagnosis, CD4 count or ART initiation in this routine dataset, and we therefore do not know how many of these children were ART-naïve. HIV-positive children in this age group should be prioritised for ART and healthcare workers should have a low threshold to re-test children born to HIV-positive mothers for HIV. TB exposure in these children should be verified at each contact with health services, as TB preventive therapy substantially reduces the risk of TB in this age group, irrespective of HIV status.[31]

Our study found an association between TB, HIV co-infection and age that differed by sex in adolescents. Amongst younger adolescents (10-14-year-olds), odds of HIV co-infection were slightly higher amongst boys than girls. The reason for this observation is unclear. Sex disparity was most pronounced in 15-19-year-olds, with the odds of HIV co-infection nearly double in older adolescent females. This is consistent with the observed higher HIV prevalence amongst

adolescent females compared to their male counterparts globally and in sub-Saharan Africa.[14, 28] In South Africa, 301,242/342,443 (88%) 15-19-year-olds who entered HIV care during 2005-2016 were female.[26] More data are needed to fully understand the sex disparity seen for TB and HIV during adolescence and explore how this can be addressed in TB services.

Routine TB surveillance data in South Africa rely on health care access, diagnosis, treatment initiation and reporting of TB by routine public services. Thus, children and adolescents who were not diagnosed, who were lost-to-follow-up prior to initiating TB treatment, or were not reported, would have been excluded from this study. The CNRs presented in this study are therefore an underestimate of the true incidence of TB in South African children and adolescents. Uptake of HIV testing in the earlier years was poor, and resulted in a short time-series of HIV-stratified TB data. The data also do not comprehensively report on pre-TB access to ART or the CD4 count at time of TB diagnosis. To minimize any bias due to the large proportion of missing HIV data in the earlier years, we restricted all HIV-analyses to the last four years of the study (2013-2016). During this time, HIV status was known for 90% of patients (156 398/173 909). The Thembisa HIV model was the only available source of age-disaggregated population and HIV prevalence estimates but lacked 95% CIs for children. Given the routine nature of the data, not all children had respiratory samples taken for bacteriological evaluation. Therefore the bacteriology results should be interpreted cautiously. Furthermore, the quality of routine data relies on how accurately and completely the data is recorded and captured by frontline healthcare workers. Excluding cases with a missing HIV status from HIV-stratified CNRs reduced the number of TB cases, and therefore resulted in more conservative estimates of HIV-stratified TB CNRs. Our findings are therefore more likely to underestimate than overestimate the true burden of TB during the study period when stratified by HIV status. Drug-resistant TB in children and adolescents are an emerging area of concern, but are captured and reported in a separate register, and were therefore not included in CNRs presented in this study.

With all HIV-positive patients in South Africa being eligible for ART, and with the imminent roll-out of shorter TB preventive therapy regimens, it will be important to evaluate the impact of these changes in guidelines and control strategies on TB CNRs in all children and adolescents beyond the broad age bands currently recommended by WHO. Such data will help to better understand

how we can plan services to improve TB prevention and treatment for children and adolescents in high TB and HIV burden settings. A successful PMTCT programme in South Africa has resulted in very low HIV prevalence in younger children. However, the maternal antenatal HIV prevalence remains high. Future research should also continue to evaluate the risk of TB in HIV-exposed uninfected children and adolescents. Small changes in the capturing of HIV data in relation to TB episodes could increase the programme's ability to respond to the TB-HIV epidemic in South Africa. Research that is responsive to local programme considerations and the epidemiological context for TB and HIV is needed to inform the design and implementation of child and adolescent-friendly TB and HIV services to better support care in affected children and adolescents.

Acknowledgements

We would like to acknowledge the South African Department of Health, National TB program and the Research, Information, Monitoring, Evaluation and Surveillance (RIMES) unit for the support and extraction of the ETR.Net data set.

Funding

Initial data extraction and cleaning was funded by URC through the TB Care II Project (USAID Co-operative Agreement No. AID-OAA-A-10-00021).

KDP is supported by the Fogarty International Center of the National Institutes of Health under Award Number K43TW011006. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ACH is financially supported by the South African National Research Foundation (NRF) South African Research Chairs Initiative (SARChI), and KDP received grant-holder linked student support. The financial assistance of the NRF towards this research is hereby acknowledged. Opinions expressed, and conclusions arrived at, are those of the authors and are not necessarily to be attributed to the NRF.

MO is supported through funding by the South African Medical Research Council (SA MRC) through its Division of Research Capacity Development under the Bongani Mayosi National Health Scholars Program from funding received from the Public Health Enhancement Fund/South African National Department of Health. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the SA MRC or the funders.

JAS is supported by a Clinician Scientist Fellowship jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement (MR/R007942/1).

Conflict of Interest

The authors has no conflict of interest to declare.

Author contributions

KDP, MO, JAS, PN and ACH conceptualised the study. RD was responsible for data management, including cleaning and preparation. KDP, MO and ZM completed data analysis. All authors contributed towards interpreting the study results. KDP completed the first draft of the manuscript, and all authors provided input on the manuscript drafts. All authors critically reviewed and approved the final version of the manuscript.

References

1. Global tuberculosis report 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
2. Snow KJ, Sismanidis C, Denholm J, Sawyer SM, Graham SM. The incidence of tuberculosis among adolescents and young adults: a global estimate. Eur Respir J **2018**; 51(2): 1702352.
3. World Health Organisation. Roadmap towards ending TB in children and adolescents. Geneva, **2018. Licence: CC BY-NC-SA 3.0 IGO. Available at http://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf?ua=1 [accessed 10 August 2020].**
4. Simbayi LC, Zuma K, Zungu N, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017. Cape Town: HSRC Press. Available at http://www.hsrc.ac.za/uploads/pageContent/10779/SABSSM%20V.pdf [accessed 10 August 2020].
5. Osman M, du Preez K, Naidoo P, et al. Key changes in the public health response to TB and HIV in South Africa. Int J Tuberc Lung Dis **2020**; 24(8): 857-9.
6. National Department of Health. Guidelines for the management of HIV in children. South Africa; 2010. Available at https://sahivsoc.org/Files/Guidelines_for_Management_of_HIV_in_Children_2010.pdf [accessed 10 Aug 2020].
7. National Department of Health. Circular Minute No 2 of 2012: Initiation of anti retroviral treatment (ART) to all HIV positive children aged 5 years and under regardless of CD4 count and/or WHO clinical staging. South Africa; 2012. Available at https://sahivsoc.org/Files/Rx%20of%20children%20under%205-Circular%20Minute%20No%202%20of%202012%20-%20ART.pdf [accessed 10 August 2020].
8. National Department of Health. Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients. South Africa; 2016. Available at https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf [accessed 10 August 2020].
9. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis **2004**; 8(4): 392-402.
10. Dodd PJ, Prendergast AJ, Beecroft C, Kampmann B, Seddon JA. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. Thorax **2017**; 72(6): 559-75.

11. Snow K, Hesseling AC, Naidoo P, Graham SM, Denholm J, du Preez K. Tuberculosis in adolescents and young adults: epidemiology and treatment outcomes in the Western Cape. Int J Tuberc Lung Dis **2017**; 21(6): 651-7.
12. Snow KJ, Cruz AT, Seddon JA, et al. Adolescent tuberculosis. Lancet Child Adolesc Health **2020**; 4(1): 68-79.
13. Seddon JA, Chiang SS, Esmail H, Coussens AK. The wonder years: what can primary school children teach us about immunity to Mycobacterium tuberculosis? Front Immunol **2018**; 9: 2946.
14. Abdool Karim Q, Baxter C, Birx D. Prevention of HIV in Adolescent Girls and Young Women: Key to an AIDS-Free Generation. J Acquir Immune Defic Syndr **2017**; 75 Suppl 1: S17-S26.
15. Sohn AH, Hazra R. The changing epidemiology of the global paediatric HIV epidemic: keeping track of perinatally HIV-infected adolescents. J Int AIDS Soc **2013**; 16: 18555.
16. Kranzer K, Bradley J, Musaazi J, et al. Loss to follow-up among children and adolescents growing up with HIV infection: age really matters. J Int AIDS Soc **2017**; 20(1): 21737.
17. Woldesenbet SA, Kufa T, Lombard C, et al. The 2017 National Antenatal Sentinel HIV Survey, South Africa, National Department of Health, **2019**.
18. Nadol P, Stinson KW, Coggin W, et al. Electronic tuberculosis surveillance systems: a tool for managing today's TB programs. Int J Tuberc Lung Dis **2008**; 12(3 Suppl 1): 8-16.
19. Coggin W. Overview of the Electronic TB Register ETR.Net: CDC South Africa. Available from: https://www.who.int/tb/err/coggin.pdf [accessed 14 July 2020].
20. National Department of Health South Africa. National Tuberculosis Guidelines 2014. Pretoria, South Africa. Available at https://sahivsoc.org/Files/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf [accessed 10 August 2020].
21. Johnson LF, May MT, Dorrington RE, et al. Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. PLoS Med **2017**; 14(12): e1002468.
22. Donald PR. Childhood tuberculosis: the hidden epidemic. Int J Tuberc Lung Dis **2004**; 8(5): 627-9.
23. Burton R, Giddy J, Stinson K. Prevention of mother-to-child transmission in South Africa: an ever-changing landscape. Obstet Med **2015**; 8(1): 5-12.
24. Newell ML, Coovadia H, Cortina-Borja M, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet **2004**; 364(9441): 1236-43.
25. Zuma K, Setswe G, Ketye T, Mzolo T, Rehle T, Mbelle N. Age at sexual debut: a determinant of multiple partnership among South African youth. Afr J Reprod Health **2010**; 14(2): 47-54.

26. Maskew M, Bor J, MacLeod W, Carmona S, Sherman GG, Fox MP. Adolescent HIV treatment in South Africa's national HIV programme: a retrospective cohort study. Lancet HIV **2019**; 6(11): e760-e8.
27. Berry KM, Rodriguez CA, Berhanu RH, et al. Treatment outcomes among children, adolescents, and adults on treatment for tuberculosis in two metropolitan municipalities in Gauteng Province, South Africa. BMC Public Health **2019**; 19(1): 973.
28. Slogrove AL, Mahy M, Armstrong A, Davies MA. Living and dying to be counted: What we know about the epidemiology of the global adolescent HIV epidemic. J Int AIDS Soc **2017**; 20(Suppl 3): 21520.
29. Mapesi H. Challenges for HIV-infected adolescents during transition from paediatric to adult HIV clinics in Africa. Int J Public Health **2020**.
30. Byamungu LN, du Preez K, Walters E, Nachega JB, Schaaf HS. Timing of HIV diagnosis in children with tuberculosis managed at a referral hospital in Cape Town, South Africa. Int J Tuberc Lung Dis **2018**; 22(5): 488-95.
31. Ayieko J, Abuogi L, Simchowitz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. BMC Infect Dis **2014**; 14: 91.

Table 1. Patient characteristics stratified by age group for all children and adolescents (0-19 years) with newly registered drug-susceptible tuberculosis reported in the ETR.Net 2004-2016 *(*n=719 400*)*

	0-4 years		5-9 years		10-14 years		15 - 19 years		Total	
	339 112	%	131 536	%	72 824	%	175 928	%	719 400	%
Sex[1]										
Male	177 439	52.3	66 458	50.5	32 558	44.7	74 056	42.1	350 511	48.7
Female	161 669	47.7	65 078	49.5	40 266	55.3	101 872	57.9	368 885	51.3
HIV status										
HIV-negative	116 141	34.2	34 535	26.3	19 244	26.4	66 655	37.9	236 575	32.9
HIV-positive	33 490	9.9	22 959	17.5	17 388	23.9	28 765	16.4	102 602	14.3
HIV unknown	189 481	55.9	74 042	56.3	36 192	49.7	80 508	45.8	380 223	52.9
TB treatment history[1]										
New	331 005	97.6	124 317	94.5	67 629	92.9	160 880	91.4	683 831	95.1
Retreatment	8 105	2.4	7 218	5.5	5 195	7.1	15 048	8.6	35 566	4.9
Site of TB Disease[1]										
PTB with/without EPTB	317 815	93.7	119 293	90.7	62 089	85.3	155 336	88.3	654 533	91.0
EPTB only	21 296	6.3	12 241	9.3	10 735	14.7	20 592	11.7	64 864	9.0
Disseminated TB[1]										
None	299 727	98.4	114 676	97.7	62 420	96.8	152 884	97.8	629 707	98.0
Present	4 966	1.6	2 671	2.3	2 036	3.2	3 384	2.2	13 057	2.0
Bacteriological investigation										
Not completed	314 031	92.6	104 536	79.5	31 048	42.6	48 014	27.3	497 629	69.2
Completed	25 081	7.4	27 000	20.5	41 776	57.4	127 914	72.7	221 771	30.8
Bacteriological status										
Bacteriologically confirmed[2]	10 473	3.1	12 940	9.8	27 113	37.2	103 729	59.0	154 255	21.4
Clinically diagnosed	328 639	96.9	118 596	90.2	45 711	62.8	72 199	41.0	565 145	78.6

[1] Missing values for the following variables: sex (n=4), TB treatment history (n=3), site of disease (n=3) and disseminated TB (n=76,636)

[2]Bacteriologically confirmed of those in whom bacteriological investigation was completed: 0-4 years=10473/25081 (42%); 5-9 years=12940/27000 (48%); 10-14 years=27113/41776 (65%); 15-19 years=103729/127914 (81%)

ETR.Net=electronic tuberculosis treatment register; EPTB=Extra-pulmonary tuberculosis; PTB=Pulmonary tuberculosis; TB=Tuberculosis.

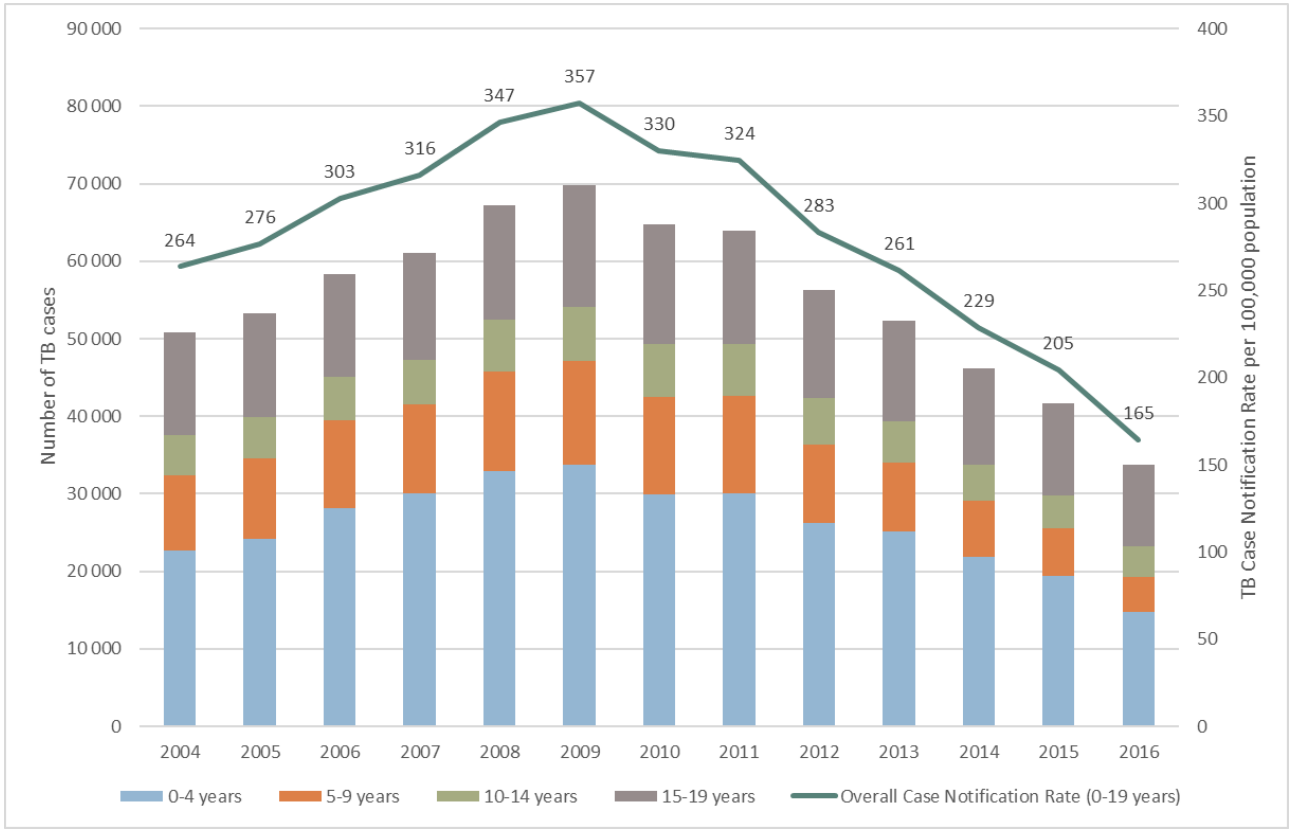

Figure 1. Overall tuberculosis case notification rate (0-19 years) and total number of reported childhood and adolescent tuberculosis cases in South Africa over time

TB=Tuberculosis

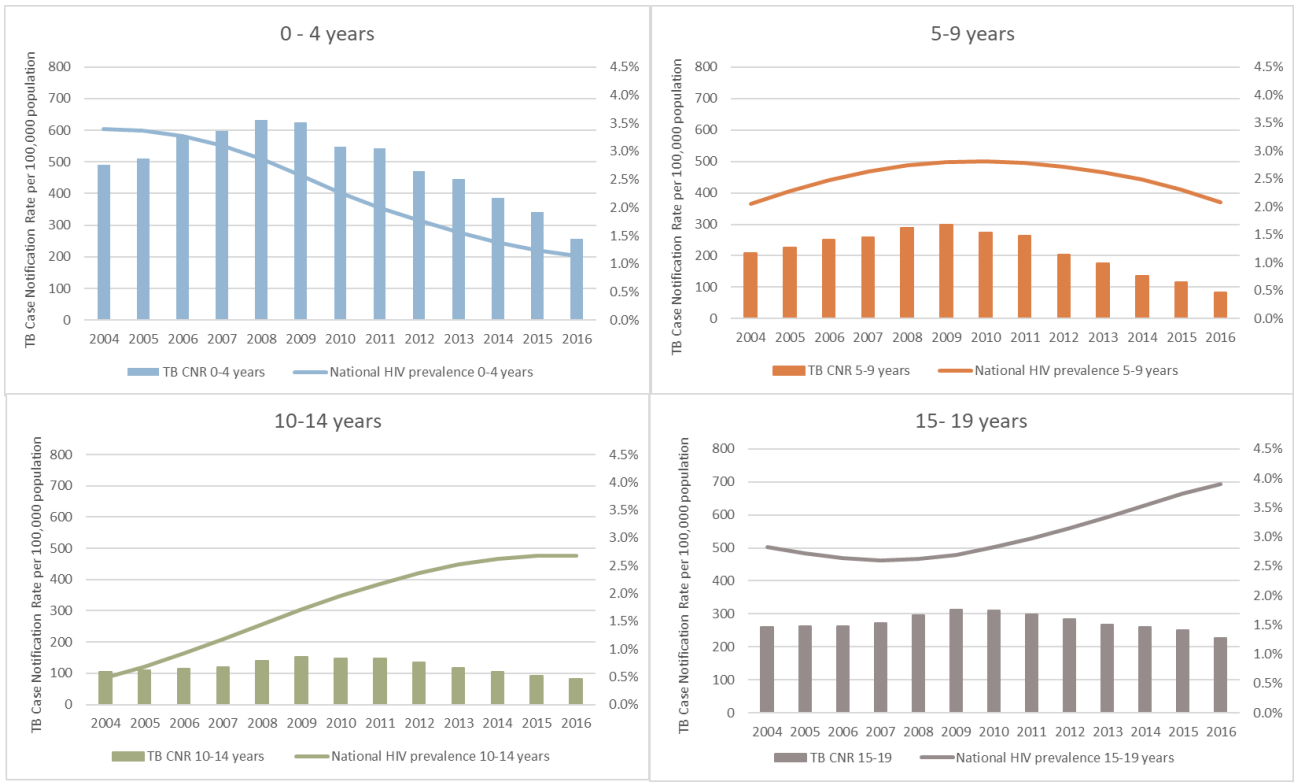

Figure 2. Tuberculosis case notification rates and estimated national HIV prevalence[1] in South Africa for each age band over time (2004-2016)

[1]HIV prevalence is calculated from the THEMBISA model and estimates HIV prevalence across the total population (reference nr 21). CNR=Case notification rate; TB=Tuberculosis.

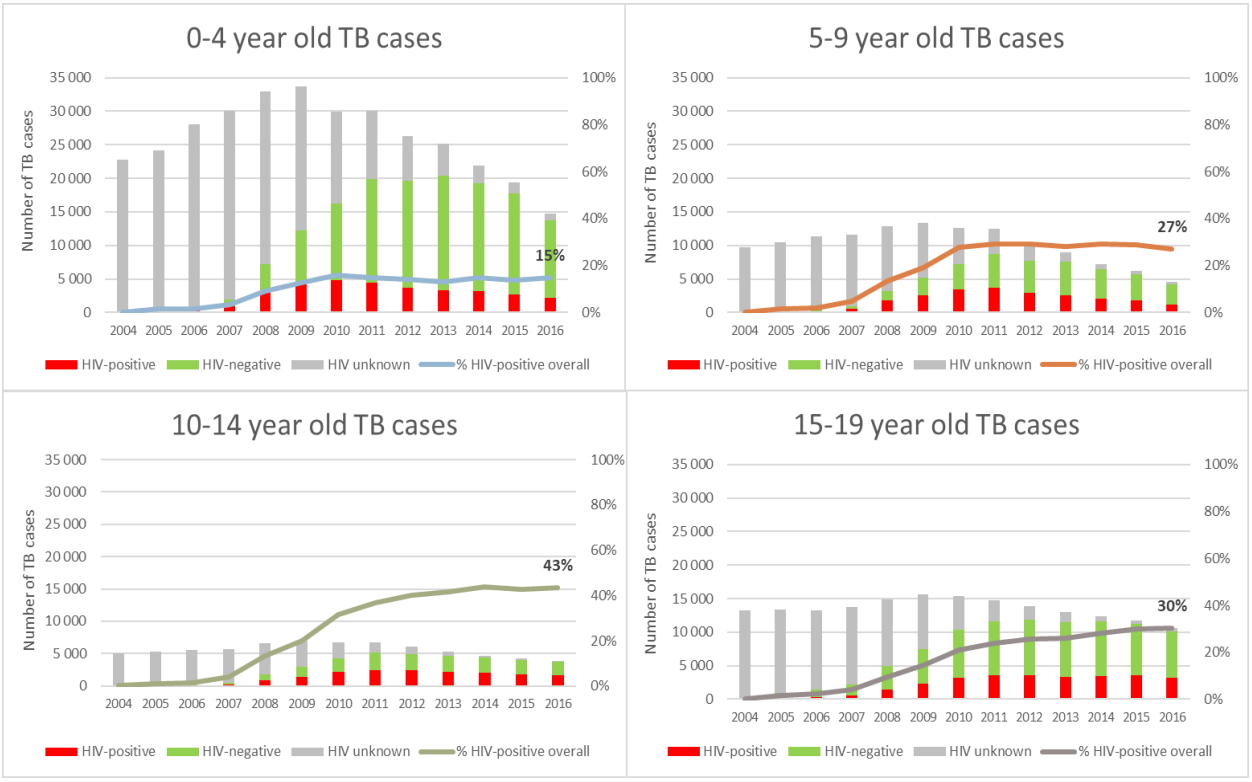

Figure 3. Uptake of HIV testing, HIV status and overall percentage HIV co-infected amongst children and adolescents treated for drug-susceptible tuberculosis in South Africa over time
TB=Tuberculosis

Table 2. Patient characteristics stratified by HIV status for all children and adolescents (0-19 years) with newly registered drug-susceptible tuberculosis reported in the ETR.Net during 2013-2016 (*n=173 909;* excluding data from 2004-2012)

	HIV-negative		HIV-positive		HIV unknown		Total	
	n=115 976	%	n=40 422	%	n=17 511	%	n=173 909	%
Sex								
Male	58 411	50.4	18 384	45.5	8 929	51.0	85 724	49.3
Female	57 565	49.6	22 038	54.5	8 582	49.0	88 185	50.7
Age bands								
0 - 4 years	59 699	51.5	11 426	28.3	10 032	57.3	81 157	46.7
5 - 9 years	16 330	14.1	7 645	18.9	2 968	16.9	26 943	15.5
10 - 14 years	8 948	7.7	7 747	19.2	1 388	7.9	18 083	10.4
15 - 19 years	30 999	26.7	13 604	33.7	3 123	17.8	47 726	27.4
TB treatment history								
New	113 261	97.7	38 027	94.1	17 166	98.0	168 454	96.9
Retreatment	2 715	2.3	2 395	5.9	345	2.0	5 455	3.1
Site of TB Disease								
PTB with/without EPTB	107 912	93.0	35 665	88.2	16 119	92.1	159 696	91.8
EPTB only	8 064	7.0	4 757	11.8	1 392	7.9	14 213	8.2
Disseminated TB[1]								
None	104 263	98.6	34 672	96.7	15 477	98.0	154 412	98.1
Present	1 427	1.4	1 186	3.3	317	2.0	2 930	1.9
Time								
2013	32 720	28.2	11 384	28.2	8 197	46.8	52 301	30.1
2014	30 738	26.5	10 922	27.0	4 503	25.7	46 163	26.5
2015	28 988	25.0	9 816	24.3	2 845	16.2	41 649	23.9
2016	23 530	20.3	8 300	20.5	1 966	11.2	33 796	19.4
Bacteriological investigation								
Not completed	78 162	67.4	22 100	54.7	13 560	77.4	113 822	65.4
Completed	37 814	32.6	18 322	45.3	3 951	22.6	60 087	34.6
Bacteriological status								
Bacteriologically confirmed[2]	28 319	24.4	9 871	24.4	2 577	14.7	40 767	23.4
Clinically diagnosed	87 657	75.6	30 551	75.6	14 934	85.3	133 142	76.6

[1]Missing values for ICD-10 classification: 16 567/173 909 (9.5%)
[2]Bacteriologically confirmed of those in whom bacteriological investigation was completed: HIV-negative=28319/37814 (75%); HIV-positive=9871/18322 (54%); HIV-unknown=2577/3951 (65%)
EPTB=extra-pulmonary tuberculosis; PTB=pulmonary tuberculosis; TB=Tuberculosis.

Table 3. Multivariable model of the association between HIV co-infection, and age, sex and other clinical characteristics, including an interaction term for effect modification between age and sex in children and adolescents treated for drug-susceptible tuberculosis in South Africa during 2013-2016 and reported in ETR.Net (n=141 548[1])

	Adjusted Odds Ratio of HIV co-infection	95% CI	p-value
Age and Sex (including an interaction term)			
0-4 Males	Reference		
0-4 Females	0.99	0.95 - 1.04	0.738
5-9 Males	2.36	2.24 - 2.48	<0.001
5-9 Females	2.31	2.19 - 2.43	<0.001
10-14 Males	4.66	4.39 - 4.94	<0.001
10-14 Females	3.47	3.28 - 3.67	<0.001
15-19 Males	1.35	1.29 - 1.42	<0.001
15-19 Females	2.49	2.38 - 2.60	<0.001
TB treatment history			
Retreatment vs. New (ref)	2.23	2.10 - 2.37	<0.001
Disseminated TB			
Disseminated disease vs. None (ref)	2.37	2.19 - 2.57	<0.001
Bacteriological investigation			
Completed vs. Not completed (ref)	1.20	1.17 - 1.24	<0.001

[1]Analysis excluded patients with a missing ICD10 code (n=14 850) and an unknown HIV status (n=17 511) during 2013-2016 (0-4 years: 10 032 [12%], 5-9 years: 2 968 [11%], 10-14 years: 1 388 [7%], 15-19 years: 3 123 [7%]).
CI=confidence interval; ref=reference; EPTB=extra-pulmonary tuberculosis; PTB=pulmonary tuberculosis; TB=tuberculosis.