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

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

Household contact tracing has been widely recommended to increase childhood tuberculosis case detection. Despite high yield,[3,4] child contact tracing has rarely been implemented in high-burden settings.[5] Methods are urgently needed to incentivize contact tracing to National Tuberculosis Programs in low-income settings. A clinical risk score was recently proposed in Taiwan, a high-income, low-prevalence setting, to increase 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 to detect 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 newly diagnosed adult tuberculosis patients in Kampala, Uganda. 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 two weeks of diagnosis and contacts were defined as spending at least seven consecutive days in the index's household three months preceding diagnosis.

Coprevalent tuberculosis was defined as tuberculosis within three 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 two years.

Contacts were grouped by age (<13 years old) and disease status to categorize data according to the scoring algorithm.[6] Contacts were given a point score based on the developed algorithm:[6] contact tuberculin skin test (TST) induration (two points if 10–14 millimeters, three points if 15–20 millimeters, and four points if ≥20 millimeters), index smear result (one point if smear positive), index sex (one point if female), and burden of residence area (two points if index lived in high-incidence area). Since all index cases in the Ugandan cohort live in a high-incidence area, all contacts were automatically given two points.

The score's discrimination and classification accuracy was compared to 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.

Institutional review boards at the Uganda National Council for Science and Technology, the Uganda National AIDS Research Subcommittee, Case Western University, and Makerere University approved this study. Informed consent was obtained for index cases; parents of contacts provided verbal assent for children. Nine-month isoniazid prophylaxis was offered to child contacts if <5 years, HIV-infected, or TST-positive.

Overall, 1941 household contacts were enrolled, of which 1032 were <13 years old and included in this analysis (Figure). Median contact age was six years; a majority had a positive TST (N=586). 74 had tuberculosis; 55 (5.3%) at baseline and 8 (0.8%)

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developed tuberculosis over two years. Of these, 65.1% were microbiological confirmed. Isoniazid preventive therapy was started on 274 children free from tuberculosis at baseline.

In 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 (Table; P_{trend}=0.528). 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 with no point score trend (P_{trend}=0.212). There were eight incident cases, five occurring in contacts with a score of 7. Compared to children with 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).

Diagnosis of tuberculosis in children remains a clinical and programmatic challenge. To guide clinicians in identifying high-risk children, a recent risk score was derived and implemented in Taiwan.[6] Although 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 this algorithm performed poorly in our cohort. First, risk factors for tuberculosis in low- and high-incidence areas may be distinct. For example, HIV-prevalence in Taiwan and Uganda are highly distinct and HIV plays a critical factor influencing the regional tuberculosis epidemic.[7,9,10] This score may be most useful in high-income, low tuberculosis burden settings where HIV-prevalence is

low. External, prospective validation in such a setting is still required to address this question. Second, case ascertainment bias is a concern because the original derivation cohort used retrospective programmatic data.

There are limitations to mention. First, without molecular genotyping, we are unable to state with certainty that contacts acquired disease due to the household exposure. However, our aim was to evaluate the disease-yield in our setting using the specified algorithm, not measure household transmission. Second, because one variable in the derived score was “high-incidence area”, evaluating this score in sub-Saharan Africa required that we designate all contacts with two points.

In conclusion, a previously derived risk score demonstrated poor predictive value in detecting coprevalent and incident tuberculosis in a large, prospective Ugandan child contact cohort. This score should be evaluated in low-burden settings to determine effectiveness in settings similar, but outside, of Taiwan. Additional clinical algorithms that more efficiently detect tuberculosis amongst child contacts are urgently needed in sub-Saharan Africa to improve case detection.

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CONFLICTS OF INTEREST. We report no conflicts of interest.

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TABLES AND FIGURES.

Table. Score Implemented in Ugandan Cohort of Household Child Contacts of Tuberculosis cases

Figure. Study profile of the Kawempe Community Health Study and participants included in primary analysis.

Table. Score Implemented in a Ugandan Cohort of Household Child Contacts of Tuberculosis cases (N = 1032)

Proposed Score	No. Contacts with Each Score	Percent Risk of All Disease Among Contacts (N events/N total)†	Percent Risk of Co-prevalent 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

Abbreviations: No., number.

* Score cutoffs were chosen as shown in the derivation to provide proper comparison between studies.

†Co-prevalent tuberculosis disease was defined as the identification of tuberculosis disease at or within three months of the baseline household visit. Incident tuberculosis disease was defined as diagnosis of tuberculosis disease at subsequent household follow-up visits, conducted at six month intervals for two years. Individuals with co-prevalent disease were excluded from analyses of incident disease. All tuberculosis disease" was the accumulation of both coprevalent and incidence tuberculosis disease.

‡ The Cochran–Armitage test was used to evaluate trends within groups

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Figure. Study profile of the Kawempe Community Health Study and participants included in primary analysis.