CORRESPONDENCE

A Prospective Validation of a Clinical Algorithm to Detect Tuberculosis in Child Contacts

To the Editor:

Over 60% of pediatric tuberculosis cases are undetected by healthcare services in low-income settings (1). Untreated children with tuberculosis have fatality rates of >20%, reaching above 40% in children <5 years old (2). Specific, effective, and validated interventions to increase case detection in children are urgently needed.

Household contact tracing has been widely recommended to increase detection of childhood tuberculosis cases. Although it can provide high yields (3, 4), child contact tracing has rarely been implemented in high-burden settings (5). Methods are urgently needed to incentivize contact tracing for national tuberculosis programs in low-income settings. A clinical risk score was recently proposed in Taiwan (a high-income, low-prevalence setting) to increase the effectiveness of child contact tracing (6). This algorithm uses a combination of contact, index, and environmental characteristics to allocate child contacts into high- and low-risk groups for secondary disease. External validation in high-burden settings has not been performed. To investigate whether this score (6) is useful for detecting tuberculosis in exposed children from Sub-Saharan Africa, we used data from a large Ugandan child contact cohort.

This was a prospective cohort study of household contacts of tuberculosis cases; the study has been described previously (7–9). Briefly, we identified adult patients in Kampala, Uganda, with a new diagnosis of tuberculosis. Index cases were microbiologically confirmed through a positive culture test and evaluated through physical examination and medical history. Households were visited by field workers within 2 weeks of diagnosis, and contacts were defined as spending at least 7 consecutive days in the index's household 3 months before diagnosis.

Coprevalent tuberculosis was defined as tuberculosis within 3 months of baseline. Contacts were evaluated for tuberculosis through a medical examination, posteroanterior chest radiographs, specimen microscopy, and mycobacterial culture. Contacts without coprevalent tuberculosis were followed for incident tuberculosis for 2 years.

Contacts were grouped by age (<13 yr old) and disease status to categorize the data according to the scoring algorithm (6). Contacts were given a point score based on the algorithm (6): contact tuberculin skin test (TST) induration (2 points if 10–14 mm, 3 points if 15–20 mm, and 4 points if ≥20 mm), index smear result (1 point if smear positive), index sex (1 point if female), and burden of residence area (2 points if index lived in a high-incidence area). Because all index cases in the Ugandan cohort lived in a high-incidence area, all contacts were automatically given 2 points.

The score's discrimination and classification accuracy was compared with results from the original derivation and internal

validation populations. Cochran-Armitage tests were used to test for trends between disease outcomes and multiple point categories in the risk score.

The institutional review boards at the Uganda National Council for Science and Technology, the Uganda National AIDS Research Subcommittee, University Hospitals Cleveland Medical Center, and Makerere University approved this study. Informed consent was obtained for index cases, and parents of contacts provided verbal assent for their children. Nine months of isoniazid prophylaxis was offered to child contacts if they were <5 years old, HIV-infected, or TST-positive.

Overall, 1,941 household contacts were enrolled; 1,032 of these contacts were <13 years old and included in this analysis (Figure 1). The median contact age was 6 years. The majority had a positive TST ($n = 586$), and 63 had tuberculosis (55 subjects [5.3%] had tuberculosis at baseline and 8 [0.8%] developed tuberculosis over 2 yr). Tuberculosis was microbiologically confirmed in 65.1% of these cases. Isoniazid preventive therapy was started in 274 children who were free of tuberculosis at baseline.

In a univariate analysis, no variable included in the risk score was a statistically significant predictor of coprevalent, incident, or any tuberculosis. The proposed algorithm had low predictive power (C-statistic, 0.54). Coprevalent tuberculosis prevalence varied from 4.8% for contacts with a score of 4 to 12.9% with a score of 8, but there was no association between the score and disease prevalence ($P_{trend} = 0.528$; Table 1). Similarly, for contacts with any disease, the observed proportion varied from 3.8% for contacts with a score of 7 to 12.9% with a score of 8, and there was no point score trend ($P_{trend} = 0.212$). There were eight incident cases, five of which occurred in contacts with a score of 7. Compared with children with a 0–4 score, children with a 5–8 score did not have statistically more coprevalent ($P = 0.405$), incident ($P = 0.237$), or any tuberculosis event ($P = 0.227$).

Making a diagnosis of tuberculosis in children remains a clinical and programmatic challenge. To guide clinicians in identifying high-risk children, a new risk score was recently derived and implemented in Taiwan (6). Although it was highly predictive among Taiwanese child contacts (C-statistic, 0.87), this algorithm had low predictive power in our large, prospective child contact cohort from Uganda.

There are several possible reasons why this algorithm performed poorly in our cohort. First, low- and high-incidence areas may have different risk factors for tuberculosis. For example, the prevalence of HIV in Taiwan is significantly different from that in Uganda, and HIV plays a critical role in influencing the tuberculosis epidemic in Africa (7, 9, 10). This score may be most useful in high-income, low-tuberculosis-burden settings where HIV prevalence is low. External, prospective validations in such settings are necessary to address this issue. Second, case ascertainment bias is a concern because the original derivation-cohort study used retrospective programmatic data.

This study has certain limitations that should be mentioned. First, without molecular genotyping, we are unable to state with certainty that contacts acquired disease owing to household exposure. However, our aim was to evaluate the disease yield in our setting using the specified algorithm, not to measure household transmission. Second, because one variable in the derived score was "high-incidence area," to evaluate this
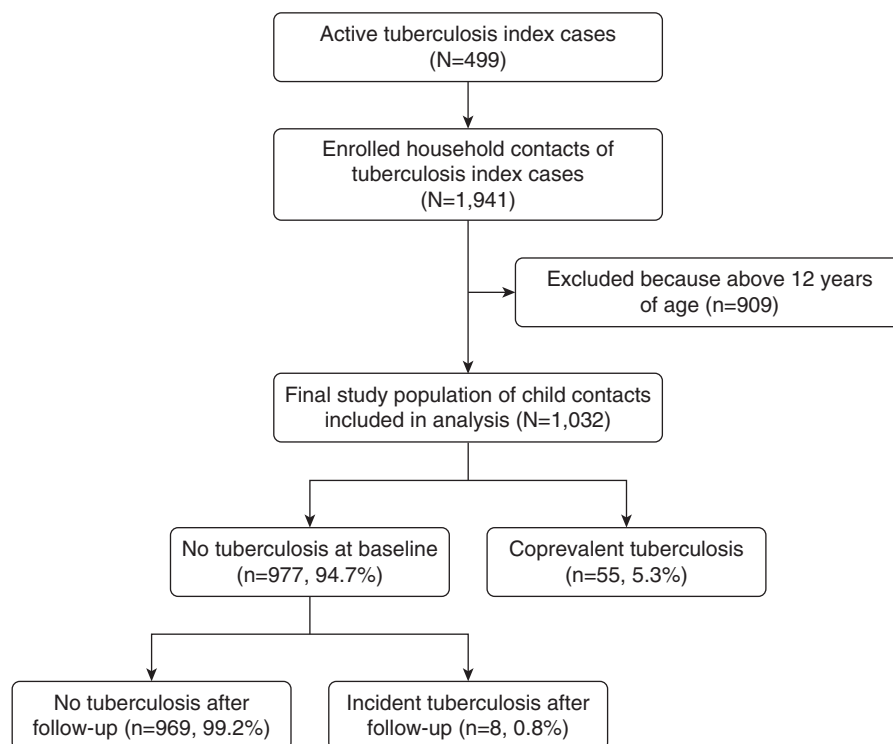
Figure 1. Study profile of the Kawempe Community Health Study and participants included in the primary analysis.

score in Sub-Saharan Africa, we had to assign 2 points to all contacts.

In conclusion, a previously derived risk score demonstrated poor predictive value for detecting coprevalent and incident tuberculosis in a large, prospective Ugandan child contact cohort. This score should be evaluated in low-burden settings to determine its effectiveness in settings similar to but outside of Taiwan. Additional clinical algorithms that can more efficiently

Table 1. Scores Implemented in a Ugandan Cohort of Household Child Contacts of Tuberculosis Cases (N = 1,032)

Proposed Score	No. of Contacts with Each Score	Percent Risk of All Disease Among Contacts (n Events/n Total)*	Percent Risk of Coprevalent Disease Cases (n Events/n Total)*	Percent Risk of Incident Disease Cases (n Events/n Total)*
8	31	12.9 (4/31)	12.9 (4/31)	0 (0/27)
7	159	6.9 (11/159)	3.8 (6/159)	3.3 (5/153)
6	240	5.8 (14/240)	5.8 (14/240)	0 (0/226)
5	133	7.5 (10/133)	6.8 (9/133)	0.8 (1/124)
4	187	4.8 (9/187)	4.3 (8/187)	0.6 (1/179)
3	224	5.4 (12/224)	4.9 (11/224)	0.5 (1/213)
2	58	5.2 (3/58)	5.2 (3/58)	0 (0/55)
1	0	—	—	—
0	0	—	—	—
P for trend[†]		0.212	0.528	0.071
High (5–8)[‡]	563	6.9 (39/563)	5.9 (33/563)	1.1 (6/530)
Low (0–4)	469	5.1 (24/469)	4.7 (22/469)	0.5 (2/447)
P for trend[†]		0.227	0.405	0.237
High (5–7)[‡]	532	6.6 (35/532)	5.5 (29/532)	1.2 (6/503)
Low (0–4)	469	5.1 (24/469)	4.7 (22/469)	0.5 (2/447)
P for trend[†]		0.327	0.585	0.21

*Coprevalent tuberculosis disease was defined as the identification of tuberculosis disease at or within 3 months of the baseline household visit. Incident tuberculosis disease was defined as diagnosis of tuberculosis disease at subsequent household follow-up visits, conducted at 6-month intervals for 2 years. Individuals with coprevalent disease were excluded from analyses of incident disease. "All disease" indicates the combination of both coprevalent and incidence tuberculosis disease.
[†]The Cochran-Armitage test was used to evaluate trends within groups.
[‡]Score cutoffs were chosen as shown in Reference 6 to provide proper comparison between studies.

detect tuberculosis in child contacts are urgently needed in Sub-Saharan Africa to improve case detection. ∎

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Blood Eosinophilia Neither Reflects Tissue Eosinophils nor Worsens Clinical Outcomes in Chronic Obstructive Pulmonary Disease

To the Editor:

The role of the blood eosinophil count as a biomarker predictor of the frequency of exacerbations and response to corticosteroid treatment in chronic obstructive pulmonary disease (COPD) has become practically a paradigm in the approach to this disease. It has been assumed all along that blood eosinophilia is a faithful representation of tissue eosinophilia. However, this assumption has not been proven conclusively (1).

We assessed prospectively the clinical outcome predictive power of blood eosinophils and the possible relation between blood and tissue eosinophils in a group of smokers older than 40 years, 294 with COPD and 178 without, followed for at least 5 years (mean, 9.6 yr) at the Hospital Universitario Miguel Servet (Zaragoza, Spain). Subjects with a history of asthma were excluded. The subjects underwent a clinical examination, spirometry, and three to five yearly blood eosinophil measurements. The annual frequency of severe (hospitalized) and moderate (medically diagnosed and treated) exacerbations was recorded. In 51 smokers with and without COPD who underwent lung resection for solitary pulmonary nodules but had no additional complications, eosinophils/mm^2 of tissue in the central and peripheral airways and lung parenchyma were counted (2), and in 36 cases correlated with blood eosinophils. Mortality was recorded throughout the study.

The median number and interquartile ranges of blood eosinophils measured upon recruitment were similar between smokers with and without COPD (156 [101–250] cells/μl vs. 160 [107–256] cells/μl), and no different from the values reported in a normal population (3).

Using the three to five available eosinophil counts, we classified the patients as having persistently high (≥150/μl), persistently low (<150/μl), or variable (oscillating above and below 150/μl)