

1 **TITLE PAGE**

2 Title: Adherence to Childhood Tuberculosis Treatment in Mozambique

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22 SUMMARY

23 Background: There is limited literature regarding adherence rates for the treatment of TB
24 in children. We aimed to describe TB treatment outcomes and adherence as well as to
25 evaluate associated factors to poor adherence in Mozambican children.

26 Methods: This is a sub-study of a community TB incidence study among children <3years
27 of age... Incomplete adherence included the sum of lost to follow-up cases plus those with
28 a delay of >3 weeks to treatment completion.

29 Results: Fifty TB treatments were assessed. Forty-four (88.0%) patients completed
30 treatment, 2(4.0%) died during treatment and 4(8.0%) were lost to follow up. Incomplete
31 adherence was observed in 31.3%(15/48) of cases and was associated with malnutrition or
32 history of a migrant mother.

33 Conclusion: Although treatment outcome is overall good, there is still a significant
34 proportion of incomplete adherence. Further larger paediatric TB cohorts and qualitative
35 approaches are needed to assess and confirm potential factors for non-adherence

36 **TEXT**

37 **BACKGROUND:**

38 According to studies performed in the smear positive adult population, tuberculosis (TB)
39 therapy requires a high adherence rate of over 90% to facilitate cure(1,2). In adults, poor
40 adherence has proven to increase the risk of morbidity, mortality and drug resistance at
41 an individual and population level (3,4). Incomplete adherence to long term therapy is
42 one of the greatest challenges towards implementing the World Health Organization
43 (WHO) End TB strategy, especially in Africa where the treatment success rate (81% in
44 2013) has not reached the Stop TB 90% target (5,6).

45

46 Children could account for 20-40% of all TB cases in high burden settings (7). Young
47 children are at highest risk of developing TB disease as well as rapid disease progression
48 and mortality if diagnosis and treatment are delayed(8). Adherence to TB treatment in
49 children is complex and is influenced by patient and healthcare system factors, among
50 others(9). It depends on the understanding and motivation of caretakers, who frequently
51 have limited awareness of the disease (3,10).

52

53 Studies on therapy for latent TB infection in children have shown low completion rates
54 ranging from 44-78%(11). Treatment outcomes for pediatric TB disease in the African
55 region have also shown high rates of poor outcomes (deaths, treatment failures and lost
56 to follow-up) ranging from 10-19%(12–17). However, there are few studies which report
57 adherence and treatment duration(11). In addition, there is very limited data on

58 associated barriers to anti-TB treatment in young children (11,18–20). Therefore, the aim
59 of this study was to describe the treatment outcomes and adherence to TB treatment and
60 to evaluate factors associated with poor adherence in Mozambican children aged less
61 than 3 years of age.

62

63

64 **METHODOLOGY**

65

66 *Settings*

67 This study was conducted at the Manhiça District, Southern Mozambique, where the
68 Manhiça Health Research Center runs a health and demographic surveillance system
69 (HDSS) (21) . This setting has a high incidence of both TB and HIV with an estimated
70 community-based incidence rate of TB among children < 3yr of 470/100,000 person-
71 years(22–24) and an estimated case detection rate of 41%(25). TB treatment is offered
72 free at no cost to the patient at the health units and pediatric fixed-dose combinations are
73 available following WHO 2010 dose recommendations(26). At the time of the study
74 implementation, pediatric TB treatment for smear negative pulmonary cases and non-
75 severe forms of extrapulmonary TB, included an intensive phase of 2 months of daily
76 Isoniazid, Rifampicin and Pyrazinamide, followed by 4 months of daily Isoniazid and
77 Rifampicin , with weekly and monthly clinical checks and drug collection respectively (27).
78 All TB cases co-infected with HIV are managed in an integrated manner with the provision
79 of cotrimoxazole preventive therapy and anti-retroviral therapy at TB clinics.

80

81 *Study Design*

82 This is a sub-study of a larger prospective cohort study that assessed the minimum
83 community incidence of TB among young children (<3 years of age) over a 1-year period
84 (October 2011- 2012), whose detailed methodology and findings have previously been
85 published(22). Briefly, all presumptive TB cases were evaluated through physical and
86 radiological examination, HIV and tuberculin skin testing, as well as smear microscopy and
87 culture of both induced sputum and gastric aspirate samples. All participants had at least
88 one follow up visit arranged within six months of recruitment. All TB cases were registered
89 with the National Tuberculosis Program (NTP) and managed according to established
90 national clinical guidelines. Treatment was always initiated at the Manhiça District
91 Hospital (MDH) and patients 'care was then transferred to their corresponding peripheral
92 health unit, if applicable. For the purpose of this analysis, TB cases were defined as any
93 case registered to initiate TB treatment at the NTP during the study period. In the
94 incidence study, TB cases followed the National Institute of Health (NIH) case definition
95 for childhood TB (28) (See Box1).

96

97 *Data Collection and analysis*

98 Demographic and clinical data were obtained at the initial visit, and follow-up clinical data
99 were recorded at every subsequent visit. Other socio-demographic data was obtained
100 through the HDSS 2012 data. Information on the WHO treatment category, follow up
101 visits, treatment outcome and adherence were retrospectively extracted from registers of

102 the NTP into a structured data collection tool. Delays in treatment completion were
103 calculated based on the registered date of treatment initiation and treatment completion.

104

105 Proportions were compared using the Fisher's exact chi-squared test. Prevalence ratio
106 (PR) and its 95% confidence intervals (CI) were calculated from poisson regression with robust
107 standard errors to measure the strength of the association between clinical and
108 demographic factors and adherence categories. Programmatic data from the NTP at the
109 MDH for other age groups during the same period was used for comparison. Statistical
110 software for analysis was Stata 11.2 (StataCorp. 2013. Stata: Release 11, StataCorp LP,
111 Statistical Software, College Station, TX).

112

113 *Ethical considerations*

114 This study was approved by the Mozambican National Bioethics Committee
115 (Ref.15/CNBS/2010). Written informed consent was obtained from the parents/caregivers
116 of all children.

117

118

119 **RESULTS**

120

121 Fifty children under the age of three years consented to participate and initiated TB
122 treatment in the district of Manhiça (**Table 1**). All were treated for drug susceptible TB, 9

123 cases were microbiologically confirmed on the basis of culture, although none of them
124 was smear positive on microscopy for acid-fast bacilli. Of all children starting treatment,
125 26 (52.0%) were male and 24 (48.0%) were HIV-infected. Although patients were
126 followed-up in ten different peripheral health care centers, over 64.0% of cases were
127 managed by two single health centers, one of which was the MDH (30.0%).

128

129 All 50 cases had documented treatment outcomes: 44(88.0%) children successfully
130 completed treatment, 2 (4.0%) died prior to treatment completion and 4 (8.0%) were lost
131 to follow up (LTFU) . There were no treatment failures nor transferred cases. Among
132 treatment success cases, 11 (25.0%) had a delay in treatment completion, 8 of which were
133 males, over half HIV infected and one microbiologically confirmed TB case. Among the
134 LTFU, 3 were males, all lived more than 2 km distance from the MDH, none fulfilled the
135 study TB case definition and all were HIV-infected. Overall incomplete adherence (delayed
136 plus LTFU) was reported in 31.3% (15 among the 48 patients who did not die) (**Table 2**).
137 **Figure 1** shows the distribution of the number of days from treatment initiation to
138 treatment completion. Eleven cases finished treatment before the expected date, 8 of
139 them 1-2 days earlier. One patient had a 74-day delay in treatment completion.

140

141 Compared to other age groups registered at the MDH NTP during the same time period,
142 we found a higher treatment success rate in children under 3 (88% versus 68,1% and
143 72,5% among patients aged 3-15 years and >15 years respectively). However, incomplete
144 adherence was similar in all groups. Figure2 shows adherence results for these three age
145 categories (final numbers exclude deaths) .

146

147 Being malnourished at enrollment and having a mother with a history of migration in the
148 previous 2 years to TB diagnosis were shown to be potential risk factors for incomplete
149 adherence (PR 2.9 ; 95%CI:1.4-6.1 and PR 2.9; 95%CI:1.4-6.0 respectively, p-value<0.05)
150 **(Table 2).**

151

152

153 **DISCUSSION**

154

155 Data on adherence to TB treatment in children is scarce. To our knowledge, this is the first
156 study describing the profile and treatment outcomes among pediatric TB cases in
157 Mozambique and one of the few reporting adherence and treatment outcomes in a well
158 characterized cohort of young children. Although the overall treatment success rate(88%)
159 was close to the 90% Stop TB target (6) there were still a significant proportion of pediatric
160 TB cases with incomplete adherence (31.3%). Being malnourished and having a migrant
161 mother were potential risk factors for incomplete adherence.

162 We have previously reported a treatment success rate of 67.3% among children <3 years
163 in Manhica during 2006-2010 (25). The significant improvement observed in the current
164 study compared to the previous years can be due to several reasons. Firstly, to the
165 substantial recent decrease in mortality as improved TB/HIV care and treatment services
166 are available at the health facilities. The proportion of patients who die during TB
167 treatment has decreased from 17% during 2006-2010 to 4% in this study(29). Secondly,

168 improved outcomes may be due to a slight decrease in the number of LTFU (from 9.6% in
169 2006-2010 to 8%) that could be influenced by the fact of being included in the
170 epidemiological incidence study. Although the study had active follow up visits which
171 could have positively influenced treatment adherence, the univariate analysis did not
172 show an association.

173 The treatment success rate reported in this study is similar to the 87% estimated by WHO
174 for all new cases in 2012 for Mozambique (5). It decreased, however, in other age groups
175 during the same period, reaching 68,1% and 72,5% in patients aged 3-15 year and >15
176 year, respectively. While other authors have also found higher success rates with younger
177 ages (11), Hailu et al. found that being above 5 years of age was a predictor of treatment
178 success (18).

179 Comparing TB treatment adherence results among different studies is difficult due to the
180 large variations in the definitions of adherence found in the literature, particularly for
181 childhood TB (11,19,17,30–33). As stated by Chang et al, it seems reasonable to consider
182 LTFU and incomplete adherence as part of the same problem, with different levels of
183 severity (34). Thus, for the purpose of this study we used a definition of incomplete
184 adherence that includes LTFU plus delayed completion. Despite the differences in the
185 definitions, the results in this study are similar to other pediatric reports from high burden
186 countries (17,32,33,35). Unpublished results from a recent meta-analysis show a
187 treatment success rate of 81% with 3% mortality, with large variations among the studies
188 included (12).

189 We have identified several factors associated with incomplete adherence, many of them
190 were expected and have been previously cited by other authors as predictors of poor
191 outcome(13,36,37). Evidence of chronic or acute malnutrition at diagnosis was associated
192 with incomplete adherence. Several studies have also reported poor TB outcomes among
193 malnourished children (36,37) but in this study malnutrition was associated both with
194 LTFU and death as well as with a delay in treatment completion. This suggests that beyond
195 the deleterious immunological impact of malnutrition on TB progression, other aspects
196 such as tolerance to drugs or, more importantly, the social context, have an impact on
197 adherence and outcome. The importance of the caregiver child relationship has been
198 shown to impact overall child survival and thus, the history of migration of the mother
199 seems to impact treatment adherence and outcomes(38). Malnutrition was significantly
200 associated with a history of a migrant mother, hospitalization at the time of diagnosis, and
201 TB case definition, and thus the specific impact of these other variables on adherence is
202 difficult to interpret.

203 HIV co-infection is also a well-known risk factor for incomplete adherence in adults (2,39–42), and
204 children(19,36),partly due to the increased pill burden and secondary effects. Because of the high
205 treatment compliance rate (90%) required to facilitate cure and reduce the risk of rapid disease
206 progression in children, the poor adherence observed among HIV-TB co-infected cases is cause for
207 concern as it could lead to increased mortality. Given the inherent difficulties in diagnosing
208 pediatric TB, caregivers may sometimes reflect their uncertainty in the diagnosis by not fulfilling
209 the treatment recommendations. This may be the underlying cause of the poorer adherence
210 observed among cases not fulfilling the study TB definition. Moreover, TB diagnostic algorithms do
211 not perform well among HIV co-infected children(28). Given the HIV co-infection rate observed

212 among confirmed and non-confirmed TB cases (10% and 51%, respectively), this may have played
213 a role in hesitance of diagnosis and adherence to treatment. The gender difference observed in
214 the current study was not statistically significant and needs to be further evaluated with larger
215 sample sizes. Some adult studies have also noted a higher rate of incomplete adherence among
216 males although this association needs to be further evaluated and may not be necessarily
217 extrapolated to the pediatric population (42–45).

218

219 There are several limitations to this study. Firstly, the small sample size of the cohort limits
220 the ability to reach statistical significance for several potential associations (no
221 multivariable logistic regression analysis was possible). Secondly, the analysis of
222 adherence was performed using data measured indirectly with a retrospective design. In
223 addition, the fact that most children starting treatment were part of a research study
224 could have had a potential positive influence on adherence, although the study was
225 focusing on case detection. Moreover, we did not register other common factors reported
226 to influence adherence such as major side effects, who the main caregiver for the child
227 was or the exact phase of the treatment where the main delay occurred. Furthermore,
228 the results may be biased given that TB under-reporting is more common in severe forms
229 of the disease which die before treatment initiation. Finally, we did not capture common
230 system failures such as drug stock rupture or health personnel absenteeism, which might
231 lead to non-patient originated poor adherence.

232

233 In conclusion, although pediatric treatment outcome is overall good, there is still a
234 significant proportion of incomplete adherence cases. This study setting may have
235 represented an improved health system scenario, so the true program performance may
236 show worse indicators. Reinforcing the importance of timely treatment completion should
237 remain a high priority. Successful treatment of pediatric TB requires the commitment and
238 involvement of the corresponding caregiver. Further larger pediatric TB cohorts and
239 qualitative research are needed to assess and eventually address potential risk factors for
240 non-adherence.

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420 **LEGENDS TO FIGURES**

421 **Figure 1. Duration of treatment among patients with treatment completion**

422 Definitions: Days of delay in treatment completion were calculated based on a standard
423 treatment duration of 180 days for retreatment cases, final day was adjusted)

424 Number of days in X axis are not in scale .

425 **Figure 2. Treatment and adherence outcomes among different age groups (2011-2012)**

426 This figure shows treatment outcome (treatment success vs. LTFU [lost to follow-up])
427 among patients who did not die and adherence results (full vs. incomplete adherence)
428 among all age groups initiating TB treatment at the National Tuberculosis Program of the
429 Manhiça Health Center (n= 867 to ≥ 15 yr; n= 82 to $< 15 - 3$ yr; n=56 to < 3 yr). Excluded
430 from this analysis are: dead and transferred cases as well as TB cases with number of
431 treatment days missing.

432 **TABLES**433 *BOX1: Relevant study definitions*

TB case: Any child registered to initiate TB treatment at the NTP during the study period.

Study TB case: Includes microbiologically confirmed plus probable cases (adapted from the standardized NIH case definition for childhood TB (28), full details on the classification are described elsewhere(22)).

Confirmed TB case: compatible symptoms plus a positive culture with *Mycobacterium Tuberculosis*.

Probable TB case: fulfilling the following 3 criteria:

(1) compatible symptoms unresolved at last clinical follow up visit (prior to any TB treatment initiation)

(2) compatible chest radiograph: ≥ 1 of the following radiographic abnormalities: airway compression, lymphadenopathy, opacification, nodular picture, effusion, cavities, spondylitis or Ghon focus (46)

(3) at least one of the following: TB exposure, positive TST (induration >5 mm for HIV or malnourished children and >10 mm for the rest of participants) or positive response to TB treatment.

HIV infection: positive antibody test in children >18 months (Determine, Abbott Laboratories and confirmed with Unigold, Trinity Biotech); or positive HIV PCR in those <18 months; or a strong clinical suspicion with positive antibody test in the absence of a PCR result.

Treatment outcomes for drug susceptible TB patients (5,47):

Treatment success: the sum of patients:

1. Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion) AND
2. Treatment completed: A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Treatment failed: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Died: A TB patient who dies for any reason before starting or during the course of treatment.

Lost to follow up: A TB patient whose treatment was interrupted for 2 consecutive months or more.

Not evaluated: A TB patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Adherence categories were defined as:

Incomplete adherence. The sum of the following two exclusive categories and calculated over those patients who did not die:

1. **Lost to follow-up** (patients whose treatment was interrupted for 2 consecutive months or more) AND
2. **Delayed completion** (patients with a delay of 3 or more weeks beyond the expected date (calculated as 6 months after treatment initiation))

Full adherence. All treatment success cases with no delay in treatment completion.

434 * NIH: National Institute of Health; NTP: National TB Program; TB: Tuberculosis; TST:
 435 tuberculin skin test
 436
 437

438 **Table 1.- Clinical and Socio-demographic characteristics of TB cases <3yr at the time of**
 439 **TB diagnosis**

Table 1A. Clinical and sociodemographic characteristics of TB cases <3yr at the time of TB diagnosis (N=50)

<i>Clinical</i>		n	(%)
<i>Sex (male)</i>	male	26	(52)
	female	24	(48)
<i>Age in months, (Median [IQR])</i>		19.8	[14.6-26.1]
<i>Age at diagnosis (months)</i>	< 12	10	(20)
	12 - 24	23	(46)
	> 24	17	(34)
<i>BCG Scar [†]</i>	<i>present</i>	43	(87.8)
	<i>absent</i>	6	(12.2)
<i>HIV-coinfected</i>	yes	24	(48)
	no	26	(52)
<i>TST ^α</i>	positive	21	(43.8)
	negative	27	(56.2)
<i>Hospitalizations in previous year to TB diagnosis</i>	yes	20	(40)
	no	30	(60)
<i>Nº outpatient consultations in previous year to TB diagnosis</i>	<10	36	(72.0)
	≥10	14	(28)
<i>Study TB cases definition</i>	<i>Confirmed</i>	9	(18)
	<i>Probable</i>	25	(50)
	<i>Possible</i>	13	(26)
	<i>MTB infection/TB unlikely</i>	3	(6)
<i>TB Compatible CXR</i>	yes	18	(36)
	no	32	(64)
<i>Symptoms</i>			
	<i>Cough >2 weeks</i>		
	yes	14	(28)
	no	36	(72)
<i>Fever>2 weeks</i>	yes	6	(12)
	no	44	(88)
<i>Wheeze</i>	yes	3	(6)
	no	47	(94)
<i>Chronic or Acute Malnutrition</i>	yes	11	(22)
	no	39	(78)
<i>Adenopathy</i>	yes	1	(2)
	no	49	(98)
<i>Contact of Pulmonary TB case (documented or reported)</i>	yes	14	(28)
	no	36	(72)
<i>Hospitalized at time of enrolment ^δ</i>	yes	9	(18)
	no	41	(82)
<i>Number of follow-up visits to the cohort study during course of TB treatment</i>			
	< 2	11	(22)
	≥ 2	39	(78)

Denominator is n=50 except for α (n=48) and † (n=49)

BCG= Bacille Calmette Guerin; HIV= human immunodeficiency virus; IQR= interquartile range; CXR= Chest X ray; TST= Tuberculin Skin Test;

Definitions: Positive TST was defined as an induration >5 mm for HIV or malnourished children and >10 mm for the rest of participants. HIV infection was defined as positive antibody test in children >18 months (Determine, Abbott Laboratories and confirmed with Unigold, Trinity Biotech); or positive HIV polymerase chain reaction in those <18 months; or a strong clinical suspicion with positive antibody test in the absence of a polymerase chain reaction result. CXR were classified as compatible if presented ≥1 of the following radiographic abnormalities: airway compression, lymphadenopathy, opacification, nodular picture, effusion, cavities, spondylitis or Ghon focus.

Sociodemographic	n	(%)
<i>Distance to Peripheral Health Care Centers in Km (Median [IQR])</i>	1,68	[1.18-2.50]
<i>Distance to Peripheral Health Care Centers</i>		
< 1	30	(60)
2-5	15	(30)
> 5	5	(10)
<i>Distance to Manhiça Health Center Km (Median [IQR])</i>	12,46	[3.9-17.4]
<i>Distance to Manhiça Health Center</i>		
< 5km	16	(32)
≥ 5 km	34	(68)
<i>Nº of people living in the house (median [IQR])</i>	6	[4-9]
<i>Nº of people living in the house</i>		
< 6	21	(42)
≥ 6	29	(58)
<i>Number of children <15y living in the house‡</i>		
1 a 3	35	(80)
≥ 4	9	(20)
<i>Children's birth order †</i>		
1 th o 2 nd	30	(68.2)
≥ 3 rd	14	(31.8)
<i>Children <15 yr at home †</i>		
1 a 4	26	(59.1)
≥ 5	18	(40.9)
<i>Orphan (death of mother)</i>	1	(2.0)
<i>Orphan (death of father)</i>	4	(8)
<i>Death in the household in the previous year</i>	14	(28)
<i>Migration of the mother in previous 2 yr</i>	8	(16)
<i>Migration of the father in previous 2 yr</i>	16	(32.0)
<i>Migration in the household member</i>	20	(40)
<i>SES†</i>		
Poorest	15	(30)
Less Poor	20	(40)

440 Denominator is n=50 except for ‡ (n=44) and † (n=35)

441 IQR= interquartile range ; SES: Socio Economic Status

442 Definitions: A household asset-based wealth index was used to categorize the household socio-economic

443 status (SES) into 5 wealth quintiles. The 2 lowest quintiles were grouped as "poorest" and the remaining 3

444 quintiles were renamed "less poor"

445

446 **Table 2. Univariate analysis of predictor factors for incomplete adherence.**

	Full Adherence [†]	Incomplete Adherence [‡]		
	n (%)	n (%)	PR (95%CI)	p value
Total	33 (68.8)	15 (31.3)		
<i>Sex *</i>				
Female	19 (82.6)	4 (17.4)	Reference	
Male	14 (56)	11 (44)	2.5 (0.9-6.9)	0.065
<i>HIV-coinfected</i>				
No	20 (80.0)	5 (20.0)	Reference	
Yes	13 (56.6)	10 (43.5)	1.9 (0.8-4.4)	0.080
<i>Study TB case definition</i>				
Possible-Unlikely	7 (50.0)	7 (50.0)	Reference	
Confirmed-Probable	26 (76.5)	8 (23.5)	0.5 (0.1-1.1)	0.072
<i>Nº outpatient consultations in previous year *</i>				
0 - 9	21 (61.8)	13 (38.2)	Reference	
≥ 10	12 (85.7)	2 (14.3)	0.4 (0.1-1.5)	0.171
<i>Hospitalized at time of enrolment *</i>				
No	30 (75.0)	10 (25.0)	Reference	
Yes	3 (37.5)	5 (62.5)	2.5 (1.2-5.4)	0.088
<i>Symptom at enrolment: malnutrition*</i>				
No	30 (76.9)	9 (23.1)	Reference	
Yes	3 (33.3)	6 (66.7)	2.9 (1.4-6.1)	0.018
<i>Migration of the mother in previous 2 yr *</i>				
No	31 (75.6)	10 (24.4)	Reference	
Yes	2 (28.6)	5 (71.4)	2.9 (1.4-6.0)	0.024
<i>Death in the household in the previous year *</i>				
No	22 (61.1)	14 (38.9)	Reference	
Yes	11 (91.7)	1 (8.3)	0.2 (0.1-1.5)	0.073
<i>Nº of people living in the house</i>				
< 6	11 (55.0)	9 (45.0)	Reference	
≥ 6	22 (78.6)	6 (21.4)	0.5 (0.2-1.1)	0.082
<i>Distance to the nearest Health Care Center</i>				
< 2 km	23 (76.7)	7 (23.3)	Reference	
≥ 2 km	10 (55.6)	8 (44.4)	1.9 (0.8-4.4)	0.127

CI= confidence intervals; PR= prevalence ratio; HIV= human immunodeficiency virus; TB= tuberculosis

[†] =Full adherence: treatment completed on time with full adherence

[‡] = Incomplete adherence includes a) delayed treatment completion plus b) treatment non completion;

p values obtained through chi-squared test or Fisher's exact test (when applicable*)

Only those variables with p-values < 0.2 are shown

A significant association was found between the variable malnutrition and hospitalization (p=0.02, migration of the mother (p=0.001) and TB case definition (P=0.002)