*Research Article*

# A Systematic Review of Clinical Diagnostic Systems Used in the Diagnosis of Tuberculosis in Children

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*Background*. Tuberculosis (TB) is difficult to diagnose in children due to lack of a gold standard, especially in resource-limited settings. Scoring systems and diagnostic criteria are often used to assist in diagnosis; however their validity, especially in areas with high HIV prevalence, remains unclear. *Methods*. We searched online bibliographic databases, including MEDLINE and EMBASE. We selected all studies involving scoring systems or diagnostic criteria used to aid in the diagnosis of tuberculosis in children and extracted data from these studies. *Results*. The search yielded 2261 titles, of which 40 met selection criteria. Eighteen studies used point-based scoring systems. Eighteen studies used diagnostic criteria. Validation of these scoring systems yielded varying sensitivities as gold standards used ranged widely. Four studies evaluated and compared multiple scoring criteria. Ten studies selected for pulmonary tuberculosis. Five studies specifically evaluated the use of scoring systems in HIV-positive children, generally finding the specificity to be lower. *Conclusions*. Though scoring systems and diagnostic criteria remain widely used in the diagnosis of tuberculosis in children, validation has been difficult due to lack of an established and accessible gold standard. Estimates of sensitivity and specificity vary widely, especially in populations with high HIV co-infection.

## 1. Background

Tuberculosis (TB) remains one of the most important causes of pediatric mortality worldwide, especially in areas with high HIV prevalence. There are approximately nine million new TB cases each year, with ten percent of those occurring in children, equaling almost one million new pediatric cases each year. Seventy-five percent of those are in twenty-two high-burden countries, which also tend to have fewer resources for diagnosis. Accurate and timely diagnosis of pediatric TB remains crucial because children are more likely than adults to progress from latent infection to active TB disease [1].

One of the largest challenges in preventing morbidity and mortality from TB among the pediatric population is the difficulty in making a timely diagnosis. Diagnostic approaches relying on symptoms, chest radiographs, tuberculin skin tests, or cultures all have particular challenges within the pediatric population. TB symptoms vary and overlap with other common pediatric diseases, especially in children who are coinfected with TB and HIV. Cough, anorexia, and weight loss are common in TB but nonspecific and might lead to overdiagnosis if used alone [2].

Chest radiography also is difficult to interpret in pediatric patients, who are less likely to have cavitations or clear radiological signs of TB. Mediastinal lymphadenopathy is often regarded as a radiologic hallmark of primary TB; however, this is difficult to diagnose on a plain chest X-ray (CXR), which may be of variable quality, particularly in some resource-limited settings. Also, significant interobserver variation exists when interpreting pediatric CXR for TB diagnosis [3].

Previous studies have shown various utility in using the tuberculin skin test (TST) in a highly BCG vaccinated population due to a concern for a high rate of false positives [4]. Though some evidence has shown that BCG-vaccinated

children with known exposure to TB have a higher rate of positive tests than community controls [5], this study did not address the utility in other populations where TST may not be as sensitive, such as HIV-infected or malnourished children.

Pediatric TB tends to be pauci-bacillary and thus it is also more difficult to diagnose using cultures, especially in children who are too young to provide sputum [1]. Attempts have been made to improve the utility of culture-proven diagnosis by using induced sputum samples or gastric aspirates. These samples can still be difficult to obtain in children. Moreover, conducting these procedures in resource-limited settings can be difficult [6]. Because of the challenges in diagnosing pediatric TB through individual clinical signs and symptoms, radiological studies, or laboratory examinations, point-based scoring systems or diagnostic criteria are often used to assist in the diagnosis of TB in children.

The first major point-based scoring system was introduced by Stegen et al. in Chile in 1969 [7] and has continued to be modified and used around the world through the present [8–14]. The Keith Edwards criteria were originally published in 1987 [15] and also have been widely used [16–19] outside the original location of Papua New Guinea. Of the many diagnostic systems developed, the World Health Organization (WHO) criteria, originally published in 1983, are the most widely used [20]. The major objective of all of the diagnostic systems is to provide a consistent and accurate way to diagnose pediatric TB, especially in resource-limited settings.

Although these scoring systems and diagnostic criteria are commonly used [21], their reliability and validity remain unclear. Different diagnostic criteria are used in different settings, and they may or may not have been validated for those locations. Moreover, the challenges of using these criteria in settings where many of the children are malnourished or coinfected with HIV have not been fully examined. Many of the diagnostic systems were developed prior to the onset of the HIV epidemic and may not perform adequately in children with coinfection. Since TB is a leading cause of mortality among the world's 2.3 million HIV-infected children, diagnosing TB among coinfected children is a particularly important challenge and may require significant adaptations of current diagnostic systems [22].

Prevention of childhood morbidity and mortality due to TB requires accurate and timely diagnosis. A previous systematic review of pediatric TB diagnostic strategies, published in 2002, recommended standardization of definitions and characteristics, pointing out the need for new diagnostic approaches [21]. Since that review, at least twenty-one new papers on pediatric TB diagnosis have been published, including several highlighting new strategies such as the Brazil Ministry of Health system [23–25] and the Marais criteria [26]. In addition, the population of children living with HIV infection has reached 2.3 million, simultaneously expanding the numbers of children vulnerable to TB disease [22]. This systematic review seeks to systematically identify, review, and compare various methods of diagnosis of TB in children in order to inform clinical practice and future research in this area. It aims to organize the scoring systems

and diagnostic criteria based on their common components, critically analyze the extent to which the criteria are validated, and highlight those that have focused specifically on children that are coinfected with HIV and TB.

## 2. Methods

We searched several bibliographic databases, including MEDLINE (through October 19, 2009), EMBASE, and relevant websites such as those for the World Health Organization. We used the following strategy: (tuberculosis/diagnosis) [MeSH heading] AND (criteria* OR screen* OR guideline* OR scor*). Three authors (S. O. Ayaya, J. F. Woodward, and E. C. Pearce) reviewed all returned titles and excluded articles that obviously did not involve children or tuberculosis. These authors then reviewed abstracts of remaining articles to determine which studies examined scoring systems or diagnostic criteria used in the diagnosis of pediatric tuberculosis. The bibliographies of all relevant articles were also reviewed for potential articles.

Two investigators (J. F. Woodward and E. C. Pearce) independently reviewed the remaining articles, independently deciding on inclusion in the review using a standard form with predetermined eligibility criteria. Disagreements were resolved by consensus. For inclusion, the articles needed to describe a descriptive or interventional study involving the use of a clinical diagnostic system to diagnose tuberculosis in pediatric patients. Only English language articles were included. Pediatric patients were described as individuals less than 18 years of age. Clinical diagnostic systems included both scoring systems and diagnostic criteria. Scoring systems were defined as point-based criteria with set numerical cutoffs for a positive diagnosis. Diagnostic criteria were defined as nonpoint-based systems in which a certain number of criteria out of the total or out of each group were needed for diagnosis. Studies analyzing the diagnosis of pediatric tuberculosis in general without using or evaluating a particular scoring system or diagnostic criteria were used as background information only for the review. Each article was analyzed to determine the study setting, study design and methods, sample characteristics, type of diagnostic system used, reference or gold standard used for comparison, and efforts at validation of the diagnostic system. We excluded duplicate publications of the same findings.

## 3. Results

The systematic literature search identified 2261 articles. The online search of MEDLINE yielded 2011 articles, and the search of EMBASE yielded 250 articles, many of which were also found by the MEDLINE search. Additional potential studies were identified through searches of bibliographies. After articles that did not address the diagnosis of tuberculosis in children were excluded, 408 articles remained. Further articles were excluded upon closer review because they did not include pediatric patients, did not include a scoring system or diagnostic criteria, or focused only on screening for latent tuberculosis. Articles that briefly mentioned a scoring

TABLE 1: Point-based scoring systems and studies evaluating these systems.

| Author | Year | Country | Scoring criteria | Changes | Study type |
|---|---|---|---|---|---|
| Stegen et al. [7] | 1969 | Chile | Kenneth Jones | New | Review with case reports |
| Mathur et al. [9] | 1974 | India | Kenneth Jones | Added marasmus to original criteria | Prospective observational |
| Nair and Philip [10] | 1981 | India | Kenneth Jones | Changed point values, took away negative points for BCG, added response to treatment | Prospective |
| Seth [11] | 1991 | India | Kenneth Jones | Used Nair's adaptation | Book excerpt |
| Shah et al. [12] | 1992 | India | Kenneth Jones | Added history of measles/whooping cough | Prospective observational |
| Mehnaz and Arif [13] | 2005 | Pakistan | Kenneth Jones | Modified multiple criteria, added and subtracted criteria | Retrospective case control |
| Oberhelmen et al. [14] | 2006 | Peru | Stegen-Toledo | No modifications | Prospective observational |
| Viani et al. [8] | 2008 | Mexico | Stegen-Toledo | Added points for positive stain | Retrospective chart review |
| Edwards [15] | 1987 | Papau New Guinea | Keith Edwards | Original | Review article |
| van Beekhuizen [16] | 1998 | Papua New Guinea | Keith Edwards | No modifications | Prospective observational |
| Weismuller et al. [17] | 2002 | Malawi | WHO score chart (modified Keith Edwards) | Added no response to malaria treatment, modified language | Cross-sectional observational study |
| van Rheenen [18] | 2002 | Zambia | Keith Edwards | Modified language | Prospective cohort |
| Narayan et al. [19] | 2003 | India | Keith Edwards | Added no response to malaria treatment | Prospective observational |
| Sant'Anna et al. [24] | 2006 | Brazil | Brazil Ministry of Health | New | Retrospective case control |
| Sant'Anna et al. [25] | 2004 | Brazil | Brazil Ministry of Health | No modifications | Retrospective |
| Pedrozo et al. [23] | 2009 | Brazil | Brazil Ministry of Health | No modifications | Prospective observational |
| Fourie et al. [27] | 1998 | Multiple | New | Set up new scoring criteria by consensus decision | Retrospective |
| Bergman [28] | 1995 | Zimbabwe | New | New | Review |

system but did not give details or include how it was used in the study were also excluded. Forty articles met the general study criteria.

*3.1. Clinical Diagnostic Systems Used for TB Diagnosis.* From the forty articles that included a clinical diagnostic system, we extracted information on the setting, location, sample size, type of system/criteria used, efforts at validation, choice of gold standard, and the effect of HIV coinfection in the population. The characteristics of these studies, including the validation strategies, are summarized in Tables 1, 2, and 3. Eighteen studies used scoring systems; these studies could be further divided into five groups based on a common initial system modified by different authors (Table 1). The three major groups were the following: (1) the Kenneth Jones/Stegen-Toledo system [7–14]; (2) the Keith Edwards system [15–19]; (3) the Brazil Ministry of Health (MOH) system [23–25]. Fourie et al. [27] and Bergman [28] also presented new systems without further published studies. Eighteen studies used diagnostic criteria. These studies could be further divided into five groups of diagnostic criteria presented by Ghidey and Habte [29], Migliori et al. [30], Mahdi et al. [31], Salazar et al. [32], Marais et al. [26], the WHO guidelines [33–42], Osborne [43], Jeena et al. [44], and Ramachandran [45] (Table 2). Four articles compared two or more scoring criteria [46–49] (Table 3).

*3.2. Validation of Clinical Diagnostic Systems for Pediatric TB Diagnosis.* Of the above forty articles, sixteen attempted to validate the diagnostic system or systems (Table 4). Gold

TABLE 2: Diagnostic classifications and studies evaluating these classifications.

| Author | Year | Country | Scoring criteria | Changes | Study type |
|---|---|---|---|---|---|
| Ghidey and Habte [29] | 1983 | Ethiopia | New | New | Prospective |
| Migliori et al. [30] | 1992 | Uganda | Migliori—revised from Ghidey and Habte | Focused towards PTB, added response to treatment as a criteria | Prospective |
| Madhi et al. [31] | 1999 | South Africa | Migliori | No change | Prospective |
| Salazar et al. [32] | 2001 | Peru | Migliori | Removed response to treatment. Created Peru criteria. | Prospective cohort |
| Marais et al. [26] | 2006 | South Africa | New | Symptom based approach | Prospective |
| World Health Organization [20] | 1983 | Multiple | New | New | New guidelines |
| Cundall [33] | 1986 | Kenya | 1983 WHO guidelines | Modifies by adding family contact | Prospective |
| Stoltz et al. [34] | 1990 | South Africa | Modified 1983 WHO guidelines | No change | Prospective |
| Beyers et al. [35] | 1994 | South Africa | 1983 WHO guidelines | No change | Prospective |
| Gie et al. [36] | 1995 | South Africa | Modified 1983 WHO guidelines | No change | Prospective |
| Schaaf et al. [37] | 1995 | South Africa | 1983 WHO guidelines | No change | Prospective |
| Houwert et al. [38] | 1998 | South Africa | 1994 WHO guidelines | No change | Prospective |
| Kiwanuka et al. [42] | 2001 | Malawi | 1983 WHO guidelines | Modified by using only certain radiological findings or positive TST for probable TB | Prospective |
| Palme et al. [39] | 2002 | Ethiopia | Modified 1983 WHO guidelines | Required 2/6 criteria | Prospective case-control |
| Theart et al. [40] | 2005 | South Africa | Modified 1983 WHO guidelines | No change | Retrospective |
| Cohen et al. [41] | 2008 | UK | 2006 WHO classification | No change | Retrospective |
| Osborne [43] | 1995 | Zambia | Lusaka's UTH Criteria | New | Review article |
| Jeena et al. [44] | 1996 | South Africa | Lusaka's UTH criteria | No change | Prospective |
| Ramachandran [45] | 1968 | India | New | New | Prospective and retrospective |

TABLE 3: Studies evaluating and comparing multiple diagnostic systems.

| Author | Year | Country | Findings |
|---|---|---|---|
| Hesseling et al. [21] | 2002 | South Africa | Analyzed 16 diagnostic systems, specifically looks at how systems have been adapted for HIV-infected and malnourished patients. |
| Edwards et al. [47] | 2007 | Congo | Analyzed 8 scoring systems, found correlation to be poor to moderate. Decision to initiate treatment for TB was dependent on scoring system used in 14% of children. Selection had a greater impact in HIV-infected patients. |
| Ahmed et al. [48] | 2008 | Bangladesh | Reviews previous scoring systems as well as Hesseling et al. [21] and Edwards et al. [47] |
| Raqib et al. [49] | 2009 | Bangladesh | Analyzed a new diagnostic test (ALS assay) detecting antibodies secreted from circulating MTB-specific plasma cells in comparison to the Kenneth Jones and WHO/Keith Edwards scoring criteria as well as clinical diagnosis. |

TABLE 4: Studies attempting validation of diagnostic systems.

| Author | Year | Country | Scoring criteria | Validation | Gold standard |
|--------|------|---------|------------------|------------|---------------|
| | | | Point-based scoring systems | | |
| Mathur et al. [9] | 1974 | India | Kenneth Jones | Sens 73% (original criteria) Sens 95% (modified criteria) | Clinical diagnosis |
| Shah et al. [12] | 1992 | India | Kenneth Jones | Compared modified criteria to previous Kenneth Jones | Previous KJ |
| Mehnaz and Arif [13] | 2005 | Pakistan | Kenneth Jones | Retrospective analysis | Clinical control and response to treatment |
| Viani et al. [8] | 2008 | Mexico | Stegen-Toledo | Retrospective analysis | Clinical diagnosis |
| van Beekhuizen [16] | 1998 | Papua New Guinea | Keith Edwards | Sens 62%, spec 95% | Improvement on anti-TB treatment or positive CXR |
| Weismuller et al. [17] | 2002 | Malawi | WHO score chart (modified Keith Edwards) | Sens 61% for all types of TB; 54% for PTB and 73% for EPTB | Clinical diagnosis—differed by various hospitals |
| van Rheenen [18] | 2002 | Zambia | Keith Edwards | Sens 88%, spec 25%, PPV 55%, NPV 67% | Diagnostic algorithm |
| Narayan et al. [19] | 2003 | India | Keith Edwards | Sens 91%, spec 88% | Clinical diagnosis |
| Sant'Anna et al. [24] | 2006 | Brazil | Brazil Ministry of Health | Sens 89%, spec 86% | Culture positive and respiratory symptoms and/or CXR improved using exclusively anti-TB drugs |
| Sant'Anna et al. [25] | 2004 | Brazil | Brazil Ministry of Health | 82% very likely, 16% possible, 2.4% unlikely | Clinical criteria and response to treatment |
| Pedrozo et al. [23] | 2009 | Brazil | Brazil Ministry of Health | Median score of TB positive groups higher than negative | Clinical criteria |
| Fourie et al. [27] | 1998 | Multiple | New | Analyzed by age and country group: sens 30–73%, spec 10–75%, PPV 50–82% | Positive radiologic or bacteriological data |
| | | | Diagnostic classification | | |
| Migliori et al. [30] | 1992 | Uganda | Migliori | Gastric aspirate: sens 96.8%, spec 92.2%, PPV 68.2%, NPV 99.4%. Response to treatment: sens 62.5%, 94.1%, PPV 57.7%, NPV 95.1% | Original Ghidey and Habte criteria |
| Salazar et al. [32] | 2001 | Peru | Migliori | Sens 92% (Migliori) versus 80% (Peru). 3/3 Peru criteria had 73% PPV | Migliori criteria (without RTT) |
| Marais et al. [26] | 2006 | South Africa | New | Children ≥3 and HIV uninfected: sens 82.3%, spec 90.2%, PPV 82.3%. Children <3 and HIV uninfected: sens 51.8%, spec 92.5%, PPV 90.1%. HIV infected: sens 56.2%, spec 61.8%, PPV 61.9% | Clinical criteria |
| Houwert et al. [38] | 1998 | South Africa | WHO provisional guidelines (1994) | PPV of all 3 criteria when present simultaneously: 63% | WHO diagnostic categories from 1994 used as the gold standard |

Sens: sensitivity; spec: specificity; PTB: pulmonary tuberculosis; EPTB: extrapulmonary tuberculosis; PPV: positive predictive value; NPV: negative predictive value.

standards used in validation varied greatly and ranged from positive cultures to clinical diagnosis to previous scoring criteria. The only study using cultures as the primary gold standard was Sant'Anna et al. [24], which found a sensitivity of 89% and specificity of 86% when evaluating Brazil Ministry of Health criteria against a standard of culture-positive patients. Sant'Anna et al. [25] also performed a retrospective analysis on a different study population using clinical consensus as the gold standard against which to compare the diagnostic criteria, resulting in similar sensitivity.

Culture for *Mycobacterium tuberculosis* is less sensitive in pediatric patients and difficult to obtain in resource-limited settings; therefore, the most common gold standard used to validate diagnostic systems was clinical diagnosis. The definition of clinical diagnosis varied widely between studies and was often not defined in detail. Because many of the studies were retrospective, clinical diagnosis was often simply defined as children who had been admitted with a diagnosis of TB [8, 34], with some studies also specifying that the children must have improved on anti-TB medication [13, 40, 41]. In one article, the study population was drawn from forty-four different hospitals, all of which used their own methods of clinical diagnosis [17]. However, in other studies, the method of clinical diagnosis was explained in depth. For example, van Rheenen described a detailed algorithm that included clinical findings, culture, CXR, TST, contact history, and response to treatment [18].

Previously described scoring criteria were also used as a gold standard; a few of the studies compared their modifications of a certain diagnostic system to the original. For example, Migliori et al. modify the criteria published by Ghidey and Habte [29] by focusing the criteria on pulmonary TB and adding response to treatment and use the original criteria as the gold standard in their analysis [30]. Salazar et al. then modified the Migliori criteria to develop the Peru criteria, and used the original Migliori criteria as the gold standard for comparison [32]. These are not traditional validation strategies as they assume the previous criteria have been validated to an extent that they may now be considered a gold standard in themselves.

Four published papers evaluated and compared multiple scoring systems and diagnostic criteria (Table 3). In a 2002 systematic review, Hesseling et al. stressed the need for standardization of definitions and point values between the various algorithms [21]. As an update on Hesseling's review, this current review includes twenty-one new studies, including those evaluating the Brazil MOH scoring system [23–25] and the Marais criteria [26]. In 2008, Ahmed et al. published a review of TB diagnosis as well as treatment, focusing mainly on the Kenneth Jones and Keith Edwards systems [48] and suggesting the need for further research. Most recently, in 2009, Raquib et al. compared a newer diagnostic test (ALS assay) to clinical diagnosis, the Kenneth Jones, and the Keith Edwards scoring criteria [49], finding that sensitivity, specificity, and overall concordance was higher when the ALS assay was compared to clinical diagnosis than to the scoring criteria.

In a 2007 article, Edwards et al. used data from a retrospective review of TB cases at a pediatric hospital with a highprevalence of HIV infection to calculate scores for eight diagnostic scoring systems [47]. The decision to initiate treatment for TB was dependent on the scoring system used, with at least one scoring system recommending not to treat for 14% of the children studied. Except for the systems derived from a common original diagnostic system, correlation was poor to moderate for agreement of when to initiate treatment based on the various scoring systems.

*3.3. Variation among Criteria.* Although all of the scoring criteria have aspects in common, their purposes and specifics have varied over the past 40 years since Stegen et al. published the original Kenneth Jones criteria. The Kenneth Jones criteria include laboratory tests but exclude clinical criteria such as cough and fever due to concerns that they would lower the specificity [7]. In contrast, the purpose of the Keith Edwards criteria was focused towards a completely clinical diagnosis, and thus excluded laboratory data except for a TST [15].

Both the Kenneth Jones and Keith Edwards criteria were designed for the diagnosis of both pulmonary and extrapulmonary tuberculosis. Because the clinical signs and symptoms of extrapulmonary tuberculosis may differ from those of pulmonary tuberculosis, several studies evaluated the ability of diagnostic strategies to identify pulmonary TB specifically (Table 5). For example, the Brazil MOH system, designed specifically for pulmonary tuberculosis [24, 25], has shown a sensitivity of 89% and a specificity of 86%. The Migliori [30] and Marais [26] diagnostic criteria, also focused on pulmonary tuberculosis, demonstrated a sensitivity of 92% [31] and 82%, respectively. While the Migliori criteria have not been tested in children with coinfection, the sensitivity of the Marais criteria decreased to 51–56% when children under three years of age and HIV infected children were included [26].

A salient difference between the various clinical diagnostic approaches was the choice of included criteria. The criteria included most commonly were the tuberculin skin test (TST) and positive history of TB contact; however, the definition of these criteria was not standardized. For example, the definition of a positive TST varies widely among studies [7, 15]. A positive history of TB contact also was defined in various ways, such as requiring confirmed sputum-positive contact [37] or only a self-report of contact [30]. In some cases, the history of contact had to be within the past two years [14]. Using both the TST and the positive contact history may also be redundant if both are included. Variability is also seen in the other criteria, such as clinical symptoms and CXR. The various definitions and subjectivity of many of the criteria included in the diagnostic approaches make it difficult to compare the diagnostic strategies and the attempts at validation. In addition, clinicians likely vary in how they implement the scoring criteria, thus, making the diagnostic thresholds even less consistent.

*3.4. Clinical Diagnostic Systems in HIV-Infected Patients.* A few studies specifically examined TB diagnosis in HIV-infected children (Table 6). In his comparison of eight

TABLE 5: Studies focusing primarily on pulmonary tuberculosis.

| Author | Year | Country | Scoring system | Percent also with EPTB | Validation |
|---|---|---|---|---|---|
| Shah et al. [12] | 1992 | India | Modified Kenneth Jones | Looked at "primary complex" (just pulmonary) versus "progressive primary complex" (pulmonary plus LAD) | Not analyzed, just used in inclusion criteria |
| Migliori et al. [30] | 1992 | Uganda | Migliori | All pulmonary | Gastric aspirate: sens 96.8%, spec 92.2%, PPV 68.2%, NPV 99.4%. Response to treatment: sens 62.5%, 94.1%, PPV 57.7%, NPV 95.1% |
| Beyers et al. [35] | 1994 | South Africa | Modified 1883 WHO criteria | All pulmonary—excluded extrapulmonary tuberculosis without lung involvement | Not evaluated |
| Salazar et al. [32] | 2001 | Peru | Migliori | All pts had PTB, 21/135 had EPTB as well: lymphadenopathy, intestinal-intraperitoneal TB, intra-abdominal lymphadenopathy, miliary disease, meningitis, and optic involvement. 3 with EPTB did not meet criteria for PTB | Sens 92% (Migliori) versus 80% (Peru). 3/3 Peru criteria had 73% PPV |
| Sant'Anna et al. [25] | 2004 | Brazil | Brazil Ministry of Health | 82% very likely, 16% possible, 2.4% unlikely | All pulmonary plus 5 pts with assoc extrapulmonary TB |
| Sant'Anna et al. [24] | 2006 | Brazil | Brazil Ministry of Health | Cut off ≥40: sens 58% and spec 98% but missed 42% of confirmed PTB. Cut off ≥30: sens 89% and spec 86% | Pulmonary |
| Oberhelmen et al. [14] | 2006 | Peru | Stegen-Toledo | Not analyzed, just used in inclusion criteria | Pulmonary |
| Marais et al. [26] | 2006 | South Africa | New | Children ≥3 and HIV uninfected: sens 82.3%, spec 90.2%, PPV 82.3%. Children <3 and HIV uninfected: sens 51.8%, spec 92.5%, PPV 90.1%. HIV infected: sens 56.2%, spec 61.8%, PPV 61.9% | Focused on pulmonary TB only |
| Viani et al. [8] | 2008 | Mexico | Stegen-Toledo | Looked retrospectively: 10/13 highly probable, 2/13 probable, 1/13 suspicious | 100% pulmonary, 54% also had disseminated |
| Pedrozo et al. [23] | 2009 | Brazil | Brazil Ministry of Health | Analyzed scoring system by looking at median scores of various groups: median score of 3a and 3b sig. higher than 1 and 2, median score also was higher than the cut off of 30 | Pulmonary only |

Sens: sensitivity; spec: specificity; PTB: pulmonary tuberculosis; EPTB: extrapulmonary tuberculosis; PPV: positive predictive value; NPV: negative predictive value.

diagnostic scoring systems, Edwards showed that HIV-infected children tended to have higher scores, especially when the Keith Edwards system was used, leading to a concern for over-diagnosis of TB in HIV-infected children [47]. Marais et al. found that the Marais diagnostic criteria were less sensitive (56% compared to 82%) and less specific (62% compared to 90%) when evaluating children with HIV as opposed to children without HIV. The positive predictive value also decreased to 62% in HIV-infected children as compared to 82% in children without HIV [26]. Viani et al. looked at a small cohort of coinfected children in Mexico retrospectively and found that 77% had scores indicating highly probable TB when using the Stegen-Toledo criteria [8]. Finally, in a 2009 analysis of the Brazil MOH criteria, Pedrozo et al. found that while coinfected children did score slightly lower than HIV-uninfected children, their scores were still significantly higher than children without TB [25].

TABLE 6: Studies that specified how many patients were coinfected with HIV.

| Author | Year | Country | Total patients | Percent HIV positive | Findings |
|---|---|---|---|---|---|
| Madhi et al. [31] | 1999 | South Africa | 130 | 40% | Did not attempt to validate scoring criteria |
| Kiwanuka et al. [42] | 2001 | Malawi | 110 | 71% (of 102 tested) | Did not attempt to validate scoring criteria |
| Palme et al. [39] | 2002 | Ethiopia | 517 | 11.2% | Did not attempt to validate scoring criteria |
| van Rheenen [18] | 2002 | Zambia | 147 | 30% | Keith Edwards scoring system: sensitivity 88% and specificity 25% in this study. Most of the children with a false positive score were malnourished (48%) or had AIDS (31%) |
| Marais et al. [26] | 2006 | South Africa | 428 | 8.8% | Sensitivity, specificity, and PPV all decreased significantly when HIV infected children included |
| Edwards et al. [47] | 2007 | Democratic Republic of Congo | 91 | 46% | Out of 8 scoring systems analyzed, 3/8 systems did not recommend treatment in 14% of HIV-infected children compared to 2% of noninfected children. Mean score tended to be higher for HIV-infected children, but only significant for Edwards score |
| Viani et al. [8] | 2008 | Mexico | 13 | 100% | Applied Stegen-Toledo criteria retrospectively but without culture results: 77% had highly probable TB, 15% probable, and 8% suspicion of TB |
| Pedrozo et al. [23] | 2009 | Brazil | 239 | 5% | Analyzed scoring system by looking at median scores of various groups: median score of 3a (TB+, HIV−) and 3b (TB+, HIV+) sig. higher than TB negative groups, median score of TB+ groups also was higher than the cutoff of 30 |

PPV: positive predictive value.

## 4. Discussion

We identified and reviewed forty different studies of twenty-two unique scoring systems or diagnostic criteria that were developed from five original scoring systems and five original diagnostic criteria. These diagnostic approaches varied in the types of clinical signs and symptoms included in the criteria, the inclusion or exclusion of laboratory testing, and even their diagnostic focus (i.e., pulmonary TB alone or pulmonary and extrapulmonary TB). Studies designed to validate the various diagnostic systems varied significantly in the gold standard chosen for comparison. Because the publication dates of the articles range over the last fifty years, some criteria were developed and evaluated prior to the HIV epidemic, while other studies focused specifically on coinfected children.

The gold standards chosen to evaluate the validity of these diagnostic strategies also varied widely. Cultures can be difficult to obtain in children. Because tuberculous disease in children is often pauci-bacillary, the diagnostic yield of cultures in children is often poor. Although one study used culture as the gold standard [25], others used positive response to treatment [13], CXR [35], or a previous scoring

criteria [30]. The most common gold standard was clinical diagnosis. Interestingly, in a study of the ALS assay for diagnosing active TB disease, the assay actually correlated better with clinical diagnosis than either the Kenneth Jones or Keith Edwards scoring criteria [49]. Unfortunately, clinical diagnosis is likely to depend strongly upon the experience and knowledge base of the clinician and thus may be less reliable in settings where clinicians have less training. To allow for comparison of criteria across different studies and settings, future studies need to employ a more consistent gold standard. Ideally, this would be culture-based, as this is a standard for validation that could be reliably replicated across settings. However, because cultures are difficult to obtain in resource-limited settings and can lead to a delay in treatment, performing studies with culture as the gold standard can be difficult.

In addition to using a variety of gold standards, the various studies often included very different sample populations. Some studies did not clearly describe the characteristics of the patient population or how they were selected. Many were retrospective, often utilizing chart review. Ideally, prospective studies of diagnostic systems would evaluate a clearly defined sample of participants with a spectrum of

disease that is representative of the patients to which the criteria would be applied in clinical practice. It is essential that researchers clearly describe the sample selection process and inclusion criteria in such studies to allow for more accurate comparisons of criteria across different populations or settings and to promote the utility of these systems in clinical practice.

Another challenge in prospective studies of TB diagnosis is the bias that is introduced when, as found in some of these studies, the inclusion or screening criteria for participants often include similar clinical features as the diagnostics systems being evaluated. For example, Pedrozo et al. used history of contact, CXR, and TST result as part of the criteria for inclusion in the study. Chest X-ray and TST were also used as part of their diagnostic gold standard to differentiate latent TB from no TB from active TB disease. All three inclusion criteria are also used in the Brazil MOH scoring system being evaluated in this study [25]. This makes it difficult to interpret the accuracy of a diagnostic system and its ability to predict a diagnosis of TB in a particular patient or patient population. This overlap also causes difficulty in determining the relative importance of particular signs or symptoms within the diagnostic system.

The largest shift in the newer diagnostic systems as compared to Kenneth Jones and Keith Edwards is the focus on pulmonary tuberculosis alone. Diagnostic systems focusing simply on pulmonary TB, such as the Brazil MOH and Marais criteria, have demonstrated higher sensitivities and specificities than those developed to diagnose both extrapulmonary and pulmonary TB. Because children have a higher incidence of extrapulmonary TB [50], using diagnostic systems targeted at pulmonary TB only addresses part of the diagnostic challenge. On the other hand, because TB presents with varied signs and symptoms depending on the site of disease, it is difficult to conceive of a single diagnostic system that could diagnose with high sensitivity and specificity the various types of tuberculosis infections (e.g., vertebral, abdominal, and pulmonary TB). Furthermore, many children with extrapulmonary TB also have pulmonary disease [51]. A new system of classification, focusing on the severity of the disease rather than location, has recently been published and may also be a more reliable and reproducible method. If this is well validated in different settings, it may allow various diagnostic systems to be better compared than is currently possible [52].

At this time, the Brazil MOH scoring system has the most studies evaluating its validity with consistently high sensitivities and specificities. In each of the three studies of this criteria, the scoring system was tested against a slightly different gold standard, ranging from clinical criteria [23, 25] to culture-proven disease [24]. Although this may make some comparisons difficult with the lack of a standard gold standard, the fact that the scoring system holds up fairly well when tested in different ways actually strengthens the evidence for its validity. Though it has not been tested outside of Brazil, it has been tested in both an inpatient [24] and outpatient setting [23, 25]. The performance of the scoring system has also been evaluated in HIV-infected patients. These coinfected children still scored significantly above the cutoff for a diagnosis of TB [23]. All of these evaluations point favorably toward the validity of this scoring system. Evaluating the Brazil MOH scoring system in additional settings worldwide should be an important next step.

The findings of this systematic review are limited by the design and quality of the studies included. The lack of consistent and sometimes clearly defined inclusion criteria among the studies makes it difficult to compare sensitivity and specificity across the different diagnostic systems. Most of the various diagnostic systems have only been evaluated in specific geographic locations or single populations; few studies evaluate a particular diagnostic system in multiple geographic regions or patient populations. Fewer studies have compared the diagnostic yield of multiple criteria in the same patient population. Finally, the increase in the prevalence of HIV during the publication range of these studies makes it difficult to compare studies from thirty years ago to those more recently published. Although this paper includes more than twenty new studies since Hesseling et al. was published in 2002 [21], the number of articles assessing the validity of each diagnostic system is still relatively small. The paper also did not include unpublished data or non-English publications.

## 5. Conclusion

Clinical diagnostic systems in use for many years (e.g., the original Kenneth Jones criteria) and those more recently developed (e.g., the Brazil MOH criteria) have generally been developed, and subsequently adapted, in an attempt to accurately and reliably diagnose tuberculosis in children. As more continues to be learned about the disease and newer, more accurate tests are developed, methods of diagnosis will likely be altered further. It remains crucial that these methods remain applicable to resource-limited settings where the majority of children with TB are still most likely to be found. Although the studies included in this paper are heterogeneous and difficult to compare, the Brazil MOH criteria seems to emerge as the best validated in children with TB alone as well as those coinfected with TB and HIV. Due to the difficulty with obtaining cultures and the expense of the newer diagnostic tests, clinical scoring systems and diagnostic criteria will likely continue to be necessary in resource-limited settings for some time. However, unless additional studies identify refined diagnostic systems with improved sensitivity and specificity, they will likely mainly be utilized as initial screening tools or adjuncts to support clinical diagnosis. Improving the accuracy of diagnosis of pediatric TB is needed to ensure appropriate and timely treatment of those with active disease and to prevent unnecessary morbidity and mortality. Validated clinical diagnostic systems that can be implemented in resource limited settings can improve the accuracy and timeliness of tuberculosis in children; however, additional well-designed studies are needed to validate the accuracy and reliability of current scoring systems and diagnostic criteria.

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