Clinical diagnosis of smear-negative pulmonary tuberculosis in low-income countries: the current evidence

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Sputum smear examination for acid-fast bacilli (AFB) can diagnose up to 50–60% of cases of pulmonary tuberculosis in well-equipped laboratories. In low-income countries, poor access to high-quality microscopy services contributes to even lower rates of AFB detection. Furthermore, in countries with high prevalence of both pulmonary tuberculosis and HIV infection, the detection rate is even lower owing to the paucibacillary nature of pulmonary tuberculosis in patients with HIV infection. In the absence of positive sputum smears for AFB, at primary care level, most cases of pulmonary tuberculosis are diagnosed on the basis of clinical and radiological indicators. This review aims to evaluate various criteria, algorithms, scoring systems, and clinical indicators used in low-income countries in the diagnosis of pulmonary tuberculosis in people with suspected tuberculosis but repeated negative sputum smears. Several algorithms and clinical scoring systems based on local epidemiology have been developed to predict smear-negative tuberculosis. Few of these have been validated within the local context. However, in areas where smear-negative tuberculosis poses a major public-health problem, these algorithms may be useful to national tuberculosis programmes by providing a starting point for development their own context-specific diagnostic guidelines.

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Tuberculosis persists as a major cause of human mortality and morbidity, affecting almost a third of the world's population.[1] Inadequate case-detection and cure rates have been identified as reasons for a mounting global tuberculosis burden.[2] Sputum microscopy and sputum culture have been advocated as two useful tools for diagnosis of pulmonary tuberculosis. However, few tuberculosis-control programmes in low-income countries have access to culture facilities in their primary-care diagnostic centres. Moreover, culture for acid-fast bacilli (AFB) takes 6–8 weeks to be interpretable, which limits the usefulness of culture as a first-line diagnostic test. Under these circumstances, sputum smear examination for AFB is the most useful test for diagnosis of pulmonary tuberculosis. However, the AFB smear examination has a sensitivity of only 50–60%,[3] partly because a positive smear requires 5000–10 000 AFB per μL sputum sample. Sputum culture requires only 10–100 AFB per μL,[4,5] and can detect pulmonary tuberculosis in around 80% of true cases.[6] The quality of microscopic performance also underlies differences in AFB smear sensitivity (30% to 80%) compared with AFB cultures.[6–8] In the absence of readily available sputum culture in low-income countries, most cases of smear-negative tuberculosis are diagnosed on the basis of clinical presentation, radiological findings, and other laboratory-based indicators.

Smear-negative tuberculosis is currently defined as symptomatic illness in a patient with at least two sputum smear examinations negative for AFB on different occasions in whom pulmonary tuberculosis is later confirmed by culture, biopsy, or other investigations.[2] Studies before the HIV epidemic estimated that there were 1·22 cases of smear-negative and extrapulmonary tuberculosis for each smear-positive case.[9] Researchers in countries with low prevalence of pulmonary tuberculosis have suggested that smear-negative tuberculosis poses less of a threat to public health than smear-positive pulmonary tuberculosis,[10] on the basis of its low infectivity potential, lesser extent of disease, and good prognosis even without treatment. The relative transmission rate from patients with smear-negative compared with smear-positive pulmonary tuberculosis is around 22%.[11] However, nearly half of all cases of pulmonary tuberculosis are smear negative, which means that the overall disease burden is substantial.

In countries with a high prevalence of HIV infection, smear-negative tuberculosis has a poorer prognosis.[12] In one study in sub-Saharan Africa, a third of patients with smear-negative tuberculosis died within a year of their initial diagnosis.[13] Roughly a third of the rest developed recurrent pulmonary tuberculosis.

Most publications on the clinical features of pulmonary tuberculosis have not distinguished between smear-negative and smear-positive disease. However, attempts have been made to identify the distinctive clinical features of smear-negative tuberculosis. This distinction, a reflection of the diverse behaviour of AFB and the human immune system, is made to assist diagnosis rather than to classify smear-negative tuberculosis as a separate clinical entity.

Various criteria, clinical scoring systems, tools, and algorithms have been developed to facilitate the diagnosis of pulmonary tuberculosis in people with suspected tuberculosis who have repeated negative sputum smears.

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The purpose of this review is to evaluate the evidence base for these tools to aid clinicians and policy-makers in tuberculosis-control programmes in low-income countries. The review considers only the use of those diagnostic tools that are available to doctors working in primary health care tuberculosis diagnostic centres in low-income countries with a high prevalence of tuberculosis. Therefore, we have not examined the use of serology, bronchoscopy, or PCR.

Methods

We identified relevant publications by searches of Medline, PubMed, Embase, HealthSTAR, and Web of Science with the keywords: "tuberculosis", "*Mycobacterium tuberculosis*", "sputum negative", "smear negative", AFB negative", "negative for AFB", "abacillary", and "diagnosis" for papers published in English from 1966 onwards. We also searched for relevant articles in the contents tables of the *International Journal of Tuberculosis and Lung Diseases* for the past 10 years. We examined the reference lists of papers identified by this strategy for further relevant studies. We contacted researchers around the world with extensive publications on the subject and members of Tuberculosis Net to locate any unpublished material.

All retrieved titles and abstracts were scrutinised for the relevance to the topic. Analytical studies that identified demographic, clinical, radiological, or simple laboratory-based indicators facilitating the diagnosis of smear-negative tuberculosis were included. An assessment of methodological quality was undertaken for each paper.

Results

We selected 15 studies that met the above criteria. Table 1 gives an outline of the studies and table 2 summarises the validity and clinical usefulness of each. Most studies validated diagnostic tools or criteria against sputum culture. However, several studies included in this review also used other less recognised methods of confirming the diagnosis of pulmonary tuberculosis.

Demographic indicators

Smear-negative tuberculosis was more common in older than younger patients in a country with low prevalence of HIV infection in one study.[16] However, countries with high HIV prevalence have an even age distribution, probably because HIV affects younger age-groups.[4] HIV is also more common in patients with smear-negative tuberculosis than in those with smear-positive disease.

Clinical indicators

Three studies aimed to identify frequently occurring clinical features in smear-negative tuberculosis in areas with high prevalence of HIV infection and tuberculosis.

In a hospital-based study in Ethiopia, loss of appetite, weight loss, fever, night sweats, chest pain, haemoptysis, and breathlessness were more common in patients with pulmonary tuberculosis (both smear positive and smear negative) than in those without pulmonary tuberculosis.[24] However, patients with smear-negative tuberculosis had night sweats for a longer time. Smear-positive patients were more likely to have fever and weight loss than the smear-negative group (odds ratios 4·1 [1·2–15·0] and 6·4 [2·3–17·8], respectively). The gold standard against which sensitivity of these indicators was measured was diagnosis by a group of tuberculosis physicians, which may have been due to lack of resources, although the authors do not clarify the reason in the paper. This feature may have introduced misclassification bias distorting the study outcomes.

Another study, in Tanzania and Burundi, identified four clinical criteria for diagnosis of smear-negative tuberculosis:[25] presence of cough for longer than 21 days (odds ratio 5·43[1·95–15·1]); presence of chest pain for longer than 15 days (1·98 [0·77–5·12]); absence of expectoration (odds ratio for expectoration 0·42 [0·15–1·18]); and absence of shortness of breath (odds ratio for breathlessness 0·26 [0·01–0·66]). Diagnosis of smear-negative tuberculosis by any two of these criteria had high sensitivity but low specificity (sensitivity 85%, specificity 67%, positive predictive value 43%, negative predictive value 94%). Use of three of the criteria improved the specificity but reduced the sensitivity (sensitivity 49%, specificity 86%, positive predictive value 50%, negative predictive value 86%). With the addition of lymphadenopathy (odds ratio 3·84 [1·38–10·7]) to two of the above criteria, the sensitivity and specificity improved further. Sputum culture, tissue histology, and positive clinical and radiological response to the antituberculosis therapy were used as the gold standard for diagnosis of pulmonary tuberculosis. However, patients with chronic lung disorders were excluded from the study, which limits the extent to which it can be generalised. The prevalence of HIV was high (71%) in both case and control groups. Community-acquired pneumonia was the most common lung disorder in the non-tuberculosis control group. These criteria can be used to differentiate smear-negative tuberculosis from community-acquired pneumonia in areas with a high prevalence of HIV infection.

A third study, in Tanzania, found that cervical lymphadenopathy was a significant feature of smear-negative tuberculosis.[26] However, that study used extrapulmonary histological samples as the standard for diagnosis of pulmonary tuberculosis, which compromises the validity of the findings.

In an area with low prevalence of HIV infection and high prevalence of tuberculosis, one study based in Senegal found no clinical features differentiating smear-negative from smear-positive tuberculosis other than the absence of cough (odds ratio 10·0 [1·96–50·0]).[16] Limitations of this study were that it had a small sample size and that the diagnosis was confirmed by means of sputum culture in only 20% of cases. The overall prevalence of HIV in both case and control groups was 8·9%.

Only one study identified in this review looked at a population with a low prevalence of both HIV infection and tuberculosis.[14] Cough with expectoration was identified as a negative predictor of smear-negative tuberculosis (odds ratio 0·3 [0·1–0·6]). This study was unable to identify any other differentiating clinical features, possibly owing to the small sample size.

Table 1. Summary of studies reviewed

Setting and ref	Objective	Design	Findings
Low HIV, low tuberculosis incidence			
CA, USA[14]	To identify clinical, demographic, and radiological predictors of smear-negative pulmonary tuberculosis; to develop a "prediction rule" to assist in the diagnosis of smear-negative pulmonary tuberculosis radiological	Hospital-based (outpatients) retrospective case-control Cases: patients with two negative sputum smears and positive cultures Controls: patients with negative sputum smears and cultures	Positive tuberculin test (odds ratio 4·8 [2·0–11·9]), dry cough, and typical chest radiograph are associated with positive tuberculosis cultures In patients with HIV infection, mediastinal lymphadenopathy is related to positive tuberculosis cultures (odds ratio 7·2 [1·4–36·0])
Denmark[15]	To relate chest radiographic changes to bacteriological results in patients with tuberculosis	Retrospective case-control hospital-based study (outpatients) Cases: patients with typical chest radiographic changes of tuberculosis Controls: patients with non-typical chest radiographic changes of tuberculosis	Most tuberculosis cases showed typical radiological signs of tuberculosis. However, in 8% the chest radiographic findings were atypical; of these, half were also smear negative. 89% of patients with cavities on chest radiography were smear positive compared with 53% without cavities ($p<0·05$)
Low HIV, high tuberculosis incidence			
Senegal[16]	To relate the clinical, radiological, and demographic findings in tuberculosis patients to their sputum smear results and HIV status	Hospital-based (outpatients) prospective cohort study	Absence of cough, absence of cavities on chest radiograph, age >40 years, CD4 count >$0·2x10^9$/L, and HIV positivity more common in smear-negative than smear-positive tuberculosis cases
High HIV, high tuberculosis incidence			
South Africa[17]	To assess the usefulness of sputum concentration for the diagnosis of smear-negative tuberculosis	Hospital-based (outpatients) prospective cohort study	Overall diagnostic sensitivity of smear microscopy was not increased by sputum liquefaction and concentration
Ethiopia[18]	To assess the usefulness of sputum concentration for the diagnosis of smear-negative tuberculosis	Hospital-based (outpatients) prospective cohort study	Overall sensitivity increased from 54·2% with direct microscopy to 63·1% after concentration ($p<0·0015$). In HIV-positive patients, sensitivity increased from 38·5% to 50·0% ($p<0·0034$)
Ethiopia[19]	To assess the usefulness of sputum concentration for the diagnosis of smear-negative tuberculosis	Hospital-based (outpatients) prospective cohort study	Sensitivity increased from 30% to 70%
Zambia[20]	To assess the usefulness of sputum concentration for the diagnosis of smear-negative tuberculosis	Hospital-based (outpatients) prospective cohort study	Sensitivity increased from 43% to 76%
South Africa[21]	To assess the value of a trial of antibiotics in the diagnosis of smear-negative tuberculosis	Hospital-based (outpatients) prospective cohort study	Diagnostic sensitivity increased from 61% to 80%, but specificity fell from 94% to 78%
South Africa[22]	To evaluate a diagnostic algorithm for pulmonary tuberculosis based on smear microscopy and response to a trial of two courses of antibiotics	Inpatient hospital-based study	Diagnostic sensitivity increased to 89% and specificity to 84%
Zimbabwe[23]	To develop a diagnostic scoring system for smear-negative tuberculosis based on clinical and radiological indicators	Hospital-based (outpatients) retrospective case-control study	Proposed diagnostic scoring system based on various indicators without validation
Ethiopia[24]	To develop a diagnostic scoring system for smear-negative tuberculosis based on clinical and radiological indicators	Hospital-based (outpatients) retrospective cohort study	Diagnostic scoring system had high sensitivity (93%) and specificity (94%)
Tanzania and Burundi[25]	To identify clinical and radiological features that characterise smear-negative tuberculosis	Retrospective case-control study based in two hospitals (outpatients) Cases: smear-negative pulmonary tuberculosis Controls: non-tuberculosis patients	Cough >21 days, chest pain, absence of sputum, and dyspnoea are common in smear-negative tuberculosis cases
Tanzania[26]	To develop criteria for diagnosis of smear-negative tuberculosis	Hospital-based inpatient prospective case-control study Cases: smear-negative tuberculosis patients Controls: non-tuberculosis patients	Developed clinical scoring system based on Mantoux test, lymphadenopathy, and chest radiographic findings.

Table 1 continued

Setting and ref	Objective	Design	Findings
High HIV, high tuberculosis incidence			
Malawi[27]	To find out prevalence of tuberculosis with normal or slightly abnormal chest radiographs among smear-negative tuberculosis suspects	Hospital-based (outpatients) prospective cohort study	21% of smear-negative patients with normal chest radiographs were diagnosed with tuberculosis by culture
Malawi[28]	To find out the prevalence of tuberculosis (smear-negative and smear positive) in patients with short duration of cough (1–3 weeks) unresponsive to antibiotics	Hospital-based (outpatients) prospective cohort study	35% patients had tuberculosis; of these two-thirds were smear negative

Cough persisting for longer than 3 weeks warrants AFB microscopy, according to the current WHO guidance. However, one study, in an area of high HIV and tuberculosis prevalence, confirmed smear-negative tuberculosis in 35% of patients with cough unresponsive to antibiotics of only 1–3 weeks duration.[28] Most of these patients had atypical changes on chest radiography. That study suggests that pulmonary tuberculosis should be considered in patients with short duration of cough associated with weight loss and lack of response to antibiotics, particularly those who live in overcrowded places in areas with high prevalence of HIV infection and tuberculosis. A cost-benefit analysis of such a strategy is needed before any implementation by tuberculosis-control programmes.

Radiographic indicators

In settings with limited microbiological services, the diagnosis of pulmonary tuberculosis depends heavily on findings of chest radiography. However, in such settings, access to specialist radiology support also tends to be limited. A survey in Malawi showed that medical officers misdiagnosed a third of clinical vignettes, which described typical radiographic signs of tuberculosis.[29]

A Danish study showed that 92% of patients with pulmonary tuberculosis (both smear negative and smear positive) in countries with low prevalence of HIV infection and tuberculosis had typical appearances on chest radiography.[15] However, in 8% of patients, the findings were atypical (lower-lobe infiltrates, miliary pattern, hilar lymphadenopathy. and occasional normal chest radiographs). Of this group, half were smear negative. 89% of patients with cavities on chest radiography were smear positive, compared with 53% without cavities ($p<0·05$). That study identified criteria differentiating pulmonary smear-negative tuberculosis from smear-positive tuberculosis. These criteria did not differentiate between smear-negative tuberculosis and non-tuberculosis disorders. Exclusion of patients with a history of HIV or previous tuberculosis from the study limits its applicability in these groups.

The California study, in a setting of low HIV prevalence, showed a negative association between lobar consolidation or diffuse changes on chest radiography and smear-negative tuberculosis (odds ratio 0·3).[14] That study identified a strong association between smear-negative tuberculosis and mediastinal lymphadenopathy in HIV-positive patients (odds ratio 7·2).

Two studies concluded that tuberculous patients with HIV infection are more likely to have atypical chest radiographic appearances (pulmonary infiltrates with no cavities, lower-lobe involvement, intrathoracic lymphadenopathy, and even normal appearance) than tuberculous patients without HIV infection.[13,30] In areas of high HIV and tuberculosis prevalence, 75% of patients with smear-negative tuberculosis are likely to have atypical chest radiographic findings.[24] Patients with smear-negative tuberculosis are less likely to have cavities on the chest radiograph (odds ratio 2·56) than patients with smear-positive tuberculosis.[16] One study found that 25% of all patients with pulmonary tuberculosis were smear negative, with few cavities on the chest radiograph.[5] The limitations of these studies were discussed earlier.

Smear-negative patients can also present with normal or only slightly abnormal chest radiographs.[27] One study confirmed pulmonary tuberculosis by sputum culture in 21% of patients with suspected tuberculosis and negative smears and normal or slightly abnormal chest radiographs. 47% of such patients developed typical radiographic features after 3 months. A third of the culture-negative patients also developed typical radiographic signs of tuberculosis during follow-up. Despite its limitations, including a significant loss to follow-up, that study suggests that close monitoring of smear-negative patients with suspected tuberculosis and normal or slightly abnormal chest radiographs is useful in areas with high prevalence of HIV infection and tuberculosis.

Sputum concentration

Many researchers have recommended sputum liquefaction and concentration through centrifugation to improve detection of AFB in negative smears through direct microscopy. Two studies have shown an increase of almost two fold in the sensitivity of AFB detection compared with direct microscopy.[19,20] However, neither looked at clinical outcomes. Studies assessing clinical outcomes have shown more modest benefit with these techniques. In one study, the overall sensitivity increased from 54·2% to 63·1% after concentration ($p<0·0015$). In HIV-positive patients, sensitivity increased from 38·5% to 50·0% after concentration ($p<0·0034$).[18,31] This improvement was less remarkable when compared with the sensitivity of direct microscopy supported by clinicians' judgment in diagnosing pulmonary tuberculosis. Another study showed no overall benefit of sputum concentration over direct microscopy in diagnosis of pulmonary tuberculosis.[17,32] Two separate sputum samples were used for the two different techniques,

Table 2. Summary of critical appraisal of the selected studies

Reference	Indicators	Validity	Clinical usefulness
Studies using tuberculosis culture to validate final diagnosis			
14	Clinical, radiological and demographic, features and "prediction rule" based on these	Low power owing to small sample size; possibility of confounding variables; information bias owing to fewer controls than cases having tuberculin tests	Limited application of the "prediction rule" in high HIV/ tuberculosis situations; however, indicators identified may be useful for clinicians to differentiate smear-negative tuberculosis from non-tuberculosis pathologies
28	Clinical: short duration of cough	Small sample size	Short duration of cough may be more relevant in high HIV/ tuberculosis areas. Need to demonstrate added benefit of diagnosing these patients early. Cost-benefit ratio of such strategy needs to be assessed before implementation
19	Sputum concentration techniques	Outcomes were related to specimens, not patients	Efficacy but not effectiveness shown
20	Sputum concentration techniques	Outcomes were related to specimens, not patients; auramine-phenol stain followed by fluorescent microscopy was used to confirm the diagnosis.	Efficacy but not effectiveness shown
18	Sputum concentration techniques	Little benefit shown compared with direct smear microscopy supported by physicians' clinical diagnoses.	..
17	Sputum concentration techniques	Separate samples were taken for the two sputum examination techniques, which may have offset the added advantage of concentration techniques.	..
21	Antibiotic diagnostic trial	Low sensitivity may have been due to confounding by superadded infection and fluctuation of tuberculosis symptoms; low specificity owing to possible confounding caused by antibiotic resistance.	Specificity might be improved if the full algorithm including subsequent chest radiography is also applied
22	Two antibiotics diagnostic trial	..	Trial was done among inpatients; the strategy may be less effective in outpatient clinics
15	Radiological signs	These criteria differentiate between pulmonary smear-negative and smear-positive tuberculosis, but do not between smear-negative tuberculosis and non-tuberculosis.	Limited owing to strict exclusion criteria; patients with history of HIV or previous tuberculosis were not included
27	Radiological signs	Substantial loss to follow-up may have affected the results.	Not applicable to areas with low HIV/tuberculosis prevalence.
Studies using tuberculosis culture, histology, and response to antituberculosis treatment to validate final diagnosis			
25	Clinical and radiological signs	Differentiates between smear-negative tuberculosis and other pulmonary pathologies.	Study restricted to hospital patients with narrow inclusion criteria.
16	Clinical, radiological, and demographic indicators	Only 20% of cases were culture confirmed among smear-negative; small sample and wide CI.	Less useful because clinicians need to differentiate smear-negative tuberculosis from non-tuberculosis not from smear-positive cases.
Studies using extrapulmonary cytology and histology samples to validate final diagnosis			
26	Scoring system based on clinical and radiological indicators	Small sample size; diagnosis based on extrapulmonary samples without sputum cultures, so validity in pulmonary tuberculosis is limited.	Case definition included pleural effusions (extrapulmonary tuberculosis).
Studies using only specialist clinical judgment to validate final diagnosis			
23	Scoring system based on clinical and radiological indicators	No details given of how the scoring system was developed or validated.	Also included children with tuberculosis.
Studies using scoring system based on clinical and radiological indicators			
24	Scoring system	Poor criteria for validation of final diagnosis.	..

which may have resulted in underestimation of the benefit of sputum concentration. The evidence supporting the use of sputum concentration is conflicting. Moreover, such techniques require centrifugation and more time and expertise, and the resource implications must be considered before recommendation to low-income countries.

Tuberculin test

The tuberculin test is of limited value in diagnosing pulmonary tuberculosis in populations with either a high prevalence of tuberculosis or a policy of BCG immunisation at an early age.[33] It may be useful in a population with low prevalence of tuberculosis and HIV infection, where it is more likely to be positive in patients with smear-negative tuberculosis than in those with other pulmonary disorders (odds ratio 4·8).[14] However, information bias (fewer controls than cases had tuberculin tests) could have contaminated these results. Similar studies in HIV-prevalent areas have shown fewer positive tuberculin tests among smear-negative patients than in low HIV prevalence

areas owing to impaired immunity.[26] Overall, smear-negative cases are less likely to be tuberculin positive than smear-positive patients. There have been many papers on the use of the tuberculin test in the diagnosis of pulmonary tuberculosis, but this issue is beyond the scope of this review.

Other laboratory markers

Apart from direct microscopy, tuberculosis diagnostic centres in low-income countries have limited access to other laboratory-based investigations. Morris and colleagues have argued that haematological and biochemical markers can be used in the diagnosis of pulmonary tuberculosis and in determining response to its treatment.[34] However, use of haemoglobin concentration, packed-cell volume, C-reactive protein concentration, and erythrocyte sedimentation rate has poor sensitivity and specificity when used in isolation.[33,35,36] When used along with other clinical criteria, only a packed-cell volume of less than 30% improved the sensitivity and specificity of the clinical diagnosis of smear-negative tuberculosis.[25]

Diagnostic drug trial

An antibiotic trial is a useful tool in excluding chest infections in the diagnostic protocol for pulmonary tuberculosis.[30] WHO advocates a single course of antibiotics for all individuals with suspected tuberculosis and two or more negative smears, to exclude chest infection.[2] According to a South African study, the sensitivity of a sputum smear test for diagnosis of pulmonary tuberculosis is increased from 61% to 80% by addition of one course of antibiotics, but the specificity decreases from 94% to 78%.[21] The low sensitivity may have been a result of confounding by the presence of superadded infection and fluctuation of the symptoms of pulmonary tuberculosis. The lower specificity could be a result of antibiotic resistance. Addition of chest radiography at this stage, as suggested by WHO, is likely to improve the specificity of the algorithm. Use of two successive courses of antibiotics has also been shown to improve the sensitivity (89%) and specificity (84%) of diagnosis of smear-negative tuberculosis:[22] patients with negative smears were first treated with amoxicillin for 5 days followed by a course of erythromycin for non-responders. This study was done in inpatients, and the strategy might be less effective in outpatient settings. Furthermore, the antibiotic-resistance patterns of community-acquired pneumonias in a particular region would need to be considered before implementation of any such strategy.

A trial of antituberculosis drugs is generally not recommended for diagnosis of smear-negative tuberculosis, because many organisms causing chest infections are also sensitive to some of these drugs. However, an algorithm based on a trial of such drugs, including ethambutol, pyrazinamide, and isoniazid has been proposed to diagnose disseminated tuberculosis in areas with high prevalence of HIV infection.[37] The benefit of such an approach has been questioned, owing to the possibility of misuse in the setting of tuberculosis-control programmes. There is also the risk that tuberculosis will not be detected in areas with high rates of isoniazid resistance. Moreover, there is little evidence that such a trial leads to improved diagnosis.[38]

Diagnostic algorithms

Researchers have attempted to develop guidelines, diagnostic prediction scoring models, and algorithms for smear-negative tuberculosis based on various indicators. Many countries have adopted the WHO guidelines; but these guidelines do not incorporate any radiographic or clinical signs in the diagnostic decision tree. In Malawi, these guidelines were modified to include three further criteria:[39] chest radiograph with unilateral lymphadenopathy or cavitations; weight loss, no response to antibiotics, and bilateral infiltrations involving three or more zones on radiography; and cough for longer than 3 weeks, weight loss, no response to antibiotics, and negative sputum smear irrespective of appearance of chest radiograph.

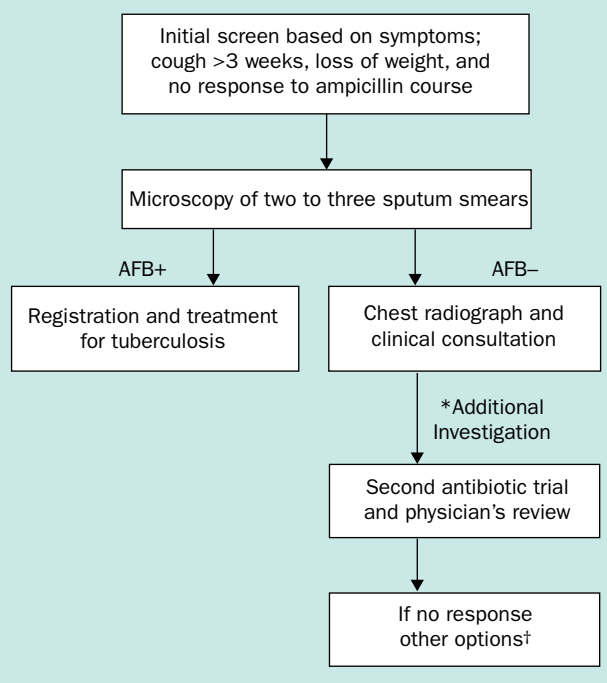
The usefulness of these criteria in the diagnosis of smear-negative tuberculosis needs to be ascertained, but they suggest situations in which pulmonary tuberculosis could be misdiagnosed with the current WHO guidance. An audit of the Malawi guidelines found that non-adherence to diagnostic criteria and errors in registering and making a clinical diagnosis resulted in overdiagnosis of smear-negative tuberculosis.

One research group validated and estimated the cost of tuberculosis case detection by two different algorithms.[40] Screening of patients with suspected pulmonary tuberculosis with chest radiography followed by sputum smear examination was compared with screening by sputum smear followed by chest radiography. Initial radiographic screening was less specific (0·31 *vs* 0·25) and more costly. Another similar algorithm is illustrated in the figure.[9] This algorithm is yet to be validated and would need to be adapted to local circumstances.

Kanaya and colleagues created a pulmonary tuberculosis prediction score (TPS) by use of four clinical predictors identified by a retrospective case-control study.[14] On the basis of the regression coefficient derived from logistic regression analysis, each predictor was given a certain TPS along with a likelihood ratio (table 3). With the TPS in this model, the probability of smear-negative tuberculosis in patients in areas with three different tuberculosis prevalences can be predicted (table 4). Information bias may have prevented the detection of other possible unmeasured and unreported diagnostic indicators. This effect was further compounded by a small sample size, leading to low power to detect all differentiating variables. Despite its limitations, the model may be a useful guide in areas of low HIV prevalence.

Aris and colleagues carried out a prospective study and proposed a diagnostic scoring system to discriminate smear-negative tuberculosis from other pathologies.[26] The diagnostic score (D) can be estimated from the following formula:

D=1·29 (matted lymph node)+0·55 (Mantoux reaction) +0·76 (cervical lymphadenopathy)+2·21 (pleural effusion)–2·19 (Kaposi's lesion)–0·51 (upper/mid zone opacities on radiograph)–1·55.



*Algorithm for managing tuberculosis suspects in developing countries. *For example, sputum induction, lymph node aspiration, etc. †In smear-negative patients with failure to respond to two courses of antibiotics, one can take the following actions: treat appropriately as smear-negative tuberculosis, consider other diagnosis, or observe and reinvestigate for tuberculosis over 3 months.*

Where the presence of each indicator=1 and absence of each indicator=0.

A particular limitation of that study was the use of extrapulmonary histological samples as the gold standard. This scoring system may be useful if validated by use of sputum cultures.

A research group in Zimbabwe developed another scoring system for the diagnosis of primary and secondary pulmonary tuberculosis.[23] It was based on the subjective assignment of scores to several clinical, radiological, and laboratory indicators observed in 1 year of follow-up among patients with smear-negative tuberculosis. However, no details were given of how these indicators were selected and how the scoring system was validated.

Table 3. TPS based on multivariate predictors*

Score	Study patients (n=47)	Control patients (n=141)	Likelihood ratio
–2	3	52	0·2
–1	9	55	0·5
0	16	26	1·8
1	14	8	7·1
2	1	0	..
3	4	0	..

*1 point=positive tuberculin skin test; –1 point=expectoration or infiltrate observed on chest radiograph not typical of tuberculosis; +2 points=both HIV-positive status and mediastinal lymphadenopathy observed on chest radiograph.

Table 4. Post-test probability of tuberculosis given the prevalence of smear-negative cases

Hypothetical score ratio	Likelihood tuberculosis (%)	Post-test probability of
High prevalence, 5% frequency of smear-negative tuberculosis		
–2	0·2	1
0	1·8	8
2	7·1	26
Moderate to low prevalence, 3% frequency of smear-negative tuberculosis		
–2	0·2	0·6
0	1·8	5
2	7·1	18
Very low prevalence, <0·1% frequency of smear-negative tuberculosis		
–2	0·2	0·02
0	1·8	0·2
2	7·1	0·7

*The risk of tuberculosis with a given score (posterior probability) was derived by multiplying the patient's risk based on the estimated prevalence of tuberculosis (prior probability) by the likelihood ratio, and converting the result (posterior odds) to posterior probability.

A group in Addis Ababa Tuberculosis Centre, Ethiopia, developed a scoring system based on weights given to each clinical and radiological indicator in patients with pulmonary tuberculosis.[24] However, the system was verified only against the final clinical diagnosis made by expert tuberculosis physicians and therefore cannot be recommended.

Discussion

We have described studies that have attempted to develop tools to assist clinicians in the diagnosis of smear-negative tuberculosis, highlighting several methodological issues that limit their validity and usefulness. All studies were hospital based, which could have led to selection bias. Various methods were used to validate diagnosis, including culture, histology, clinical judgment, and response to tuberculosis therapy. Small sample size, variable exclusion criteria, and heterogeneity between studies also cast doubt on the validity and usefulness of these diagnostic tools.

The problem of diagnosis of smear-negative tuberculosis has become urgent because the number of patients with paucibacillary pulmonary tuberculosis in countries with an HIV epidemic is increasing rapidly.[41] However, the solution is a challenge given the atypical presentation of pulmonary tuberculosis in HIV-infected patients (eg, dry cough, absence of haemoptysis).[30]

The current evidence suggests that in areas with high prevalence of HIV infection and tuberculosis, the presence of cough for longer than 3 weeks with repeated negative AFB smears, chest pain, cervical lymphadenopathy, absence of expectoration, and shortness of breath suggests pulmonary tuberculosis rather than community-acquired pneumonia.[25] Clinicians are less likely to find typical radiological signs of pulmonary tuberculosis in areas with high prevalence of HIV infection than in those with lower rates. The index of suspicion should still be high if there are

pulmonary infiltrates with no cavities, lower-lobe involvement, intrathoracic lymphadenopathy, and even a normal appearance on chest radiograph. Tuberculin test, erythrocyte sedimentation rate, C-reactive protein concentration, and other basic laboratory tests are likely to give non-specific results. Sputum concentration techniques, if found to be cost-beneficial, may be useful in low-income countries in assisting clinicians in the diagnosis. Although a single course of an appropriate antibiotic can be recommended in excluding chest infection, strategies based on two courses of antibiotics require further investigation in outpatient settings. A trial of antituberculosis drugs is a theoretically attractive option but is unsupported by evidence of effectiveness and may carry the dangers of increased multi-drug resistance and underdiagnosis of pulmonary tuberculosis. The clinical scoring systems developed for countries with high HIV prevalence are based on weak evidence and cannot be recommended to clinicians before further validation.

In countries with low prevalence of HIV infection and tuberculosis, clinicians should expect typical chest radiographic signs in cases of smear-negative tuberculosis. The specificity of the tuberculin test can be increased when combined with other clinical criteria in these settings. The scoring system suggested by Kanaya and colleagues can also be useful in such situations.

Although there is little current evidence of effectiveness of any of the diagnostic tools described above, they can provide a starting point for the development of diagnostic protocols by tuberculosis-control programmes. Policy-makers intending to use such tools need to assess their suitability in a given situation. They need to consider the local epidemiology, such as the prevalence of HIV, tuberculosis, and other pulmonary disorders, and antibiotic-resistance patterns, before implementation.

Search strategy and selection criteria

These are described in detail in the Methods section.

Published work may be useful in stimulating discussion among health professionals and other stakeholders. These groups can then incorporate local experience and data to develop or modify their own guidelines for tuberculosis management. Modified algorithms may include certain radiological or clinical features (varying in each setting) to develop a diagnostic decision-tree model. Once validated, these context-specific guidelines can be adopted more widely.

Rates of misdiagnosis of smear-negative tuberculosis can be reduced by development of diagnostic tools, which incorporate the diagnosis of other non-tuberculosis pulmonary disorders. Where current WHO guidelines have been implemented, clinical audits have the potential to improve the quality of diagnosis of smear-negative tuberculosis.

This review has also identified several research needs. New diagnostic techniques are required in addition to AFB microscopy for the identification of smear-negative tuberculosis. These need to be appropriate for use in low-income countries.[41] Research into development of more cost-effective microbiological and serological diagnostic solutions is under way. However, until such tests are widely available, diagnostic scoring systems and algorithms must be developed and validated to assist clinicians working in resource-poor settings. Research collaboration is required between countries with similar HIV prevalence to address these research needs and to develop joint management guidelines, which can be applied and evaluated in different situations.

Conflicts of interest

None declared.

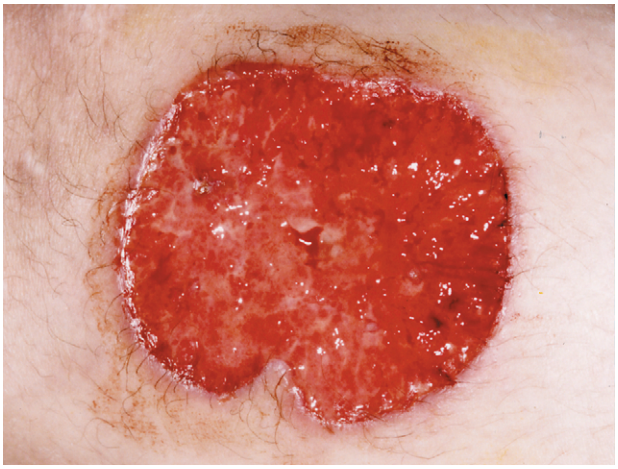
References

1 Lauzardo M, Ashkin D. Phthisiology at the dawn of the new century. *Chest* 2000; **117:** 1455–73.
2 Maher D, Chalet P, Spinaci S, Harries AD. Treatment of tuberculosis: guidelines for national programmes, 2nd edn. Geneva: WHO, 1997.
3 Aber VR, Allen BW, Mitchison DA, Ayuma P, Edwards EA, Keyes AB. Quality control in tuberculosis bacteriology: 1, laboratory studies on isolated positive cultures and the efficiency of direct smear examination. *Tubercle* 1980; **61:**123–33.
4 Parry CM. Sputum smear negative pulmonary tuberculosis. *Trop Doct* 1993; **23:** 145–46.
5 Kim TC, Blackman RS, Heatwole KM, Kim T, Rochester DF. Acid-fast bacilli in sputum smears of patients with pulmonary tuberculosis: prevalence and significance of negative smears pretreatment and positive smears post-treatment. *Am Rev Respir Dis* 1984; **129:** 264–68.
6 Levy H, Feldman C, Sacho H, van der MH, Kallenbach J, Koornhof H. A reevaluation of sputum microscopy and culture in the diagnosis of pulmonary tuberculosis. *Chest* 1989; **95:** 1193–97.
7 Alausa KO, Osoba AO, Montefiore D, Sogbetun OA. Laboratory diagnosis of tuberculosis in a developing country 1968–1975. *Afr J Med Med Sci* 1977; **6:** 103–08.
8 Petersen KF, Urbanczik R. [Microscopic and cultural methods for the laboratory diagnosis of tuberculosis: a short historical review (author's transl)]. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 1982; **251:** 308–25.
9 Colebunders R, Bastian I. A review of the diagnosis and treatment of smear-negative pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2000; **4:** 97–107.
10 Long R. Smear-negative pulmonary tuberculosis in industrialized countries. *Chest* 2001; **120:** 330–34.
11 Behr MA, Warren SA, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet* 1999; **353:** 444–49.
12 Hargreaves NJ, Kadzakumanja O, Whitty CJ, Salaniponi FM, Harries AD, Squire SB. 'Smear-negative' pulmonary tuberculosis in a DOTS programme: poor outcomes in an area of high HIV seroprevalence. *Int J Tuberc Lung Dis* 2001; **5:** 847–54.
13 Banda H, Kang'ombe C, Harries AD, et al. Mortality rates and recurrent rates of tuberculosis in patients with smear-negative pulmonary tuberculosis and tuberculous pleural effusion who have completed treatment. *Int J Tuberc Lung Dis* 2000; **4:** 968–74.
14 Kanaya AM, Glidden DV, Chambers HF. Identifying pulmonary tuberculosis in patients with negative sputum smear results. *Chest* 2001; **120:** 349–55.
15 Wilcke JT, Askgaard DS, Nybo JB, Dossing M. Radiographic spectrum of adult pulmonary tuberculosis in a developed country. *Respir Med* 1998; **92:** 493–97.
16 Samb B, Sow PS, Kony S, et al. Risk factors for negative sputum acid-fast bacilli smears in pulmonary tuberculosis: results from Dakar, Senegal, a city with low HIV seroprevalence. *Int J Tuberc Lung Dis* 1999; **3:** 330–36.
17 Wilkinson D, Sturm AW. Diagnosing tuberculosis in a resource-poor setting: The value of sputum concentration. *Trans R Soc Trop Med* 1997; **91:** 420–21.
18 Bruchfeld J, Aderaye G, Palme IB, Bjorvatn B, Kallenius G, Lindquist L. Sputum concentration improves diagnosis of tuberculosis in a setting with a high prevalence of HIV. *Trans R Soc Trop Med Hyg* 2000; **94:** 677–80.
19 Habeenzu C, Lubasi D, Fleming AF. Improved sensitivity of direct microscopy for detection of acid-fast bacilli in sputum in developing countries. *Trans R Soc Trop Med Hyg* 1998; **92:** 415–16.
20 Gebre N, Karlsson U, Jonsson G, et al. Improved microscopical diagnosis of pulmonary tuberculosis in developing countries. *Trans R Soc Trop Med Hyg* 1995; **89:** 191–93.
21 Wilkinson D, De Cock KM, Sturm AW. Diagnosing tuberculosis in a resource-poor setting: the value of a trial of antibiotics. *Trans R Soc Trop Med Hyg* 1997; **91:** 422–24.
22 Wilkinson D, Newman W, Reid A, Squire SB, Sturm AW, Gilks CF. Trial-of-antibiotic algorithm for the diagnosis of tuberculosis in a district hospital in a developing country with high HIV prevalence. *Int J Tuberc Lung Dis* 2000; **4:** 513–18.
23 Bergman NJ. A "treatment score" for primary and pulmonary tuberculosis. *Cent Afr J Med* 1995; **41:** 1–6.
24 Tessema TA, Bjune G, Assefa G, Bjorvat B. An evaluation of the diagnostic value of clinical and radiological manifestations in patients attending the Addis Ababa tuberculosis centre. *Scand J Infect Dis* 2001; **33:** 355–61.
25 Samb B, Henzel D, Daley CL, et al. Methods for diagnosing tuberculosis among in-patients in eastern Africa whose sputum smears are negative. *Int J Tuberc Lung Dis* 1997; **1:** 25–30.
26 Aris EA, Bakari M, Chonde TM, Kitinya J, Swai AB. Diagnosis of tuberculosis in sputum negative patients in Dar es Salaam. *East Afr Med J* 1999; **76:** 630–34.
27 Harries AD, Banda HT, Boeree MJ, et al. Management of pulmonary tuberculosis suspects with negative sputum smears and normal or minimally abnormal chest radiographs in resource-

poor settings. *Int J Tuberc Lung Dis* 1998; **2:** 999–1004.
28 Banda HT, Harries AD, Welby S, et al. Prevalence of tuberculosis in TB suspects with short duration of cough. *Trans R Soc Trop Med Hyg* 1998; **92:** 161–63.
29 Nyirenda TE, Harries AD, Banerjee A, Salaniponi FM. Accuracy of chest radiograph diagnosis for smear-negative pulmonary tuberculosis suspects by hospital clinical staff in Malawi. *Trop Doct* 1999; **29:** 219–20.
30 Harries AD, Maher D, Nunn P. An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high-HIV-prevalence settings in sub-Saharan Africa. *Bull World Health Organ* 1998; **76:** 651–62.
31 Sherman LF, Fujiwara PI, Cook SV, Bazerman LB, Frieden TR. Patient and health care system delays in the diagnosis and treatment of tuberculosis. *Int J Tuberc Lung Dis* 1999; **3:** 1088–95.
32 Toyota M. [Validity of "the risk index" to predict the infectiousness of tuberculosis patients]. *Kekkaku* 1994; **69:** 375–77.
33 Cowie RL, Escreet BC. The diagnosis of pulmonary tuberculosis. *S Afr Med J* 1980; **57:** 75–77.
34 Morris CD, Bird AR, Nell H. The haematological and biochemical changes in severe pulmonary tuberculosis. *QJM* 1989; **73:** 1151–59.
35 Yanagisawa N, Takahashi M, Namiki M, Okajima S, Ichinose Y, Toyama K. [Study of erythrocyte sedimentation rate in patients with pulmonary tuberculosis]. *Kansenshogaku Zasshi* 1996; **70:** 955–62.
36 Al Marri MR, Kirkpatrick MB. Erythrocyte sedimentation rate in childhood tuberculosis: is it still worthwhile? *Int J Tuberc Lung Dis* 2000; **4:** 237–39.
37 Harries AD, Hargreaves NJ, Kumwenda J, Kwanjana JH, Salaniponi FM. Trials of anti-tuberculosis treatment in areas of high human immunodeficiency virus prevalence in sub-Saharan Africa. *Int J Tuberc Lung Dis* 2000; **4:** 998–1001.
38 Fourie B, Weyer K. Trials of anti-tuberculosis treatment as a diagnostic tool in smear-negative tuberculosis are of questionable benefit. *Int J Tuberc Lung Dis* 2000; **4:** 997.
39 Harries AD, Hargreaves NJ, Kwanjana JH, Salaniponi FM. Clinical diagnosis of smear-negative pulmonary tuberculosis: an audit of diagnostic practice in hospitals in Malawi. *Int J Tuberc Lung Dis* 2001; **5:** 1143–47.
40 Harries AD, Kamenya A, Subramanyam VR, et al. Screening pulmonary tuberculosis suspects in Malawi: testing different strategies. *Trans R Soc Trop Med Hyg* 1997; **91:** 416–19.
41 Foulds J, O'Brien R. New tools for the diagnosis of tuberculosis: the perspective of developing countries. *Int J Tuberc Lung Dis* 1998; **2:** 778–83.

Clinical picture

Cutaneous histoplasmosis in a patient with systemic lupus erythematosis



A 49-year-old woman presented with a 6 by 4 cm swelling of her distal left lateral thigh. She was born in Belize and moved to New York State at 18 years, then to Europe at 23 years. She was diagnosed with systemic lupus erythematosis (SLE) with antiphospholipid syndrome 4 years before admission. She was on warfarin for a pulmonary embolus and prednisolone 5 mg/day and hydroxychloroquine 200 mg/day for SLE. She had been treated with azathioprine and had six doses of pulsed cyclophosphomide 2 years previously.

The lesion was thought to be a haematoma and the patient was managed conservatively. The lesion did not improve and 6 weeks later she had an incision and drainage. Culture of the fluid was negative. The lesion did not heal and ulcerated despite a course of antibiotics (figure). Two skin grafts failed.

2 years after admission the woman developed multiple cutaneous ulcers and nasal ulceration, which was biopsied and showed organisms within macrophages that were typical of *Histoplasma capsulatum*. The organism was grown from the nose and thigh ulcer. Serology for histoplasma showed a positive M-line immunodiffusion test. She was markedly lymphopenic with a CD4 count of 11/μL.

The patient was started on sodium cholesteryl sulphate-amphotericin complex (Amphocil, 1 mg/kg), which was not tolerated, and switched to liposomal amphotericin B (Ambisome, 1 mg/kg per day increasing to 3 mg/kg per day) for 2 weeks, and then oral liquid itraconazole 400 mg per day for 6 weeks. The skin and nasal lesions completely resolved. Despite a continuously low CD4 count the patient elected to stop prophylaxis due to side-effects. 8 months on she developed further cutaneous ulcerations with isolation of *H capsulatum*. She was retreated with liposomal amphotericin B for 21 days and switched to voriconazole with maintenance at 200 mg twice daily. She has not developed further lesions.

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