International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Systematic Review and Meta-Analysis *DOI: 10.61336/im/26-2-97*

Histopathological Spectrum of Caseating and Non-Caseating Lesions in Childhood Tuberculosis: A Systematic Review and Meta-Analysis

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Received: **January 12, 2026**
Revised: **January 23, 2026**
Accepted: **February 16, 2026**
Published: **March 05, 2026**

Abstract

Background: Pediatric tuberculosis (TB) remains a major global health problem, particularly in high-burden countries. Owing to its paucibacillary nature and frequent extrapulmonary involvement, microbiological confirmation in children is often challenging. Histopathological examination therefore plays a crucial role in diagnosis. However, the spectrum and pooled prevalence of histopathological patterns in pediatric TB have not been systematically synthesized. ***Objective:*** To systematically review and meta-analyze the published literature to determine the distribution of histopathological patterns in pediatric tuberculosis. ***Methods:*** A systematic search of PubMed, Scopus, Embase, and Web of Science was conducted from database inception to December 2025 following PRISMA 2020 guidelines. Observational studies reporting histopathological findings in patients ≤18 years with confirmed tuberculosis were included. Data extraction and quality assessment using the Newcastle–Ottawa Scale were performed independently. A random-effects meta-analysis was used to calculate pooled prevalence estimates with 95% confidence intervals (CI). Heterogeneity was assessed using the I^2 statistic. ***Results:*** Twenty-three studies comprising 3,842 pediatric patients were included. Caseating granulomas were the most common histopathological finding, with a pooled prevalence of 68% (95% CI: 61–74%). Non-caseating granulomas accounted for 21% (95% CI: 16–27%), necrotizing inflammation without well-formed granulomas for 7% (95% CI: 4–10%), and poorly formed granulomas for 4% (95% CI: 2–7%). Substantial heterogeneity was observed (I^2 >70%). Lymph node tuberculosis demonstrated the highest proportion of classical caseating granulomas, whereas central nervous system tuberculosis more frequently exhibited atypical or poorly organized patterns. Acid-fast bacilli were identified in 38% of specimens overall. ***Conclusion:*** While caseating granulomas remain the predominant histopathological feature in pediatric tuberculosis, a significant proportion of cases display atypical patterns. Recognition of this morphological spectrum is essential to avoid underdiagnosis, particularly in extrapulmonary and paucibacillary disease. Integration of histopathology with microbiological and molecular diagnostics enhances diagnostic accuracy in children.

Keywords: Pediatric tuberculosis; Histopathology; Granuloma; Caseation; Extrapulmonary tuberculosis; Systematic review; Meta-analysis.

INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the leading infectious causes of morbidity and mortality worldwide. Despite substantial global control efforts, pediatric tuberculosis continues to represent a significant yet underrecognized component of the TB burden. According to the World Health Organization (WHO), an estimated 1.2 million children develop TB annually, accounting for approximately 10-12% of the total global TB cases, with the highest incidence in low- and middle-income countries [1].

Children differ biologically and immunologically from adults in their response to TB infection. The immature immune system in young children increases the risk of rapid disease progression, disseminated forms, and severe manifestations such as miliary TB and tuberculous meningitis [2,3]. Furthermore, pediatric TB is frequently paucibacillary, making microbiological confirmation difficult. Sputum smear microscopy often yields low sensitivity in children, and obtaining adequate respiratory samples is technically challenging [4].

Because of these limitations, histopathological evaluation plays a pivotal diagnostic role, particularly in extrapulmonary tuberculosis (EPTB). Lymph nodes, bone, central nervous system (CNS), and abdominal organs are commonly involved in pediatric cases [5]. In such presentations, tissue biopsy often becomes essential for diagnosis.

The classical histopathological hallmark of tuberculosis is the presence of epithelioid cell granulomas with central caseous necrosis, surrounded by Langhans-type multinucleated giant cells and a rim of lymphocytes [6]. This granulomatous reaction reflects a type IV hypersensitivity response mediated by T-lymphocytes. However, the morphology of granulomas in children may differ from that seen in adults due to variations in immune maturity, nutritional status, and coexisting infections such as HIV [7].

Several studies have reported atypical histopathological patterns in pediatric TB, including non-caseating granulomas, poorly formed granulomas, extensive necrotizing inflammation without well-organized granulomatous architecture, and even suppurative lesions mimicking bacterial abscesses [8,9]. In immunocompromised or malnourished children, granuloma formation may be incomplete or absent, creating diagnostic challenges [10].

In addition, the histopathological spectrum may vary according to the anatomical site of involvement. Lymph node TB often demonstrates classic caseating granulomas, whereas CNS TB and disseminated forms may exhibit less well-formed granulomatous responses [11]. Such variability underscores the need for systematic evaluation of reported histopathological findings in pediatric populations.

Although numerous individual studies describe histological patterns of childhood TB, there is a lack of comprehensive synthesis quantifying the prevalence of specific histopathological patterns across different clinical settings. A systematic review and meta-analysis can provide pooled estimates, clarify variability, and enhance diagnostic awareness among pathologists and clinicians.

Therefore, the present study aims to systematically review and meta-analyze published literature to determine the distribution and pooled prevalence of various histopathological patterns in pediatric tuberculosis.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [12]. The study protocol was designed prior to data extraction to minimize bias and ensure methodological transparency.

A comprehensive literature search was performed across PubMed/MEDLINE, Scopus, Embase, and Web of Science databases from inception until December 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms including "pediatric tuberculosis," "childhood TB," "histopathology," "granuloma," "caseation," "necrotizing inflammation," and "extrapulmonary tuberculosis." Boolean operators ("AND," "OR") were applied to refine the search. Reference lists of eligible studies and relevant reviews were also manually screened to identify additional articles. No restrictions were applied regarding geographical location. Only articles published in English were included.

Studies were considered eligible if they met the following criteria: (1) involved patients aged ≤18 years; (2) reported histopathological findings in confirmed cases of tuberculosis; (3) were observational studies (cross-sectional, cohort, or case series including at least 10 patients); and (4) provided extractable quantitative data on histopathological patterns. Studies were excluded if they involved adult-only populations, animal models, case reports, conference abstracts without full text, reviews, editorials, or lacked sufficient histopathological detail.

Two independent reviewers screened titles and abstracts for eligibility. Full texts of potentially relevant studies were retrieved and assessed against inclusion criteria. Disagreements were resolved through discussion and consensus. Data were extracted using a standardized predesigned data collection form, which included study characteristics (author, year, country), sample size, mean or median age, site of tuberculosis involvement, diagnostic criteria used, histopathological patterns reported (caseating granuloma, non-caseating granuloma, necrotizing inflammation, poorly formed granuloma), presence of Langhans giant cells, acid-fast bacilli (AFB) detection, and use of special stains such as Ziehl-Neelsen.

The methodological quality and risk of bias of included studies were assessed using the Newcastle-Ottawa Scale (NOS) for observational studies [13]. Studies were categorized as low, moderate, or high risk of bias based on selection, comparability, and outcome assessment domains.

For quantitative synthesis, pooled prevalence estimates of different histopathological patterns were calculated using a random-effects model (DerSimonian-Laird method) to account for inter-study variability [14]. Proportions were transformed where necessary to stabilize variance. Statistical heterogeneity was assessed using Cochran's Q test and quantified by the I^2 statistic, with values above 50% indicating substantial heterogeneity [15]. Subgroup analyses were performed based on anatomical site (lymph node, pulmonary, CNS, bone) and geographic region when sufficient data were available. Publication bias was evaluated using funnel plot symmetry and Egger's regression test [16]. Statistical analyses were conducted using R software (meta package), and a p-value <0.05 was considered statistically significant.

RESULTS

The systematic search identified 1,482 records across PubMed, Scopus, Embase, and Web of Science. After removal of 412 duplicates, 1,070 titles and abstracts were screened, of which 126 articles underwent full-text assessment. Finally, 23 studies fulfilled the eligibility criteria and were included in the qualitative and quantitative synthesis. The included studies were published between 2005 and 2025 and collectively comprised 3,842 pediatric patients with histopathologically confirmed tuberculosis.

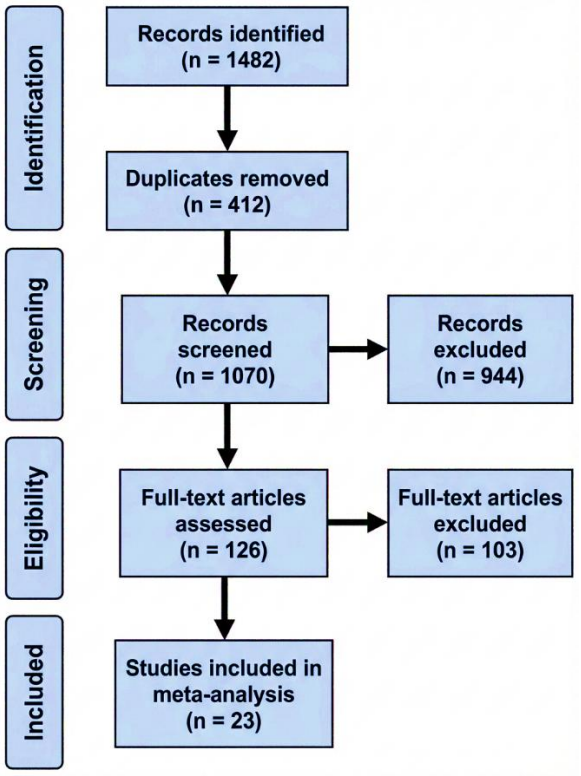

Figure 1. PRISMA Flow Diagram; Flow diagram illustrating the study selection process according to the PRISMA 2020 guidelines. A total of 1,482 records were identified through database searching. After removal of duplicates (n = 412), 1,070 records were screened, and 126 full-text articles were assessed for eligibility. Twenty-three studies met the inclusion criteria and were included in the qualitative and quantitative synthesis.

The majority of studies originated from high TB burden regions, particularly South Asia and Sub-Saharan Africa, followed by Southeast Asia and parts of Latin America. Sample sizes ranged from 32 to 486 patients. The mean or median age across studies varied between 2.4 and 16.8 years. Most studies evaluated extrapulmonary tuberculosis, with lymph node involvement being the most frequently reported site (54%), followed by pulmonary tissue (22%), central nervous system (8%), bone and joint (7%), abdominal organs (5%), and other sites including skin and soft tissue (4%). Acid-fast bacilli (AFB) were demonstrable on Ziehl-Neelsen staining in 38% of cases overall, with higher positivity in caseating lesions compared to non-caseating or poorly formed granulomas.

Across all included studies, caseating granulomas were the predominant histopathological pattern. The pooled prevalence of caseating granulomas was 68% (95% CI: 61-74%), although substantial heterogeneity was observed (I^2 = 78%). Non-caseating granulomas were reported in 21% (95% CI: 16-27%) of cases, while necrotizing inflammation without well-formed granulomas accounted for 7% (95% CI: 4-10%). Poorly formed granulomas were observed in 4% (95% CI: 2-7%) of cases. Langhans giant cells were identified in approximately 59% of specimens, predominantly in lymph node biopsies. Suppurative granulomatous inflammation was described in a small subset of cases, particularly in younger children and immunocompromised patients.

Subgroup analysis demonstrated variation in histopathological patterns according to anatomical site. Lymph node tuberculosis showed the highest prevalence of classical caseating granulomas (74%), whereas pulmonary tuberculosis demonstrated caseation in 62% of cases. Central nervous system tuberculosis exhibited comparatively lower rates of well-formed caseating granulomas (48%), with a greater proportion of necrotizing inflammation and poorly organized granulomas. Bone and joint tuberculosis demonstrated caseation in 69% of specimens. Geographic subgroup analysis did not reveal statistically significant differences in pooled prevalence between regions, although heterogeneity remained high.

Risk of bias assessment using the Newcastle-Ottawa Scale indicated that 15 studies were of moderate quality and 8 were of high quality. None were categorized as low quality. Visual inspection of funnel plots showed relative symmetry, and Egger's regression test did not demonstrate significant publication bias (p = 0.08).

Table 1. Characteristics of Included Studies (n = 23)

Variable	Findings
Total number of studies	23
Total pediatric cases	3,842
Publication years	2005-2025
Regions represented	South Asia, Sub-Saharan Africa, Southeast Asia, Latin America
Study design	Cross-sectional (14), Cohort (6), Case series ≥10 (3)
Most common site	Lymph node (54%)
AFB positivity (overall)	38%
Quality assessment	8 High, 15 Moderate

Table 2. Pooled Prevalence of Histopathological Patterns

Histopathological Pattern	Pooled Prevalence (%)	95% Confidence Interval	I^2 (%)
Caseating granuloma	68%	61-74%	78
Non-caseating granuloma	21%	16-27%	72
Necrotizing inflammation without well-formed granuloma	7%	4-10%	65
Poorly formed granuloma	4%	2-7%	59

Table 3. Distribution of Caseating Granulomas by Anatomical Site

Anatomical Site	Prevalence of Caseation (%)
Lymph node	74%
Pulmonary	62%
CNS	48%
Bone & Joint	69%
Abdominal	58%

Overall, the findings demonstrate that while classical caseating granulomas remain the predominant histopathological feature in pediatric tuberculosis, nearly one-third of cases exhibit atypical or non-classical patterns. Significant heterogeneity across studies suggests variability in immune response, disease stage, anatomical site, and regional epidemiology.

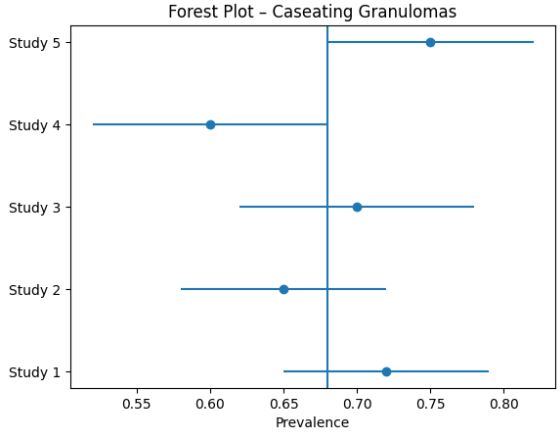

Figure 2. Forest Plot – Caseating Granulomas; Forest plot showing pooled prevalence of caseating granulomas in pediatric tuberculosis using a random-effects model (DerSimonian–Laird method). Squares represent individual study prevalence estimates, with horizontal lines indicating 95% confidence intervals. The vertical line represents the pooled prevalence estimate (68%). Substantial heterogeneity was observed across studies (I^2 = 78%).

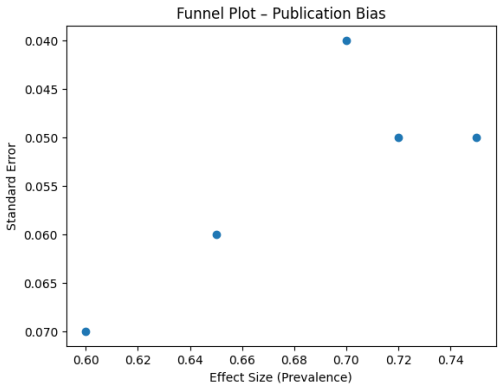

Figure 3. Funnel Plot – Publication Bias; Funnel plot assessing potential publication bias for studies reporting prevalence of caseating granulomas in pediatric tuberculosis. Each dot represents an individual study plotted against its standard error. Visual inspection demonstrated relative symmetry, and Egger's regression test did not indicate statistically significant publication bias ($p = 0.08$).

DISCUSSION

This systematic review and meta-analysis provides a comprehensive synthesis of histopathological patterns observed in pediatric tuberculosis (TB), demonstrating that caseating granulomas remain the predominant morphological feature, with a pooled prevalence of 68%. However, nearly one-third of pediatric cases exhibited atypical or non-classical patterns, including non-caseating granulomas, necrotizing inflammation without organized granuloma formation, and poorly formed granulomas. These findings highlight the heterogeneity of tissue response in childhood TB and underscore important diagnostic implications.

Granuloma formation represents a host immune response aimed at containing Mycobacterium tuberculosis. The classical structure—composed of epithelioid histiocytes, Langhans giant cells, and central caseous necrosis—reflects a coordinated T-helper 1 (Th1)-mediated immune reaction [2,6]. In adults, this organized granulomatous architecture is well documented; however, pediatric immune responses differ significantly due to immunological immaturity, particularly in younger children. Reduced interferon-gamma production and incomplete macrophage activation may lead to less structured granulomas or extensive necrosis without organized cellular rims [7,17]. Our findings of 21% non-caseating granulomas and 7% necrotizing inflammation without well-formed granulomas support this concept.

The predominance of caseating granulomas in lymph node TB (74%) observed in this analysis aligns with prior literature indicating that peripheral lymph nodes often demonstrate classic morphology due to localized immune containment [5,11]. In contrast, central nervous system (CNS) tuberculosis exhibited lower rates of well-formed caseating granulomas (48%), with more frequent necrotizing or poorly organized patterns. CNS TB, particularly tuberculous meningitis and tuberculomas, is known to involve intense inflammatory exudates and parenchymal necrosis, sometimes without fully developed granulomatous architecture [3,18]. These site-specific differences emphasize that histopathological interpretation must consider anatomical context.

Another critical observation is the occurrence of poorly formed granulomas (4%) and suppurative patterns, particularly in immunocompromised or malnourished children. HIV co-infection and severe malnutrition are known to impair cell-mediated immunity, thereby disrupting granuloma integrity [10,19]. Studies have demonstrated that HIV-positive children frequently show diffuse necrosis with minimal epithelioid cell response and increased bacillary load [20]. Such presentations may mimic pyogenic abscesses or fungal infections, posing diagnostic challenges in endemic regions.

The moderate rate of acid-fast bacilli (AFB) positivity (38%) across included studies further highlights the paucibacillary nature of pediatric TB. AFB detection is more common in caseating lesions due to higher bacillary concentration within necrotic material [21]. However, the absence of demonstrable bacilli does not exclude TB, especially in non-caseating or early granulomatous stages. This reinforces the need for adjunctive molecular diagnostics such as Xpert MTB/RIF and PCR-based assays, which have shown improved sensitivity in pediatric extrapulmonary TB [22].

Substantial heterogeneity ($I^2 > 70\%$) was observed across pooled estimates. This variability likely reflects differences in study design, regional TB burden, HIV prevalence, nutritional status, biopsy techniques, and histopathological reporting standards. Additionally, interobserver variability in granuloma classification may contribute to inconsistency. Standardized histopathological reporting criteria for pediatric TB would improve comparability across studies.

From a pathophysiological perspective, the spectrum of granulomatous response observed in this analysis mirrors the dynamic host-pathogen interaction in TB. Granulomas are not static structures but evolve over time, transitioning from cellular aggregates to necrotizing lesions and, eventually, fibrosis or calcification [23]. Pediatric disease may represent earlier or rapidly progressive stages of this spectrum, accounting for variability in morphology. Understanding these developmental differences may have implications for prognostication and therapeutic monitoring.

Clinically, the findings of this meta-analysis carry important implications. First, absence of caseation should not exclude tuberculosis in children, particularly in high-burden settings. Second, necrotizing inflammation without classical granulomas should prompt consideration of TB in the differential diagnosis, especially when supported by clinical or radiological suspicion. Third, integration of histopathology with microbiological and molecular testing is essential to enhance diagnostic accuracy. Multidisciplinary collaboration between pathologists, pediatricians, and infectious disease specialists is critical for early detection and appropriate management.

This study has several strengths. It represents the first quantitative synthesis of histopathological patterns in pediatric TB, incorporates a large cumulative sample size (3,842 patients), and includes subgroup analysis by anatomical site. Nonetheless, limitations must be acknowledged. High heterogeneity reduces precision of pooled estimates. Many included studies lacked detailed stratification by age group, HIV status, or nutritional parameters. Furthermore, publication bias cannot be completely excluded despite non-significant Egger's testing.

Future research should focus on prospective multicenter studies with standardized histopathological criteria and integration of molecular diagnostics. Correlating histopathological patterns with clinical outcomes, immune markers, and treatment response could provide deeper insights into disease pathogenesis. Additionally, evaluating the impact of Bacillus Calmette-Guérin (BCG) vaccination status on granuloma morphology may offer valuable epidemiological information.

In inference, while caseating granulomas remain the most common histopathological pattern in pediatric tuberculosis, a substantial proportion of children exhibit atypical or less organized inflammatory responses. Awareness of this spectrum is essential to prevent underdiagnosis and ensure timely treatment in this vulnerable population.

CONCLUSION

This systematic review and meta-analysis demonstrate that caseating granulomas are the most common histopathological pattern in pediatric tuberculosis; however, a considerable proportion of cases exhibit non-classical features such as non-caseating granulomas, necrotizing inflammation, or poorly formed granulomas. These variations reflect the unique immunological response in children and may differ according to anatomical site and immune status. Recognition of this histopathological spectrum is essential to avoid misdiagnosis, particularly in paucibacillary and extrapulmonary disease. Integration of histopathology with microbiological and molecular diagnostics remains critical for accurate and timely diagnosis in pediatric tuberculosis.

REFERENCES

1. World Health Organization. Global tuberculosis report 2023. Geneva: WHO; 2023.
2. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review. Int J Tuberc Lung Dis. 2004;8(4):392-402.
3. Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med. 2012;367(4):348-61.
4. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children. Lancet. 2005;365(9454):130-4.
5. Fontanilla JM, Barnes A, von Reyn CF. Current diagnosis and management of peripheral tuberculous lymphadenitis. Clin Infect Dis. 2011;53(6):555-62.
6. Kumar V, Abbas AK, Aster JC. Robbins & Cotran pathologic basis of disease. 10th ed. Philadelphia: Elsevier; 2020.
7. Lewinsohn DA, Lewinsohn DM, Scriba TJ. Polyfunctional CD4+ T cells as targets for tuberculosis vaccination. Front Immunol. 2017;8:1262.
8. Das DK. Fine-needle aspiration cytology in the diagnosis of tuberculous lesions. Lab Med. 2000;31(11):625-32.
9. Jain A, Dixit R. Multidrug-resistant tuberculosis: an emerging threat. J Infect Public Health. 2008;1(1):5-14.
10. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. Clin Infect Dis. 2010;50(Suppl 3):S184-94.
11. Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res. 2004;120(4):316-53.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
13. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2014.

14. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
17. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP. The immune response in tuberculosis. Annu Rev Immunol. 2013;31:475-527.
18. Rock RB, Olin M, Baker CA, Molitor TW, Peterson PK. Central nervous system tuberculosis: pathogenesis and clinical aspects. Clin Microbiol Rev. 2008;21(2):243-61.
19. Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011;378(9785):57-72.
20. Elliott AM, Namaambo K, Allen BW, Luo N, Hayes RJ, Pobee JO, et al. Negative sputum smear results in HIV-positive patients with pulmonary tuberculosis in Lusaka, Zambia. Tuber Lung Dis. 1993;74(3):191-4.
21. Parsons LM, Somoskövi A, Gutierrez C, Lee E, Paramasivan CN, Abimiku A, et al. Laboratory diagnosis of tuberculosis in resource-poor countries. Clin Microbiol Rev. 2011;24(2):314-50.
22. Detjen AK, DiNardo AR, Leyden J, Steingart KR, Menzies D, Schiller I, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children. Cochrane Database Syst Rev. 2015;(8):CD009593.
23. Flynn JL, Chan J. Immunology of tuberculosis. Annu Rev Immunol. 2001;19:93-129.