The Child Ecosystem and Childhood Pulmonary Tuberculosis: A South African Perspective

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Abstract

Introduction This study investigates drivers of childhood pulmonary tuberculosis (PTB) using a childhood ecosystem approach in South Africa. An ecosystem approach towards identifying risk factors for PTB may identify new directions for intervention. Methods Data were collected as part of a prospective cohort study of children presenting at a primary care facility or tertiary hospital with suspected TB. Characterization of the childhood ecosystem included proximal, medial and distal determinants. Proximal determinants included child characteristics that could impact PTB outcomes. Medial determinants included relational factors such as caregiver health that might impact interactions with the child. Distal determinants included macro-level determinants of disease such as socioeconomic status and food insecurity. Children started on TB treatment were followed for up to 6 months. Multivariate regression models tested independent associations between factors associated with PTB in children. Results Of 1,738 children enrolled in the study, 242 (20%) of children had confirmed PTB, 756 (63%) were started on TB treatment, and 444 (37%) had respiratory conditions other than TB. In univariate analyses, childhood malnutrition and caregiver smoking were associated with treated or confirmed PTB. In multivariate analyses, proximal factors such as male gender and hospitalization and low socio-economic status as a distal factor were associated with PTB. Conclusions Interventions may need to target subgroups of children and families at elevated risk for PTB. Screening for risk factors such caregiver health may guide targeting, and provision of social protection programs to bolster economic security may be important interventions for attenuating childhood exposure to risk factors.

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Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written, informed consent was obtained from a parent or legal guardian and assent from children older than seven years. The study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town.

Abstract

Introduction

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Methods

Data were collected as part of a prospective cohort study of children presenting at a primary care facility or tertiary hospital with suspected TB. Characterization of the childhood ecosystem included proximal, medial and distal determinants. Proximal determinants included child characteristics that could impact PTB outcomes. Medial determinants included relational factors such as caregiver health that might impact interactions with the child. Distal determinants included macro-level determinants of disease such as socioeconomic status and food insecurity. Children started on TB treatment were followed for up to 6 months. Multivariate regression models tested independent associations between factors associated with PTB in children.

Results

Of 1,738 children enrolled in the study, 242 (20%) of children had confirmed PTB, 756 (63%) were started on TB treatment, and 444 (37%) had respiratory conditions other than TB. In univariate analyses, childhood malnutrition and caregiver smoking were associated with treated or confirmed PTB. In multivariate analyses, proximal factors such as male gender and hospitalization and low socio-economic status as a distal factor were associated with PTB.

Conclusions

Interventions may need to target subgroups of children and families at elevated risk for PTB. Screening for risk factors such caregiver health may guide targeting, and provision of social protection programs to bolster economic security may be important interventions for attenuating childhood exposure to risk factors.

Introduction

Childhood tuberculosis (TB) is a major global health problem. There are an estimated 1.1 million children living with TB[1] and 250,000 deaths caused by TB annually[2]. Tuberculosis ranks among the top ten global causes of death for children, including children under five years[3]. The prevalence of TB is especially high among children and adults from low- and middle-income countries such as South Africa[4; 5]. South Africa has one of the highest country burdens of TB globally with over 300,000 people falling ill with TB in 2018, of which 9% were children[1].

Conceptual hierarchical frameworks are useful to characterize etiology of chronic health conditions such as TB. Previous studies have utilized frameworks that organize determinants of chronic disease into proximal, medial and distal levels of the ecosystem[6; 7]. Consideration of these ecosystem dimensions of health can guide efforts to reduce disease burden for priority populations in the TB epidemic such as children. Attention towards the ecological aspects of TB health for children is vital for several reasons. Diagnosis and appropriate treatment of TB among children are dependent on having an effective, healthy caregiver. Individuals and families affected by TB are often faced with challenging economic environments. These adverse economic environments can contribute to psychological distress, reduce access to protective resources and increase individual vulnerability to poor TB outcomes[8; 9]. Such environments can predispose children to malnutrition, which can increase the risk of childhood TB[10-12]. More directly, caregiver health including psychological distress and substance abuse has been linked to TB non-adherence among adults; these caregiver factors may also affect TB outcomes among children. Therefore, the overarching child ecosystem may affect childhood TB incidence and outcomes.The child ecosystem, including caregiver health and the broader social and economic environment are vital factors to address.

The aim of this study was to investigate factors associated with PTB in children and explore health markers that characterize the ecosystem of childcare to better understand the links between the childhood ecosystem and PTB**.**

Methods

Study design and Setting

Data were derived from a prospective study of children enrolled with suspected TB disease in a TB diagnostic study at two sites in Cape Town, South Africa: 1) Nolungile Clinic, a primary health care clinic in an urban low socioeconomic area, and 2) Red Cross War Memorial Children's Hospital, a tertiary care referral hospital[13; 14]. Children with suspected pulmonary TB (PTB) were followed at 1, 3 and 6 months for response to treatment. Ethical approval for the study was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences at University of Cape Town (UCT HREC:045/2008). Written informed consent was obtained from a parent or legal guardian, and verbal assent was obtained from children 7 years or older.

Enrollment and Participant Consent

Inclusion criteria were: 1) children less than 15 years old with suspected TB based on cough of any duration and one of the following: household TB contact; 2) recent weight loss; 3) positive tuberculin skin test or a chest radiograph suggestive of PTB[13; 14]. TB therapy was initiated at the discretion of the treating doctor. Follow-up visits were done at 1, 3 and 6 months for children on TB therapy and at 1 and 3 months for those not treated.

Outcome measures

Outcome measures used in our child-ecosystem framework include TB diagnostic category and TB treatment. To look for patterns among TB related determinants using the childhood ecosystem approach, malnutrition was selected as an outcome measure for an additional analysis given the known risk factors between malnutrition and childhood TB. PTB diagnostic categorization was based on clinical and microbiological investigations, in line with National Institute of Health (NIH) consensus definitions as 'confirmed PTB' (microbiologically confirmed), 'unconfirmed TPB' (microbiologically negative, clinically diagnosed) and 'unlikely PTB' (lower respiratory disease not due to TB with improvement on follow-up in the absence of TB treatment)[15]. We also examined treatment for those clinically diagnosed with PTB. Children falling in the category 'unlikely' served as controls compare to those children falling into the categories of confirmed and likely (but unconfirmed) PTB.

Ecosystem Measures

Determinants of TB diagnostic category and TB treatment were organized into proximal, medial and distal levels as part of our hierarchical framework for understanding the childhood ecosystem for TB in South Africa. Proximal determinants were understood as factors that were specific to the individual child characteristics including demographic factors that were hypothesised to impact child TB outcomes such as gender and TB treatment. Medial determinants including factors relating to interpersonal factors that might impact childhood TB. These factors included aspects of caregiver health that might impact interactions with the child (psychological health, substance use, stress) and other interpersonal measures such as social support. Distal determinants included macro-level determinants of disease such as socioeconomic status (SES) and food insecurity.

Child-focused measures

Clinical diagnostics for children other than TB diagnosis and treatment were operationalized as proximal measures in PTB consistent with how they were operationalized in the chronic disease context by Egger and Dixon[6]. Measures include gender and previous hospitalization for TB.

Caregiver Questionnaire

To capture the medial and distal measures of the child-ecosystem, caregivers completed a self-administered questionnaire at enrolment to assess risk factors for TB. The questionnaires included assessment of SES[8], substance abuse, psychological distress, perceived stress, social support and on caregiver health including substance use was collected. Six measures were used to contextualize the child ecosystem measuring health status for caregivers, including the following.

Kessler's psychological distress scale

Kessler's psychological distress scale (K10)[16] was used to measure caregivers' psychological distress. For K10 a total score was calculated; a score [?] 30 was indicative of severe psychological distress. The K10 scale has been previously validated among adults in South Africa, ages 18 or older with moderate discriminate validaity[17].

Perceived stress

The Cohen Perceived Stress Scale (PSS)[18] was used to measure caregivers' perceived stress level. For the PSS, a total score was calculated; a score $>$ 20 was indicative of high stress levels.

Perceived Social Support

A modified Multidimensional Scale of Perceived Social Support[19] (MSPSS) was used to assess caregivers' access to social support, comprising 12 questions with a four-point scaling a total score was calculated; three levels of support were generated, $<$28 high, 28 $-$ 38 moderate and $>$38 low.

Substance abuse

The Alcohol Use Disorders Identification Test-C (AUDIT-C)[20] was used to collect information about alcohol use and the Fagerström Test for Nicotine Dependence (FTND) information about cigarette smoking[21]. The AUDIT-C is a 3-item version of the longer AUDIT scale[20]. Studies have found high comparability between the AUDIT-C and the full AUDIT[22].

The FTND is an instrument used to assess the intensity of physical addiction to nicotine[21]. The measure consists of 6 questions with scores of 0 to 1 for yes/no items and scores of 0-3 for multiple-choice items. The thresholds for dependence are the following: scores 1-2: low, 3-4: low to moderate, 5-7: moderate, $>$8: high. A limited number of substance abuse questions were completed by caregivers resulting in missing data. For the FTND, only classification of caregivers as smoker or non-smokers was possible.

Nutritional Status

To capture the distal factors of the child ecosystem, we examined food insecurity. Specifically, we examined child malnutrition as a proxy for food insecurity. We examined childhood nutrition by calculating height-for-age (HAZ), weight-for-age (WAZ) and weight/height-for-age (WHZ) z scores using World Health Organization (WHO) Child Growth Standards[23]. Under-weight-for-age was defined as a weight-for-age z score $<$-2, malnutrition as weight-for-age $<$-3, stunting as height-for-age z score $<$-2, and severe stunting as a height-for-age z score of $<$-3.

Socioeconomic Status & Educational Attainment

To capture distal factors, SES was assessed using a list of 14 common household items and amenities, adapted from an SES scoring system used in social epidemiology in South Africa[8]. The median number of assets reported by the caregivers was 7 assets and a cut point was established. Lower SES was defined as a household with 7 or fewer assets and higher SES defined as a household with 8 or more. An additional measure of monthly income was assessed to further understand caregiver resources. Caregiver monthly income was categorized based on the three follow categories $<$\$68, \$68-340, and $>$\$340 USD. In addition, caregiver education was explored as a risk factor for childhood TB. Education was classified as $<$10 or [?]10 years of schooling.

Data Analyses

Data analyses were performed using STATA 15.1[24]. Exploratory data analysis of categorical and continuous variables included frequency tables and histograms of continuous variables to determine distribution. Simple descriptive statistics were used to characterize the study population. Normally distributed continuous data were summarized by mean and standard deviations (SD); non-normally distributed continuous data by median and interquartile range (IQR). Categorical data were summarized as number and proportion. Statistical tests included chi-square test of equal proportions and Kruskal-Wallis comparison of medians. Separate multivariate regression models were developed to futher investiage the collective relationship between independent variables in the childhood ecosystem mode and PTB in children, TB treatment and malnourished children. Only variables that were significant in the univariate models in addition to age and gender were included in multivariate models. Results of the regression models are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Separate regression analyses looked at factors related to non-adherence to follow-up visits. Statistical tests were two-sided at $\alpha = 0.05$.

Results

Between September 2010 and July 2017, 1,738 children were enrolled at the two study sites [Figure I]. 1,202 (69%) caregivers completed questionnaires; 80% were completed by the mother, 5% by the father, 9% by another family member. Six percent of caregivers were not a family member or were not specified. Nearly all (94%) caregivers were female, with a median (IQR) age of 30 (25 - 37) years. Less than <1% of the caregivers were younger than 18 years. Overall, 34% of caregivers reported being HIV-infected [Table II]. Nearly a quarter (24%) of caregivers were previously treated for TB. Most (73%) caregivers completed at least ten years of schooling.

Characteristics of Children

Most children, n=833 (69%) were hospitalized; n=369 (31%) presented as an outpatient at a clinic not needing hospitilization.The median (IQR) age was 2.9 (1.5 - 5.5) years; 50% were male and 14% were HIV-infected. The median (IQR) z-score for weight-for-age was -0.7 (-1.6 - 0.2), and height-for-age -1.0 (-2.0 - 0.2). Twenty-six percent were classified as stunted, 17% as under-weight-for age, 12% as severely stunted and 7% as malnourished [Table I].

Proximal Factors

Child TB Disease

There were 242 (20%) of children with confirmed PTB, 560 (47%) with unconfirmed TB and 400 (33%) with unlikely TB. Overall, n=756 (63%) of children were started on TB treatment [Table I]. Treated PTB was associated with the following child characteristics in univariate analyses: male ($p = 0.004$), previous hospitalization ($p < 0.001$), lower weight-for-age z score ($p = 0.001$), lower height-for-age z score ($p <= 0.003$) [Table III]. Previous TB treatment was found to be protective against being started on TB treatment ($p = 0.028$). In the multivariate analysis, male gender ($p = .0004$) and previous hospitalization ($p < 0.001$) remained significantly associated with treated PTB as proximal factors.

Adherence to the 3-month follow-up visit

Of the 1,202 children whose caregiver completed the psychosocial questionnaire at baseline, 6 (0.5%) children died before the 3-month visit, and 27 (2%) were disenrolled due to relocation. Overall, adherence in this study was high, approaching 94%. Of the remaining 1,169, 6% did not attend the 3-month visit and were considered lost-to-follow-up (LFTU) [Table I]. LTFU was associated with children with severe stunting ($p = 0.017$), hospitalization ($p < 0.001$), caregiver smoking ($p = 0.009$) or severe psychological distress as assessed based on the Kesler 10 questionnaire administered to the caregiver questionnaire ($p = 0.019$) in univariate analyses. In a multivariate logistic regression model, severe stunting was independently associated with non-adherence to the three-month follow-up visit [Supplemental Table VI].

Medial Factors

Caregiver Characteristics

Overall, 233 (23%) caregivers reported smoking while 166 (22%) consumed alcohol; 308 (45%) of caregivers were classified as experiencing high stress [Table II]. Of all caregivers, 61% perceived that they had high social support, 32% moderate social support and 8% low social support [Table II]. Active smoking (p=0.019) was a caregiver characteristic associated with treated childhood TB in univariate analyses. Previous TB treatment of the caregiver was protective (p = 0.050) [Table III]. A similar association was found when analyzed by microbiologically-confirmed PTB [Table V].

Psychological Distress

Of all caregivers, 863 (72%) completed all questions on the K-10 questionnaire. The median score (IQR) was 23 (15 – 30); 40% were classified as being well, 15% as having mild distress, 14% as having moderate distress and 31% as having severe distress (K-10 score [?]30). There was no difference in the proportion of caregivers with severe psychological distress across the three categories of children with PTB (p = 0.249) [Table II]. For the outcome of malnutrition, severe psychological distress was associated with malnutrition among children in both the univariate and multivariate analyses (p=0.028) and (p=0.015), respectively [Table IV].

Distal Factors

Socioeconomic Status

Overall, 648 (62%) of households were classified as of low SES. When examined by monthly income, 59% of caregivers earned less than $68, 38% earned between $68 - 340 and 3% earned more than $340 per month [Table II]. Socio-economic status was measured in several ways, caregiver monthly income was associated with differences in childhood TB status (p=0.003); as was caregiver educational attainment of less than 10 years (p=0.010) [Table II]. Both relationships remained significant in the unadjusted model for PTB in children. Monthly income was not included in multivariate analyses due to missing data. Inclusion of this measure did not impact findings in supplementary analyses. In the univariate analyses monthly income below $68 USD and educational attainment below 10 years were also associated with microbiologically confirmed TB [Table V]. Low SES remained statistically significant in the multivariate analyses for children with microbiologically confirmed PTB (p=0.036), further highlighting the importance of this distal risk factor.

Nutritional Status

Nutritional status was looked at in two ways. First, it was used as a proxy for food insecurity to explore the impact of this distal factor on PTB. Second, it was used as an outcome variable to look at patterns between TB determinants and risk factors related to TB . Among children with malnutrition, suboptimal nutritional status, defined as weight-for-age <-3 was associated with the following child characteristics: younger age (p = 0.016), HIV infection (p = 0.001), hospitalization (p <0.001) and the following caregiver characteristics: less than 10 years of schooling (p = 0.005), HIV infection (p=0.008), smoking (p <0.001) and severe psychological distress, (p = 0.028). In a multivariate logistic regression model, child HIV-infection (p <0.001), hospitalization (p = 0.018), caregiver active smoking (p <0.001) and caregiver with severe psychological distress (p = 0.015) were independently associated with childhood malnutrition [Table IV].

Discussion

Our findings indicate that several proximal, medial and distal factors in a child's ecosystem may impact on the risk of childhood PTB and nutritional status. Proximal risk factors for childhood TB included sex and previous hospitalization. Consistent with this, young male South African children have been reported to be at higher risk for tuberculin skin test conversion, TB disease and LRTI, which may reflect a biological susceptibility due to hormonal or other factors[25]. Medial risk factors included caregiver tobacco use. While caregiver tobacco use was not associated with childhood PTB beyond univariate analyses, caregiver tobacco use is a known risk factor for PTB. Tuberculosis and second-hand smoke exposure have a severe negative impact on the respiratory system. A meta-analysis conducted on second hand smoke (SHS) exposure and TB risk has shown that children have more than 3-fold increased risk of SHS-associated active TB compared to those not exposed to SHS[26]. Similarly, caregiver psychological distress was not associated with childhood PTB. However, severe psychological distress among caregivers was common. This may reflect the burden of caring for a child with illness and environmental stressors inherent in living in poverty[1; 3]. The high number of caregivers surviving on a subsistence budget in our study may compound the elevated levels of psychological distress. This is consistent with the literature, that has found an association between caregiver psychological distress and socioeconomic status[8].

Finally, we examined distal factors linked to childhood TB. Caregivers with less than 10 years of schooling, a monthly income of less than <$68 per month were distal determinants associated with childhood TB. As evidenced through the outcome of mycobacteriologically confirmed TB limited monetary resources and educational attainment underscore the structural barriers some caregivers experience when caring for a child with TB.

Malnutrition is a known risk factor for childhood TB[5]; however, this link was only evidenced by our findings that low-weight or low-height for age were associated with childhood TB in the univariate analyses. This may also reflect that our control group were children sick with non-TB respiratory illnesses, for which malnutrition may also be a risk factor. Medial factors observed for the outcome of TB diagnostic category and TB treatment related to caregiver characteristics were also associated with childhood malnutrition at baseline. Caregiver smoking was an important risk factor for childhood malnutrition with a 3-fold increased risk for childhood malnutrition. Malnutrition, was more than twice as likely to be present in children of caregivers who suffered from severe psychological distress. Given the nuanced links between childhood TB and proximal, medial and distal risk factors in our data, child malnutrition appears to be a distal risk factor for childhood TB that needs further exploration. Additional studies using a child ecosystem approach are needed to confirm our findings in relation to child nutrition.

The proximal, medial and distal factors identified in our ecosystem analysis help to provide an important context to the high prevalence of TB among children in this population. Promisingly, adherence in this study was extremely high. Despite the high adherence rates, rates of lost-to-follow-up shed light on a subpopulation in our study that could benefit from family-ecosystem oriented interventions. Of the 6% of children that did not attend the 3-month visit, loss-to-follow-up was associated with proximal, medial and distal factors associated with childhood TB and childhood malnutrition that we identified using a childhood ecosystem framework. These findings indicate that caregivers with less schooling and suboptimal mental health may need additional support from healthcare systems to ensure that adherence for their children's TB treatment stays high.

The high rates of psychological distress among caregivers is concerning. These data are consistent with reported rates of psychological distress in studies of adult TB patients in South Africa[9-11], and how this may relate to childhood TB including adherence to follow-up visits is an avenue that warrants further exploration.

Limitations include that questionnaires were self-completed by caregivers. As such, prevalence of smoking, alcohol use or psychological distress may have been underestimated.That notwithstanding, a strong association was shown between these risk factors as organized through the childhood ecosystem approach and TB diagnosis, TB treatment and childhood malnutrition. Second, only 69% of the caregivers of children consented to completing the questionnaires. Caregivers that elected to not participate in this study may have been less healthy [Supplemental Table VII]. Our reported prevalence rates represent the minimum prevalence for psychological distress or substance use. Reasons for not consenting were not recorded. No differences in age, level of schooling or gender between those that consented and those that did not consent were found.

Despite these limitations, the findings emerging from this study provide a clearer picture of risks for childhood TB. Our findings highlight the need for broad interventions to provide appropriate support protection strategies to reduce this burden, such as labor market supports such as job training or temporary subsidies to families in need. Additional research is required to explore the impact of the child ecosystem during transitional points in the development trajectory. For example, the role of family, peers, and individuals in the educational ecosystem may have varying points of prominence depending on what stage of development the child is in. Interventions should consider developmental milestones that may be leveraged for maximum intervention effect. Such studies may provide a more nuanced understanding and approach to risk reduction of transmission, diagnosis or management of TB.

Conclusion

Our findings indicate the importance of proximal factors (e.g. male gender, sicker children e.g. those hospitalize, medial factors (e.g. caregiver tobacco use) and distal factors (e.g. educational attainment, economic stability, nutritional status) in childhood PTB. Our results underscore important entry points to leverage in future interventions. Current, childhood TB interventions are primarily focused on the continuum of care in terms of prevention, adherence and treatment. While these are critical components in achieving TB prevention, our findings suggest that other entry points include a more holistic family approach such as the impact of distal factors on childhood TB. Future interventions may need to target subgroups of children and families who are elevated risk for TB diagnosis and treatment. Within TB endemic settings, screening for risk factors such as psychological distress or tobacco counseling among caregivers with children who are at high risk for TB or who have TB, as well as provision of social protection programs to bolster economic security may be critical in limiting children's exposure to TB risk factors.

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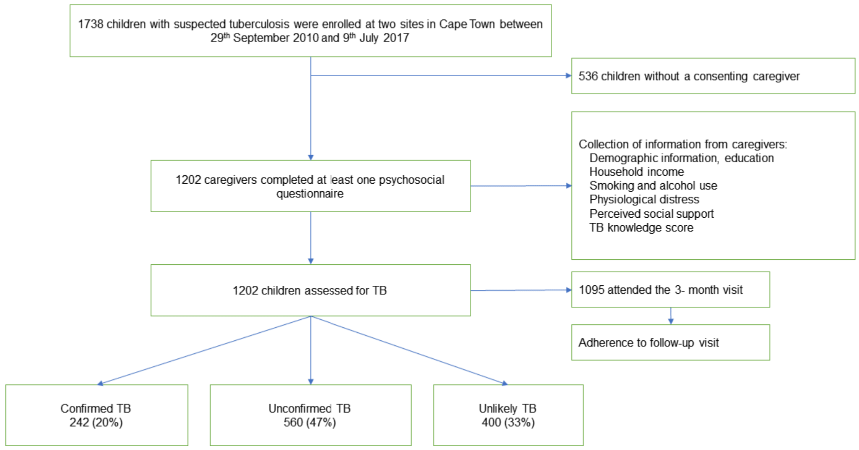
Figure 1: Flow diagram of childhood tuberculosis diagnosis across study sites



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