ORIGINAL ARTICLE

Community-wide Screening for Tuberculosis in a High-Prevalence Setting

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ABSTRACT

BACKGROUND

The World Health Organization has set ambitious targets for the global elimination of tuberculosis. However, these targets will not be achieved at the current rate of progress.

METHODS

We performed a cluster-randomized, controlled trial in Ca Mau Province, Vietnam, to evaluate the effectiveness of active community-wide screening, as compared with standard passive case detection alone, for reducing the prevalence of tuberculosis. Persons 15 years of age or older who resided in 60 intervention clusters (subcommunes) were screened for pulmonary tuberculosis, regardless of symptoms, annually for 3 years, beginning in 2014, by means of rapid nucleic acid amplification testing of spontaneously expectorated sputum samples. Active screening was not performed in the 60 control clusters in the first 3 years. The primary outcome, measured in the fourth year, was the prevalence of microbiologically confirmed pulmonary tuberculosis among persons 15 years of age or older. The secondary outcome was the prevalence of tuberculosis infection, as assessed by an interferon gamma release assay in the fourth year, among children born in 2012.

RESULTS

In the fourth-year prevalence survey, we tested 42,150 participants in the intervention group and 41,680 participants in the control group. A total of 53 participants in the intervention group (126 per 100,000 population) and 94 participants in the control group (226 per 100,000) had pulmonary tuberculosis, as confirmed by a positive nucleic acid amplification test for *Mycobacterium tuberculosis* (prevalence ratio, 0.56; 95% confidence interval [CI], 0.40 to 0.78; P<0.001). The prevalence of tuberculosis infection in children born in 2012 was 3.3% in the intervention group and 2.6% in the control group (prevalence ratio, 1.29; 95% CI, 0.70 to 2.36; P=0.42).

CONCLUSIONS

Three years of community-wide screening in persons 15 years of age or older who resided in Ca Mau Province, Vietnam, resulted in a lower prevalence of pulmonary tuberculosis in the fourth year than standard passive case detection alone. (Funded by the Australian National Health and Medical Research Council; ACT3 Australian New Zealand Clinical Trials Registry number, ACTRN12614000372684.)

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During 2015, tuberculosis developed in 10.4 million persons worldwide, and 1.8 million persons died from the disease.[1] In response, the World Health Organization (WHO) adopted the "END TB" strategy. The targets of the strategy include reducing the number of deaths from tuberculosis by 95% and the incidence of tuberculosis by 90%, as compared with 2015 levels, by 2035.[2]

The long-standing global strategy for tuberculosis control focuses on improving access to diagnosis, treatment, and supportive services to ensure that patients with symptomatic tuberculosis disease receive an appropriate diagnosis and treatment. Although there have been substantial gains in tuberculosis control in some countries,[3] the decline in the incidence of tuberculosis is slow in many countries, and the prevalence of tuberculosis remains high in those countries,[4] which ensures ongoing transmission. Barriers to the implementation of the current strategy include weak health systems[5,6] and the fact that many patients with pulmonary tuberculosis do not report typical symptoms[4,7,8] or may delay seeking treatment.[9] As a consequence, in 2017, an estimated 3.6 million persons with tuberculosis worldwide did not receive a diagnosis and were not treated.[3] Unless effective new approaches are identified and implemented, the high social and economic costs of tuberculosis will continue, with little progress toward the targets of the END TB strategy, despite substantial ongoing investment of resources in tuberculosis-control programs.[10-12]

There is consensus among experts that progress in controlling tuberculosis in high-burden countries requires enhanced case detection.[13] Active case finding, in which persons who are not seeking health care for symptoms are invited to be screened for tuberculosis disease, has played an important role in tuberculosis control in higher-income countries for more than half a century.[14-18] Previous attempts at active case finding have focused mainly on screening high-risk subgroups of the population, primarily known contacts of persons with active tuberculosis.[19] However, most cases of tuberculosis in areas where tuberculosis is highly endemic occur in persons without recognized risk factors.[20] Hence, the effect of screening high-risk groups alone on the pool of prevalent cases of tuberculosis will be relatively small.[21] We hypothesize that in areas with a high burden of tuberculosis it will be necessary to screen the entire population and treat all, or nearly all, prevalent cases of tuberculosis to reduce transmission.

The Active Case Finding for Tuberculosis 3 (ACT3) trial aimed to assess the effectiveness of a community-wide active case-finding intervention in reducing the prevalence of tuberculosis and tuberculosis infection in a high-prevalence area. The intervention was performed with the use of a rapid nucleic acid amplification test (Xpert MTB/RIF, Cepheid)[22,23] to detect *Mycobacterium tuberculosis* in spontaneously expectorated sputum samples.

METHODS

TRIAL PROCEDURES

A community-based, cluster-randomized, controlled trial was conducted in Ca Mau Province, Vietnam (Fig. 1) from March 2014 through February 2018. The cluster sampling unit was the subcommune, which is roughly equivalent to a village or suburb with an average population of approximately 1000 persons 15 years of age or older. Subcommunes were randomly selected and randomly assigned to the community-wide screening intervention (60 subcommunes in the intervention group) or no intervention (60 subcommunes in the control group). Random selection was stratified according to district, with the probability of being selected proportional to the size of the subcommune at baseline (see the Supplementary Appendix, available with the full text of this article at NEJM.org). In the first 3 years of the trial, the active screening intervention was performed annually in the intervention group and no intervention was performed in the control group. The participants in either trial group who received a diagnosis of tuberculosis were treated in accordance with the policy of the National Tuberculosis Program.

The protocol, available at NEJM.org, was approved by the Human Research Ethics Committee of the University of Sydney and the institutional review board of the National Lung Hospital, Vietnam Ministry of Health. Further details of ethical approval, participant-consent procedures, trial registration, trial funding, and the involvement of the sponsor are provided in the Supplementary Appendix. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

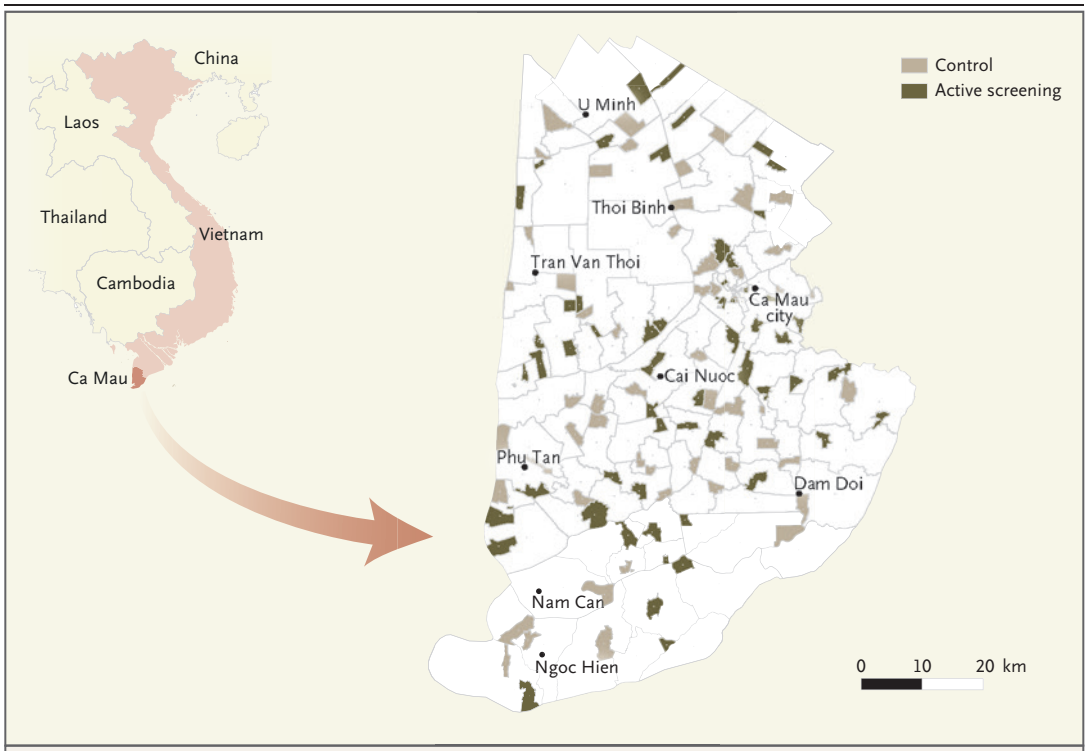

Figure 1. Map of the 9 Districts and 949 Subcommunes in Ca Mau Province, Vietnam.

Shown are the randomly selected subcommunes that were randomly assigned to the active community-wide screening intervention (active screening) or to no intervention (control). The smaller map in the top left corner shows the location of Ca Mau Province in Vietnam.

TRIAL GROUPS

Intervention Group

The participants in each subcommune in the intervention group were screened annually, at approximately the same time of year and at no cost to them. In each subcommune, the intervention proceeded through a series of phases. We conducted a house-to-house survey (census) of the entire population of persons 15 years of age and older in the participating subcommunes. Oral consent for participation in tuberculosis screening was obtained from all the participants. Screening included a brief questionnaire about typical symptoms of tuberculosis (cough, sputum, and hemoptysis) and smoking status and a request to provide a sputum sample, regardless of the response to these questions (Fig. S1 in the Supplementary Appendix). A randomly selected subsample of participants comprising 10% of the trial population completed an extended questionnaire. Sputum samples, collected from the participants who consented and were able to provide a sample, were transferred to the laboratory. Samples that had a volume of at least 0.5 ml were deemed suitable for examination with the Xpert MTB/RIF test, which was performed within 24 to 36 hours after collection. From the end of the second year of the trial, sputum samples were pooled in pairs before Xpert testing. Participants who had sputum samples that tested positive for *M. tuberculosis* on the Xpert test were requested by the trial field staff to provide two additional spontaneously expectorated sputum samples for mycobacterial microscopy, culture, and drug-susceptibility testing and to attend the Provincial Tuberculosis Hospital for chest radiography and clinical assessment by the tuberculosis program medical staff. The decision about whether to recommend treatment for tuberculosis was made by the attending clinician.

Control Group

Community-wide active screening was not performed in the control group during the first 3 years of the trial. Residents of the subcommunes in the

control group who presented to government tuberculosis clinics with typical symptoms of the disease were assessed for a diagnosis of tuberculosis, which was confirmed by a sputum smear positive for acid-fast bacilli on microscopic examination and, when clinically indicated, by findings on chest radiography. Those who received a diagnosis of tuberculosis were treated in accordance with the policy of the National Tuberculosis Program. Oral consent for participation in tuberculosis screening in the fourth-year survey was obtained from all the participants.

TRIAL OUTCOMES

Primary Outcome

The primary outcome was the prevalence of microbiologically confirmed pulmonary tuberculosis in the fourth year of the trial. In accordance with WHO recommendations,[24] microbiologically confirmed pulmonary tuberculosis was defined as a sputum sample positive for *M. tuberculosis* on the Xpert test. Prevalence was estimated according to the findings from a whole-population survey that was conducted in both the intervention group and the control group with the same method used in the screening intervention (see the Supplementary Appendix). The subcommunes in the intervention group and the control group were evaluated synchronously within each district.

In a sensitivity analysis, two subsidiary outcomes of tuberculosis prevalence were measured in the fourth-year prevalence survey. In one subsidiary outcome, confirmed tuberculosis was defined as an initial sputum sample positive for *M. tuberculosis* on the Xpert test plus at least one mycobacterial culture that grew *M. tuberculosis*. In the other subsidiary outcome, confirmed tuberculosis was defined as a sputum sample positive for *M. tuberculosis* on the Xpert test plus at least one mycobacterial culture that grew *M. tuberculosis* or chest radiographic findings that were reported to be consistent with tuberculosis by both the attending clinician and a second reader who was an expert in tuberculosis care and unaware of the trial-group assignment and the report by the attending clinician.

Secondary and Post Hoc Outcomes

The secondary outcome was the prevalence of latent tuberculosis infection in the fourth year of the trial among all children in the selected subcommunes who were born during 2012. An interferon gamma release assay (QuantiFERON-TB Gold Plus, Qiagen) was used to diagnose latent tuberculosis infection in children. The test was performed and interpreted in accordance with the manufacturer's instructions (see the Supplementary Appendix).

After the analysis of the findings for this secondary outcome, it became apparent that the prevalence of latent tuberculosis infection in children born in 2012 was lower than expected. Hence, we subsequently decided to repeat the assessment of this secondary outcome in a randomly selected sample of children in the selected subcommunes who were born between January 1, 2004, and December 31, 2011. This survey was undertaken during 2018 and was performed with the same methods used in the survey of children born in 2012.

STATISTICAL ANALYSIS

Analyses were performed according to the intention-to-treat principle with the use of a hierarchical approach to account for the clustered design. A log-binomial regression model was used, with the subcommune clusters treated as normally distributed random intercepts. No adjustment for covariates was performed in the main analysis. However, we performed supplementary analyses with adjustment for age, sex, and smoking status. The trial was reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for cluster-randomized trials.[25]

Using data from the previous Vietnam National Tuberculosis Prevalence Survey, we estimated that the prevalence of culture-proven tuberculosis in the control group was 350 per 100,000 population.[4] We estimated that each trial group would need to include 55 subcommunes, each with a population of 1000 persons 15 years of age or older (i.e., approximately 55,000 participants) to provide the trial with 90% power to detect a prevalence ratio for microbiologically confirmed pulmonary tuberculosis of 0.6 or lower, assuming a type 1 error rate (alpha level) of 0.05.[26] We planned to select 60 subcommunes for each trial group (total of 120) to provide a margin for error and to allow for nonparticipation. Further details of the sample size and power calculations are provided in the Supplementary Appendix.

Table 1. Participation in the Intervention Screening and the Prevalence Survey.*

Variable	Community-wide Screening Intervention			Fourth-Year Prevalence Survey	
	Year 1	Year 2	Year 3	Intervention Group	Control Group
Households — no.	18,787	20,762	21,478	21,593	18,238
Persons ≥15 yr of age — no. (%)	51,460 (100)	55,080 (100)	56,895 (100)	56,763 (100)	48,345 (100)
Persons contacted to seek consent — no. (%)	44,129 (85.8)	44,364 (80.5)	44,645 (78.5)	42,515 (74.9)	42,068 (87.0)
Persons capable of giving consent — no. (%)	43,781 (85.1)	44,117 (80.1)	44,343 (77.9)	42,219 (74.4)	41,777 (86.4)
Persons who gave oral consent to participate — no. (%)	43,425 (84.4)	44,082 (80.0)	44,311 (77.9)	42,150 (74.3)	41,680 (86.2)
Persons in whom sputum collection was attempted — no. (%)	40,050 (77.8)	37,548 (68.2)	35,415 (62.2)	31,396 (55.3)	32,881 (68.0)
Persons with adequate sputum sample for Xpert testing — no. (%)†	23,282 (45.2)	22,375 (40.6)	19,890 (35.0)	18,837 (33.2)	19,687 (40.7)

* Among 949 subcommunes (roughly equivalent to a village or suburb with an average population of approximately 1000 persons ≥15 years of age) in Ca Mau Province, Vietnam, 120 were randomly selected to be included in the trial. Random selection was stratified according to district, with the probability of being selected proportional to the size of the subcommune at baseline. The subcommunes were randomly assigned to the community-wide screening intervention (intervention group) or no intervention (control group), with 60 subcommunes in each group.

† Sputum samples that had a volume of at least 0.5 ml were deemed adequate for examination with the Xpert MTB/RIF test (Cepheid), a rapid nucleic acid amplification assay.

RESULTS

TRIAL PARTICIPANTS

Among the eligible participants in the intervention group, 43,425 (84.4%) in the first year, 44,082 (80.0%) in the second year, and 44,311 (77.9%) in the third year provided oral informed consent, of whom 23,282, 22,375, and 19,890, respectively (45.2%, 40.6%, and 35.0% of the total number of participants), produced sputum samples that were suitable for Xpert testing (Table 1). In the fourth-year prevalence survey, 42,150 eligible participants (74.3%) in the intervention group and 41,680 eligible participants (86.2%) in the control group provided oral informed consent, of whom 18,837 (44.7%) and 19,687 (47.2%), respectively, produced sputum samples that were suitable for testing (Table 1).

The trial population in the fourth-year prevalence survey included slightly more female participants than male participants (Table 2). Most participants had no additional training after leaving school, and the most common participant-reported occupations, apart from domestic duties, were laborer and agricultural worker. Approximately half the participants had health insurance coverage. The prevalence of participant-reported diabetes was 0.55% in the intervention group and 0.54% in the control group. The prevalence of participant-reported cough on the day of testing was 5.4% in the intervention group and 6.0% in the control group.

PRIMARY OUTCOME

Among the participants in the intervention group, 169 in the first year (389 per 100,000 population), 136 in the second year (308 per 100,000), 78 in the third year (176 per 100,000), and 53 in the fourth-year prevalence survey (126 per 100,000) had sputum samples positive for *M. tuberculosis* on the Xpert test (Table S1 in the Supplementary Appendix). Among the participants in the control group, 94 (226 per 100,000) in the year 4 prevalence survey had sputum samples positive for *M. tuberculosis* on the Xpert test.

Among the participants who had sputum samples positive for *M. tuberculosis* on the Xpert test, the percentage of those who also had at least one mycobacterial culture that grew *M. tuberculosis* ranged from 52.1% in the control group in the fourth year to 75.6% in the intervention group in the third year. In each year of the trial, chest ra-

Table 2. Demographic, Clinical, and Social Characteristics of the Trial Population in the Fourth-Year Prevalence Survey (2017–2018).*

Characteristic	Intervention Group (N=42,150)	Control Group (N=41,680)
Age — yr	43.6±16.1	43.2±16.5
Male sex — no. (%)	19,343 (45.9)	19,082 (45.8)
Participant-reported symptoms — no. (%)		
Cough on day of testing	2264 (5.4)	2506 (6.0)
Cough every day during the past 2 wk	532 (1.3)	812 (1.9)
Sputum on day of testing	1631 (3.9)	1817 (4.4)
Sputum every day during past 2 wk	365 (0.9)	532 (1.3)
Blood-stained sputum	78 (0.2)	97 (0.2)
Smoking status — no. (%)		
Daily	7547 (17.9)	7285 (17.5)
Occasionally	576 (1.4)	438 (1.1)
Not at all	34,027 (80.7)	33,957 (81.5)
Highest level of education attained — no./total no. (%)		
Did not attend school at all	30/4193 (0.7)	23/4072 (0.6)
Did not complete primary school	52/4193 (1.2)	43/4072 (1.1)
Completed primary school	1664/4193 (39.7)	1449/4072 (35.6)
Completed secondary school, grades 6 to 9	1579/4,193 (37.7)	1737/4072 (42.7)
Completed high school, grades 10 to 12	631/4193 (15.0)	573/4072 (14.1)
Completed college or higher	237/4193 (5.7)	247/4072 (6.1)
Occupation — no./total no. (%)†		
Student	201/4193 (4.8)	214/4072 (5.3)
Unemployed	67/4193 (1.6)	93/4072 (2.3)
Indoor manual laborer	845/4193 (20.2)	878/4072 (21.6)
Outdoor manual laborer	275/4193 (6.6)	286/4072 (7.0)
Agricultural worker	798/4193 (19.0)	636/4072 (15.6)
Fisherman	214/4193 (5.1)	215/4072 (5.3)
Office worker	223/4193 (5.3)	226/4072 (5.6)
Domestic duties	1477/4193 (35.2)	1331/4072 (32.7)
Small trader	401/4193 (9.6)	381/4072 (9.4)
Retired	26/4193 (0.6)	26/4072 (0.6)
Transportation worker‡	94/4193 (2.2)	87/4072 (2.1)
Participant-reported health insurance coverage — no./total no. (%)	2446/4193 (58.3)	2183/4072 (53.6)
Participant-reported diabetes — no./total no. (%)	22/3983 (0.6)	21/3889 (0.5)

* Plus–minus values are means ±SD. Information on educational attainment, occupation, health insurance coverage, and history of diabetes was sought from a randomly selected subsample of participants comprising 10% of the trial population.
† Participants could report more than one occupation.
‡ Transportation worker includes drivers of vehicles (e.g., motor bikes, taxis, boats, and cars).

diography was performed in more than 90% of the participants who had a sputum sample positive for *M. tuberculosis* on the Xpert test. Among these participants, the percentage of those with chest radiographic findings that were reported to be consistent with tuberculosis by both readers ranged from 66.2% in the intervention group in the first year to 69.9% in the intervention group

in the third year. Further details on the mycobacterial and radiographic findings are provided in Tables S2 through S5 in the Supplementary Appendix.

The prevalence ratio for microbiologically confirmed tuberculosis (i.e., a sputum sample positive for *M. tuberculosis* on the Xpert test) in the intervention group, as compared with the control group, was 0.56 (95% confidence interval [CI] 0.40 to 0.78; P<0.001) (Table 3). The number of persons needed to have been screened annually for 3 years to prevent one prevalent case of tuberculosis in the fourth year was 1002.

In the sensitivity analysis, when confirmed tuberculosis was defined as a sputum sample positive for *M. tuberculosis* on the Xpert test plus at least one culture positive for *M. tuberculosis* or radiographic findings reported to be consistent with tuberculosis by two readers (one of the two subsidiary outcomes), the prevalence ratio was the same as that observed in the primary analysis (0.56; 95% CI, 0.39 to 0.79) (Table 3). When confirmed tuberculosis was defined as a sputum sample positive for *M. tuberculosis* on the Xpert test plus at least one culture positive for *M. tuberculosis* (the other subsidiary outcome), the effect size was smaller (prevalence ratio, 0.65; 95% CI, 0.41 to 1.02). Adjustment for age, sex, and smoking status did not substantially alter the findings for the primary outcome (Table S6 in the Supplementary Appendix).

SECONDARY AND POST HOC OUTCOMES

A total of 1217 children in the intervention group and 1006 in the control group were born during 2012, as enumerated in the fourth year of the trial. Among these children, the prevalence of tuberculosis infection was assessed with the use of an interferon gamma release assay (QuantiFERON-TB Gold Plus) in 702 (57.7%) in the intervention group and in 707 (70.3%) in the control group (Table S7 in the Supplementary Appendix). A total of 23 children in the intervention group (3.3% of those with valid test results) and 18 children in the control group (2.6% of those with valid test results) had positive QuantiFERON tests (Table 4). The prevalence ratio for a positive QuantiFERON test among the children in the intervention group, as compared with those in the control group, was 1.29 (95% CI, 0.70 to 2.36) (P=0.42).

A total of 1290 children in the intervention group and 1229 in the control group were randomly selected to be included in a post hoc analysis of children born between January 1, 2004, and December 31, 2011. Among these children, the prevalence of tuberculosis infection was assessed with the use of the QuantiFERON test in 781 (60.5%) in the intervention group and in 770 (62.7%) in the control group. A total of 32 children in the intervention group (4.1% of those with valid test results) and 64 children in the control group (8.3% of those with valid test results) had positive QuantiFERON tests. The prevalence ratio for a positive QuantiFERON test among the children in the intervention group, as compared with those in the control group, was 0.50 (95% CI, 0.32 to 0.78).

DISCUSSION

The ACT3 trial has shown that a community-wide active case-finding intervention, in which a nucleic acid amplification assay was used to detect *M. tuberculosis* in spontaneously expectorated sputum samples collected annually from persons 15 years of age or older, regardless of symptoms, for 3 years, was effective in reducing the prevalence of microbiologically confirmed pulmonary tuberculosis. Our finding is broadly consistent with the 41% decline in culture-confirmed pulmonary tuberculosis observed between baseline and postintervention assessments in the DETECTB trial (performed in Zimbabwe), in which two community-wide active case-finding methods were compared in an area with a high prevalence of human immunodeficiency virus.[27] In our trial, the analogous observation (i.e., the reduction in the prevalence of Xpert test–positive, culture-confirmed pulmonary tuberculosis from the first year to the fourth-year prevalence survey) was 64% (Table S1 in the Supplementary Appendix). The Zambia South Africa TB and HIV Reduction (ZAMSTAR) study,[28] also performed in sub-Saharan Africa, did not include a study group that received usual care or standard passive case detection, and it did not show a significant effect of either of the tested interventions on the prevalence of tuberculosis. The findings from our trial are most consistent with those observed over 50 years ago in a trial performed in Alaska.[18] However, it is not possible to distinguish the separate effects of active case finding and treatment of latent tuberculosis infection (with isoniazid) in

Table 3. Prevalence of Pulmonary Tuberculosis in the Fourth-Year Prevalence Survey According to Outcome Definition.*

Outcome Definition	Prevalence in the Intervention Group (N=42,150)	Prevalence in the Control Group (N=41,680)	Prevalence Ratio (Intervention vs. Control)†	Prevalence Difference (Control – Intervention)	No. Needed to Have Been Screened Annually for 3 Years to Prevent 1 Prevalent Case of Tuberculosis in the Fourth Year‡
	no. in trial group (no. per 100,000)		*estimate (95% CI)*	*no. per 100,000*	
Sputum sample positive for *M. tuberculosis* on Xpert testing	53 (126)	94 (226)	0.56 (0.40–0.78)§	100	1002
Sputum sample positive for *M. tuberculosis* on Xpert testing plus at least one culture that grew *M. tuberculosis*	33 (78)	50 (120)	0.65 (0.41–1.02)	42	2400
Sputum sample positive for *M. tuberculosis* on Xpert testing plus at least one culture that grew *M. tuberculosis* or radiographic findings reported to be consistent with tuberculosis by two readers	50 (119)	89 (214)	0.56 (0.39–0.78)	95	1054

* Prevalence was evaluated among the persons who provided oral consent to participate in the trial.
† The prevalence ratio was estimated with the use of a log-binomial hierarchical model that adjusted for clustering by subcommune.
‡ The number needed to have been screened was calculated as 100,000 divided by the absolute difference in prevalence per 100,000 population.
§ $P<0.001$.

that trial. In contrast, in our trial the intervention was limited to active case finding.

The incremental effect of the intervention observed in our trial, if converted to an annualized rate of decline in tuberculosis prevalence, would be nearly 15% per annum during the implementation of annual active screening, which is higher than the 3% to 7% annual rate of decline observed in countries where two or more prevalence surveys have been conducted[29-32] and also higher than the current worldwide rate of decline in incidence, estimated by the WHO to be 2% per annum.[3] Furthermore, the number of persons needed to have been screened annually for 3 years to prevent one prevalent case of tuberculosis in the fourth year was 1002. Hence, this trial provides evidence to support the implementation of community-wide active case finding as an intervention to substantially accelerate progress toward the goal of tuberculosis elimination. However, further research is required to clarify the appropriate type, duration, and timing of screening, the effect on disease transmission, and the durability of the benefits.

The prevalence of tuberculosis infection among children born 1 to 2 years before the intervention started (a prespecified secondary outcome) was not lower in the intervention group than in the control group. However, a post hoc analysis of older children, who were 3 to 10 years of age in the first year of the intervention, showed that the prevalence of tuberculosis infection was 50% lower among the children in the intervention group than among those in the control group. The difference in findings between these two age cohorts implies that the older children, but not the younger children, benefited from reduced transmission consequent to the reduced prevalence of tuberculosis among persons 15 years of age or older.

Our trial has several limitations. Some of the results of the Xpert MTB/RIF tests of the sputum samples were likely to have been false positive or false negative, and only approximately half the participants were able to spontaneously produce a suitable volume of sputum for testing. These findings have implications for both the intervention (because the Xpert MTB/RIF test was used as the primary diagnostic tool) and the assessment of effectiveness (because the Xpert MTB/RIF test was used to assess the primary outcome in the prevalence survey in the final year). We have pre-

Table 4. Prevalence of Latent Tuberculosis Infection among Children.*

Analysis Population	Prevalence in the Intervention Group	Prevalence in the Control Group	Prevalence Ratio (Intervention vs. Control)
	no. of positive tests/no. of valid test results (% [95% CI])		*estimate (95% CI)*
Children born during 2012	23/701 (3.3 [2.0–4.6])	18/705 (2.6 [1.4–3.7])	1.29 (0.70–2.36)†
Children born between January 1, 2004, and December 31, 2011	32/779 (4.1 [2.7–5.5])	64/769 (8.3 [6.4–10.3])	0.50 (0.32–0.78)

* The prevalence of tuberculosis infection was determined with the use of an interferon gamma release assay (QuantiFERON-TB Gold Plus, Qiagen).
† P=0.42.

viously shown, using mycobacterial culture and plain chest radiographic findings from the first year of the screening intervention in this trial,[33] that the positive predictive value of the Xpert MTB/RIF test for the detection of *M. tuberculosis* in the context of community-wide screening for tuberculosis in Ca Mau Province, Vietnam, is between 61% and 84%, depending on the reference standard that was applied, and that the estimated specificity of the test is between 99.78% and 99.93%. Although it is possible that some participants were treated for tuberculosis unnecessarily, the algorithm used by the clinicians who made treatment decisions for the participants with screen-detected tuberculosis who were referred to them makes this relatively unlikely. The reported overall sensitivity of the Xpert MTB/RIF test is 89% (95% credible interval, 85 to 92), with higher sensitivity in cases with an acid-fast bacilli–positive smear (98%; 95% credible interval, 97 to 99).[34] It is possible that our procedure for pooling two sputum samples before testing may have slightly reduced the sensitivity, although there is evidence that this is unlikely.[35,36] It is probable that some cases of active pulmonary tuberculosis will have been missed with the use of this active screening algorithm because of either the inability of the participant to produce a suitable sputum sample or false negative Xpert tests. Nevertheless, it is likely that patients with tuberculosis who are most infectious to others — and who are the most important to identify and treat — will have been able to produce a spontaneous sputum sample, which will have had a high bacillary burden[37] and hence a high probability of testing positive for *M. tuberculosis* on the Xpert test.[34] It is also possible that false positive and false negative results for *M. tuberculosis* on Xpert tests may have affected the prevalence estimates in the fourth-year survey. This may have attenuated the magnitude of the observed effect. Further discussion of the limitations in this trial is provided in the Supplementary Appendix.

The strengths of this trial include its implementation in collaboration with the National Tuberculosis Program of Vietnam. Locally employed staff implemented the screening procedure, and the local tuberculosis program undertook the management of all screen-detected cases, which were further assessed in the regional reference laboratory of the National Tuberculosis Program. Together with the high participation rate in the screening intervention, this collaboration lends support to the potential scalability of the intervention. The high participation rate in the fourth-year prevalence survey reduces the risk that the findings were adversely affected by selection bias. The application of the Xpert MTB/RIF test as the initial diagnostic tool in this trial, in place of the more conventional plain chest radiograph, proved to be feasible.[33]

A number of issues require investigation before this community-wide active case-finding method is further implemented and scaled up to national tuberculosis control programs. The generalizability of these findings needs to be assessed in other settings and populations, as does the feasibility of scaling up screening with the nucleic acid amplification tests, such as the Xpert MTB/RIF test. The role of alternative first-stage screening tests, such as less expensive or more sensitive nucleic acid amplification tests performed on sputum samples,[38] blood tests,[39] or chest radiography, including the possible use of artificial intelligence algorithms to interpret the findings,[40] needs to be evaluated, as does the effect of alter-

native schedules for screening (i.e., longer or shorter intervals between screenings) and the appropriate duration of the screening period. This trial was conducted in an area with a strong, centrally managed National Tuberculosis Program. The feasibility of implementing this approach in areas without such a program remains to be established. Finally, the role, if any, of population-wide treatment of latent tuberculosis infection, as an adjunct to active case finding, needs to be assessed.[18,41] We need to know more about the relation between these variables, as well as their costs and effectiveness, including the cost savings from the prevention of future cases, to be able to make recommendations to national and global policy agencies.

In conclusion, we found that annual community-wide screening for tuberculosis in an area in which tuberculosis is endemic was more effective than standard passive case detection alone in reducing the prevalence of tuberculosis in the population.

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REFERENCES

1. Global tuberculosis report 2017: report no. WHO/HTM/TB/2017.23. Geneva: World Health Organization, 2017 (http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1&ua=1).
2. The END TB Strategy: report no. WHO/HTM/TB/2015.19. Geneva: World Health Organization, 2015 (https://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1).
3. Global tuberculosis report 2018: report no. WHO/CDS/TB/2018.20. Geneva: World Health Organization, 2018 (http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?ua=1).
4. Hoa NB, Sy DN, Nhung NV, Tiemersma EW, Borgdorff MW, Cobelens FG. National survey of tuberculosis prevalence in Viet Nam. Bull World Health Organ 2010;88:273-80.
5. Lönnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. Lancet 2010;375:1814-29.
6. Ayé R, Wyss K, Abdualimova H, Saidaliev S. Patient's site of first access to health system influences length of delay for tuberculosis treatment in Tajikistan. BMC Health Serv Res 2010;10:10.
7. Laifer G, Widmer AF, Simcock M, et al. TB in a low-incidence country: differences between new immigrants, foreign-born residents and native residents. Am J Med 2007;120:350-6.
8. Ayles H, Schaap A, Nota A, et al. Prevalence of tuberculosis, HIV and respiratory symptoms in two Zambian communities: implications for tuberculosis control in the era of HIV. PLoS One 2009;4(5):e5602.
9. Long NH, Johansson E, Diwan VK, Winkvist A. Fear and social isolation as consequences of tuberculosis in VietNam: a gender analysis. Health Policy 2001;58:69-81.
10. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med 2009;68:2240-6.
11. Houben RMGJ, Menzies NA, Sumner T, et al. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. Lancet Glob Health 2016;4(11):e806-e815.
12. Watkins DA, Yamey G, Schäferhoff M, et al. Alma-Ata at 40 years: reflections from the Lancet Commission on Investing in Health. Lancet 2018;392:1434-60.
13. Getahun H, Raviglione M. Active case-finding for TB in the community: time to act. Lancet 2010;376:1205-6.
14. Wallace JM. Changes in the pattern of respiratory tuberculosis in an urban community following a mass radiography campaign. Tubercle 1964;45:7-16.
15. Oommen AV. Review of mass radiography services; a report by the Joint Tuberculosis Council. Tubercle 1964;45:255-66.
16. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis 2005;9:1183-203.
17. Mason PH, Oni T, van Herpen MM, Coussens AK. Tuberculosis prevention must integrate technological and basic care innovation. Eur Respir J 2016;48:1529-31.
18. Comstock GW, Ferebee SH, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. Am Rev Respir Dis 1967;95:935-43.
19. Fox GJ, Nhung NV, Sy DN, et al. Household-contact investigation for detection of tuberculosis in Vietnam. N Engl J Med 2018;378:221-9.
20. Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. Lancet 2004;363:212-4.
21. Kasaie P, Andrews JR, Kelton WD, Dowdy DW. Timing of tuberculosis transmission and the impact of household contact tracing: an agent-based simulation model. Am J Respir Crit Care Med 2014;189:845-52.
22. Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet 2011;377:1495-505.
23. Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational "how-to"; practical considerations. Geneva: World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf).
24. World Health Organization. Definitions and reporting framework for tuberculosis — 2013 revision, updated December 2014: report no. WHO/HTM/TB/2013.2. Geneva: World Health Organization, 2013 (http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/accra2013_9_revised_who_definitions_falzon.pdf?ua=1).
25. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. BMJ 2012;345:e5661.
26. Donner A, Klar N. Design and analy-

sis of cluster randomization trials in health research. London: Arnold, 2000.
27. Corbett EL, Bandason T, Duong T, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. Lancet 2010; 376:1244-53.
28. Ayles H, Muyoyeta M, Du Toit E, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. Lancet 2013;382: 1183-94.
29. Mao TE, Okada K, Yamada N, et al. Cross-sectional studies of tuberculosis prevalence in Cambodia between 2002 and 2011. Bull World Health Organ 2014; 92:573-81.
30. Tupasi TE, Radhakrishna S, Chua JA, et al. Significant decline in the tuberculosis burden in the Philippines ten years after initiating DOTS. Int J Tuberc Lung Dis 2009;13:1224-30.
31. Hong YP, Kim SJ, Lew WJ, Lee EK, Han YC. The seventh nationwide tuberculosis prevalence survey in Korea, 1995. Int J Tuberc Lung Dis 1998;2:27-36.
32. Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990-2010: a longitudinal analysis of national survey data. Lancet 2014;383:2057-64.
33. Ho J, Nguyen PTB, Nguyen TA, et al. Reassessment of the positive predictive value and specificity of Xpert MTB/RIF: a diagnostic accuracy study in the context of community-wide screening for tuberculosis. Lancet Infect Dis 2016;16:1045-51.
34. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 2014;1:CD009593.
35. Ho J, Jelfs P, Nguyen PT, Sintchenko V, Fox GJ, Marks GB. Pooling sputum samples to improve the feasibility of Xpert® MTB/RIF in systematic screening for tuberculosis. Int J Tuberc Lung Dis 2017;21:503-8.
36. Phuong NTB, Anh NT, Van Son N, et al. Effect of two alternative methods of pooling sputum prior to testing for tuberculosis with genexpert MTB/RIF. BMC Infect Dis 2019;19:347.
37. Churchyard G, Kim P, Shah NS, et al. What we know about tuberculosis transmission: an overview. J Infect Dis 2017; 216:Suppl 6:S629-S635.
38. Schumacher SG, Sohn H, Qin ZZ, et al. Impact of molecular diagnostics for tuberculosis on patient-important outcomes: a systematic review of study methodologies. PLoS One 2016;11(3):e0151073.
39. Blauenfeldt T, Heyckendorf J, Graff Jensen S, et al. Development of a one-step probe based molecular assay for rapid immunodiagnosis of infection with M. tuberculosis using dried blood spots. PLoS One 2014;9(9):e105628.
40. Maduskar P, Muyoyeta M, Ayles H, Hogeweg L, Peters-Bax L, van Ginneken B. Detection of tuberculosis using digital chest radiography: automated reading vs. interpretation by clinical officers. Int J Tuberc Lung Dis 2013;17:1613-20.
41. Comstock GW. Isoniazid prophylaxis in an undeveloped area. Am Rev Respir Dis 1962;86:810-22.