Abstract

Background: In Colombia, epidemiological and clinical information related to pediatric tuberculosis (TB) is scarce. Data are needed to define the impact of the disease and to strengthen measures for detection and treatment. It is proposed to analyze the pediatric population diagnosed with pulmonary TB in a national reference institution. Methods: Retrospective observational study including pediatric patients with pulmonary and miliary TB, and pulmonary and extrapulmonary involvement, treated between January 1, 2008 and December 31, 2016. A descriptive analysis of the selected variables was done. Results: A total of 93 cases of diagnosed TB were identified, of which 61 cases were classified as pulmonary (65.6%). The location of TB occurred only in lungs in 51 patients (83.6%), was miliar in 3 (4.9%), pulmonary and extrapulmonary involvement in 7 patients (11.5%). The mean age was 7.5 years (0.5–18 years). Clinical criteria used for diagnosis was related to 98.3% of the cases, whereas radiological criteria in 90.2%. Bacteriological criterion was met in 42.6% of the cases. The most frequent symptoms were coughing (83.6%), fever (63.9%), and weight loss (26.2%); human immunodeficiency virus co-infection occurred in 3 cases (4.9%). During treatment, 5 mortality cases were recorded, although they were not attributable to TB. Conclusions: The epidemiological characterization of pediatric patients with pulmonary TB helps to achieve a better diagnostic approach in this population. Improving monitoring and follow-up activities in children with pulmonary TB, as well as promoting actions for adequate prevention and treatment is highly necessary.

Keywords: Epidemiology, microbiology, military, pediatrics, pulmonary, tuberculosis, tuberculosis

Introduction

Due to the difficulty for microbiological isolation, particularly in contexts in which resources are limited, the burden of tuberculosis (TB) disease in children is underestimated.[1] Pulmonary TB is the most frequent presentation in patients of all ages, accounting for up to 80% of cases.[2] In Colombia, epidemiological information related to pediatric TB and issued by Sistema Nacional de Vigilancia en Salud Pública (National Public Health Surveillance System) is scarce. Strong regional data are needed to define the impact of the disease and to strengthen measures for timely detection and treatment.[3] The epidemiological characterization of pediatric patients with pulmonary TB presented in this research, helps to achieve a better diagnostic approach in this population. This investigation aims at analyzing the status of this disease by assessing demographic, clinical, therapeutic, and diagnostic strategies directed to children with pulmonary TB in a region with intermediate prevalence of the disease.

Methods

The medical records of patients under age 18, with in- or out-patient treatment from a national pediatric reference institution, between January 2008 and December 2016, registered with TB diagnosis according to the International Classification of Diseases 10th Revision in any location, were retrospectively identified.

For the inclusion of patients, bacteriologically confirmed cases were defined as those with a positive biological sample by smear microscopy, culture, or molecular test; clinically diagnosed patients are those that do not meet the criteria...
for bacteriological confirmation but have been diagnosed with active TB by a physician, and have been administered a complete cycle of anti-TB treatment. This definition includes cases diagnosed based on X-ray abnormalities and/or suggestive histopathology, and/or with epidemiological nexus, and/or with a positive tuberculin test (contact with a confirmed TB case).[4]

Pulmonary TB was considered in any bacteriological or clinically diagnosed case involving the pulmonary parenchyma or the tracheobronchial tree; miliary TB was classified as pulmonary TB. Cases without radiographic lung involvement or intrathoracic (mediastinal and/or hilar) lymph node TB were not included in the study. Cases with pulmonary and extrapulmonary involvement were considered cases of pulmonary TB.[5]

Diagnostic criteria comprised clinical, bacteriological, histological, tuberculin, and radiological criteria. The definitions were based on the public health surveillance protocol entitled TB, published by Instituto Nacional de Salud (National Institute of Health, Colombia).[6] For assessment based on previous antituberculous treatment, patients were classified as a new patient and previously treated patient (after relapse, after failure, recovered after loss of follow-up, other previously treated patients). To evaluate the results of the treatment, the following categories were used: Cured and completed treatment, finished treatment, failure, death, loss in follow-up, not evaluated.[7]

For data collection, the clinical records of all patients were reviewed, and those that met the criteria described were selected. The following variables were obtained: Demographic data (age, sex, TB exposure, ethnicity), clinical data (weight, height, clinical manifestations, and comorbidities) and paraclinical tests (microbiology of biological samples, human immunodeficiency virus (HIV) status, images, and histopathology). The analysis of the nutritional status was performed through anthropometric measurements recorded in the clinical history at the time of TB diagnosis and was done using the World Health Organization (WHO) tool Anthro and Anthro Plus software, version 3.2.2, (Geneva: WHO) 2011, and interpreted according to the parameters of the WHO.[8] The information collected was transferred to a Microsoft Excel 2007 database, and a descriptive analysis of the variables was performed using the tools provided by the statistical support of the SPSS program, (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).[9] Frequencies and averages are reported for the variables of interest. No treatment’s outcome association was determined because the data about follow-up were not complete.

This project follows the public research policies that provide the standards for research, which are based on principles of justice, respect, nonmaleficence, beneficence, autonomy and capacity. It complies with international standards – particularly the Helsinki Declaration – as well as with the ethical guidelines for biomedical research prepared by the Council for International Organizations of Medical Sciences, and the Resolution 8430 of 1993 by the Ministry of Health of Colombia.

The project was assessed and approved by the Ethics and Research Committee of the institution where the project was carried out.

**Results**

During the study, 93 patients were diagnosed with TB; 61 patients (65.6%) presented with pulmonary TB, of which 51 (83.6%) presented this condition only in lungs; 3 cases (4.9%) were classified as miliary, and 7 cases (11.5%) with pulmonary and extrapulmonary location. 60 patients (98.3%) were classified as new patient and 1 (1.7%) as a previously treated patient.

**Demographic and general clinical data**

There is no gender-specific distribution (52.5% men, 47.5% women). The mean age was 7.5 years, ranging between 0.5 and 18 years with the highest prevalence among the 0–5 years of age group (41%). 4 cases (6.6%) occurred in the indigenous population. In 31 cases (50.8%), TB was associated with other comorbidity, the most frequent being hematologic comorbidity (childhood leukemias and lymphomas (21.3%) and malnutrition (13.1%). Three (4.9%) cases were co-infected with HIV (1 patient had miliary TB, and 2 pulmonary TB).

**Epidemiological nexus, history of vaccination and tuberculin test**

Epidemiological Nexus was documented in 23 cases (37.7%). No additional contact information was obtained. In 27 (44.3%) cases, a history of BCG vaccination was confirmed, and in the remaining cases, the history was unknown since no information was found in the medical records. The Mantoux tuberculin skin test (TST) was performed in 38 cases, being positive for 29 (76.3%) patients [Table 1].

**Clinical presentation**

Clinical criteria were met in 98.4% of the cases. The most frequent symptoms were coughing (83.6%), fever (63.9%), and weight loss (26.2%). The chronicity of the symptoms was not recorded [Table 2].

**Diagnostic tools**

**Microbiological evaluation**

Smear microscopy was performed in 59 cases (96.7%). The samples used were sputum (22%), gastric juice (GJ) (25.5%), and bronchoalveolar lavage (BAL) (13.5%). A combined sputum or GJ and BAL study were performed in 23 cases (39%). The positivity of the bacilloscopy was 16.9% (6 in GJ, 3 in sputum, 1 in BAL). GJ, sputum, BAL or tissue biopsies (lung, lymph node) cultures were performed in 51 cases (83.6%). Nine (17.6%) positive cultures were obtained for *M. tuberculosis*, 1 in GJ, 3 in sputum, 3 in BAL, and 2 in lymph nodes.
A molecular study using polymerase chain reaction (available since 2010 in the institution) was carried out in 29 cases: 3 in GJ, 20 in BAL, 3 in lung tissue, 1 in lymph node, 1 in peritoneal fluid, and 1 in pleural fluid. Positivity was 58.6%.

A histopathological study was done in lungs, lymph, mastoids, and skin samples in 12 cases (19.7%), finding granuloma and caseous necrosis in 6 cases (50%).

**Diagnostic imaging**

Radiological criteria were met in 55 patients (90.2%). A chest radiograph was performed in 59 cases (96.7%), and abnormal findings were documented in 84.7% of the cases. Two patients did not have chest radiograph, but one of them had a computed tomography (CT). In 42 cases (68.8%), chest CT was performed, yielding abnormal results in 80.9% of the cases. The findings were diverse, with single opacity, multilobar opacity, lymphadenopathy, and calcifications as the most frequent results for both studies. The 6 cases (9.8%) that did not meet the radiological criteria had normal radiographs, although only one of the cases required an additional chest CT, which was interpreted as normal; the 4 remaining cases did not have studies with images complementary to radiography [Table 3].

Other images, specific for each location, were utilized in cases of pulmonary and extrapulmonary TB. In the case of vertebral TB, a lumbar spine CT was performed reporting the destruction of the vertebral body of L5; in the case of mastoid TB, CT reported mastoiditis with bone erosion.

**Diagnostic criteria**

Clinical criterion was met in 98.3% of pulmonary TB cases, and was followed by radiological (90.2%), tuberculin (49.2%), epidemiological (37.7%), bacteriological (42.6%), and histopathological criteria (9.8%) [Table 4].

In all cases the most frequent combination of criteria for diagnosis was clinical, radiological and tuberculin criteria. In pulmonary and extrapulmonary TB cases, the most frequent combination was clinical, bacteriological, and radiological criteria.

**Treatment**

Only one case did not initiate any treatment due to death caused by compromise associated with other comorbidities. Patients who received treatment were classified as treated in 14 (22.9%) cases and treatment in 22 (36.1%) cases; failure was reported in 1 (1.6%) case. Results for no institutional follow-up are unknown in 19 cases (31.2%). Five mortality cases were not attributable to TB (8.2%). There is only one adverse effects record associated with anti-TB drugs, namely, ototoxicity to amikacin and gastrointestinal intolerance to ethionamide. No other cases of drug toxicity were reported [Table 5].

**Resistant TB**

Two patients received second-line treatment. One case had a positive sputum smear at the end of treatment so there was a suspicion of multidrug-resistant TB (MDR-TB); second-line treatment with kanamycin, cycloserine, moxifloxacin, ethionamide, and pyrazinamide was initiated. However, institutional follow-up was done until

Table 1: General demographic and clinical characteristics

| Variable                        | n (%) |
|---------------------------------|-------|
| Sex                             |       |
| Female                          | 29 (47.5) |
| Male                            | 32 (52.5) |
| Age at diagnosis (years)        |       |
| 0-5                             | 25 (41) |
| 5-10                            | 13 (21.3) |
| 10-15                           | 13 (21.3) |
| 15-18                           | 10 (16.4) |
| Case classification             |       |
| New                             | 60 (98.3) |
| Relapse                         | 1 (1.7) |
| Location                        |       |
| Only                            | 51 (83.6) |
| Pulmonary                       | 51 (100) |
| Multiple                        | 10 (16.4) |
| Pulmonary/lymph node             | 1 (10) |
| Pulmonary/vertebral              | 1 (10) |
| Pulmonary/skin/hematologic      | 1 (10) |
| Miliar/pleural                  | 1 (10) |
| Miliar/lymph node/mastoid       | 1 (10) |
| Pulmonary/pleural/peritoneal    | 1 (10) |
| Pulmonary/meningeal             | 1 (10) |
| Pulmonary/miliar                | 3 (30) |
| BCG vaccination status          |       |
| Unknown                         | 34 (55.7) |
| Yes                             | 27 (44.3) |
| Epidemiological nexus           |       |
| Yes                             | 23 (37.7) |
| No                              | 37 (60.7) |
| Unknown                         | 1 (1.6) |
| Tuberculin*                     |       |
| Positive                        | 29 (47.5) |
| Negative                        | 9 (14.8) |
| Unknown                         | 23 (37.7) |
| Comorbidities                   |       |
| No                              | 30 (49.2) |
| Yes                             | 31 (50.8) |
| Single/multiple comorbidities   |       |
| Single                          | 14 (45.1) |
| Multiple                        | 17 (54.9) |
| Types of comorbidities          |       |
| Hematologic**                   | 13 (21.3) |
| Malnutrition                    | 8 (13.1) |
| Other***                        | 12 (19.7) |
| Pulmonary                       | 5 (8.2) |

*For the assessment of the tuberculin test, a reaction of ≥10 mm is considered positive. In children younger than 15 years and in children infected with HIV, a reaction of ≥5 mm is considered positive, **Leukemia and pediatric lymphoma cases, ***Hemolytic anemia, systemic sclerosis, and epilepsy cases. BCG: Bacillus Calmette–Guérin
the second month of treatment, and the clinical outcome and susceptibility tests are unknown. The second case classified as treatment failure was a miliary TB. The drug susceptibility test documented poli-resistant TB (resistance to streptomycin and isoniazid) and treatment was continued with moxifloxacin, ethionamide, pyrazinamide, amikacin and rifampicin. The outcome of the treatment is unknown since institutional follow-up was not done. In 2 more cases, susceptibility testing was performed without documented resistance.

**Table 2: Symptoms**

| Findings          | n (%) | Chest X-ray | n (%) | Chest CT | n (%) |
|-------------------|-------|-------------|-------|----------|-------|
| Coughing          | 51 (83.6) | 50 (84.7) | 34 (81) | 39 (90)  | 9 (15.2) |
| Fever             | 50 (84.7) | 39 (63.9) | 16 (26.2) | 39 (63.9) | 16 (26.2) |
| Weight loss       | 11 (18)       | 11 (18)       | 11 (18)       | 11 (18)       | 11 (18)       |
| Hiporexia         | 8 (13)        | 9 (15.2) | 4 (6.8) | 5 (8.2) | 5 (8.2) |
| Lymphadenopathy   | 5 (8.2)        | 5 (8.2) | 5 (8.2) | 5 (8.2) | 5 (8.2) |
| Failure to thrive | 10 (16.4) | 10 (16.4) | 10 (16.4) | 10 (16.4) | 10 (16.4) |
| Others*           | 12 (19.7) | 12 (19.7) | 12 (19.7) | 12 (19.7) | 12 (19.7) |

*Hepatosplenomegaly, diarrhea, seizure

**Table 3: Radiological criteria**

| Findings          | Chest X-ray | Chest CT |
|-------------------|-------------|----------|
| Abnormal          | 50 (84.7) | 34 (81) |
| Normal            | 9 (15.2) | 8 (19) |
| Description       |           |         |
| Single opacity    | 27 (45.7) | 16 (38.1) |
| Multilobar opacity| 13 (22) | 7 (16.6) |
| Adenopathy        | 5 (8.5) | 12 (28.6) |
| Nodule            | 4 (6.8) | 12 (28.6) |
| Calcification     | 5 (8.5) | 7 (16.6) |
| Pleural effusion  | 4 (6.8) | 2 (4.7) |
| Cavity            | 1 (1.7) | 2 (4.7) |
| Micronodular      | 3 (5.1) | 6 (12.3) |
| Others*           | 19 (32.2) | 3 (7.1) |

*Atelectasis, peribronchial thickening, interstitial infiltrates, bronchial inflammatory process, ground glass. CT: Computed tomography

**Table 4: Evidence used for diagnosis**

| Location according to each case | Clinical, n (%) | Bacteriological, n (%)*** | Histopathological, n (%)*** | Epidemiological, n (%) | Tuberculin, n (%) | Radiological, n (%)*** |
|---------------------------------|-----------------|---------------------------|-----------------------------|------------------------|------------------|------------------------|
| Pulmonary                       | 50 (98)         | 18 (35.3)                 | 4 (7.8)                     | 20 (39.1)              | 26 (50.9)        | 45 (88.2)              |
| Miliary                         | 3 (100)         | 2 (66.6)                  | 0                           | 0                      | 2 (66.6)         | 3 (100)                |
| Pulmonary/lymph node            | 1 (100)         | 1 (100)                   | 0                           | 0                      | 1 (100)          | 1 (100)                |
| Pulmonary/vertebral             | 1 (100)         | 1 (100)                   | 0                           | 1 (100)                | 1 (100)          | 1 (100)                |
| Pulmonary/skin/hematological    | 1 (100)         | 1 (100)                   | 0                           | 1 (100)                | 0                | 1 (100)                |
| Military/pleural                | 1 (100)         | 1 (100)                   | 0                           | 0                      | 0                | 1 (100)                |
| Military/lymph node/mastoid     | 1 (100)         | 1 (100)                   | 1 (100)                     | 0                      | 0                | 1 (100)                |
| Pulmonary/pleural/peritoneal    | 1 (100)         | 1 (100)                   | 0                           | 1 (100)                | 0                | 1 (100)                |
| Pulmonary/meningeal             | 1 (100)         | 1 (100)                   | 0                           | 1 (100)                | 0                | 1 (100)                |
| Total                           | 61 (98.3)       | 26 (42.6)                 | 6 (9.8)                     | 23 (37.7)              | 30 (49.2)        | 55 (90.2)              |

*Bacteriological criteria include bacilloscopy, culture or molecular detection tests (polymerase chain reaction). **Histopathological criteria include biopsy of any tissue that demonstrates granulomas with caseous necrosis (active) and positive Zielh–Neelsen. ***Radiological criteria include findings on chest radiography, chest tomography with findings suggestive of TB. TB: Tuberculosis

**Discussion**

The scenario of pediatric TB poses challenges, in which a combination of clinical suspicion and diagnostic aids (direct and indirect tests of infection) is required to build up the case, considering that microbiological confirmation rates are low in this population.[10] In Colombia, according to the epidemiological bulletin of the National Institute of Health, in 2016,[11] 13,626 cases of TB in all forms were reported. The incidence rate in Colombia for all forms of TB was 25.3/100,000 inhabitants, and in Bogotá, it was 14/100,000 inhabitants. Of the total number of cases reported in the country that year, 4.2% (584 cases) were younger than 15 years. There are reports of incidence of TB with positive bacilloscopy in pediatric patients in 2008 of 2/100,000 inhabitants and 1.2/100,000 inhabitants of TB with negative sputum smear microscopy.[12]

Pulmonary TB was the most common form of the disease in this study, which coincides with the reports found in the literature.[13-15] In the pediatric population, age is one of the risk factors for progression to active disease;[19] cases observed in this study report that the highest infection rates are found in children under 5 years of age.[13]

In most patients, clinical criteria could be documented, finding that the most common symptoms were similar to those found in other studies.[16,17] Although a history of epidemiological nexus was identified in few children, an active search for pediatric cases from index cases continues to represent one of the most effective tools for identifying the infection.[18]

HIV co-infection is the most studied comorbidity in pediatric patients; Krauss et al.[19] reported a prevalence of 9.2% in Latin America, which is similar to the results presented in this study. However, this association was not the most common comorbidity in the study, in which approximately half of the patients had concomitant conditions, being the most frequent hematological malignancies and malnutrition.

Information about TB in children with cancer is scarce and comes from case reports;[20] in addition, there is a limitation...
for extrapolating such information to the results of this study since most of these records come from regions with low TB prevalence. Additional studies are necessary to evaluate the behavior of TB in this population in regions with intermediate and high burden of disease.

On the other hand, undernutrition and TB are frequently associated conditions in children, and both represent a public health issue worldwide. Documentation of both entities varies according to the region studied; the findings in this study were significant when compared with reports in similar populations.\textsuperscript{21,22}

Microbiological performance in the casuistry of this hospital was close to what was found in the literature.\textsuperscript{23,24} The performance of each biological sample used for the bacteriological study varies according to the reference consulted. Although most studies suggest that the isolation rate is higher in GJ (20\%–40\%) compared to BAL (10\%–16\%),\textsuperscript{25} which coincides with the population in this study that presented the highest frequency of GJ isolates.

Since the return rate is still low, studies such as Hong-Ren \textit{et al.}\textsuperscript{23} evaluate the simultaneous use of samples such as GJ and BAL, and find that the combination of both studies increases the frequency of isolations up to 100\%, which differs from the findings of this study. Although about half of the cases have both types of samples, the frequency of microbiological confirmation did not increase, suggesting that possible technical factors associated with patient sampling and conditions may modify the performance of the tests.

In this series, 50\% of bacteriologically confirmed cases were obtained through molecular tests; it is noteworthy that in more than half of these patients isolates were not obtained with conventional microbiological studies (Ziehl–Neelsen and cultures), similar to those reported by other authors,\textsuperscript{26,27} who document a greater sensitivity of the molecular study than conventional microbiological studies for the diagnosis of pulmonary TB in children. The above validates the importance of the routine use of molecular biology tools to improve diagnostic performance. Currently, new methodologies, such as GeneXpert MTB/RIF\textsuperscript{®} which simultaneously detects microorganisms and resistance to rifampicin, are available to provide additional features.\textsuperscript{28,29} However, by the time of completion of this study, there was not a relevant amount of patients with this test to draw conclusions regarding its usefulness.

The diagnostic value of chest X-ray in pulmonary TB has been documented in asymptomatic patients with a positive tuberculin test for identifying disease-related alterations, as well as in patients with clinical suspicion of the disease. Therefore, it constitutes a routine study.\textsuperscript{30} The frequency of radiographic alterations coincides with reports in other similar investigations.\textsuperscript{29} Findings were widely variable since the literature does not report radiographic alterations in a pathognomonic way in different series.

In a study conducted in Lima\textsuperscript{31} in a 25-year old sample, the findings varied according to age, although bilateral infiltrates, cavitation and intrathoracic adenopathies were more frequent, which differs from this study due to the variability of the presentation of the entity.

The systematic use of chest CT remains controversial. Some authors propose its use in symptomatic patients with normal or doubtful chest X-ray.\textsuperscript{32} However, in pediatrics, the risk of systematic exposure to radiation is a limitation. Similar to findings in other series, the percentage of cases with normal radiography was <10\%, and only one of these cases underwent a complementary tomographic study, which did not present alterations either; with this in mind, providing recommendations or drawing conclusions regarding the use of routine CT scans in pediatric patients with suspected TB and normal chest X-ray is not possible. Mortality in this study was 8.2\%, but there was no association between death and TB infection.

One of the limitations of this study is the impossibility of extrapolating results since data come from a single hospital center, which is a national reference in pediatrics, pediatric oncology and neurology. Conclusions about the outcome of treatment in the studied population cannot be made since follow-up records are not available in a significant proportion of cases. Data is insufficient to analyze the behavior of resistance in the pediatric population.

Pulmonary TB in the pediatric population is a diagnosis that derives from the interaction between establishing clinical suspicion and conducting multiple complementary studies through direct and indirect evidence of the disease. Molecular biology tools increase the diagnostic yield; however, in regions with moderate or low health resources, its systematic implementation represents a challenge. Imaging studies are complementary in the evaluation of the disease; the role of CT scans in patients with clinical suspicion and normal radiographs are still unclear. Multicenter studies in the country are necessary to characterize the child population affected by this entity; however, standardizing diagnostic behaviors that include the use of molecular biology tools is

### Table 5: Characteristics of the treatment

| Variable                  | n (%) |
|---------------------------|-------|
| Treatment                 | 60 (98.4) |
| Treatment results         |       |
| In treatment              | 22 (36.1) |
| Without institutional follow-up | 19 (31.1) |
| Treaty                    | 14 (23)  |
| Treatment failure         | 1 (1.6)  |
| Deceased***               | 5 (8.2)  |

*No treatment is initiated because of death due to complications associated with comorbidities, **Mortality not attributable to TB.

TB: Tuberculosis
necessary to address this entity and to achieve higher rates of microbiological confirmation and early treatments.

**CONCLUSION**

The epidemiological characterization of pediatric patients with pulmonary TB presented in this research, helps to achieve a better diagnostic approach in this population. In this study, molecular biology tools increased the diagnostic yield.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Marais BJ. Tuberculosis in children. J Paediatr Child Health 2014;50:759-67.
2. Gousset P, Gie R. The role of bronchoscopy in the diagnosis and management of pediatric pulmonary tuberculosis. Expert Rev Respir Med 2014;8:101-9.
3. Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. Paediatric tuberculosis. Lancet Infect Dis 2008;8:498-510.
4. Ministry of health and social protection. Technical annex 1. Programmatic definitions for tuberculosis adapted from the document “Definition and Reporting Framework for Tuberculosis” Bogotá, Colombia; 2014. Available from: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/circular-externa-0007-de-2015.pdf. [Last cited on 2017 Jan 09].
5. World Health Organization (WHO). Global Tuberculosis Report. 20th ed. Geneva: WHO; 2015.
6. National health institute. Protocolo de Vigilancia en Salud Pública. Tuberculosis. Bogotá, Colombia; 2016. Available from: http://www.ins.gov.co/lineas-de-accion/Subdireccion-Vigilancia/sivigila/Protocolos%20SIVIGILA/PRO%20Tuberculosis.pdf. [Last cited on 2017 Jan 09].
7. World Health Organization (WHO). Definitions and reporting framework for tuberculosis – 2013 revision. WHO/HTM/TB/2013.2. Geneva: World Health Organization; 2013.
8. de Onis M, Garza C, Vitora C, Bhan MK, Norum KR. The WHO Multicentre Growth Reference Study (MGRS): Rationale, planning, and implementation. Food Nutr Bull 2004;25 Suppl 1:S3-84.
9. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.
10. Turel O, Kazanci S, Gonen I, Aydogmus C, Karaoğlan E, Siraneci R. Paediatric tuberculosis at a referral hospital in İstanbul: Analysis of 250 cases. Biomed Res Int 2016;2016:6896279.
11. National Health Institute. Boletín Epidemiológico Semana 52. Bogotá, Colombia; 2016. Available from: http://www.ins.gov.co/boletin-epidemiologico/Boletin%20Epidemiologico/2016/520Bolet%C3%ADn%20Epidemiologico%20Semanal%20%2052%20-521.pdf. [Last cited on 2017 Jan 09].
12. Rodríguez DA, Gil NA, Vera NR. Tuberculosis situation in Colombia 2007-2008 with emphasis in pediatric cases and coinfection TB-VIH. Infectio 2010;14:195-205.
13. Swaminathan S, Rekha B. Pediatric tuberculosis: Global overview and challenges. Clin Infect Dis 2010;50 Suppl 3:S184-94.
14. Alavi SM, Salzmanzadeh S, Bakhthiyariyina P, Albagi A, Hemmatnia F, Alavi L. Prevalence and treatment outcome of pulmonary and extrapulmonary pediatric tuberculosis in Southwestern Iran. Caspian J Intern Med 2015;6:213-9.
15. Devrim I, Aktürk H, Bayram N, Apa H, Tulumoglu S, Devrim F, et al. Differences between pediatric extra-pulmonary and pulmonary tuberculosis: A warning sign for the future. Mediterr J Hematol Infect Dis 2014;6:e2014058.
16. Galli L, Lancelli L, Tersigni C, Venturini E, Chiappinni E, Bergamini BM, et al. Pediatric Tuberculosis in Italian Children: Epidemiological and Clinical Data from the Italian Register of Pediatric Tuberculosis. Int J Mol Sci 2016;17:960.
17. Bisero E, Luque G, Borda ME, Melillo K, Zapata A, Varela S. Tuberculosis in a Pediatric Population Treated at a Public Hospital. Adherence to Treatment. Descriptive Study. Rev Am Med Resp 2013;4:184-89.
18. Franke MF, del Castillo H, Pereda Y, Lecca L, Cárdenas L, Fuertes J, et al. Modifiable factors associated with tuberculosis disease in children: A case-control study. Pediatr Infect Dis J 2014;33:109-11.
19. Krauss MR, Harris DR, Abreu T, Ferreira FG, Ruiz NP, Worrell C, et al. Tuberculosis in HIV-infected infants, children, and adolescents in Latin America. Braz J Infect Dis 2015;19:23-9.
20. Lancioni C, LaBeaud AD, Esper F, Abughali N, Auletta J. Pulmonary tuberculosis presenting as fever without source in a pediatric patient with acute lymphoblastic leukaemia. Pediatr Blood Cancer 2009;53:1318-20.
21. Orozco I, Nesbitt C, Gonzalez S. Tuberculosis in pediatrics: Epidemiology. Rev Enfermedad Infecciosas Pediatría 2009;22:83-90.
22. Rodríguez MG, Patallo CP, Rizzotti VA, Moscoloni MA, Ballester DS. Pulmonary tuberculosis at a reference hospital during the 2004-2008 period. Rev Argent Microbiol 2011;43:37-41.
23. Hong-Ren Y, Kuang-Che K, Wei-Ju L, Kao-Sheng H. Bronchoalveolar lavage is useful for the diagnosis of pulmonary tuberculosis in children. J Pediatr Resp Dis 2015;11:35-9.
24. Ramos JM, Pérez-Butragueño M, Tisiano G, Yofranes T, Reyes F, Górgolas M. Evaluation of Ziehl-Neelsen smear for diagnosis of pulmonary tuberculosis in childhood in a rural hospital in Ethiopia. Int J Mycobacteriol 2013;2:171-3.
25. Swaminathan S, Ramachandran G. Challenges in childhood tuberculosis. Clin Pharmacol Ther 2015;98:240-4.
26. Tiwari S, Natraj G, Kanade S, Mehta P Diagnosis of pediatric pulmonary tuberculosis with special reference to polymerase chain reaction based nucleic acid amplification test. Int J Mycobacteriol 2015;4:48-53.
27. Osman AL, Saeed NS, Elhassan MM. Polymerase Chain Reaction targeting insertion sequence IS6110 for the diagnosis of pulmonary tuberculosis among Sudanese children and young adults. Int J Mycobacteriol 2014;3:252-8.
28. Holberg M, Zabala C, Gutiérrez S, Sisto G, Sosa M, Giachetto G. Prevalence and clinical-epidemiological characteristics of child tuberculosis diagnosed with an index case. Uruguay 2012-2014. Arch Pediatr Uruguay 2016;5 Suppl 1:3-10.
29. Hasan Z, Arif F, Shokoor S, Mehrnaz A, Akber A, Kanji A, et al. Effective testing for pulmonary tuberculosis using Xpert MTB/RIF assay for stool specimens in immunocompetent Pakistani children. Int J Mycobacteriol 2016;5 Suppl 1:S8-S9.
30. Gwee A, Pantazidou A, Ritz N, Tebueeg M, Connell TG, Cain T, et al. To x-ray or not to x-ray? Screening asymptomatic children for pulmonary TB: A retrospective audit. Arch Dis Child 2013;98:401-4.
31. Del Castillo-Barrientos H, Centeno-Luque G, Univeros-Tello A, Simms B, Lecca L, Nelson AK, et al. Clinical presentation of children with pulmonary tuberculosis: 25 years of experience in Lima, Peru. Int J Tubere Lung Dis 2014;18:1066-73.
32. Garrido JB, Alias Hernández I, Bonillo Perales A, Ruíz Ruiz T, González Jiménez Y, González-Ripoll Garzón M, et al. Usefulness of thoracic CT to diagnose tuberculosis disease in patients younger than 4 years of age. Pediatr Pulmonol 2012;47:895-902.