**Title**: “Tuberculosis on the rise: incidence risk from 1997 to 2012 in a southern province of Mozambique”

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**ABSTRACT:**

Objectives:

Methods:

Results:

Conclusion:

**INTRODUCTION:**

Mozambique is one of the few high tuberculosis (TB) burden countries where TB figures have not improved in recent years with TB/HIV co-infection rates of 58% of all notified TB cases. The estimated TB incidence in 2013 was 552 cases per 100.000 population and together with Afghanistan, Bangladesh, the Democratic Republic of the Congo, Nigeria and Zimbabwe it has the lowest case detection rates of the world, around 37% according to the World Health Organization (1).

The National Tuberculosis Control Program (NTP) in Mozambique was launched in 1977, as part of the Mutual Assisted Programme of the International Union Against Tuberculosis and Lung disease (IUATLD) and started to be applied on nationwide basis in 1985 (2)(3). The TB patient registration system began in 1984 and short course therapy followed in the late 80´s (3)(4), even if the country was facing the adverse context of a civil war, with shortage of qualified medical staff, supplies and transports inside de country. With the emergence of the HIV also in 1980´s and its impact in industrialised countries, TB regained importance as a public health problem, and DOTS strategy (direct observed therapy, short-course therapy) was launched in the early 1990´s, developed and promoted by WHO as best practices for TB control (5). In 1996, almost all districts of Mozambique were covered by the national guidelines, with complete coverage in 2000(4).

The aim of this study is to evaluate how the TB incidence rate and other key indicators for TB control evolved from 1997 to 2012 in a rural district of Southern Mozambique, which has recently reported very high rates of TB and HIV (6)(7). Analysing the trends of tuberculosis in Manhiça as well as its characterization over time will contribute to better understand the current TB epidemic in Southern Mozambique and thus might shed some light on potential key areas for public health action.

**METHODS:**

Study design and data collection

This is a longitudinal retrospective descriptive study using tuberculosis patients’ data from the registry books of the National Tuberculosis Control Program (NTP) for the district of Manhiça in the period of 1997 to 2012. All patients starting TB treatment were registered in these registry books.

Throughout the years some variables included in the books changed: in 2006 HIV status began to be registered in the tuberculosis registry books; TB case definitions changed, and multi drug resistant tuberculosis (MDR-TB) began to be registered in 2011.

Tuberculosis control program in the District of Manhiça

In Manhiça district, registry books of the National Tuberculosis Program exist since 1986 and patients were registered in the two main health centres: Manhiça´s District Hospital and Xinavane Rural Hospital, separated 52 kilometres away. Nowadays, there are also 14 peripheric health care centres, which refer samples and patients to these two hospitals. After diagnosis, patients were registered in the main centres and after the first intake of medication, they were referred to their closest peripheral health centre where treatment is supervised under a modified DOT (once weekly). In the district of Manhiça, due to the geographical dispersion of the population, TB patients can be assigned a “godfather” (normally a relative) who will be accountable for the intake of the patients´ medication, which is given on a weekly basis during both the initiation or continuation phase. The smear controls were done in the two main hospitals.

Case definitions

TB case definitions have changed during the study period. In this analysis we used the WHO definitions, revised in 2013 and updated in 2014 (8). TB cases were classified as new, previously treated or unknown TB treatment history. Previously treated patient category includes: relapse (true relapse or reinfection), treatment after failure, treatment after lost to follow up and other previously treated patients. During the study period, the registry books of NTP program in Mozambique also used other terms: “recurrent TB”, “chronic TB”, which were recoded as “previously treated TB patients”, as well as for “MDR-TB” patients.

Following WHO definitions for incident cases we considered all new cases and relapse cases as incident cases. For the purpose of this study we also considered the former classification of “recurrent case” as an incident case (9).

Smear positivity was defined according to the IUTLD smear grading scheme, considering scanty in at least one slide as a positive result, and smear negative patient as patients having two sputum smear negative in two different occasions according to the local guidelines since 2004 (10).

Regarding treatment outcomes patients were classified as cured, treatment completed, treatment failed, died, lost to follow up and not evaluated; treatment success was defined as the sum of “cured” and “treatment completed”.

Data analysis

Data from registry books were double entered using electronic software (Openclinica. [www.openclinica.org](http://www.openclinica.org/)) and information was checked, cleaned and analysed using SPSSv20. Descriptive statistics were used to describe TB profile in the district during the study period.

Population at risk for each year of our study period was based on annual demographic estimates of the National Institute of Statistics from Mozambique. Population projections were based on the two last national census, which took place in 1997 and 2007 and were available by age group and gender.

We grouped all the study period in a 4 year time bands, in order to minimize the effect of circumstantial situations (low human resources, heavy rains…) which could affect some of the TB indicators. We have also stratified the population by age groups, according to the WHO classification and the data we had from the census. TB-HIV analysis was only possible since 2007 onwards, when HIV testing was fully implemented at the NTP offices.

Ethics considerations

The Manhiça Health Research Centre approved this research proposal for ethic and scientific integrity. Formal permission to use official information contained in the books was granted by the Manhiça District Health Officer.

**RESULTS:**

Overall and demographic characteristics:

Over the 16 year period of the study, 9576 cases of tuberculosis were registered by the National Program of Tuberculosis Control in the district of Manhiça, 70,4% (6739 cases) of them in Manhiça District Hospital and 29,6% (2834 cases) in Rural Hospital of Xinavane. The mean age of registered TB patients was 34,1 years old (standard deviation of 17,3), the median was 33,0 (interquartile range: 24,0- 45,0) and the mode was 30,0 years old. Absolute number of cases was higher in men along all the study period. Children from 5-14 years old have the lowest proportion of cases (table 1).

During the study period, the population of the district increased from 134,587 in 1997 to 141,167 inhabitants in 2012 (5% increase), while the absolute number of tuberculosis cases registered in 2008-2012 was approximately 3 times higher compared to 1997-2000 (3774 and 1247 cases respectively).

Incidence risk

During our study period there were 8986 incident cases (94,1%). The tuberculosis incidence risk has been increasing over the years of the study, for all age groups, from a total of 155 cases per 100.000 habitants in 1997 to 700 incident cases per 100.000 population at risk in 2012. Incidence was highest for men aged from 30 to 49 years old being this information consistent along all the study period; from 2002 to 2012, approximately each one out of fifty men had tuberculosis. The incidence in men almost doubles the incidence in women for the same age range. In table 2 we detail the incidence risks stratified by years, gender and age group.

In figure 1, we can observe that after a slow increase from 2003 to 2008, incidence risk has a rapid rise especially for men from 2008 to 2012, passing from 558 cases to 917 cases of tuberculosis per a 100.000 population.

Children from 5-14 years old have the lowest incidence risk for both males and females.

HIV status and TB

Until 2006 only 5 patients had their HIV status recorded in the registry books from the NTP, however from 2008 onwards the HIV status was recorded in more than 95% of the patients (in 2006 and 2007, 11% and 91%, respectively). The total number of TB patients with known HIV infection during the study period was 3512, representing 70,4% of tested patients; 52,7% (1851 cases) were male. Patients aged from 15 to 49 years old represented 80% (2810 cases) of all TB/HIV-infected patients.

TB type and smear testing

The total number of registered pulmonary cases was 8014 (83,8% of total number of cases) (table 1), out of which 6681 cases (83,4%) had a smear result, and 5018 cases (75,1%) had a smear positive result.

The amount of TB patients starting treatment who were tested for a smear test increased from 1997 until 2003, when 82,2% of them underwent AFB smear at diagnosis. Afterwards proportions decreased until 2009 with 69,2% (566 cases), and for 2012 73,2% (751 cases) patients had a smear test done was ( figure 2).

The proportion of smear negative results (among the pulmonary cases having a smear test) has increased during the study period, with 40% of pulmonary TB being smear negative in 2009-2012 (figure 3). Chi-square for trend.

Regarding HIV infection, 78,3% (923 cases) smear negative pulmonary TB were HIV-infected, while in smear positive pulmonary TB this proportion was 67,3% (1464 cases). p-value?

Extrapulmonary TB (EPTB) accounted for 16,2% (1548 cases) of the total number of cases (table 1). From all the EPTB having an HIV status (879 cases), 666 cases (75,8%) were HIV-infected. Among HIV-infected patients the proportion of EPTB along the years was: 15,5% (58 cases), 21,6% (91 cases), 21,0 % (117 cases), 18,0 % (126 cases), 19,0% (134 cases) and 19,2% (132 cases) in the period of 2007 to 2012 respectively. Any test?

Previously treated vs new patients

Along the study period 8496 cases (88,7%) were classified as new, 878 (9,2%) were previously treated patients (table 1). For 202 patients (2,1%) the previous TB treatment history was not known.

In figure 2 we observe that the proportion of previously treated patients did not greatly vary along the years with a mean value of 9% (table 1). Among the previously treated patients having an HIV status, 74,6% (364 cases) were HIV-infected.

From all previously treated patients within the study period, 44,0% (386 cases) were relapses, 13,6% (119 cases) were lost to follow up and 5,7% (50 cases) treatment failure. The remaining 36,7% (323 cases) were classified as “other” , “recurrent” or “MDR”. There were 3 diagnosed cases of MDRTB, 1 in 2011 and 2 in 2012.

Treatment failure along the years…

Treatment outcomes

Over the study period the overall proportion of treatment success for registered patients was 70,8% (6534 cases), the proportion of cured patients decreased while treatment completed increased (figure 4). A total of 1478 patients starting TB treatment died (16,0%) during the study period.

Overall women had a higher proportion of treatment success 73,5% of cases (2966) compared to 68,7% (3568) in men, and less number of deaths: 14,7% (595 cases) compared to 17,0% (883), respectively. Lost to follow up as treatment outcome was also more frequent in men: 10,9% (568 cases) than in women 8,2% (329 cases). This outcome was also more frequent in children aged 0 to 4 (14.9% of all cases initiating treatment). Simple Chi-square

Among patients with known HIV status, death was almost 2 times more frequent in HIV-positive patients: 17,3% (604 cases) against 8,7% (126 cases) (figure 5). OR, confidence interval and p-value. The age group having the highest proportions of deaths (among different outcomes) was people older than 65 with 18,0% (76 cases), followed by people of 30-49 years old with 17,8% (692 cases).

Treatment failed in similar proportions in HIV-positive patients and HIV negative patients: 1,1% (26 cases) against 1% (14 cases), respectively; and also for men and women: 1,2% (64 cases) and 1,3% (51 cases), respectively. Simples chi-square

**DISCUSSION:**

This study shows that the incidence of tuberculosis in the District of Manhiça is increasing, in fact, the incidence rate has tripled over a 16 year period. According to our findings tuberculosis patients were mainly HIV positive young adults having a newly diagnosed pulmonary tuberculosis with an increasing trend of bacteriologically unconfirmed disease. Incidence was higher in men than in women, not only because of higher number of absolute cases, but also, as said before, female population doubling the male population in some age ranges (referencia). Although our incidence analysis does not differentiate HIV positive and negative patients as it is done elsewhere (11), we observed that people aged from 30-49 are the ones having the highest incidence for both genders, probably related to higher rates of HIV infection (12).

The increasing number of smear negative tuberculosis patients, difficulties in implementing genexpert

Missing data regarding IPT, CPT.

Other TB incidence studies in neighbouring countries

In 2005 the rapid roll-out of combined antiretroviral therapy (cART), initially held by a vertical “day hospital” approach, but soon decentralised to the existing public sector network permitted the National Tuberculosis Program to integrate HIV testing, counselling and ART initiation(13), constituting an step forward in unveiling the characteristics of tuberculosis patients.

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**TABLES AND FIGURES:**

1) Table 1. Characteristics of TB patients starting treatment in the District of Manhiça (1997-2012)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variables/ Years** |  | **1997-2000** | | **2001-2004** | | | **2005-2008** | | | **2009-2012** | | | **Total** | |
|  |  | N | % | N | % | N | | % | N | | % | N | | % |
|  |  |  |  |  |  |  | |  |  | |  |  | |  |
| **Age groups** | **0 a 4** | 194 | 15,6 | 145 | 7,4 | 212 | | 8,2 | 287 | | 7,6 | 838 | | 8,8 |
|  | **5 a 14** | 43 | 3,5 | 70 | 3,6 | 134 | | 5,2 | 145 | | 3,9 | 392 | | 4,1 |
|  | **15 a 29** | 275 | 22,1 | 579 | 29,6 | 707 | | 27,4 | 923 | | 24,5 | 2484 | | 26 |
|  | **30 a 49** | 444 | 35,7 | 783 | 40,1 | 1067 | | 41,3 | 1720 | | 45,7 | 4014 | | 42,1 |
|  | **50 a 64** | 222 | 17,8 | 292 | 14,9 | 354 | | 13,7 | 513 | | 13,6 | 1381 | | 14,5 |
|  | **> 65** | 66 | 5,3 | 85 | 4,4 | 109 | | 4,2 | 175 | | 4,7 | 435 | | 4,6 |
|  |  |  |  |  |  |  | |  |  | |  |  | |  |
| **Gender** | **Men** | 737 | 58,8 | 1139 | 58,1 | 1444 | | 55,8 | 2068 | | 54,8 | 5388 | | 56,3 |
|  | **Women** | 517 | 41,2 | 822 | 41,9 | 1142 | | 44,2 | 1707 | | 45,2 | 4188 | | 43,7 |
|  |  |  |  |  |  |  | |  |  | |  |  | |  |
| **Type of TB** | **Pulmonary** | 1068 | 85,4 | 1684 | 86,1 | 2158 | | 83,5 | 3104 | | 82,4 | 8014 | | 83,8 |
|  | **EPTB** | 183 | 14,6 | 273 | 13,9 | 427 | | 16,5 | 665 | | 17,6 | 1548 | | 16,2 |
|  |  |  |  |  |  |  | |  |  | |  |  | |  |
| **Smear** | **Positive** | 726 | 82,5 | 1321 | 86,5 | 1462 | | 72,7 | 1548 | | 56,9 | 5057 | | 70,8 |
|  | **Negative** | 154 | 17,5 | 206 | 13,5 | 549 | | 27,3 | 1173 | | 43,1 | 2082 | | 29,2 |
|  |  |  |  |  |  |  | |  |  | |  |  | |  |
| **Co-infection HIV** | **Positive** | - | - | - | - | 855 | | 67,4 | 2655 | | 71,5 | 3510 | | 70,4 |
|  | **Negative** | - | - | - | - | 414 | | 32,6 | 1059 | | 28,5 | 1473 | | 29,6 |
|  |  |  |  |  |  |  | |  |  | |  |  | |  |
| **Type of TB** | **New** | 1136 | 93,3 | 1689 | 89,5 | 2355 | | 91,8 | 3316 | | 89,5 | 8496 | | 90,6 |
|  | **Retreatment\*** | 81 | 6,7 | 199 | 10,5 | 210 | | 8,2 | 388 | | 10,5 | 878 | | 9,4 |

\*Retreatment is the same as previously treated patients.

Note: Some of the totals within each category do not sum the total number of patients mentioned in the text as missing data wasn´t taken into account.

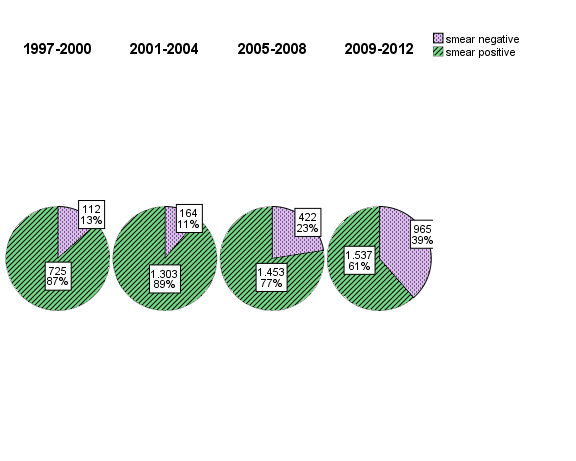
3) Figure 1. Incidence risk for Tuberculosis per 100.000 population for men and women in Manhiça District from 1997 to 2012.

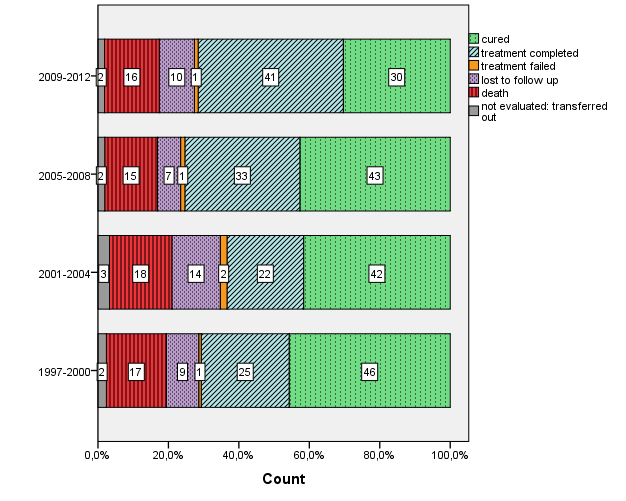
4) Table 2. Incidence risk for Tuberculosis per 100.000 population stratified by age group and gender from 1997-2012.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 1997-2000 | | | 2001-2004 | | | 2005-2008 | | | 2009-2012 | | | total | |
|  | men | women | men | | women | men | | women | men | | women | men | | women |
| 0-4 | 229 | 230 | 167 | | 152 | 246 | | 249 | 405 | | 305 | 262 | | 234 |
| 5-14 | 39 | 22 | 48 | | 53 | 93 | | 110 | 97 | | 115 | 69 | | 75 |
| 15-29 | 188 | 158 | 368 | | 306 | 461 | | 400 | 602 | | 589 | 405 | | 363 |
| 30-49 | 632 | 279 | 1039 | | 440 | 1407 | | 573 | 2062 | | 844 | 1285 | | 534 |
| 50-64 | 776 | 198 | 1017 | | 241 | 1105 | | 377 | 1406 | | 606 | 1076 | | 356 |
| >65 a | 446 | 102 | 623 | | 77 | 821 | | 104 | 1254 | | 208 | 786 | | 123 |
| total | 284 | 162 | 418 | | 242 | 552 | | 343 | 791 | | 503 | 511 | | 312 |

4) Figure 2. Trends in Tuberculosis in Manhiça District (1997-2012)

Some variables were complementary to each other: *pulmonary and extrapulmonary, new and retreatment*. For the variable *HIV+TB patients, Smear done* and *Smear positive (all patients)* the denominator was all TB patients registered. For the variable *Smear + (tested)* the denominator was smear tested patients.

5) Figure 3. Trends in smear results for pulmonary tuberculosis (absolute numbers and percentages)

6) Figure 4. Proportions of different treatment outcomes for tuberculosis treatment from 1997 to 2012

7) Figure 5. Treatment outcome for tuberculosis (in %) stratified by HIV status