



The burden and outcomes of childhood tuberculosis in Cotonou, Benin

S. Ade,¹ A. D. Harries,^{2,3} A. Trébuq,² S. G. Hinderaker,⁴ G. Ade,¹ G. Agodokpessi,¹ D. Affolabi,¹ S. Koumakpaï,⁵ S. Anagonou,¹ M. Gninafon¹

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Setting: The National Tuberculosis Programme (NTP) and the paediatric ward of the General Hospital (GH), Cotonou, Benin.

Objective: To describe the burden of tuberculosis (TB), characteristics and outcomes among children treated in Cotonou from 2009 to 2011.

Design: Cross-sectional cohort study consisting of a retrospective record review of all children with TB aged <15 years.

Results: From 2009 to 2011, 182 children with TB were diagnosed and treated (4.5% of total cases), 153 (84%) by the NTP and 29 (16%) by the GH; the latter were not notified to the NTP. The incidence rate of notified TB cases was between 8 and 13 per 100 000 population, and was higher in children aged >5 years. Of 167 children tested, 29% were HIV-positive. Treatment success was 72% overall, with success rates of 86%, 62% and 74%, respectively, among sputum smear-positive, sputum smear-negative and extra-pulmonary patients. Treatment success rates were lower in children with sputum smear-negative TB (62%) and those with HIV infection (58%).

Conclusion: The number of children being treated for TB is low, and younger children in particular are under-diagnosed. There is a need to improve the diagnosis of childhood TB, especially among younger children, and to improve treatment outcomes among HIV-TB infected children, with better follow-up and monitoring.

Globally, childhood tuberculosis (TB) has received limited priority in National TB Programmes (NTPs) due to the fact that children tend to be smear-negative and are therefore perceived to have limited infectiousness; also, numbers are often thought to be few.¹ The numbers of children reported with TB may also be inaccurate due to difficulties in diagnosing both pulmonary and extra-pulmonary TB.

Children aged <15 years constitute about 11% of the estimated 9 million TB cases worldwide,² and up to 15% in low-income countries.³ Although this proportion may seem small, TB in children aged <5 years, particularly those aged <2 years, has been shown to cause high mortality and morbidity.⁴ Globally, TB has been reported to be one of the most important causes of death among children,² and treatment outcomes among children with TB have also been found to be poor.⁵

In Benin, information about the burden of TB in children is limited. While children with TB are registered and their outcomes are recorded in the NTP's TB register, only sputum smear-positive pulmonary cases

(grouped together into the 0–14 year age group) are specifically identified in the NTP's quarterly reports. At the General Hospital (GH) in Cotonou, the economic capital, children are diagnosed and treated on the basis of information recorded in their personal medical files, but are never notified to the NTP, for a variety of reasons. NTP data on children are therefore incomplete and cannot be used to estimate the true burden of childhood disease in Benin.

The aim of the present study was to describe the burden of TB and characteristics and outcomes along children treated in Cotonou, Benin. Specific objectives were to determine: 1) the total number of TB cases recorded in the NTP TB registers, and of these, the number of children aged <15 years; 2) the incidence rate of notified TB cases among children aged <15 years; 3) the number of children notified with TB in the NTP TB register and the number of children recorded in the GH medical files (who are not notified in the NTP TB register) and, in each of these groups, stratification by sex, age, type of TB and human immunodeficiency virus (HIV) status; and 4) the treatment outcomes among these children stratified by place of treatment, sex, age, type of TB and HIV status, from 2009 to 2011.

STUDY POPULATION, DESIGN AND METHODS

Study design

This was a cross-sectional, retrospective cohort study of children with TB in Cotonou based on reviews of NTP TB registers and the medical files of the GH.

Setting

Benin is a small country in West Africa with a population of 9 million and a gross national income of US\$780 per capita (<http://data.worldbank.org/about/country-classifications>). The NTP notifies about 3500 TB cases each year. The national incidence rate of notified new TB cases has been stable over the last 10 years, at 41–46 per 100 000 population. The NTP follows the DOTS strategy and uses internationally recognised criteria for diagnosing and treating patients with TB.^{6,7} The NTP has a central unit responsible for policy and strategy, while diagnosis, registration and care are decentralised to 57 public or private basic management units (BMUs) in the country.

The present study was conducted in Cotonou and its suburbs, which has a population of about 1 million. There are five BMUs in Cotonou, all of which have a TB register and use TB treatment cards. The GH has a

AFFILIATIONS

- 1 National Tuberculosis Programme, Cotonou, Benin
- 2 International Union Against Tuberculosis and Lung Disease, Paris, France
- 3 London School of Hygiene & Tropical Medicine, London, United Kingdom
- 4 University of Bergen, Bergen, Norway
- 5 Paediatric Service, Centre National Hospitalier et Universitaire, Cotonou, Benin

CORRESPONDENCE

Serge Ade
National Tuberculosis Programme
Cotonou, Benin
Tel: (+229) 9654 5760
e-mail: adeserg@yahoo.fr

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KEY WORDS

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paediatric department and a paediatric surgery department, where children are also diagnosed and treated for TB, but are not notified to the NTP.

Diagnosis and treatment of tuberculosis

Children are suspected of TB if they have chronic symptoms such as cough for >3 weeks, persistent fever, malnutrition, weight loss and/or failure to thrive. The presence of an adult with sputum smear-positive TB living in the same household as the child may be an indication of TB due to contact with the index case. Child TB suspects are investigated using sputum smear microscopy, if they can produce sputum, or, if feasible, gastric lavage, chest radiography (interpreted by radiologists and chest physicians) and tuberculin skin testing. *Mycobacterium tuberculosis* culture from sputum or other specimens is occasionally performed. Lack of response to non-specific antibiotics may also indicate a diagnosis of TB. If the child's health status is poor, treatment is started immediately.

At both the NTP facilities and the GH, diagnosed children are classified as pulmonary (smear-positive and smear-negative) and extra-pulmonary TB, and as new and previously treated cases, according to national and international guidelines.^{6,7} All diagnosed children are supposed to be registered with a BMU close to their homes, and to receive standardised treatment. Children aged <8 years receive rifampicin (RMP), pyrazinamide and isoniazid (INH) for the 2-month initial phase, followed by RMP and INH for the 4-month continuation phase. Treatment for children aged ≥8 years is similar, except that ethambutol is added to the initial phase to make a total of four drugs. At the GH in Cotonou, however, the anti-tuberculosis regimens used do not always follow these recommendations.

For diagnosis, less than US\$1 is usually, but not necessarily, required as payment for sputum smear examination at both the GH and the NTP. Treatment is free, and anti-tuberculosis drugs are provided by the NTP (they are not available in private pharmacies). Treatment outcomes are monitored using treatment cards and paper registers at both the NTP and the GH, and NTP outcomes are reported in quarterly reports.

Healthy children aged <5 years and living in the same household as an adult with sputum smear-positive TB are given INH preventive therapy (IPT) for 9 months.

Patients

All children aged 0–14 years who were diagnosed and treated for TB in Cotonou and its suburbs between 1 January 2009 and 31 December 2011 were included in the study. Children who were receiving IPT were excluded.

Data collection

Sources of data were the NTP TB registers and the GH medical files. Diagnosis was made by general practitioners and chest physicians in the NTP and by paediatricians at the GH. Data from each individual patient were collected using a standardised paper-based study questionnaire. To avoid errors, each data variable was collected by two different investigators.

The following data were collected: epidemiological characteristics of the child (sex, age), type and category of TB, HIV status (positive, negative, indeterminate and unknown) and standardised treatment outcomes. For these variables, standardised definitions of the International Union Against Tuberculosis and Lung Disease (The Union) and the World Health Organization (WHO) were used by both the GH and the NTP.⁸ If the treatment outcome was not known, it was classified as 'unknown'. Treatment outcomes were

'successful' if the children were cured or had completed treatment, and 'unsuccessful' if the children died, were lost to follow-up, failed treatment, were transferred out or unknown. A child was classified as 'still on treatment' if treatment had not yet been completed.

Statistical analysis

Data from the questionnaire were double-entered into EpiData version 3.1 (EpiData Association, Odense, Denmark). Using frequency analysis, demographic and clinical characteristics and site of diagnosis and care were analysed in relation to treatment outcomes using the χ^2 test, relative risks (RRs) and 95% confidence intervals (95% CIs). Comparisons were made using Epi Info, version 6.04dfr (Centers for Disease Control and Prevention, Atlanta, GA, USA). Levels of significance were set at 5%.

Ethics

The study was approved by the Ethics Advisory Group of The Union and the Ethics Committee of the Benin NTP.

RESULTS

Epidemiological characteristics

The number of children treated for TB, all forms, in Cotonou from 2009 to 2011 was 182 (67, 42 and 73 cases respectively in 2009, 2010 and 2011), representing 4.5% of all TB cases notified annually (Table 1). The male:female sex ratio was 0.94; 58 (32%) children were aged <5 years and 124 (68%) were aged between 5 and 14 years. The incidence rate of notified TB cases among children in Cotonou was between 8 and 13/100 000, much lower than that observed among adults ($P < 0.01$). Reported cases were higher among children aged >5 years (Table 2). One hundred and fifty-three children (84%) were treated at NTP facilities, while 29 children (16%) were treated at the GH but were not notified. Thus, during these 3 years, 16% of all TB cases diagnosed among children were omitted from national figures because they were not notified to the NTP.

Diagnosis of tuberculosis

Table 3 shows TB case notifications by place of treatment (NTP facilities, GH and all sites), stratified by age, sex, type of TB and HIV status. Five times more patients were treated at the NTP facilities than at the GH, and significantly more new sputum smear-positive pulmonary TB (PTB) patients were diagnosed at NTP facilities ($P < 0.01$), while significantly more extra-pulmonary TB (EPTB) cases were diagnosed at the GH ($P < 0.01$). HIV status was known for 167 (92%) children, of whom 49 were positive (29%). Significantly more children in the GH did not have their HIV status assessed compared with NTP facilities ($P < 0.01$).

Table 4 shows the number of children with different types of EPTB. There were 45 children with EPTB at one site alone, 34 with both PTB and EPTB (registered as PTB cases) and 3 children with

TABLE 1 TB cases, all forms and childhood, in Cotonou, Benin, 2009–2011

| Year | Notified TB cases <i>n</i> | Paediatric TB cases <i>n</i> | Proportion of paediatric cases among total cases % |
|------|-------------------------------|---------------------------------|---|
| 2009 | 1503 | 67 | 4.5 |
| 2010 | 1383 | 42 | 3.1 |
| 2011 | 1495 | 73 | 4.9 |

TB = tuberculosis.

TABLE 2 Estimated population, notified TB cases and incidence of TB in childhood, Cotonou, Benin, 2009–2011

| Year | Estimated child population* | | | Notified cases | | | Incidence/100 000 children | | | | Incidence/100 000 adults | |
|------|-----------------------------|----------|------------|----------------|----------|------------|----------------------------|----------|------------|----------------|--------------------------|-----------------|
| | Total | <5 years | 5–14 years | Total | <5 years | 5–14 years | Total | <5 years | 5–14 years | <i>P</i> value | ≥15 years | <i>P</i> value† |
| 2009 | 506 728 | 194 709 | 312 019 | 67 | 17 | 50 | 13.2 | 8.7 | 16.0 | <0.01 | 177.7 | <0.01 |
| 2010 | 517 046 | 199 850 | 317 196 | 42 | 16 | 26 | 8.1 | 8.0 | 8.2 | 0.01 | 160.5 | <0.01 |
| 2011 | 527 267 | 204 404 | 322 863 | 73 | 25 | 48 | 13.8 | 12.2 | 14.9 | <0.01 | 165.5 | <0.01 |

*Source: Statistical yearbook of Health Ministry of Benin, 2009, 2010 and 2011.

†Comparison between children and adults.

TB = tuberculosis.

EPTB at two sites. The most common sites for EPTB were the lymph nodes, vertebrae and pleura.

Treatment outcomes

Of the 182 patients diagnosed, 163 had completed treatment and 19 were still on treatment at the time of data collection. Treatment outcomes, stratified by place, age, sex, type of TB and HIV status, are shown in Table 5. The cure rate was higher among children in the NTP facilities than among those from the GH ($P < 0.01$), where the rate of unknown outcome was higher. In com-

paring successful (cure and/or treatment completed) and unsuccessful (death, loss to follow-up and unknown) treatment outcomes between the different groups, successful treatment outcomes were lower in smear-negative than in smear-positive children (RR 0.72, 95%CI 0.58–0.90, $P < 0.01$), and in HIV-positive compared with HIV-negative children (RR 0.73, 95%CI 0.56–0.96, $P < 0.01$). All of the HIV-TB co-infected children were on cotrimoxazole preventive therapy. Information about antiretroviral treatment (ART) was not, however, collected during the study. In all other respects, there were no significant differences between the groups.

TABLE 3 TB cases in children stratified by age, sex, type of TB and HIV status, Cotonou, Benin, 2009–2011

| Characteristic | NTP facilities <i>n</i> (%) | General hospital <i>n</i> (%) | All sites <i>n</i> (%) | <i>P</i> value* |
|---------------------------|--------------------------------|----------------------------------|---------------------------|-----------------|
| Total | 153 | 29 | 182 | |
| Age, years | | | | |
| 0–4 | 45 (29) | 13 (45) | 58 (32) | 0.08 |
| 5–14 | 108 (71) | 16 (55) | 124 (68) | 0.08 |
| Sex | | | | |
| Male | 73 (48) | 15 (52) | 88 (48) | 0.69 |
| Female | 80 (52) | 14 (48) | 94 (52) | 0.69 |
| Type of TB | | | | |
| New sputum smear-positive | 53 (35) | 3 (10) | 56 (31) | <0.01 |
| New sputum smear-negative | 69 (45) | 12 (41) | 81 (44) | 0.71 |
| New EPTB | 31 (20) | 14 (49) | 45 (25) | <0.01 |
| HIV status | | | | |
| Positive | 43 (28) | 6 (21) | 49 (27)† | 0.41 |
| Negative | 106 (69) | 12 (41) | 118 (65) | <0.01 |
| Unknown | 4 (3) | 11 (38) | 15 (8) | <0.01 |

*Comparison between NTP and the General Hospital.

†Of the total 182 cases, 27% were HIV-positive; of the 167 cases tested, 29% were HIV-positive.

TB = tuberculosis; HIV = human immunodeficiency virus; EPTB = extra-pulmonary TB; NTP = National TB Programme.

TABLE 4 Number of patients with extra-pulmonary tuberculosis by site of disease, Cotonou, Benin, 2009–2011

| Site | <i>n</i> (%) |
|----------------------------|--------------|
| Lymph node | 22 (27) |
| Vertebral | 20 (24) |
| Pleural | 17 (21) |
| Miliary | 9 (11) |
| Peritoneal | 4 (5) |
| Bone (excluding vertebral) | 3 (4) |
| Neuro-meningeal | 2 (2) |
| Pericardial | 2 (2) |
| Cutaneous | 2 (2) |
| Renal | 1 (1) |
| Total | 82 (100) |

DISCUSSION

The study is the first in Benin to describe the burden of TB and treatment outcomes among children in Cotonou, and this in turn has a direct influence on results at a national level. Our main findings were a treatment rate among children that was lower than WHO global estimates (4.5% vs. 11% of total cases) and a higher proportion of children treated in the age group 5–14 years than among younger children (68% vs. 32%). Approximately 16% of the children were diagnosed and treated at the GH and were not notified, contributing to an underreporting of the true burden of

TABLE 5 Distribution of treatment outcomes stratified by place of treatment, age, sex, type of TB and HIV status, Cotonou, Benin, 2009–2011

| Category | Total <i>n</i> | Cure and/or treatment completed <i>n</i> (%) | Death <i>n</i> (%) | LTFU <i>n</i> (%) | Outcome unknown <i>n</i> (%) |
|-----------------------|-------------------|---|-----------------------|----------------------|------------------------------------|
| All cases | 163* | 118 (72) | 14 (9) | 12 (7) | 19 (12) |
| Place | | | | | |
| NTP facilities | 138 | 109 (79) | 12 (9) | 10 (7) | 7 (5) |
| General Hospital | 25 | 9 (36) | 2 (8) | 2 (8) | 12 (48) |
| Age, years | | | | | |
| 0–4 | 52 | 34 (65) | 6 (12) | 5 (10) | 7 (14) |
| 5–14 | 111 | 84 (76) | 8 (7) | 7 (6) | 12 (11) |
| Sex | | | | | |
| Male | 79 | 60 (76) | 5 (6) | 4 (5) | 10 (13) |
| Female | 84 | 58 (69) | 9 (11) | 8 (10) | 9 (11) |
| Type of TB | | | | | |
| New smear-positive TB | 49 | 42 (86) | 3 (6) | 0 | 4 (16) |
| New smear-negative TB | 71 | 44 (62) | 9 (13) | 9 (13) | 9 (13) |
| New EPTB | 43 | 32 (74) | 2 (5) | 3 (7) | 6 (14) |
| HIV status | | | | | |
| Positive | 45 | 26 (58) | 6 (13) | 5 (11) | 8 (18) |
| Negative | 104 | 82 (79) | 8 (8) | 5 (5) | 9 (9) |
| Unknown | 14 | 0 | 10 (71) | 2 (14) | 2 (14) |

*Number of children who completed follow-up for treatment.

TB = tuberculosis; HIV = human immunodeficiency virus; LTFU = loss to follow-up; NTP = National TB Control Programme; EPTB = extra-pulmonary TB.

childhood TB in Cotonou and Benin. As a greater proportion of children at the GH were diagnosed with EPTB, this type of TB is particularly underreported. This may also be due to misdiagnosis due to lack of training in childhood TB among health care workers, as training in TB generally focuses on the detection of smear-positive TB in adults.

Reports about TB prevalence being higher in younger children are conflicting.^{9–14} Although younger children are at greater risk of progressing to active TB once infected with *M. tuberculosis*, they were underrepresented in our study, possibly due to misdiagnosis.^{15–18} For example, TB in younger children presenting with acute pneumonia or malnutrition may be missed due to clinical overlap with other common child illnesses, and die due to TB. In addition, collecting adequate sputum specimens in this young age group is very difficult. Studies increasingly advocate the implementation of other sampling methods, such as induced sputum, in primary health care settings.^{19,20}

This study was conducted in an urban setting, with a low rate of children being diagnosed and treated for TB. We assume that this rate is even lower in rural settings due to the shortage of specialists and difficulty in accessing health care services.

The predominance of lymph node, pleural and spinal TB among EPTB patients (72%) is similar to that reported in Malawi (62%).²¹ We found TB meningitis to be rare, however, in contrast to the higher rates reported elsewhere.²² Reasons for this may include difficulty in confirming the diagnosis, and bacille Calmette-Guérin vaccination coverage of almost 100% in Benin, which protects children against severe forms of TB such as TB meningitis and miliary disease.^{23,24}

It should be noted that although Benin is not a high-burden country for HIV (1.7%), HIV prevalence among children with TB was high (29%), and much higher than in adults (15%). A limitation of our study is that data on ART were not recorded. However, WHO recommendations for ART were applied on the whole.²⁵ The number of maternity wards involved in preventive mother-to-children treatment is increasing (61% in 2012), and there is a transition to three-drug prophylaxis. However, full coverage of pregnant women has not yet been achieved (51% in 2010).

Treatment outcomes among the children were reasonable. The overall treatment success rate, at 72%, was higher than that reported in Malawi (45%),²¹ but lower than in Djibouti in 2010 (84%).²⁶ A higher treatment success rate of 86% in smear-positive cases was close to that reported for adults (90%);² overall better treatment outcomes could be obtained through better monitoring systems to reduce loss to follow-up and unknown outcomes, and possibly by more accurate diagnosis. For example, unknown outcomes were particularly common in children registered and treated at the GH. This may be related to misdiagnosis (with consequent discontinuation) or lack of information on treatment duration. Referring children to BMUs (where health care workers trace all patients lost to follow-up) for their treatment monitoring may be one solution. Appointments would also be set with the GH practitioner. Unsurprisingly, worse outcomes were observed in smear-negative and HIV-infected children, as the TB diagnosis in both cases was doubtful.

In conclusion, childhood TB makes up a small proportion of all reported TB cases in Cotonou, Benin. While treatment outcomes are reasonable, particularly for smear-positive cases, better follow-up and monitoring is needed during treatment to reduce the high burden of loss to follow-up and unknown outcomes.

Greater collaboration between the NTP and the General Hospital is required to improve case notification and treatment outcomes, and we have been working to address these issues since the completion of the study.

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Contexte : Les services du Programme National de la Tuberculose (PNT) et les services pédiatriques de l'hôpital général (GH) à Cotonou, Bénin.

Objectif : Décrire le fardeau de la tuberculose (TB), les caractéristiques et les résultats chez les enfants traités à Cotonou entre 2009 et 2011.

Schéma : Etude transversale de cohorte basée sur une revue rétrospective des dossiers de tous les enfants âgés de <15 ans atteints de TB.

Résultats : Entre 2009 et 2011, on a diagnostiqué et traité 182 enfants tuberculeux (4,5% de l'ensemble des cas) : 153 (84%) dans les services du PNT et 29 (16%) traités au GH mais non déclarés au PNT. Le taux d'incidence des cas déclarés de TB se situe entre 8 et 13/100 000 ; il est plus élevé chez les enfants âgés de >5 ans. Dans l'ensemble, 29% des 167 enfants testés étaient séropositifs pour le VIH. Le taux

de succès est de 72% dans l'ensemble, avec 86% chez les enfants à bacilloscopie positive des frottis de crachats, 62% chez les enfants à bacilloscopie négative et 74% chez les enfants extra-pulmonaires. On a noté des taux moins bons de succès du traitement chez les enfants atteints de TB à bacilloscopie négative (62%) et chez les enfants atteints d'une infection par le VIH (58%).

Conclusion : Le nombre d'enfants traités pour TB est faible. Les carences de diagnostic portent principalement chez les enfants plus jeunes. Il est nécessaire d'améliorer à la fois le diagnostic de la TB infantile, particulièrement parmi les enfants plus jeunes, ainsi que les résultats du traitement chez les enfants co-infectés par le TB-VIH, en améliorant le suivi et la surveillance de ces patients.

Marco de referencia: Los centros del Programa Nacional contra la Tuberculosis (PNT) y los servicios de pediatría en el Hospital General (GH) de Cotonou, en Benin.

Objetivos: Describir la carga de morbilidad por tuberculosis (TB), las características de los niños tratados en Cotonou y los desenlaces clínicos de la enfermedad entre el 2009 y el 2011.

Métodos: Fue este un estudio de cohortes transversal de todos los niños con diagnóstico de TB <15 años de edad, basado en la análisis retrospectivo de archivos.

Resultados: Entre el 2009 y el 2011 se diagnosticaron 182 niños con TB (4,5% de todos los casos): 153 en los establecimientos del PNT (84%) y 29 (16%) en el GH que no se notificaron al PNT. La tasa de incidencia de casos notificados osciló entre 8 y 13 en 100 000 y fue más alta en los niños >5 años de edad. El 29% de los 167 niños con

prueba diagnóstica del virus de la inmunodeficiencia humana (VIH) obtuvo un resultado positivo. La tasa global de tratamiento exitoso fue 72%, en los casos con baciloscopia positiva fue 86%, en los casos con baciloscopia negativa fue 62% y 74% de los niños con diagnóstico de TB extrapulmonar alcanzaron un desenlace favorable. Las tasas más bajas de éxito terapéutico se observaron en los niños con TB baciloscopia negativa (62%) y en los niños que sufrían coinfección por el VIH (58%).

Conclusión: La cantidad de niños tratados por TB es baja en este entorno. El diagnóstico se pasa por alto sobre todo en los niños de más corta edad. Es preciso mejorar el diagnóstico y el desenlace terapéutico de la TB en la infancia, mediante una mayor atención al tratamiento de la infección por el VIH y un mejor seguimiento.