

THE LANCET

Respiratory Medicine

Supplementary appendix

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Supplement to: Martinez L, Shen Y, Handel A, et al. Effectiveness of WHO's pragmatic screening algorithm for child contacts of tuberculosis cases in resource-constrained settings: a prospective cohort study in Uganda. *Lancet Respir Med* 2017; published online Dec 19. [http://dx.doi.org/10.1016/S2213-2600\(17\)30497-6](http://dx.doi.org/10.1016/S2213-2600(17)30497-6).

SUPPLEMENTARY APPENDIX.

Effectiveness of WHO's Pragmatic Screening Algorithm for
Child Contacts of Tuberculosis Cases in Resource-constrained Settings:
A Prospective Cohort Study from Uganda

Leonardo Martinez, PhD, MPH, Ye Shen, PhD, Andreas Handel, PhD,
Srijita Chakraborty, MS, Catherine M. Stein, PhD,
LaShaunda L. Malone, MSPH, W. Henry Boom, MD, Frederick D. Quinn, MS, PhD,
Moses L. Joloba, MBChB, PhD, Christopher C. Whalen, MD, MS†,
Sarah Zalwango, MBChB, MPH†

† Co-last authors.

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ADDITIONAL METHODOLOGICAL INFORMATION.

Diagnosis of Pediatric Tuberculosis in Contacts.

Identification of tuberculosis amongst child contacts was conducted using a multi-pronged approach. All household contacts were evaluated for active tuberculosis through a medical examination and posteroanterior chest radiographs examined independently by two experienced pulmonary physicians. Specimen microscopy and mycobacterial culture were obtained if the child was under six years of age, symptomatic, had suggestive chest radiograph findings, or HIV-seropositive. If a sputum sample could not be collected, alternative testing sites (including gastric aspiration, nasopharyngeal aspiration, pleural fluid, cerebrospinal fluid, and lymph node aspiration) was administered. Culture was performed (LJ slants/BACTEC) in triplicate at the baseline evaluation and sick visits, as well as at initiation of therapy and then months 1, 2, and 5 and the end of treatment. Clinical diagnosis was based on two or more of the following in the context of a positive response to tuberculosis therapy: (1) tuberculosis-specific symptoms; (2) TST induration ≥ 10 millimeters; (3) chest radiography consistent with active tuberculosis; or (4) failure to respond to empiric antibiotics in two weeks.

Definite tuberculosis was defined as culture-confirmed disease (five or more *M. tuberculosis* colonies). Probable tuberculosis was defined as a clinical illness consistent with tuberculosis based on ≥ 2 of the following: results of chest radiography consistent with pulmonary tuberculosis, smear of tissue or secretions positive for acid-fast bacilli, or a response to antituberculosis therapy.

Coprevalent and incident tuberculosis were defined as definite or probable tuberculosis only; coprevalent disease occurred at baseline or within three months of

the initial evaluation. Contacts classified without tuberculosis at baseline were followed and assessed for active tuberculosis at six-month intervals for two years.

All available information on contacts suspected to have tuberculosis was reviewed by a study outcome committee consisting of two or more clinicians. Suspects were subsequently classified as definite, probable, possible, and unlikely tuberculosis.

ADDITIONAL RESULTS.

Method of Diagnosis in Asymptomatic Exposed Children.

Of 39 asymptomatic contacts diagnosed with coprevalent tuberculosis, 28 (72%) children were microbiologically diagnosed using culture. Two contacts (15.1%) were detected by chest radiography and positive smear results but had negative culture results. Three contacts (7.7%) were diagnosed with chest radiography alone while six contacts were diagnosed with smear alone.

Of 9 asymptomatic contacts diagnosed with incident tuberculosis, 5 (56%) were diagnosed using culture. The remaining four were diagnosed using smear and chest radiography.

Supplementary Table 1. Demographic differences between pediatric tuberculosis found and not found following World Health Organization's pragmatic guidelines.

Variable	World Health Organization's Pragmatic Guidelines		P-value
	Pediatric coprevalent cases found [n(%)]	Pediatric coprevalent cases missed [n(%)]	
Household contact characteristics			
N	85 (69.1)	41 (32.5)	0.007
Age group, years			
0 – 4	70 (82.4)	23 (56.1)	
5 – 9	11 (12.9)	14 (34.2)	
10 – 15	4 (4.7)	4 (9.8)	
Male sex	48 (56.5)	23 (56.1)	
BCG vaccinated††	57 (67.9)	24 (75.0)	
Relation to index case			
Child	70 (84.3)	32 (78.1)	
Sibling	1 (1.2)	1 (2.4)	
Other	12 (14.5)	8 (19.5)	
Past active tuberculosis	2 (2.4)	0 (0)	
Closeness to index case			
Share bed	14 (16.5)	5 (12.2)	
Share room, not bed	44 (51.8)	20 (48.8)	
Different room	26 (30.6)	16 (39.0)	
Missing	1 (1.2)	0 (0)	
Index case characteristics‡			
Age group, years			0.176
18 – 29	49 (57.7)	14 (35.2)	
30 – 39	32 (37.7)	23 (56.1)	
40 – 49	3 (3.5)	3 (7.3)	
≥50	1 (1.2)	1 (2.4)	
Male sex	41 (48.2)	20 (48.8)	0.954
Cigarette smoker	19 (22.4)	8 (19.5)	0.716
Cavitory disease§	63 (74.1)	29 (70.7)	0.688

HIV-seropositive	33 (38.8)	9 (22.0)	0.060
Household characteristics			
Housing type			0.311
Multi-family household	59 (69.4)	32 (78.1)	
Single family household	26 (30.6)	9 (22.0)	
Charcoal or fire smoke exposure			0.48
Inside household	2 (4.9)	5 (12.2)	
Outside household	74 (87.1)	34 (82.9)	
None	1 (1.2)	2 (4.9)	
Missing	1 (1.2)	0 (0)	
Household size (persons/home)			0.690
1 – 5	49 (57.7)	24 (58.5)	
6 – 10	31 (36.5)	16 (39.0)	
>10	5 (5.9)	1 (2.4)	

Abbreviations. IQR, interquartile range. BCG, Bacillus Calmette-Guérin.

Supplementary Table 2. Diagnostic markers for World Health Organization guidelines for the management of child contacts of tuberculosis cases, overall and stratified by important subgroupings

Outcome and Stratification	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Positive Likelihood Ratio (95% CI)
Coprevalent tuberculosis					
Main manuscript analysis† HIV-serostatus‡	67.5 (58.5, 75.5)	82.5 (80.5, 84.3)	23.4 (20.6, 26.4)	97.0 (96.1, 97.6)	3.9 (3.3, 4.5)
HIV-seropositive contacts only	84.6 (54.6, 98.1)	70.7 (54.5, 83.9)	47.8 (35.1, 60.9)	93.6 (80.0, 98.1)	2.9 (1.7, 4.9)
HIV-seronegative contacts only	65.4 (55.6, 74.4)	80.8 (78.5, 82.9)	22.5 (19.6, 25.8)	96.5 (95.5, 97.3)	3.4 (2.9, 4.1)
Age, years					
0-4 years old	75.3 (65.2, 83.6)	70.9 (66.7, 74.9)	33.2 (29.3, 37.3)	93.7 (91.3, 95.5)	2.6 (2.2, 3.1)
5-15 years old	45.5 (28.1, 63.7)	87.5 (85.4, 89.4)	9.8 (6.8, 14.0)	98.2 (97.5, 98.7)	3.7 (2.4, 5.5)
Culture-confirmed cases used only	61.8 (50.0, 72.8)	80.7 (78.7, 82.6)	12.9 (10.8, 15.4)	97.9 (97.2, 98.4)	3.2 (2.6, 3.9)

Supplementary Table 3. Comparative effectiveness of World Health Organization guidelines for management of contact tracing of household exposed children versus a modified algorithm suggested by Marais and Pai (2007)‡ and a more restrictive algorithm§.

Variable	Coprovalent tuberculosis†			
	N	Contacts with tuberculosis (% prevalence)	Number needed to screen*	Percent of all cases detected
All Household Contacts	1718	126 (7.3)	13.7	100
Children included in algorithm				
Restrictive symptom algorithm, no HIV	101	33 (32.7)	3.1	26.2
Restrictive symptom algorithm, HIV	108	34 (31.5)	3.2	27.0
Modified algorithm, Marais and colleagues				
Symptomatics	364	85 (23.4)	4.3	67.5
High-risk asymptomatics	223	14 (6.3)	15.9	11.1
Low-risk asymptomatics	1131	27 (2.4)	41.7	21.4
Main manuscript analysis	364	85 (23.4)	4.3	67.5
All Household Contacts <5 years old	578	93 (16.1)	6.2	100
Children included in algorithm				
Restrictive symptom algorithm, no HIV	63	28 (44.4)	2.3	30.1
Restrictive symptom algorithm, HIV	67	28 (41.8)	2.4	30.1
Modified algorithm, Marais and colleagues				
Symptomatics	211	70 (33.2)	3.0	75.3
High-risk asymptomatics	202	13 (6.4)	15.6	14.0
Low-risk asymptomatics	165	10 (6.1)	16.4	10.8
Main manuscript analysis	211	70 (33.2)	3.0	75.3
All Household Contacts ≥5 years old	1140	33 (2.9)	43.5	100
Children included in algorithm				
Restrictive symptom algorithm, no HIV	38	5 (13.2)	7.6	15.2

Restrictive symptom algorithm, HIV	41	6 (14.6)	6.8	18.2
Modified algorithm, Marais and colleagues				
Symptomatics	153	15 (9.8)	10.2	45.5
High-risk asymptomatics	22	1 (4.6)	21.7	3.0
Low-risk asymptomatics	966	17 (1.8)	55.6	51.5
Main manuscript analysis	153	15 (9.8)	10.2	45.5

Variable	Incident tuberculosis†			
	N	Contacts with tuberculosis (% incidence)	Number needed to screen*	Percent of all cases detected
All Household Contacts	1592	24 (1.5)	66.7	100
Children included in algorithm				
Restrictive symptom algorithm, no HIV	68	6 (8.8)	11.4	25.0
Restrictive symptom algorithm, HIV	74	7 (9.5)	10.6	29.2
Modified algorithm, Marais and colleagues				
Symptomatics	279	14 (5.0)	20.0	58.3
High-risk asymptomatics	210	3 (1.4)	71.4	12.5
Low-risk asymptomatics	1104	7 (0.6)	166.7	29.2
Main manuscript analysis	279	14 (5.0)	20.0	58.3
All Household Contacts <5 years old	477	8 (1.7)	58.8	100
Children included in algorithm				
Restrictive symptom algorithm, no HIV	35	3 (8.6)	11.6	37.5
Restrictive symptom algorithm, HIV	39	4 (10.3)	9.7	50.0
Modified algorithm, Marais and colleagues				
Symptomatics	141	6 (4.3)	23.3	75.0
High-risk asymptomatics	189	2 (1.1)	90.9	25.0
Low-risk asymptomatics	155	0 (0)	NA	0.0
Main manuscript analysis	141	6 (4.3)	23.3	75.0

All Household Contacts ≥ 5 years old	1107	16 (1.5)	66.7	100
Children included in algorithm				
Restrictive symptom algorithm, no HIV	33	3 (9.1)	11.0	18.8
Restrictive symptom algorithm, HIV	35	3 (8.6)	11.7	18.8
Modified algorithm, Marais and colleagues				
Symptomatic	138	8 (5.8)	17.2	50.0
High-risk asymptomatics	21	1 (4.8)	20.8	6.3
Low-risk asymptomatics	949	7 (0.7)	142.9	43.8
Main manuscript analysis	138	8 (5.8)	17.2	50.0

§ Children were included to be screened under the restrictive algorithm if they had persistent cough for at least 3 weeks duration with at least one other tuberculosis-related symptom (night sweats, failure to gain weight, fever, hemoptysis, or poor appetite). Two restrictive symptom-based algorithms are described: 1) HIV-seropositivity as an additional characteristic included (therefore HIV-seropositive children with cough would be included) in the algorithm and 2) HIV-seropositivity not included in the algorithm. Children were included in the main manuscript analysis if they were HIV-seropositive or had any tuberculosis-related symptom (hemoptysis, fever, chronic cough, weight loss, night sweats, poor appetite). Although incident tuberculosis is evaluated here the main algorithm does not recommend following-up children with symptoms if without disease at baseline. We present these results however note that this is not in the World Health Organization guideline.

† Coprevalent tuberculosis was defined as the identification of tuberculosis at or within 3 months of the baseline household visit. Incident tuberculosis was defined as diagnosis of tuberculosis 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

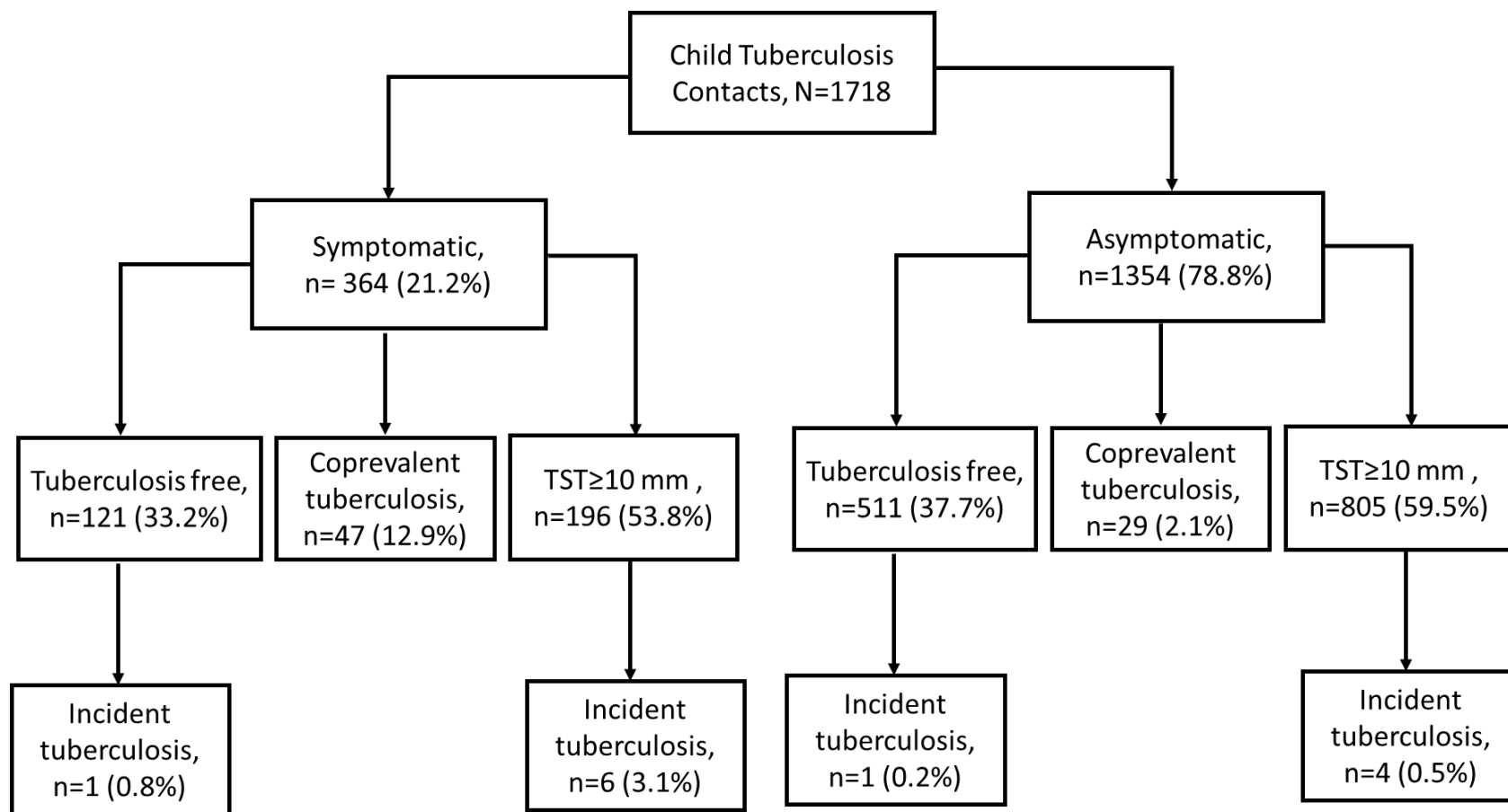
‡ This algorithm recommends screening of all symptomatic contacts regardless of age or immunocompetency; asymptomatic contacts should be grouped into “high-risk” (<3 years of age or immunocompromised) and “low-risk” (≥ 3 years of age and immunocompetent) children. This algorithm was first proposed in the 2007 manuscript: Marais, B.J. and Pai, M., 2007. New approaches and emerging technologies in the diagnosis of childhood tuberculosis. *Paediatric respiratory reviews*, 8(2), pp.124-133.

* This is the number of child contacts in the specified row that is needed to screen in order to detect one active tuberculosis case. This is calculated by dividing 100 by the row-specific disease prevalence. For example, 7.3% of all child contacts had coprevalent tuberculosis. Therefore, 14 (13.7 is specified in this row) contacts need to be screened to detect one coprevalent tuberculosis case among the total child contact cohort (N=1718 child contacts).

Supplementary Table 4. Definitions of tuberculosis-related symptoms used.

Tuberculosis-related symptom	Definition used
Chronic cough	a continuous, nonremitting cough present for >3 weeks.
Weight loss or failure to thrive	reporting of weight loss or failure to thrive with confirmatory evidence from the child's growth chart
Fever	body temperature of >38°C for 14 days, after exclusion of common causes (malaria or pneumonia)
Loss of appetite	Self-reported from parents and guardians
Night sweats	Self-reported from parents and guardians
Hemoptysis	expectoration of blood from the lung airways or parenchyma

Supplementary Figure 1. Flowchart of microbiologically-confirmed tuberculosis-related outcomes§ stratified by World Health Organization child contact screening recommendations

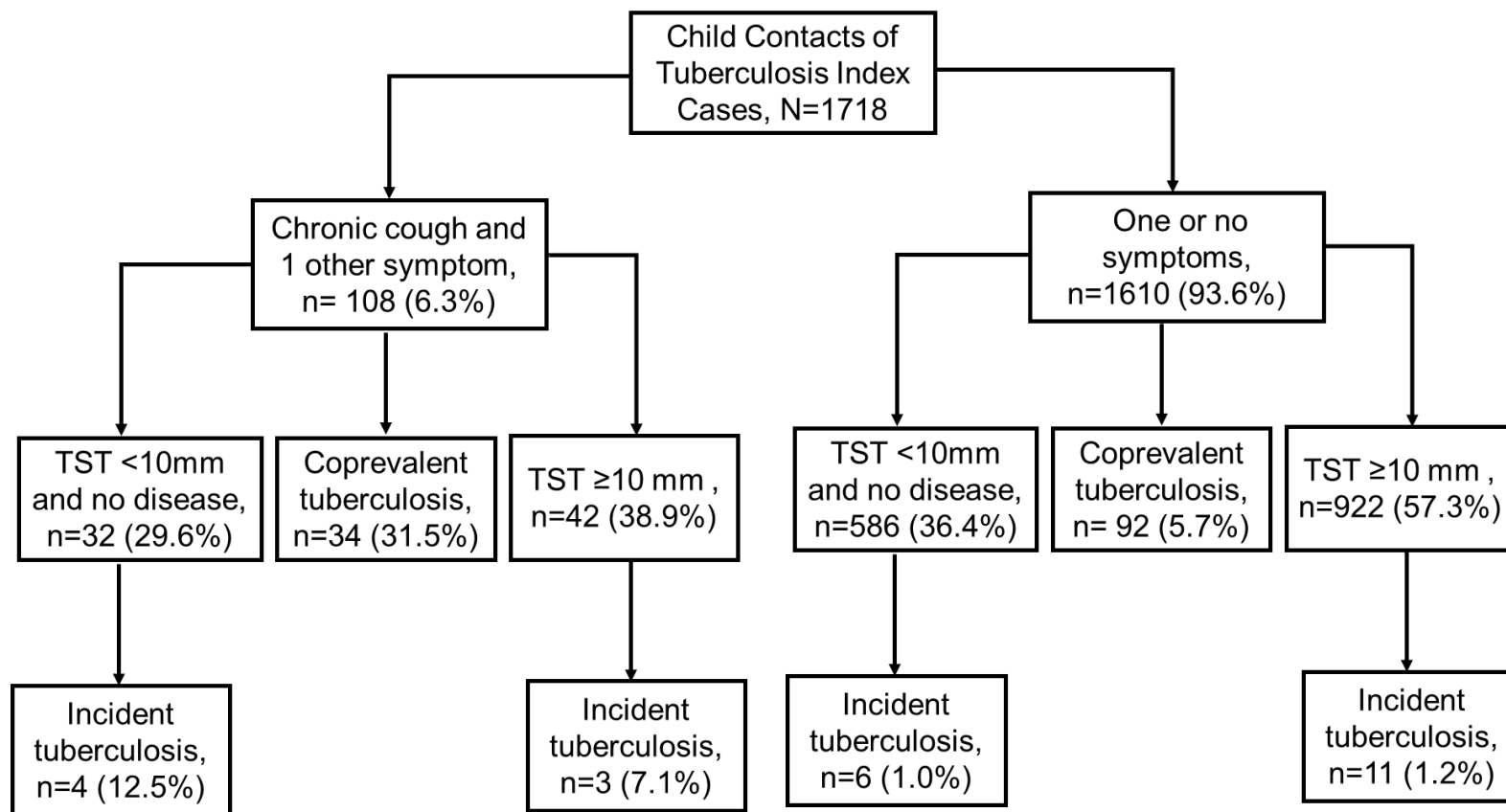


§ In this analysis, only culture-confirmed child cases are included. Coprevalent tuberculosis was defined as the identification of tuberculosis at or within 3 months of the baseline household visit. Incident tuberculosis was defined as diagnosis of tuberculosis at subsequent household follow-up visits, conducted at 6-month intervals for 2 years. Individuals with coprevalent disease were excluded from analyses of incident disease. In this analysis, latent tuberculosis was

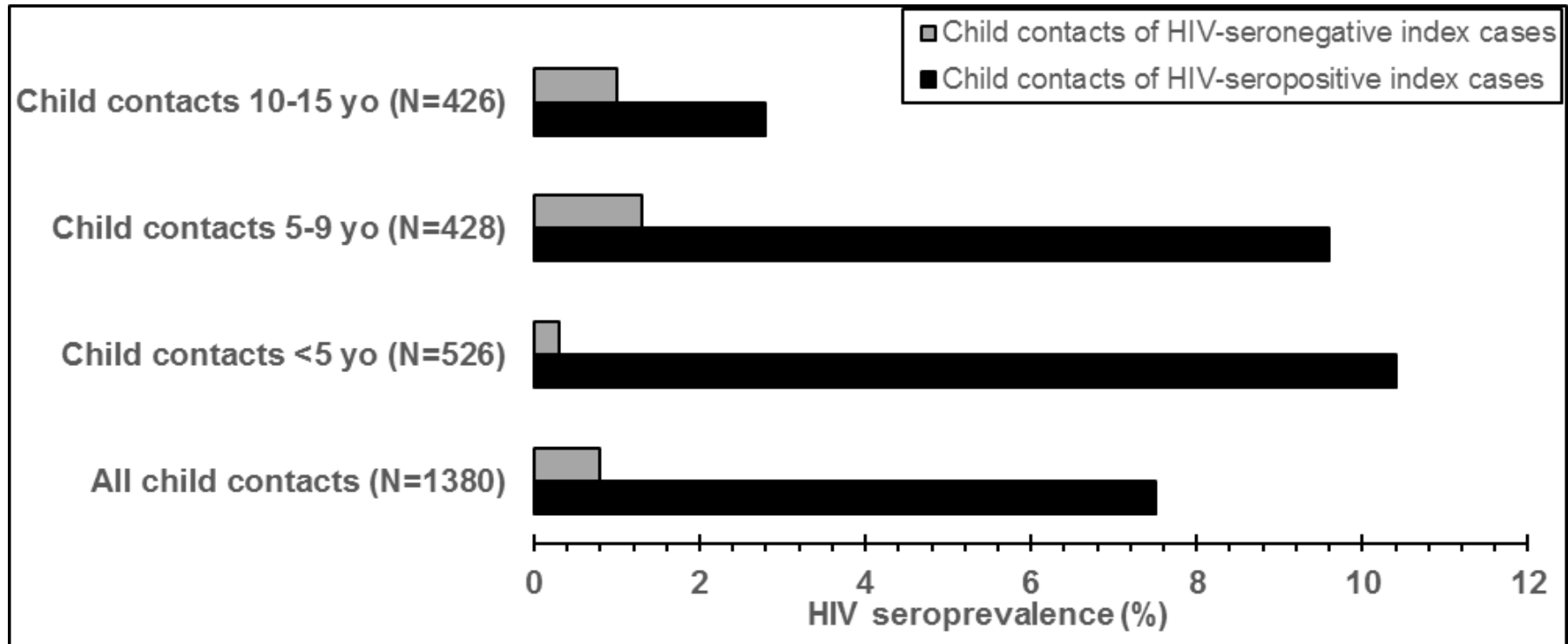
defined as a tuberculin skin test induration response of ≥ 10 millimeters. Percentages may not total 100% because within-characteristic percentages were rounded to the nearest integer.

†The difference between coprevalent tuberculosis among symptomatic and asymptomatic contacts was statistically different (12.9% versus 2.1%, $P < 0.0001$). The difference between incident tuberculosis among symptomatic and asymptomatic contacts was also statistically different (1.8% versus 0.4%, $P_{exact} = 0.004$).

Supplementary Figure 2. Flowchart of tuberculosis outcomes stratified by a restrictive screening algorithm.



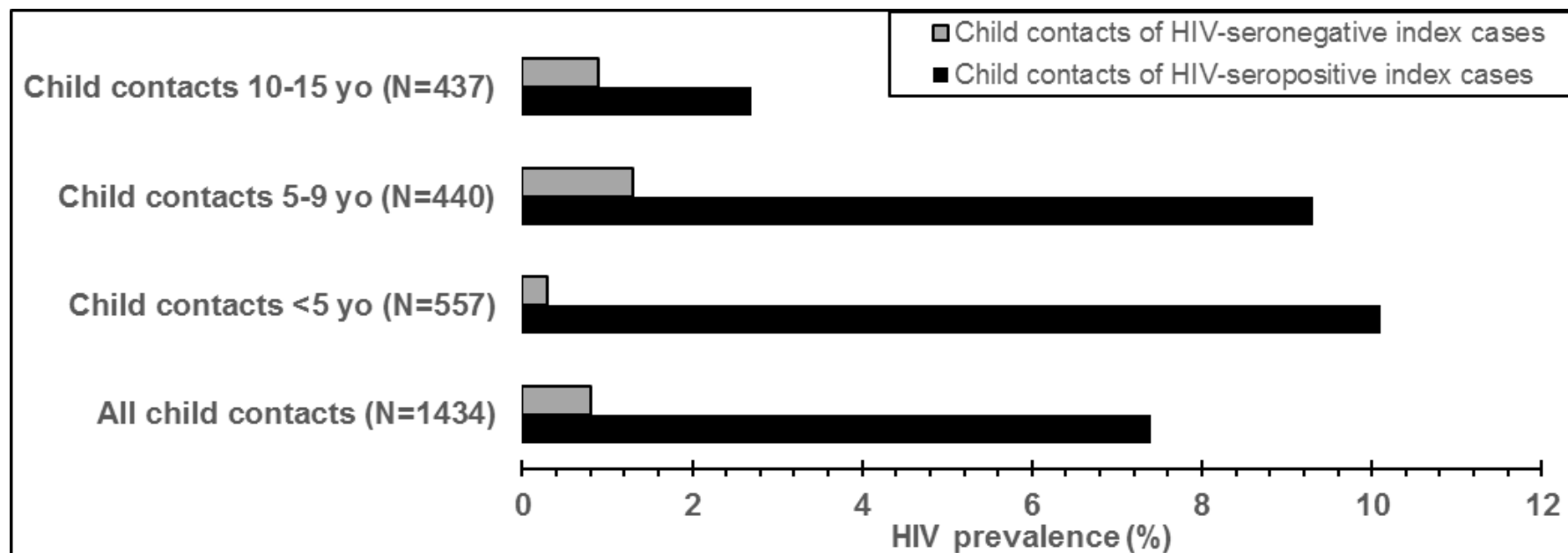
Supplementary Figure 3. HIV seropositivity in 1380 contacts§ of HIV-seropositive and HIV-seronegative tuberculosis index cases



Abbreviations. yo, years old. HIV, Human immunodeficiency virus.

§ This analysis included 1380 child contacts that took an HIV test and had a tuberculosis index case with a HIV test result. Using both HIV-tests and self-reported HIV (through either the guardian and/or the child) displayed similar results which are shown in Figure 1 in the supplementary appendix.

Supplementary Figure 4. HIV prevalence in household child contacts of HIV-seropositive and HIV-seronegative tuberculosis index cases§



Abbreviations. yo, years old. HIV, Human immunodeficiency virus.

§ This includes 1434 child contacts that either took an HIV test or self-reported (through either the guardian and/or the child) their HIV status and additionally had a tuberculosis index case with a HIV test result. In the entire sample, HIV-seropositivity was found almost exclusively in contacts of HIV-seropositive tuberculosis cases (48/651, 7.4% versus 6/783, 0.8%). Contacts of HIV-seropositive index cases represented 89% of all HIV-seropositive contacts. This relationship was magnified in contacts <5 years of age (10.1% versus 0.3%, $P<0.0001$) and contacts between 5–9 years of age (9.3% versus 1.3%, $P<0.0001$). Contacts ≥ 10 years of age with an HIV-seropositive index case were also at increased likelihood of HIV-infection but this association did not reach statistical significance (2.7% versus 0.8%, $P=0.159$).