Evaluation of Latent Class Analysis and Decision Thresholds to Guide the Diagnosis of Pediatric Tuberculosis in a Rwandan Reference Hospital

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Setting: A pediatric ward of a university hospital in Kigali, Rwanda, a region with a high HIV seroprevalence.

Objective: To estimate the diagnostic accuracy of symptoms, signs, and paraclinical investigations for tuberculosis in children, and to propose a clinical rule based on the results.

Design: During a 2-year period all children with cough for more than 2 weeks and/or fever for more than 2 weeks and/or reported weight loss were prospectively included. A set of clinical and paraclinical data were analyzed with latent class analysis. Comparison of post-test probability based on this analysis with a therapeutic threshold for TB was used to develop a guideline.

Results: In the 309 children HIV prevalence was 56%, bacteriology was positive in 9%, and the tuberculin skin test (TST) was >10 mm in 20%. TB prevalence was 32%. Bacteriology and TST had a specificity of 97% and cough had a sensitivity of 91%. Decision analysis suggests treating children presenting one of the inclusion criteria, combined with positive bacteriology or TST >10 mm or contact with a TB patient.

Conclusions: Latent class analysis confirmed earlier identified predictors for TB and allowed development of an easy to use clinical rule, applicable in reference hospitals of countries with high HIV endemicity.

Key Words: tuberculosis, diagnostic accuracy, latent class analysis, pediatrics, threshold, guideline, sub-Saharan Africa

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Tuberculosis (TB) remains one of the most challenging diagnoses in children in sub-Saharan Africa, because the clinical presentation is elusive and bacteriologic confirmation not often obtained. In Rwanda a TB incidence rate of 89 per 100,000 was recorded in 2005 and only 3% of all bacteriologically confirmed cases were children.[1] Statistics for pediatric TB are difficult to obtain.[1–3] Figures vary from 10% to 20% of all TB cases. One of the key factors for the wide heterogeneity in pediatric TB notification is the low sensitivity of bacteriologic tests and the absence of a standard.[2,3] Direct smear microscopy has an estimated sensitivity of 20% and culture 40%.[4]

Diagnosis of TB in children is often based on a pattern of clinical symptoms and signs: contact with an infected adult, persistent fever and cough, weight loss, positive tuberculin skin test (TST), chest radiograph findings.[5–8] Specificity of these signs and symptoms is often low, especially in countries with high prevalence of human immunodeficiency virus (HIV) infection.[4] Use of TST is generally not recommended, as its interpretation is difficult given the widespread BCG vaccination at birth and the prevalence of HIV-related immune depression, the first enhancing the TST response, the latter weakening it.[9,10] Interferon-γ/T cell assays have a higher specificity for a comparable sensitivity and might constitute a valuable tool in the future, but its cost is still prohibitive.[11]

The sensitivity of chest radiograph reaches 62% to 67% if hilar or mediastinal lymph nodes, a miliary pattern or cavities are all taken into account.[12,13] Chest radiograph may be normal in 10% of children with positive bacteriology.[14] Lymphoid interstitial pneumonia might mimic miliary TB.[15] The value of the polymerase chain reaction (PCR) is unclear: sensitivity varies from 4% to 80%, and specificity from 80% to 100%.[16] Not only has the absence of a widely accepted reference standard made interpretation of PCR difficult, but evaluations of the diagnostic performance of PCR often suffer from the confusion between mycobacterial infection and TB disease. Serologic tests have been developed, but their overall diagnostic accuracy is poor.[16]

Several diagnostic guidelines have been developed.[17,18] Their problem remains the lack of a diagnostic standard to validate them, and the applicability at different health system levels and in countries with both high and low HIV prevalence.[19,20]

Different methods have been developed to overcome the absence of a diagnostic standard. Latent class analysis (LCA) estimates the prevalence of the disease and the sensitivity and specificity of key findings based on patterns of clinical signs and tests.[21] As in multivariate analysis, where symptoms, signs and tests are evaluated for their classification accuracy given a predefined disease status, LCA builds a model with a hypothetical disease as a reference standard.

A therapeutic threshold is the probability of disease where the risk of treating is equal to the risk of withholding treatment, where the harm done to false positives is in balance with the harm done to false negatives. Applying such a threshold means treating all children who have a disease probability higher than this threshold. Often it is confounded with the proportion of false positives treated in a cohort: this is not the case, since most diseased children will have a much higher probability, and most nondiseased a much lower probability, depending on the accuracy of the test(s). Few studies on thresholds for medical decision making have been published, although this methodology has been developed since more than 20 years.[22–24] We intended to determine TB prevalence and diagnostic accuracy of key findings in children in a setting with both high TB and HIV burden, awaiting results of the ongoing quest for a diagnostic standard.[19,25] Based on the results, we propose a guideline for use at reference level in countries with a high HIV infection burden.

MATERIALS AND METHODS

From January 1, 2005 until December 31, 2006, we included all children ≤15-year-old, admitted to the pediatric ward of the University Hospital in Kigali with at least one of the following symptoms: cough >2 weeks or fever >2 weeks or weight loss, all as reported by the parents. Children already on TB treatment were excluded.

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The following data were prospectively collected: fever, weight loss, cough, contact with a TB patient, loss of appetite, weakness, night sweats, hemoptysis, vaccination scar, and lymph nodes. Anteroposterior chest roentgenogram was done for all children and read independently by a radiologist (blinded to clinical diagnosis) and at least one pediatrician. In case of different readings a consensus was reached together with a second clinician. Mediastinal or hilar lymphadenopathy, a miliary pattern, cavities, and pleural effusion were labeled as "suggestive." An abdominal ultrasound performed by a radiologist blinded to clinical and chest radiograph information was labeled as "suggestive" in case of multiple lymph nodes or the presence of ascites.

For older children with productive cough 3 sputum specimens were examined on direct smear with Ziehl-Nielsen staining, and inoculated on Löwenstein media. For smaller children or children with dry or absent cough a nasogastric aspiration was done on 3 consecutive days. Direct smear was considered positive if at least 2 samples showed >10 mycobacteria per 100 fields.[18,26,27] A variable "bacteriologically positive" was composed from direct smear and culture results: if one of both was positive, we considered the case as bacteriologically confirmed.

For TST, standard instructions consisted of injection of 0.1 mL of PPD-RT23.[18] Diameter of swelling was measured after 72 hours. Both intradermal injection and reading were done by the same clinician for all children. In addition, an "adjusted TST" value as proposed by WHO was calculated but abandoned because of lack of improvement of statistical models.[10,27]

HIV serostatus was analyzed with a rapid test (Determine, Abbott laboratories, Abbott Park, IL), if positive confirmed with a second rapid test (Unigold, Trinity Biotech plc, Wicklow, Ireland). For <18 months old infants a DNA–PCR (Amplicor version 1.5, Roche Molecular Systems, Pleasanton, CA) was performed. For all HIV-positive children a CD4 count was done (FACSCalibur, BD Bioscience, Becton, Dickinson and company, Franklin Lakes, NJ).

The decision to treat for TB was taken in consensus by at least 2 pediatricians, based on available clinical and paraclinical evidence.

We used LCA to estimate TB prevalence and sensitivity and specificity of markers. LCA assumes that the study subjects can be classified in 2 subgroups: the ones with the disease and the ones without. Disease status is a so-called "latent variable," as it is not directly observed in the study, because there is no diagnostic standard among the study variables. We can assume that the clinical signs and test results of the study subjects are—each taken alone—an imperfect measure of the disease status. Taken together, those markers combine in a number of patterns (eg, for 3 tests A, B, and C, subjects are A+B+C+; A+B+C−; A+B−C−; …etc). The observed frequencies of those test patterns allow for the construction of loglinear models with a latent variable (disease) and yield estimates for the prevalence of the disease, and the sensitivity and specificity of each marker.[28,29]

Descriptive statistical analyses were performed using SPSS 10.1 (Chicago, IL). We estimated the latent class models using a Bayesian fixed effects model using WinBugs 1.4 (MRC Statistical Unit Cambridge, Cambridge, United Kingdom) called from within R 2.3.1 (R Foundation for Statistical Computing, Vienna, Austria).[30–32]

For identifying the best latent class model we started with a model with 3 known predictors suggested in the literature: bacteriology, contact with a TB patient and suggestive radiology.[5,8,25,33] Successively we added age, sex, malnutrition, longstanding fever, weakness, palpable lymph nodes, hemoptysis, chronic cough, ultrasound, HIV serologic status, and TST to the model, to evaluate their predictive value. Only findings with a positive likelihood ratio more than 2 or a negative likelihood ratio less than 0.5 were retained in the model. The conditional independence assumption between these markers was checked using graphical posterior predictive checks and Bayesian lack-of-fit test, where a low P value indicates an incorrect model. Results of the final model were summarized using posterior means and 95% credible (or probability) intervals (95% CIs) for sensitivities, specificities, and positive/negative likelihood ratios.[34]

From the observed number of patients in each pattern and the model-derived probability of being diseased for each response pattern, we computed the expected number of false positives that would occur if the patients with that pattern would be treated. We did the same for false negatives in case of withholding treatment. Cumulative sums of both were computed for different decision thresholds.

For a therapeutic threshold we relied on earlier work, where we computed thresholds for TB treatment in Rwandan adults, based on data from a questionnaire for medical officers and clinicians involved in treatment and treatment guidelines.[35] Questions included mortality and morbidity of disease and treatment, efficacy, and cost of treatment. For comparison between mortality and morbidity we asked how much a certain disease would subtract of the "vital capacity," full vital capacity being 1 and death 0. For the value of life estimated as a cost we asked what the interviewee would be willing to pay to stop an imminent life-threat against him or herself (willingness to pay). Finally, we asked how many times a death due to unnecessary treatment was worse than a natural death (relative weight given to false positives; commission regret).

When using the following formula, a threshold of 12% was estimated.

$$x = \frac{\text{treatmort*weightprov} + \text{treatmorb*morbweight*weightprov} + \text{treatcost/lifecost}}{\text{diseasemort} - \text{failuremort} + \text{diseasemorb*morbweight}}$$

where: diseasemorb: probability of morbidity due to a nontreated tuberculosis; lifecost: value of life estimated as a cost; morbweight: weighed value of morbidity with respect to mortality; treatcost: direct cost of a short course treatment; treatmorb: probability of morbidity due to treatment; weightprov: value of a provoked death, weighed relative to a natural death.

TABLE 1. History, Clinical, and Paraclinical Findings in Patients Admitted to the Pediatric Ward of the University Hospital Kigali (Rwanda, 2005–2006)*

Markers	Frequency (n = 309)
Cough for more than 2 wk	256 (83%)
Fever for more than 2 wk	155 (50%)
Weight loss	235 (76%)
Night sweats	210 (68%)
Weakness	203 (66%)
Loss of appetite	135 (44%)
Enlarged peripheral lymph nodes	108 (35%)
History of contact with tuberculosis patient	97 (31%)
Haemoptysis	19 (6%)
HIV-test positive	172 (56%)
Bacteriology positive	27 (9%)
Culture positive	16 (5%)
Smear positive	22 (7%)
Tuberculin intradermal reaction (IDR)	
<5 mm	241 (78%)
5–9 mm	4 (1%)
10–14 mm	11 (4%)
≥15 mm	53 (17%)
Adjusted IDR ≥10 mm	61 (20%)
Unadjusted IDR ≥10 mm	64 (21%)
Chest x-ray suggestive of TB	104 (34%)
Abdominal ultrasound suggestive of TB	49 (16%)

*With at least one of the following symptoms: cough >2 wk, fever >2 wk, or weight loss.

The study was approved by the ethical clearance body of the University Hospital of Kigali. All examinations were done as part of routine investigations for any child with the inclusion criteria. For HIV testing, counseling was offered and informed consent obtained from the parents.

RESULTS

General

Of 309 patients included 147 were female and 162 male. Median age was 29.5 months (interquartile range: 15–87.5). Table 1

TABLE 2. Sensitivity, Specificity, and Positive/Negative Likelihood Ratios of Findings Included in the Final Latent Class Model in 309 Children Admitted to a Pediatric Ward With Persistent Cough, Fever, or Reported Weight Loss (Rwanda, 2005–2006)

Finding	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
Bacteriology positive	23 (14–34)	97 (93–100)	51.4 (2.5–148.8)	0.80 (0.68–0.91)
Cough for >2 wk	91 (83–97)	22 (16–28)	1.2 (1.0–1.3)	0.43 (0.12–0.90)
Contact with TB patient	65 (51–82)	84 (76–94)	4.9 (2.6–10.5)	0.41 (0.22–0.59)
Chest x-ray suggestive	53 (41–66)	75 (68–84)	2.2 (1.4–3.4)	0.63 (0.45–0.82)
Ultrasound suggestive	24 (15–36)	88 (82–93)	2.1 (1.0–3.9)	0.86 (0.72–1.01)
Unadjusted IDR >10 mm	60 (40–86)	97 (91–100)	92.0 (6.0–371.1)	0.42 (0.14–0.62)
Prevalence	32 (19–47)			

Prevalence, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio estimated using Bayesian latent class analysis with noninformative (uniform) priors. Posterior means and 95% credible intervals are presented. Bayesian Lack of Fit *P* value of the model 0.297.

TABLE 3. Frequency of Observed Test Patterns and Estimated Probability of Having TB in Children Admitted to a Pediatric Ward With Persistent Cough, Fever or Reported Weight Loss (Rwanda, 2005–2006)

Patterns						Analysis			
Bacteriology	Cough	Contact	X-ray	Ultrasound	IDR	Obsfreq	ProbD	FN	FP
+	+	+	+	−	+	4	1.00	99	0
+	+	+	−	+	+	2	1.00	95	0
+	+	+	−	−	+	3	1.00	93	0
+	+	−	+	+	+	1	1.00	90	0
−	+	+	+	+	+	4	0.99	89	0
−	+	+	+	−	+	10	0.99	85	0
−	−	+	+	+	+	1	0.98	75	0
−	+	+	−	+	+	1	0.98	74	0
+	+	+	+	+	−	1	0.97	73	0
+	−	−	+	−	+	1	0.97	72	0
−	−	+	+	−	+	1	0.96	71	0
+	+	−	−	−	+	1	0.96	70	0
−	+	+	−	−	+	14	0.95	69	0
−	+	−	+	+	+	3	0.94	56	1
+	+	+	+	−	−	2	0.94	53	1
−	−	+	−	−	+	1	0.88	51	1
−	+	−	+	−	+	6	0.88	50	1
−	+	−	−	+	+	5	0.82	45	2
+	+	+	−	−	−	3	0.82	41	3
−	+	+	+	+	−	2	0.76	38	4
−	+	−	−	−	+	4	0.67	37	4
−	−	−	−	+	+	1	0.61	34	5
+	+	−	+	−	−	7	0.60	33	6
−	+	+	+	−	−	12	0.59	29	9
−	+	+	−	+	−	4	0.47	22	14
−	−	−	−	−	+	1	0.41	20	16
−	−	+	+	−	−	5	0.32	20	16
+	+	−	−	−	−	2	0.30	18	20
−	+	+	−	−	−	23	0.29	18	21
−	+	−	+	+	−	5	0.24	11	37
−	+	−	+	−	−	30	0.12	10	41
−	−	+	−	−	−	4	0.12	6	68
−	−	−	+	+	−	3	0.09	6	71
−	+	−	−	+	−	14	0.08	5	74
−	−	−	+	−	−	6	0.04	4	87
−	+	−	−	−	−	93	0.04	4	92
−	−	−	−	+	−	2	0.03	0	182
−	−	−	−	−	−	27	0.01	0	184

Only observed test patterns (39 out of a possible 64) are shown.

The threshold for TB treatment in adults is indicated by a white line space.

FP, FN indicates predicted number of false positives and false negatives if the threshold for diagnosis at individual level is set at the predicted disease probability for pattern of findings; Obsfreq, observed number of patients with this combination of findings; ProbD, probability of TB, predicted by LCA.

gives the clinical and paraclinical data: all 3 inclusion criteria were very frequent, only one-third had a history of contact with a TB patient; bacteriologically confirmed cases were rare (9%) and 56% were HIV-positive.

Correlation between direct smear and culture was poor: 11 patients had a positive smear but a negative culture (Cohen's kappa 0.55; CI: 0.34–0.74).

Latent Care Analysis

The final latent class model included 6 markers with assumed conditional independence among them: bacteriology positive, cough >2 weeks, contact with TB patient, suggestive chest radiograph, suggestive ultrasound, and unadjusted TST >10 mm. The model showed a good fit to the data ($P = 0.271$) and posterior predictive graphs indicated that the observed distribution of patients over the response patterns was consistent with the latent class model. Other models, eg, latent class models with more or less than 6 markers and models relaxing the conditional independence assumption showed similar results (data not shown) to the selected model.

Table 2 shows the results of the latent class model. The prevalence of TB was 32%. No single test showed both good sensitivity and specificity. Cough >2 weeks had a good sensitivity (91%) but a poor specificity (22%). All other tests had at most moderate sensitivity. Bacteriology and TST had high test specificity (both 97%), but very poor (23%) to moderate sensitivity (60%) respectively. Bacteriology and TST showed high positive likelihood ratios, none of the tests showed a good negative likelihood ratio. Overall, contact with a TB patient and TST were the best predictors.

Table 3 shows the different observed test patterns with the number of patients in each pattern and the post-test probability of having TB as estimated by the latent class model.

Figure 1 shows the distribution of the patients following their post-test probability of being TB infected. Patients form 2 groups at the extremes of probability, with few patients with intermediate probabilities of being TB infected. This indicates that the combination of the 6 markers generally allows a good discrimination between subjects that are unlikely to be infected and those that are likely to be infected.

Patients were stratified for HIV infection, and LCA was applied to both groups. Marker sensitivities and specificities were similar in the 2 subgroups (overlapping 95% probability intervals; Table 4). Consequently, the pooled latent class model can be used for both the HIV-positive and negative subjects; the estimated prevalence of TB was 32% in both subgroups.

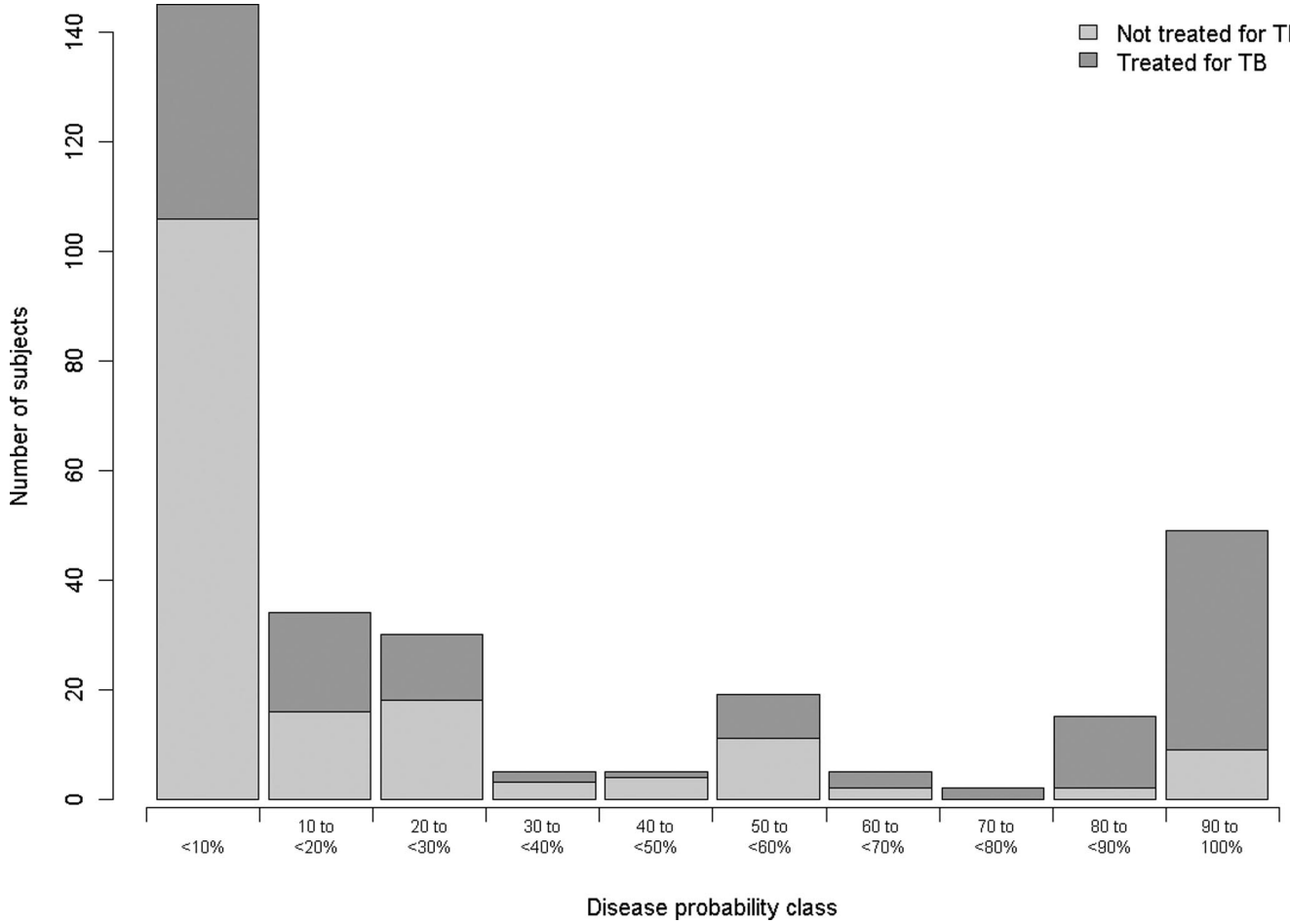

FIGURE 1. Distribution of patients according to post-test probability of having TB by treatment actually received. On the x-axis post-test probability classes are shown. The y-axis gives the number or patients in each class. The graph suggests 2 groups at the extremes of probability, representing patients with a high and low post-test probability, with few patients in the intermediate classes. Disease probability estimated with the Bayesian latent class model summarized in Table 3.

Treatment

One hundred and thirty-eight patients (45%) were actually treated. The proportion of patients treated increased with increasing probability of being TB diseased (Fig. 1). In patterns having a disease probability >90%, 7 of 8 patients that were not treated had negative bacteriology, suggesting a possible bias through this test result (3/7 were under 5).

Assuming a threshold of 12%, 130 patients (42%) would have been treated, with 38 false positives for 12 false negatives, a ratio of 3 to 1 (Table 3). Figure 2 shows the number of patients that would be treated with varying decision thresholds. Hypothetically, at a therapeutic threshold of 80%, only 64 patients would be treated. If the threshold would be lowered from 80% to 20%, 66 additional patients would be treated. Around the threshold we applied, small variations would have serious implications: lowering the threshold to 10% would suggest treating 34 more patients, 30 more false positives for 4 truly positives. In 21 of these 34 patients hilar adenopathies was the additional finding suggesting treatment, and 18 were treated by the clinicians.

HIV seropositive patients were more commonly treated (59%) than HIV seronegative patients (26%), even at low TB probabilities (Fig. 3).

TABLE 4. Estimated Sensitivity and Specificity of Findings for Pediatric Tuberculosis in Children Admitted to a Pediatric Hospital With Persistent Cough, Fever, or Reported Weight Loss (Rwanda, 2005–2006) Stratified by HIV-Status

	HIV Negative (n = 137)		HIV Positive (n = 172)	
Finding	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bacteriology positive	20 (7–40)	94 (88–99)	30 (14–54)	96 (91–100)
Cough for >2 wk	92 (78–100)	25 (17–36)	86 (71–97)	17 (10–24)
Contact with TB patient	67 (46–92)	76 (65–90)	79 (53–99)	87 (76–98)
Chest x-ray suggestive	62 (40–88)	76 (65–88)	49 (31–68)	70 (61–80)
Ultrasound suggestive	28 (11–54)	92 (85–97)	22 (7–40)	81 (73–89)
Unadjusted IDR >10 mm	71 (38–98)	93 (84–100)	62 (38–90)	92 (84–99)

Sensitivity and specificity estimated using separate Bayesian latent class analyses with noninformative (uniform) priors in HIV seronegative and seropositive subjects. Posterior mean and 95% probability intervals are presented.
Bayesian Lack of Fit P = 0.261 (HIV−) and 0.301 (HIV+).

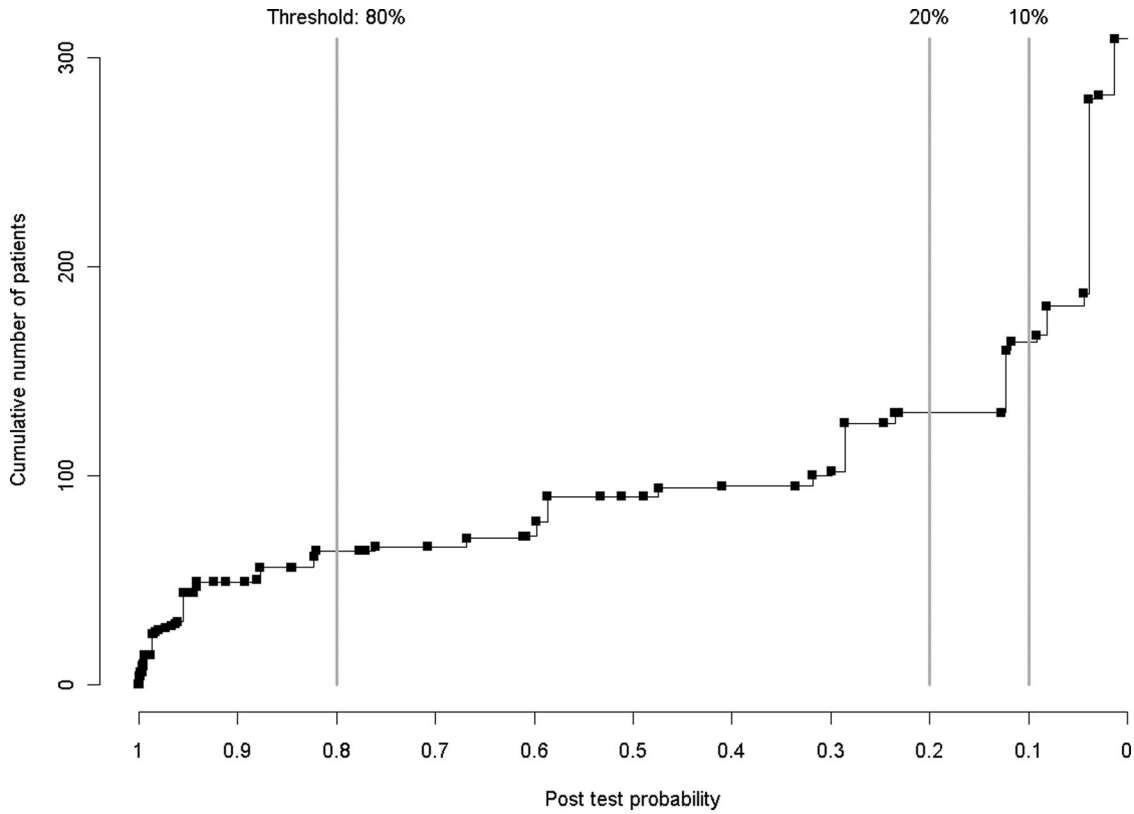

FIGURE 2. Cumulative numbers of patients that would be treated against 3 hypothetical thresholds. The number of patients is added in descending order of posttest probabilities. The cumulative distribution starts from those reaching the highest post-test probability to those reaching the lowest. Vertical lines represent 3 hypothetical treatment thresholds.

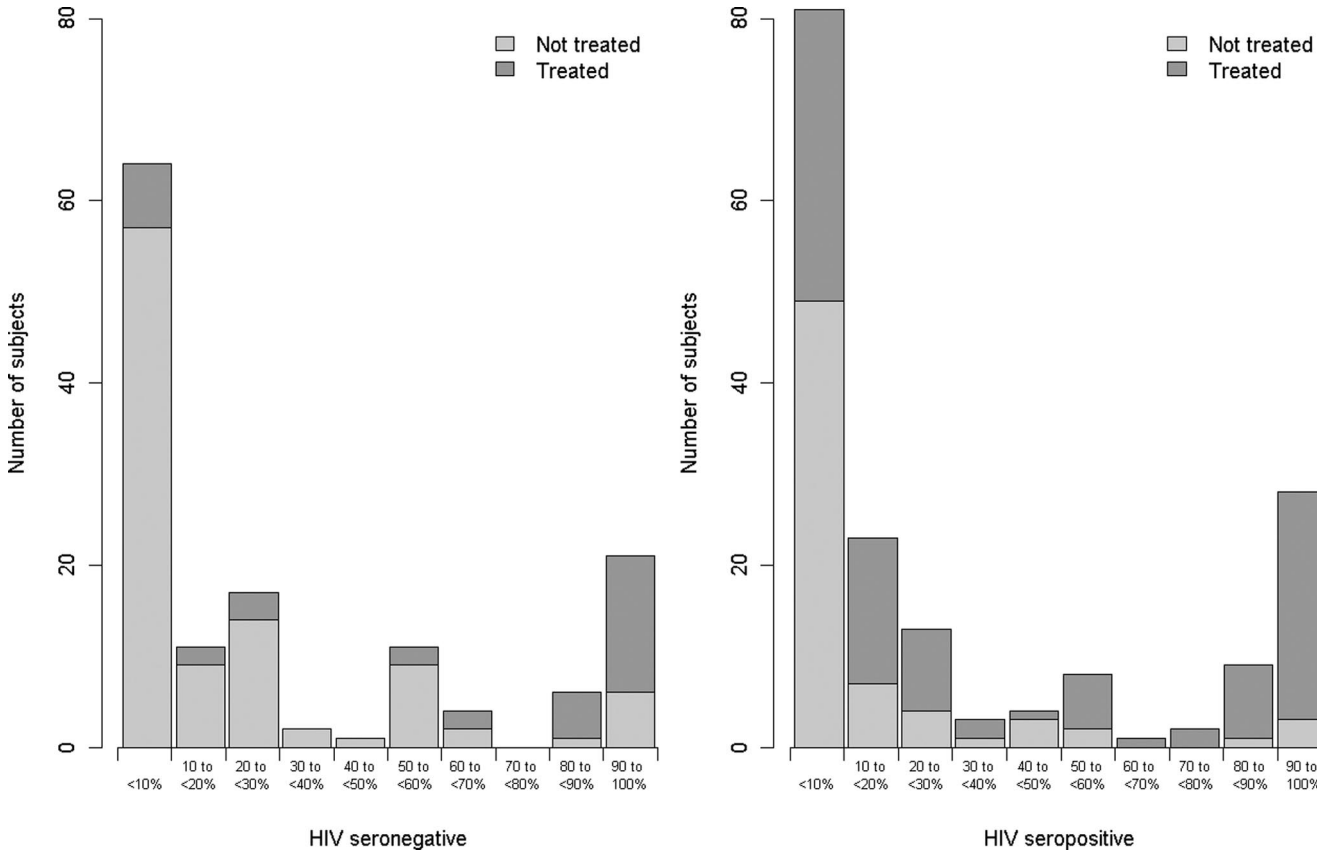

FIGURE 3. TB treatment by HIV-status and post-test probability distribution. On the x-axis posttest probability classes are shown. The y-axis gives the number or patients in each class. The graph shows that HIV+ patients are more easily treated then HIV− patients. For example, at a probability of TB less than 10%, 11% of HIV-patients are treated compared with 40% of HIV+ patients. Disease probability estimated with the Bayesian latent class model summarized in Table 3.

Clinical Treatment Rule

Assuming a threshold of 12%, an easy-to-use guideline based on analysis of Table 3 suggests treating any child with one of the 3 study inclusion criteria plus positive bacteriology or TST >10 or notion of contact with a TB patient. This guideline would result in a disease probability >12% for all but 4 selected patients, and ≤12% for all but 5 not selected. Sensitivity of this guideline would be 96% and specificity 97%, taking as diagnostic standard the threshold.

Applying this rule to HIV-positive patients would cause no false positives or negatives. Applying to HIV-negative patients would result in a disease probability >12% for all but 19 selected, and ≤12% for all but 2 not selected, giving a sensitivity of 95% and a specificity of 79%, taking the threshold as the reference.

DISCUSSION

This study of a cohort of children suspected of TB in a national reference pediatric ward in a country with high HIV prevalence shows that 32% have TB disease, that bacteriologic confirmation is rare, that contact with a TB patient, bacteriology and TST are important predictors, and that HIV infected children are more readily treated than noninfected.

Given the paucity of culture positive cases, we opted for LCA which has been criticized for the liberal choice of findings and the subjective interpretation of different models. More fundamental is the possibility to obtain completely different results for the same model.[36] To avoid gambling with models, we started with 3 well-known predictors, and investigated the accuracy of the others by adding them one by one to the basic model. Models with more or less markers than those with an important association with the latent variable or with correction for conditional dependence resulted in similar values for prevalence, sensitivity, and specificity in this study.

We estimated TB prevalence at 32%, which is plausible given the inclusion criteria and the setting. Elenga et al found a prevalence of 24% in HIV infected children in Côte d'Ivoire.[37] Bacteriology alone would have diagnosed only 9%.

More patients had 2 positive smears than positive cultures. This might be explained by the small absolute numbers, with possibly overlapping confidence intervals, and by decontamination, which might lower considerably the yield of cultures.[38,39] Classic symptoms are known to have low diagnostic accuracy for TB, especially in regions with high HIV prevalence.[4,40,41] Other authors identified almost the same set of predictors as we did.[25]

In contrast to other studies, malnutrition, fever, and HIV were not shown predictive for TB, probably because the first 2 were part of the inclusion criteria for the study. We might hypothesize that between the non tuberculous children in this cohort at a referral hospital, a substantial part are there because of HIV infection and immune depression. HIV infection causes several symptoms and signs often found in TB: failure to thrive, fever, night sweats, weakness, peripheral, hilar, and abdominal lymph

nodes. Disease manifestations of TB are said to be less pronounced in HIV infected: although in our cohort, no difference is found in the discriminative power of relevant predictors.

Some bacteriologically+ patients were assigned low to moderate disease probability, whereas bacteriology is commonly assumed to be the reference standard. False positives do exist, and facing the absence of other discriminative findings, false positivity becomes more probable.

We applied a threshold designed for treatment of pulmonary TB in adults. We hypothesize that it should not be very different from that in children: mortality might be higher in children, but risk of spread of disease is much lower. Small differences however, could have important consequences, as shown by the exercise of lowering the threshold a few points. In the middle field of the probability distribution lowering would not cause substantial effects, since this field is almost empty,[29] but at the lower extremity many more patients would be treated (Fig. 1). This would avoid not treating some really diseased, but for the price of treating many more nondiseased.

The clinicians treated more patients than the prevalence actually predicted by LCA (45% vs. 32%). This is explainable by the threshold concept: in order not to miss some false negatives, a number of false positives should be tolerated. The fact that clinicians treated about the same number of patients as the LCA model combined with the Basinga threshold suggests is reassuring, but there is quite an important discordance in decisions for individual patients. Further research should address the question why clinicians treat or not.

Pediatricians have a tendency of treating more readily HIV infected children (Fig. 3). Discussion of these results with the treating physicians revealed 3 reasons: avoiding an immune reconstitution syndrome in the future; treating at least one of both conditions in putative coinfection; and taking into account that HIV is a known risk factor for TB disease, increasing the post-test probability. This is a nice example how a predictor could influence both the post-test probability and the threshold. HIV was not found to be a predictor in this model, but HIV positivity lowers considerably the threshold. To what extent might be a topic for future research.

Applicability of the results of this study is certainly restricted to a comparable setting, taking into account that reference hospitals often serve also as a district hospital. This setting specificity is one reason why we did not compare our guideline with other published scores. A second reason is the variety of findings taken into account in the different scoring systems, and the different target conditions (pulmonary versus all presentations of TB).[6] But the most important reason is the diagnostic standard, the reference test used: this is different in the different published studies, and up until now nobody used LCA as surrogate for disease definition.

CONCLUSIONS

Latent class analysis confirms earlier identified predictors for TB and allowed us, applying also threshold theory, to develop an easy to use clinical rule, applicable in reference hospitals of countries with high HIV endemicity.

The world is in absolute and urgent need of a reliable test for TB, especially in children. In the mean time diagnostic guidelines should be improved, not only to give a more scientific base to TB treatment, but also to convince pediatricians that their intuitive "overtreatment" is justified, given the high mortality and morbidity of the disease, and the low cost and toxicity of the treatment.

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