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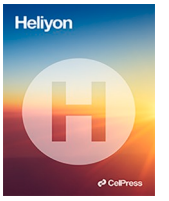

Research article

Pediatric tuberculosis in a high burden setting: Socio-spatial distribution, blood elements features, and outcomes

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ABSTRACT

Background: The childhood tuberculosis (TB) epidemic has been long neglected. Data on pediatric tuberculosis is needed to develop effective strategies against TB.
Methods: We retrospectively reviewed 200 medical records from children aged 0–15 years who suffered from tuberculosis between 2011 and 2021 in Libreville, Gabon. We collected and analyzed socio-demographic data and clinical data.
Results: 141 children files were selected (43 % girls and 57 % boys). The mean age of the patients was 9.2 years (CI: 8.5–10). Sixty per cent (60 %) of cases were from precarious housing areas, 35.34 % from mixed housing areas, and 4.51 % from residential. The cure rate was 75.24 %, 9.52 % relapsed, and 15.24 % died. Deaths were significantly higher in older children (Dunn's post-test $p < 0.01$). Children who recovered had higher haemoglobin and platelet counts than those who died (Dunn's test: haemoglobin $p < 0.0001$; thrombocytes $p < 0.05$). The haemoglobin threshold value of 5.5 g/dL identified children death with up to 80 % sensitivity and 86 % specificity. Thrombocytes count identified children's death with a sensitivity of 80 % and a specificity of 51 %.
Conclusion: Precariousness is associated with childhood tuberculosis. The directly observed therapy (DOTS) in older children should be reinforced to limit tuberculosis-associated deaths. Haemoglobin concentration and platelet are vital prognosis markers in pediatric tuberculosis.

1. Introduction

A quarter of the world's population is infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) [1]. With more than 10 million new

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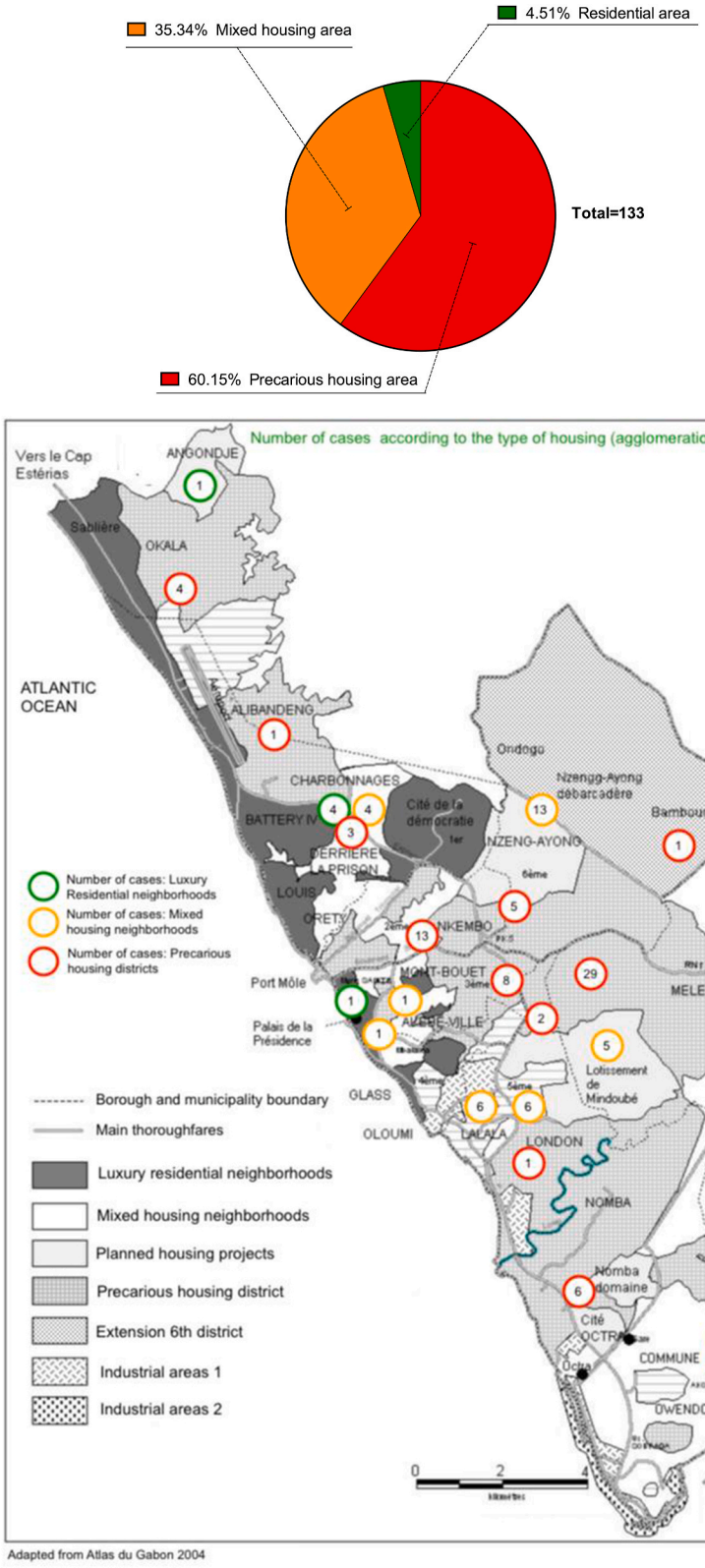

Fig. 1. (a) Global distribution of patients by residential areas; (b) detailed distribution according to the districts of the Libreville agglomeration.

tuberculosis (TB) cases per year worldwide, tuberculosis remains a major global health problem [2]. Despite the availability of a partially effective vaccine and reasonably effective but lengthy drug treatment, this disease still claims more than one million deaths each year [1,2].

Pediatrically, the childhood tuberculosis epidemic has been neglected for a long time. Therefore, its magnitude is not yet fully known and cannot be minimized [3]. In 2020, childhood TB accounted for 11 % of all TB cases, and 16 % (143,000) of TB deaths globally were children (under 15 years of age) [1]. The treatment success rate in children (ages 0–14) was 88 % in 2019 [1]. Gabon is one of 30 countries with a high prevalence of tuberculosis. In 2020, 5 % of all TB cases in Gabon were children under the age of 15 [4].

Social inequalities have been associated with the burden of tuberculosis in general [5–8]. Moreover, it has been argued that living conditions rather than the exact poverty level are the determinants of TB incidence rates [9]. Mapping TB cases is therefore necessary to strategize an adequate response.

Regarding the disease physiopathology, studies investigating blood elements in children with TB are scarce in the literature. A study done in South Africa reported anaemia, neutrophilia, and monocytosis as the most common haematological abnormalities in children with TB [10].

Very few data on pediatric tuberculosis exist in this high-burden Gabonese setting. Because understanding pediatric tuberculosis's socio-spatial and physiopathological specificities is necessary for developing effective strategies to fight against this scourge, we investigated the characteristics of this epidemic in Gabonese children. Our objectives were to establish the socio-spatial distribution of pediatric TB cases in Libreville and characterize the physiopathological specificities of pediatric tuberculosis in our setting.

2. Methods

We retrospectively analyzed medical records from the TB-specialized hospital in Libreville. Which is the main hospital caring for TB patients. The target population of our study consisted of children aged 0–15 years old who suffered from tuberculosis between 2011 and 2021. About 250 to 316 children are diagnosed with active tuberculosis every year at the TB-specialized hospital in Libreville. For this study, a convenience and random sampling of two hundred patient files was done and the selected files were reviewed. We collected and analyzed socio-demographic data, and data on chest x-ray, sputum smear (Ziehl-Neelsen staining), Xpert MTB/RIF test, haemoglobin concentration, full blood count, platelets (thrombocytes) as well as anti-tuberculosis treatment data. We also collected data on the socio-spatial origins of cases (residential district, mixed district (mixture of precarious and residential housing), and lean districts). To be included in the study patients should have an actual physical medical record including at least age, sex, clinical symptoms associated with TB, and a chest x-ray suggestive of pulmonary bacillosis.

2.1. Data analysis and statistics

Patients' extracted data were analyzed using the software Prism version 6 from GraphPad Inc. (USA). The differences between the groups (cured, relapsed, and died) were analyzed using the Kruskal-Wallis test (ANOVA), and a p-value of less than 0.05 was considered statistically significant. The ROC was used to evaluate the discriminative power analyzed parameters on treatment outcome. We computed the Post hoc study power, using G*Power 3.1.

2.2. Ethics

The research was done following Gabonese ethical guidelines and regulations, and approval was obtained from the Gabonese

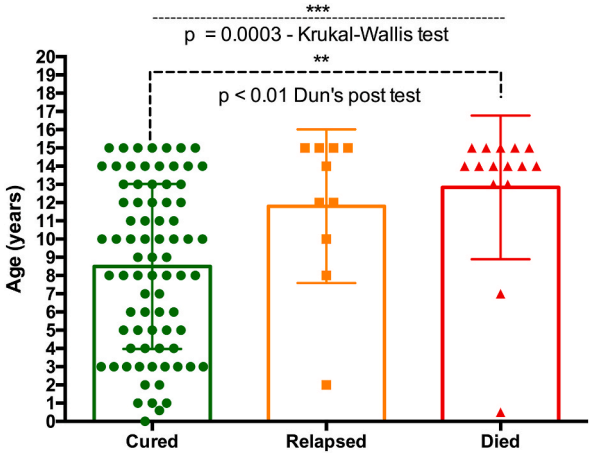

Fig. 2. Age and outcome of anti-tuberculosis treatment: child's age impacts anti-tuberculosis treatment outcome (Krukal-Wllis test $p = 0.0003$). Deaths are significantly higher in older children (Dunn's test $p < 0.01$).

National Ethics Committee and registered under the number: PROT-N°0089/2019/PR/SG/CNER.

3. Results

After reviewing the initial 200 patient files, 141 children aged between 0 and 15 were retained for the study. Fifty-nine (59) files were excluded for missing critical data. The mean age of the patients was 9.2 years (CI: 8.5–10). The study population was composed of 43 % (n = 61) girls and 57 % (n = 80) boys.

3.1. Socio-spatial origin of active tuberculosis cases

Sixty per cent (60.15 % (80/133)) of childhood tuberculosis cases came from precarious housing areas (districts), 35.34 % (47/133) from mixed housing areas, and 4.51 % (6/133) from residential areas (Fig. 1a & b).

3.2. Laboratory diagnostic positivity rate

Eighty-nine (89) patients were tested by Ziehl-Neelsen stained smear microscopy. Of those patients, eighty (80) were positive, and nine (9) were negative, corresponding to a 90 % (80/89) positivity rate (Fig. 2). Fifteen (15) patients were tested with the Xpert MTB/RIF molecular biology assay. Fourteen (14) tested positive, and one (1) tested negative, representing a positivity rate of 93 % (14/15). The patients who tested negative and those who did not benefit from a biological diagnosis were declared positive for active tuberculosis based on the clinic.

3.3. Outcomes of TB treatment in children

Treatment outcomes were available for 105 children. The total cure rate (without relapse) was 75.24 % (n = 79), the relapse rate was 9.52 % (n = 10), and the death rate was 15.24 % (n = 16). Analysis of treatment outcomes by gender revealed no significant differences.

3.4. Age and TB treatment outcomes in children

Data analysis reveals that the age of children significantly influences the outcome of anti-tuberculosis treatment (ANOVA Krukal-Wllis test p = 0.0003) and that the number of deaths was significantly higher in older children (Dunn' post-test p < 0.01) (Fig. 2).

3.5. Laboratory parameters and outcomes of anti-tuberculosis treatment in children

Our results show a link between children's haemoglobin levels and the outcome of their anti-tuberculosis therapy. Indeed, there is a significant difference in the haemoglobin and thrombocytes (platelets) levels of children depending on the outcome of the treatment (ANOVA Krukal-Wllis test: haemoglobin p < 0.0001; thrombocytes p = 0.002) (Fig. 3a and b). An in-depth analysis of our data shows that children who recover have much higher haemoglobin and platelets counts than those who die (Dunn's test: haemoglobin p < 0.0001; thrombocytes p < 0.05)) (Fig. 3a and b). No significant difference in leukocyte count was observed between children who recovered and those who died (Fig. 3c). The Post hoc power calculation showed that the effect size for identifying haemoglobin as a segregator was 0.71 and the study power was 0.99. Also, the effect size for identifying platelets, as a segregator was 16.8 and the study power was 1. Exogenous variables have a very big effect on platelets.

Additional analysis (ROC curve analysis) showed a haemoglobin threshold value of 5.5 g/dL segregated young patients at risk of death with up to 80 % sensitivity and 86 % specificity (Fig. 4a and Table 1). Thrombocytes, also with a sensitivity of 80 % and a specificity of 51 %, could identify children with a high risk of mortality (Fig. 4b and Table 1).

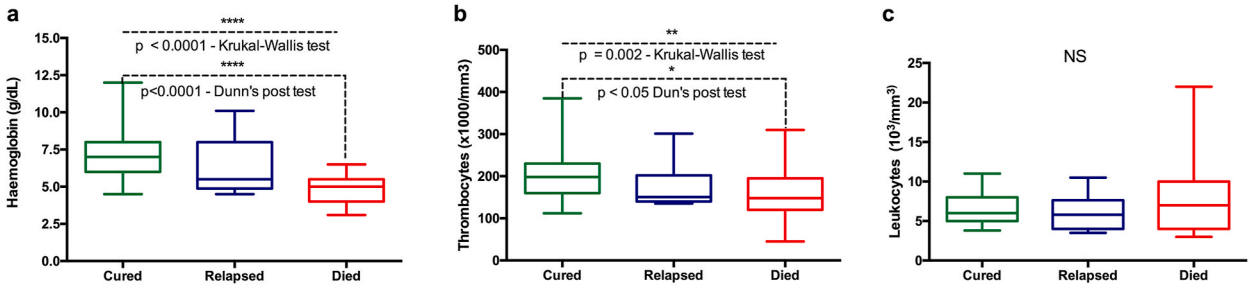

Fig. 3. (a) Hemoglobin concentration, (b) thrombocytes count, and (c) white blood cell count based on the outcome of anti-tuberculosis treatment outcomes (cure, relapse and death).

4. Discussion

The goal of the international TB community is that no child should die of TB [3]. Understanding the local socio-epidemiological and physiopathological specificities of pediatric tuberculosis is crucial for the development of effective strategies for the control of pediatric tuberculosis.

Mapping TB cases' origins showed spatial variability based on housing conditions. More than half of the cases (60 %) were children from precarious housing areas or neighbourhoods, and more than a third (35.34 %) came from mixed housing areas (precarious and decent). Very few cases were from residential areas (4.51 %). Studies done in Brazil also showed that socio-spatial equity is associated with TB onset [5,11]. Our study confirms once again that poverty fuels tuberculosis and that the fight against tuberculosis cannot be done on the sidelines of the fight against poverty and development [12–14].

Regarding the performance of the diagnostic tools used, in our context, the positivity rate of smear stained with Ziehl-Neelsen was 90 %, and that of the Xpert MTB/RIF molecular biology test was 93 %. If, in our context, the observed performance of microscopy is superior to what is generally accepted (≤75 % positivity), that of the Xpert MTB/RIF test is comparable to data published in the literature [15,16]. However, this study sample size restriction due to cases with the completeness of data warrants caution regarding the positivity rates of Ziehl-Neelsen staining and Xpert MTB/RIF tests.

The total recovery rate (without relapsing) was 75.24 %, the relapse rate was 9.52 %, and the death rate was 15.24 %. We note an increase of just over 20 % in therapeutic success among children suffering from tuberculosis in Gabon. Indeed, a previous study carried out in the same hospital as us, covering five (5) years (1997–2001), showed that the therapeutic success rate was 54 %, with the mortality going up to 37 % [17]. The capacity building of biologists and technicians, the introduction of modern diagnostic methods, and the revision of clinical and biological algorithms have undoubtedly improved the management of tuberculosis patients in Gabon.

Furthermore, our data show that the number of deaths is significantly higher among older children. This could be explained by the difference in compliance with taking medication. For the youngest, the parents are certainly the ones administering the drugs. For the older ones, it could be that they were trusted to self-taking their treatment, which could affect compliance to a lengthy treatment (6 months) and is not without side effects. This observation is key to devising better age-based drug administration in children. Adolescent unsupervised self-administration of anti-TB should not be recommended.

On the biological or physiopathological level, our results reveal significant differences in the haemoglobin and thrombocytes (platelets) levels of children depending on the outcome of the treatment. Data showed that children who recover have much higher haemoglobin and platelet counts than those who die. No differences were seen between cured patients and those who relapsed; neither between those who relapsed and those who died. The post hoc analysis showed that the study had sufficient power to avoid type II errors. However, Exogenous factors seemed to have a very big effect on platelets. The haemoglobin concentration and the platelet count could predict the outcome of anti-tuberculosis treatment. Indeed, there is a significant difference in haemoglobin and thrombocytes (platelets) between fully cured and deceased children. Children who recovered had higher haemoglobin and platelet counts than those who died. The haemoglobin level would identify young patients at risk of death with up to 80 % sensitivity and 86 % specificity. Thrombocytes, also with a sensitivity of 80 % and a specificity of 51 %, could help identify children at risk of mortality. Severe anaemia (Hb < 5 g/dL) associated with thrombocytopenia (platelets <190) would indicate an unfavourable outcome. Previous studies have shown a link between severe anaemia and the severity of active TB infection. Severe anaemia indicates a high mortality risk [18,19].

Our study's limited number of medical records may constitute our study limit. In addition, the retrospective nature of the survey and the relatively small sample size may have introduced certain biases that may have influenced our results. Nevertheless, all sense of proportion kept, this study has the merit of sketching out selected TB-associated characteristics in children and reaffirming the link between TB, poverty and development.

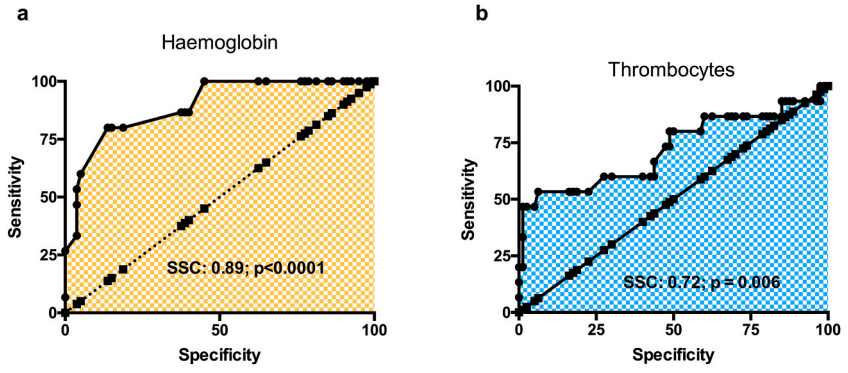

Fig. 4. ROC curve of haemoglobin and thrombocytes as markers of anti-tuberculosis treatment outcome: (a) haemoglobin level (area under the curve (AUC): 0.89; $p < 0.0001$); (b) Thrombocyte count (area under the curve (AUC): 0.72; $p = 0.006$).

Table 1
Haemoglobin and thrombocyte as markers of the outcome of anti-tuberculosis treatment: threshold values, sensitivities, specificities and odds ratio (ROC curve analysis).

	Cut-off	Sensitivity%	95 % CI	Specificity%	95 % CI	Odds ratio
Haemoglobin	<5.5	80	52 %–96 %	86	77 %–93 %	6
	<5.7	80	52 %–96 %	85	75 %–92 %	5
Thrombocytes	<191	73	45 %–92 %	52	41 %–64 %	1,5
	<195.5	80	52 %–96 %	51	40 %–62 %	1,6

5. Conclusion

In a high-burden setting like ours, precariousness remains strongly associated with the development of tuberculosis. The directly observed therapy (DOTS) in older children should be reinforced to limit the number of deaths associated with tuberculosis in this population. Also, clinical management of anaemia and nutritional interventions in children with tuberculosis should be considered to improve their clinical course. Finally, the haemoglobin concentration and the platelet count could help determine the vital prognosis of children with tuberculosis.

Ethics

The research was done following Gabonese ethical guidelines and regulations, and approval was obtained from the Mother and Child University Hospital Scientific Board and ethics committee.

CRediT authorship contribution statement

Célestin Bilolo: Writing – review & editing, Methodology, Investigation, Data curation. **Juliette Atsame Ndong:** Methodology, Formal analysis, Data curation. **Eliane Kuissi Kamgaing:** Writing – review & editing, Visualization, Supervision, Investigation. **Anicet Christel Maloupazoa Siawaya:** Writing – review & editing, Supervision, Project administration, Investigation. **Ofilia Mvoundza Ndjindi:** Supervision, Resources, Investigation. **Amandine Mveang Nzoghe:** Visualization, Supervision, Resources. **Marielle Lebouenyi:** Visualization, Resources. **Bénédicte Ndeboko:** Visualization, Supervision, Resources. **Simon Ategbo:** Writing – review & editing, Visualization, Supervision, Resources. **Joel Fleury Djoba Siawaya:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Global Tuberculosis Report 2021, World Health Organization, Geneva, 2021.
[2] Global Tuberculosis Report 2017, World Health Organization, Geneva, 2017.
[3] OMS, Tuberculose de l’enfant : feuille de route : objectif zero deces, OMS, Geneva, 2016.
[4] World Health Organization, Tuberculosis Profile: Gabon, 2021. https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22GA%22.
[5] H.L.P. De Andrade, L.H. Arroyo, M. Yamamura, A.C.V. Ramos, J.A. Crispim, T.Z. Berra, M.S. Neto, I.C. Pinto, P.F. Palha, A.A. Monroe, K.A. Alexander, R. A. Arcêncio, Social inequalities associated with the onset of tuberculosis in disease-prone territories in a city from northeastern Brazil, Journal of infection in developing countries 15 (10) (2021) 1443–1452.
[6] D. Pathak, G. Vasishtha, S.K. Mohanty, Association of multidimensional poverty and tuberculosis in India, BMC Publ. Health 21 (1) (2021) 2065.
[7] P.D. Davies, The worldwide increase in tuberculosis: how demographic changes, HIV infection and increasing numbers in poverty are increasing tuberculosis, Ann. Med. 35 (4) (2003) 235–243.
[8] J. Grange, A. Zumla, Tuberculosis and the poverty-disease cycle, J. R. Soc. Med. 92 (3) (1999) 105–107.
[9] B.J. Marais, A.C. Hesseling, M.F. Cotton, Poverty and tuberculosis: is it truly a simple inverse linear correlation? Eur. Respir. J. 33 (4) (2009) 943–944.
[10] G. Wessels, H.S. Schaaf, N. Beyers, R.P. Gie, E. Nel, P.R. Donald, Haematological abnormalities in children with tuberculosis, J. Trop. Pediatr. 45 (5) (1999) 307–310.
[11] S. Verônica Melo Almeida Lima, J. Victor Muniz Rocha, K. de Araújo, M. Antonio Prado Nunes, C. Nunes, Determinants associated with areas with higher tuberculosis mortality rates: an ecological study, Trop. Med. Int. Health 25 (3) (2020) 338–345.
[12] S.R. Benatar, R. Upshur, Tuberculosis and poverty: what could (and should) be done? Int. J. Tubercul. Lung Dis. 14 (10) (2010) 1215–1221.
[13] D.P. Spence, J. Hotchkiss, C.S. Williams, P.D. Davies, Tuberculosis and poverty, BMJ (Clinical research ed.) 307 (6907) (1993) 759–761.
[14] G. Carrasco-Escobar, A. Schwalb, K. Tello-Lizarraga, P. Vega-Guerovich, C. Ugarte-Gil, Spatio-temporal co-occurrence of hotspots of tuberculosis, poverty and air pollution in Lima, Peru, Infectious Diseases of Poverty 9 (1) (2020) 32.

[15] A.J. Caulfield, N.L. Wengenack, Diagnosis of active tuberculosis disease: from microscopy to molecular techniques, Journal of clinical tuberculosis and other mycobacterial diseases 4 (2016) 33–43.
[16] J. Creswell, Z.Z. Qin, R. Gurung, B. Lamichhane, D.K. Yadav, M.K. Prasai, N. Bista, L.M. Adhikari, B. Rai, S. Sudrungrot, The performance and yield of tuberculosis testing algorithms using microscopy, chest x-ray, and Xpert MTB/RIF, Journal of clinical tuberculosis and other mycobacterial diseases 14 (2019) 1–6.
[17] E. Engohan alloghe, M. Toung mve, S. Ramarojoana, J. Iba ba, D. Nkoghe, Epidémiologie de la tuberculose infantile au centre antituberculeux de Libreville de 1997-2001, Med. Trop. 66 (5) (2006) 469–471.
[18] L. Chernick, I.S. Kalla, M. Venter, Clinical, radiological, and laboratory predictors of a positive urine lipoarabinomannan test in sputum-scarce and sputum-negative patients with HIV-associated tuberculosis in two Johannesburg hospitals, South. Afr. J. HIV Med. 22 (1) (2021) 1234.
[19] S. Sharma, R. Sarin, G. Sahu, G. Shukla, Demographic profile, clinical and microbiological predictors of mortality amongst admitted pediatric TB patients in a tertiary referral tuberculosis hospital, Indian J. Tubercul. 67 (3) (2020) 312–319.