Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial

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Summary

Background Southern Africa has had an unprecedented increase in the burden of tuberculosis, driven by the HIV epidemic. The Zambia, South Africa Tuberculosis and AIDS Reduction (ZAMSTAR) trial examined two public health interventions that aimed to reduce the burden of tuberculosis by facilitating either rapid sputum diagnosis or integrating tuberculosis and HIV services within the community.

Methods ZAMSTAR was a community-randomised trial done in Zambia and the Western Cape province of South Africa. Two interventions, community-level enhanced tuberculosis case-finding (ECF) and household level tuberculosis–HIV care, were implemented between Aug 1, 2006, and July 31, 2009, and assessed in a 2×2 factorial design between Jan 9, 2010, and Dec 6, 2010. All communities had a strengthened tuberculosis–HIV programme implemented in participating health-care centres. 24 communities, selected according to population size and tuberculosis notification rate, were randomly allocated to one of four study groups using a randomisation schedule stratified by country and baseline prevalence of tuberculous infection: group 1 strengthened tuberculosis–HIV programme at the clinic alone; group 2, clinic plus ECF; group 3, clinic plus household intervention; and group 4, clinic plus ECF and household interventions. The primary outcome was the prevalence of culture-confirmed pulmonary tuberculosis in adults (≥18 years), defined as *Mycobacterium tuberculosis* isolated from one respiratory sample, measured 4 years after the start of interventions in a survey of 4000 randomly selected adults in each community in 2010. The secondary outcome was the incidence of tuberculous infection, measured using tuberculin skin testing in a cohort of schoolchildren, a median of 4 years after a baseline survey done before the start of interventions. This trial is registered, number ISRCTN36729271.

Findings Prevalence of tuberculosis was evaluated in 64 463 individuals randomly selected from the 24 communities; 894 individuals had active tuberculosis. Averaging over the 24 communities, the geometric mean of tuberculosis prevalence was 832 per 100 000 population. The adjusted prevalence ratio for the comparison of ECF versus non-ECF intervention groups was 1·09 (95% CI 0·86–1·40) and of household versus non-household intervention groups was 0·82 (0·64–1·04). The incidence of tuberculous infection was measured in a cohort of 8809 children, followed up for a median of 4 years; the adjusted rate ratio for ECF versus non-ECF groups was 1·36 (95% CI 0·59–3·14) and for household versus non-household groups was 0·45 (0·20–1·05).

Interpretation Although neither intervention led to a statistically significant reduction in tuberculosis, two independent indicators of burden provide some evidence of a reduction in tuberculosis among communities receiving the household intervention. By contrast the ECF intervention had no effect on either outcome.

Funding Bill & Melinda Gates Foundation.

Published **Online** August 1, 2013 http://dx.doi.org/10.1016/S0140-6736(13)61131-9

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(13)61568-8

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Introduction

The past two decades have seen an unprecedented rise in the burden of tuberculosis in southern Africa. Mathematical modelling[1] and molecular epidemiology[2–4] suggest that continuing transmission of tuberculosis, in the context of HIV infection, is the driving force. Community-based prevalence surveys have shown that much undiagnosed tuberculosis exists in communities,[5–8] with consequent transmission to the susceptible HIV-infected population.[9] An estimated 80% of the world's cases of HIV-tuberculosis co-infection are in southern Africa; the estimated incidence of tuberculosis in South Africa is more than 900 per 100 000 people per year.[10]

Although there have been substantial advances in recommended strategies for management of tuberculosis in people with HIV infection,[11] approaches that are currently recommended remain focused on services provided for individuals presenting with cough to local health services or those known to have HIV infection. The rationale for this clinic-based approach was reinforced by various studies of community-based case-finding from the era before HIV emerged as the predominant driver of coepidemics in southern Africa.[12]

In recognition of the fact that focusing solely on individuals who present to health facilities has not reduced tuberculosis, and the many barriers to access to health services, the Stop TB Partnership has included increased community involvement in the diagnosis and management of tuberculosis as part of the global plan to stop tuberculosis.[13] Several interventions have been proposed or tested mostly involving case finding[14–16] or case management.[17–19] However, none of these studies has provided robust evidence for policy change. Assessment of the effect of interventions for tuberculosis at a public health level is challenging. Randomised study designs of interventions delivered within existing health services need to allocate whole communities to the same intervention group, and the outcomes must be measured in sufficiently large units to capture herd effects attributable to continuing transmission within the population. Studies of approaches to reduce the burden of tuberculosis in communities with a high prevalence of HIV have therefore tended to be observational[20] or to use proxy outcomes, such as the number of cases found.[14]

See Online for appendix

The ZAMSTAR (Zambia, South Africa Tuberculosis and AIDS Reduction) trial was a community-randomised trial of two interventions with the hypothesis that taking interventions beyond health services could significantly reduce the prevalence and transmission of tuberculosis.[21] The interventions were embedded within existing health services, applied across a population of about 1 million people, and were assessed with robust measures of the burden of tuberculosis at community level (prevalence of tuberculosis and incidence of tuberculous infection).

Methods

Setting and participants

24 communities in Zambia and the Western Cape province of South Africa were purposively selected such that the tuberculosis notification rate, according to official data, was at least 400 per 100 000 per year, and that each health facility offered tuberculosis diagnosis and treatment to a catchment population of at least 25 000. Population-level HIV data did not exist and therefore we developed a protocol that solicited expert opinion from local and national health officials about each community's HIV profile and combined this information with available data from antenatal services and voluntary counselling and testing services and surveys. This strategy defined all the communities that were selected as having an HIV prevalence higher than estimated for the whole country (Zambia) or province (Western Cape).

Interventions

Two complex interventions were implemented between Aug 1, 2006, and July 31, 2009. The first intervention was a community-level enhanced case-finding (ECF) intervention, which focused on a strategy of community mobilisation and promotion of increased access to sputum examination using smear microscopy (ECF intervention). The second intervention was a strategy of combined tuberculosis-HIV activities at the household level, based around the activities included in the WHO guidelines for collaborative tuberculosis–HIV care in clinics. Newly diagnosed patients with tuberculosis were used as a gateway to households at risk of tuberculosis and HIV (household intervention). The appendix provides more detail of the interventions. Additionally, all communities had a strengthened tuberculosis–HIV programme implemented at the clinic, in line with WHO policy for collaborative tuberculosis–HIV activities, which involved strengthening of laboratory diagnosis for tuberculosis, augmentation of the tuberculosis registration system, HIV testing offered to all patients with referral for HIV care and antiretroviral therapy, increased tuberculosis screening for individuals with HIV infection, and provision of isoniazid preventive therapy.[11]

24 communities were randomly allocated to one of four trial groups (six communities per group): group 1, strengthened tuberculosis–HIV programme at the clinic alone (clinic group); group 2, clinic plus ECF (ECF group); group 3, clinic plus household intervention (household group); and group 4, clinic plus ECF and household interventions (ECF plus household group).

Outcomes

The objectives of the ZAMSTAR study were to establish whether either of the two interventions (ECF or household) reduced the prevalence of tuberculosis and the incidence of tuberculous infection at the community level. The study had a 2×2 factorial design such that the primary analyses compared communities with and without each of the interventions.[21] Thus analysis of the effect of ECF compared groups 2 and 4 with groups 1 and 3, whereas analysis of the effect of household compared groups 3 and 4 with groups 1 and 2.

The primary outcome was the prevalence of culture-confirmed pulmonary tuberculosis in adults (≥18 years), defined as *Mycobacterium tuberculosis* isolated from one respiratory sample irrespective of clinical symptoms, measured between 3·5 and 4·5 years after the start of interventions in a survey of 4000 randomly selected adults in each community in 2010. The secondary outcome was the incidence of tuberculous infection, measured using tuberculin skin testing (TST) in a cohort of 15 583 schoolchildren, about 4 years after a baseline survey done before the start of interventions. Testing procedures for this outcome were in line with standard guidelines for tuberculin surveys,[22] as previously described.[23] For the purpose of this trial, incident tuberculous infection was defined as a change in induration from 0 mm at baseline to 15 mm or greater at follow-up. The appendix provides detailed methods for the two outcome measures.

Assent for a community to be included in the trial was obtained from local leaders, including health authorities,

district commissioners, local councillors, and traditional leaders before randomisation occurred. The trial was approved by the ethics committees of the London School of Hygiene and Tropical Medicine, Stellenbosch University, and the University of Zambia. Permission for the study was given by the Ministry of Health in Zambia and the Western Cape Provincial Department of Health.

For the household intervention, individual written informed consent was obtained from each patient with tuberculosis before any study staff member visited her or his house and from all household members who took part in the household counselling intervention. Parental written informed consent was obtained from parents of children involved in the household intervention. For the prevalence survey, individual informed consent was obtained from all participants, and separate written informed consent was needed for HIV testing. For the TST surveys (incidence of tuberculous infection in children), written informed consent was obtained from the parent or guardian of each child and assent obtained from each child.

Randomisation and masking

Randomisation of intervention was stratified by country and the prevalence of tuberculous infection (as measured by baseline TST surveys and categorised as high or low within countries). Additionally, randomisation was restricted to ensure balance of prevalence of tuberculosis infection, HIV prevalence (high or less high), urban or rural location, social context (defined as open or closed), and geographical location. Full details of the randomisation methods have previously been described.[24] A list of 1000 possible allocations of communities to four groups was drawn as a random sample from a total of about 7 million allocations that met restriction criteria.[24] A two-stage public randomisation ceremony was done, first to select one of 1000 possible allocations of the 24 communities to four groups (labelled A, B, C, and D), and second to allocate each of the four trial groups to one of the letters A, B, C, or D.

Analysis of sputum samples collected in the prevalence survey was done blinded to group assignment.

Statistical analysis

Sample size calculation used the formula for cluster randomised trials.[25] On the basis of data from our pilot prevalence surveys done in neighbouring areas,[5] we assumed a prevalence of pulmonary tuberculosis in adults of 1% in the control group. We powered our study to be able to detect a 30% reduction in the primary outcome of prevalence of tuberculosis attributable to each intervention individually and a 51% reduction in tuberculosis prevalence when the two interventions were combined. To achieve 80% power to detect a significant difference (two-sided $p<0·05$), with an assumed between-community coefficient of variation $k=0·20$ (after stratification for country and low or high prevalence of tuberculosis infection), we needed 24 communities (six per group) and to sample 4000 adults per community.

For the secondary outcome of incidence of tuberculous infection during 4 years after a baseline survey in 2005, we aimed to detect a 30% reduction associated with either intervention. The sample size was calculated to provide 80% power to detect a 30% difference (two-sided

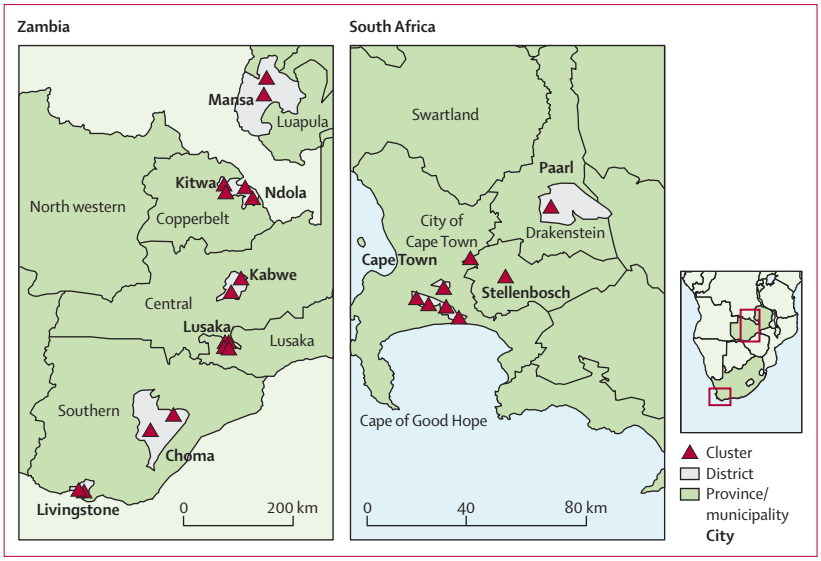

Figure 1: **Map of cluster locations**

	Group 1: Clinic	Group 2: Clinic plus ECF	Group 3: Clinic plus household	Group 4: Clinic plus ECF and household
Number of communities	6	6	6	6
Population in catchment area of health facility	368 578	327 337	402 781	381 500
Population in intervention area*	257 698	148 090	257 729	299 138
ECF				
ECF participants who submitted sputum	..	7817	..	13 420
ECF participants with smear-positive sputum result	..	672	..	1068
Household				
Households involved in household intervention	..	..	4573	5304
Household members enumerated†	..	..	19 874	18 225
Household members consenting to the intervention	..	..	17 461	16 025
Household members screened for tuberculosis	..	..	12 860	10 687
Incident cases of tuberculosis identified	..	..	126	110
Individuals tested for HIV infection‡	..	..	7168	5867

ECF=enhanced case-finding. *Estimated population included in the intervention delivered by the ZAMSTAR trial. For large populations, sections of the catchment area of the health facility were selected so that the communities were a more even size. †Adults and children. ‡Adults only.

Table 1: **Population and process data by study group**

	Group 1: Clinic	Group 2: Clinic plus ECF	Group 3: Clinic plus household	Group 4: Clinic ECF plus household
Overall				
Prevalence of positive TST test, 2005 survey				
Crude	5443 (9·7%)	5119 (10·3%)	5613 (10·8%)	5218 (11·3%)
Age-sex adjusted	5443 (9·7%)	5119 (10·5%)	5613 (10·7%)	5218 (11·0%)
HIV prevalence, 2010 survey				
Serology (crude)	13 412 (16·4%)	11 154 (17·9%)	13 670 (16·4%)	11 211 (16·8%)
Serology (age-sex adjusted)	13 412 (17·0%)	11 154 (18·1%)	13 670 (17·4%)	11 211 (17·4%)
Zambia				
Prevalence of positive TST test, 2005 survey				
Crude	3408 (7·4%)	2976 (5·9%)	3156 (7·9%)	3282 (8·0%)
Age-sex adjusted	3408 (7·3%)	2976 (5·5%)	3156 (7·8%)	3282 (7·6%)
HIV prevalence, 2010 survey				
Serology (crude)	9908 (15·0%)	8522 (17·5%)	9176 (16·0%)	10 109 (17·5%)
Serology (age-sex adjusted)	9908 (15·9%)	8522 (18·0%)	9716 (16·8%)	10 109 (17·6%)
Western Cape, South Africa				
Prevalence of positive TST test, 2005 survey				
Crude	2035 (14·3%)	2143 (19·0%)	2457 (16·6%)	1936 (17·8%)
Age-sex adjusted	2035 (14·5%)	2143 (20·6%)	2457 (16·6%)	1936 (17·9%)
HIV prevalence, 2010 survey				
Serology (crude)	3504 (19·2%)	2632 (18·7%)	3909 (17·2%)	1102 (15·5%)
Serology (age-sex adjusted)	3504 (19·2%)	2632 (18·4%)	3909 (18·5%)	1102 (16·9%)

Data are n (%). HIV prevalence was calculated for each of the 24 communities, based on individuals who consented to give blood for HIV testing in the 2010 tuberculosis prevalence survey. For example, in the six communities in group 1, HIV prevalence estimates were 15·6% (366 of 2353), 18·7% (532 of 2841), 12·3% (300 of 2443), 13·3% (302 of 2271), 19·1% (459 of 2400), and 19·3% (213 of 1104) . Taking the average of these six HIV prevalence values gives the estimate of HIV prevalence for group 1—ie, 16·4%. Prevalence of positive TST test means prevalence of TST induration ≥15 mm, based on the 2005 baseline survey. Prevalence of a positive TST test was calculated in the same way as for HIV prevalence—ie, first the prevalence of a positive TST test was calculated for each of the 24 communities, and then the value for each of groups 1, 2, 3, and 4 was calculated as the average of the six communities in each group. ECF=enhanced case-finding. TST=tuberculin skin test.

Table 2: **Community tuberculosis and HIV characteristics, by country and trial group**

p<0·05), with k=0·20. Under these assumptions, and with an assumed 3% cumulative incidence of tuberculous infection over 3 years in the control group and allowance for 20% loss to follow-up, we needed to recruit 800 children in each community.

As a cluster-randomised trial with a large number of individuals per community, but less than 30 communities, the analysis was done in two stages according to a predefined analysis plan.[25] The analysis gave each community equal weight, and accounted for the stratification by country and baseline prevalence of tuberculosis infection, and clustering by community. The appendix provides detailed statistical methods. This trial is registered, number ISRCTN36729271.

Role of the funding source

The funders of the study were involved in discussions about study design but had no role in data collection, data analysis, data interpretation, or writing of the report. The authors made the final decision to submit for publication.

Results

The trial took place in 24 communities in Zambia (16 communities) and the Western Cape province of South Africa (eight communities; figure 1). The estimated total population in the areas where the intervention was applied (the intervention area) was 962 655, with an average population per community of 40 110. Table 1 shows the results of the randomised allocation and the numbers of individuals who directly participated in the interventions.

Table 2 shows how community-level HIV prevalence varied across the groups and countries. As expected, socioeconomic factors measured at the household level showed differences between Zambian and South African communities, and within countries we identified some differences by trial group (appendix). Individual risk factors for tuberculosis differed between the countries; notably, a significantly higher number of individuals reported previous tuberculosis in South Africa than in Zambia, but within each country differences by trial group were small (table 3). Participation was higher in women than men in all trial communities, but much the same across trial groups (table 3).

In the ECF intervention groups (ECF group and ECF plus household group), 21 237 individuals (4·7% of the total population in these intervention areas) brought sputum for examination via the ECF process and

1740 were shown to have smear-positive tuberculosis. The cases identified accounted for 29·7% of the 5864 smear-positive cases notified in these communities in the same period.

In the household intervention groups (household group and ECF plus household group), 9877 households of patients with tuberculosis participated in household counselling sessions. 33 486 individuals (20 007 adults and 13 310 children, 169 age unknown; 6·1% of the total population in these intervention areas) received tuberculosis–HIV education and 23 547 (4·2%) were screened for tuberculosis. Additionally, 13 035 adults (65·2% of adults) accepted counselling and testing for HIV infection, with 7233 (55%) testing positive. Those who were HIV positive were referred for antiretroviral therapy and, if not already diagnosed with tuberculosis, were referred for isoniazid preventive therapy. Figure 2 shows examples of the geographical coverage of the intervention.

Recruitment of prevalence survey participants occurred from Jan 9, to Dec 6, 2010. 55 344 houses were visited, with the head of the household being asked for consent to enrol the household in the study; 48 395 (87·4%) agreed and all adults in these households were enumerated, resulting in a total of 123 790 eligible adults. Individual written informed consent was obtained from 90 601 (73·2%). Of these individuals, 64 463 (71·2%) had fully evaluable data and were included in the analysis. Figure 3 shows the breakdown by study group and reasons for non-inclusion. Although much the same numbers of participants consented in the two countries, some samples from Zambia were deemed non-evaluable because some batches did not meet our predefined quality assurance standards, mostly because the positive control did not grow. 18 103 samples were excluded because they did not meet predefined quality assurance standards, with additional samples excluded because they were lost or contaminated (figure 3). 502 DNA archives of *M tuberculosis* positive samples from a total of 202 batches (26 Zambia, 176 Western Cape) fulfilled the criteria for spoligotyping to test for possible cross contamination (appendix). In eight cases (one in Zambian batches and seven in Western Cape batches) the spoligotypes were the same and cross contamination was deemed a possibility, although all these spoligotypes were those commonly identified in this population. This finding equates to a possible maximum occurrence of cross contamination of less than 1%. Sensitivity analysis, excluding these samples, did not change the results and these samples were kept in for analysis (appendix).

894 adults had prevalent culture-confirmed pulmonary tuberculosis, giving an overall geometric mean of prevalent tuberculosis of 832 per 100 000 adult population, 501 in Zambian communities and 2288 in South African communities. Table 4 shows crude prevalence by trial group. After adjustment, the prevalence ratio for the comparison of household versus non-household groups was 0·82 (95% CI 0·64–1·04, p=0·095, permutation test p=0·063) and for ECF versus non-ECF was 1·09 (0·86–1·40, p=0·44, permutation test p=0·48). The estimated value of the coefficient of between-community variation (k) was 0·29, taking into account stratification by country and baseline prevalence of tuberculosis infection.

Comparison of individuals with evaluable samples with those with non-evaluable samples in Zambia, stratified by community, showed them to be much the same (appendix). To investigate the potential for the missing data to introduce bias in the analysis of trial intervention effects, imputation of data for culture-positive tuberculosis was done for individuals in Zambia whose sample was not evaluable because of being included in a batch that failed quality control.

	Group 1: Clinic (N=14 204)	Group 2: Clinic plus ECF (N=17 170)	Group 3: Clinic plus household (N=16 253)	Group 4: Clinic plus ECF and household (N=16 836)
Sex				
Men	4880 (34·4%)	6256 (36·4%)	5918 (36·4%)	5881 (34·9%)
Women	9324 (65·6%)	10 914 (63·6%)	10 335 (63·6%)	10 955 (65·1%)
Age group (years)				
18–24	4584 (32·3%)	5592 (32·6%)	5240 (32·2%)	5572 (33·1%)
25–29	2430 (17·1%)	2999 (17·5%)	2739 (16·9%)	2891 (17·2%)
30–34	1820 (12·8%)	2234 (13·0%)	2041 (12·6%)	2142 (12·7%)
35–39	1419 (10·0%)	1671 (9·7%)	1549 (9·5%)	1528 (9·1%)
40–49	1707 (12·0%)	2294 (13·4%)	2156 (13·3%)	2062 (12·2%)
50–59	1089 (7·7%)	1298 (7·6%)	1401 (8·6%)	1331 (7·9%)
≥60	1051 (7·4%)	944 (5·5%)	1055 (6·5%)	1204 (7·2%)
Unknown	104 (0·7%)	138 (0·8%)	72 (0·4%)	106 (0·6%)
Education				
None or grade 1–2	822 (5·8%)	1184 (6·9%)	1122 (6·9%)	1186 (7·0%)
Grade 3–6	1539 (10·8%)	1945 (11·3%)	1997 (12·3%)	2383 (14·2%)
Grade 7–10	5815 (40·9%)	7360 (42·9%)	7351 (45·2%)	7723 (45·9%)
Grade 11–12	5001 (35·2%)	5453 (31·8%)	4617 (28·4%)	4749 (28·2%)
College or university	1027 (7·2%)	1228 (7·2%)	1166 (7·2%)	795 (4·7%)
Marital status				
Single	7993 (56·3%)	7375 (43·0%)	7673 (47·2%)	8038 (47·7%)
Married	4776 (33·6%)	7969 (46·4%)	6910 (42·5%)	6956 (41·3%)
Widowed	959 (6·8%)	1086 (6·3%)	941 (5·8%)	1021 (6·1%)
Separated	476 (3·4%)	740 (4·3%)	729 (4·5%)	821 (4·9%)
Smoking				
Never	12 117 (85·3%)	13 942 (81·2%)	12 779 (78·6%)	13 725 (81·5%)
Ex-smoker	1112 (7·8%)	1752 (10·2%)	2175 (13·4%)	1321 (7·8%)
Current smoker	975 (6·9%)	1476 (8·6%)	1299 (8·0%)	1790 (10·6%)
Previous tuberculosis*				
No	12 944 (91·1%)	15 573 (90·7%)	14 716 (90·5%)	15 438 (91·7%)
Yes, once	1012 (7·1%)	1298 (7·6%)	1272 (7·8%)	1098 (6·5%)
Yes, twice or more	248 (1·7%)	299 (1·7%)	265 (1·6%)	300 (1·8%)

Data are n (%). ECF=enhanced case-finding. *Self-reported previous tuberculosis.

Table 3: **Characteristics of participants with evaluable sputum sample in prevalence survey, by trial group**

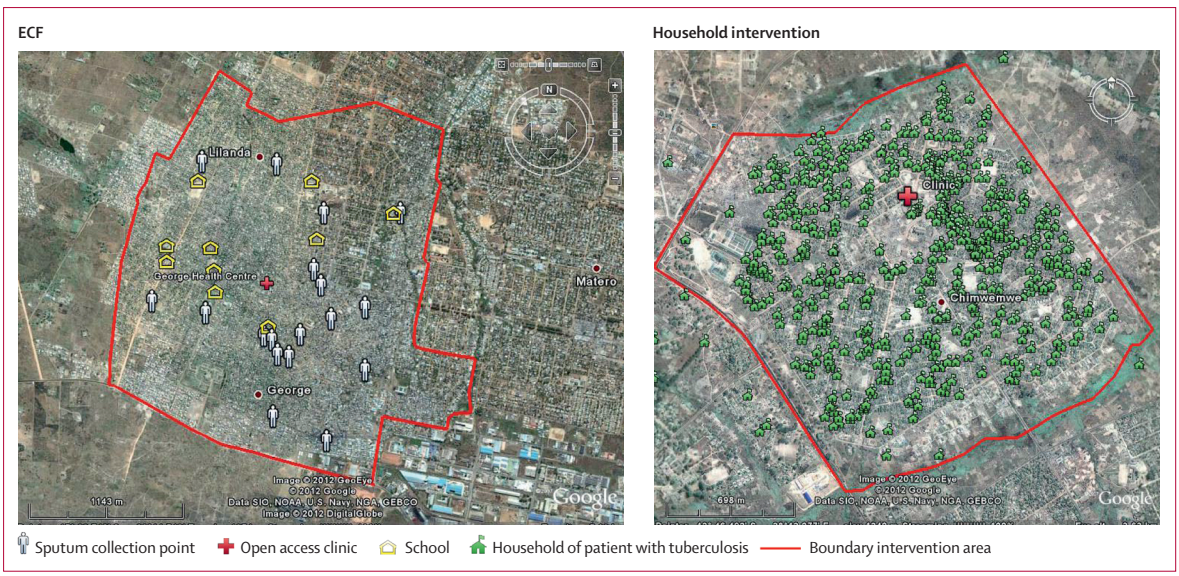

Figure 2: **Examples of coverage of intervention**
ECF=enhanced case-finding.

The imputation model included the same household and individual-level explanatory variables that were included in the adjusted analysis, and additionally tuberculosis symptoms and the community where the individual lived. 50 imputed datasets were created. Analysis of intervention effects was repeated with the imputed datasets, and gave point estimates of intervention effect that were very close to those obtained in the analysis that was restricted to individuals with evaluable samples (appendix).

Sputum smear positivity in prevalent tuberculosis cases was 43% (382 of 894). This finding did not differ by country (Zambian communities 42% [80 of 192], South African communities 43% [302 of 702]), by trial group (household 43% [189 of 443] *vs* non-household 43% [193 of 451], ECF 43% [216 of 505] *vs* non-ECF 43% [166 of 389]), or by HIV status (with HIV 43% [66 of 153 *vs* without HIV 42% [99 of 233]).

21 393 children were included in the initial TST survey in 2005 (parental consent obtained, TST done, and TST result read).[23] Of these children, 15 583 (72·8%) had 0 mm induration; they formed the total evaluation cohort. Of the children in this evaluation cohort (median follow-up time 4 years, IQR 3·5–4·7), 8809 (56·5%) had a repeat TST read in 2009. Figure 4 shows reasons for losses to follow-up. Loss to follow-up increased with child age at baseline, was much the same for boys and girls, and was slightly lower in trial groups with the household or ECF intervention than the clinic alone group.

733 children had incident tuberculous infection, giving an overall geometric mean of incidence of infection of 1·22 per 100 person-years, 0·66 in Zambian communities and 4·15 in South African communities. Table 5 shows incidence by trial group.

After adjustment, the incidence of tuberculous infection rate ratio for household versus non-household groups was 0·45 (95% CI 0·20–1·05, p=0·063, permutation test p=0·10) and for ECF versus non-ECF groups was 1·36 (0·59–3·14, p=0·45, permutation test p=0·55; table 5). The estimated value of the coefficient of between-community variation (k) was 0·53, stratified by country and baseline prevalence of tuberculous infection. Figure 5 summarises the effects of each of the two interventions on both prevalence of culture positive tuberculosis and transmission of tuberculous infection at the community level.

Discussion

We assessed prevalence of tuberculosis in 24 communities in Zambia and South Africa, after 3 years of ECF or household interventions for tuberculosis control. Of 64 463 randomly selected individuals, 894 individuals had active tuberculosis. Averaging over 24 communities the geometric mean of tuberculosis prevalence was 832 per 100 000 population. We also measured the incidence of tuberculous infection in a cohort of 8809 children, followed up for a median of 4 years. The adjusted prevalence ratio for prevalence and the adjusted rate ratio for incidence did not differ significantly for the ECF versus non-ECF or for the household versus non household groups. However, for the household versus non-household groups the upper bounds of the CI for both prevalence ratio and incidence rate ratio were close to unity. The concordance of two robust outcome measures, measured in different population groups and with different methods suggests that the household intervention did have some effect on the burden of tuberculosis in these communities.

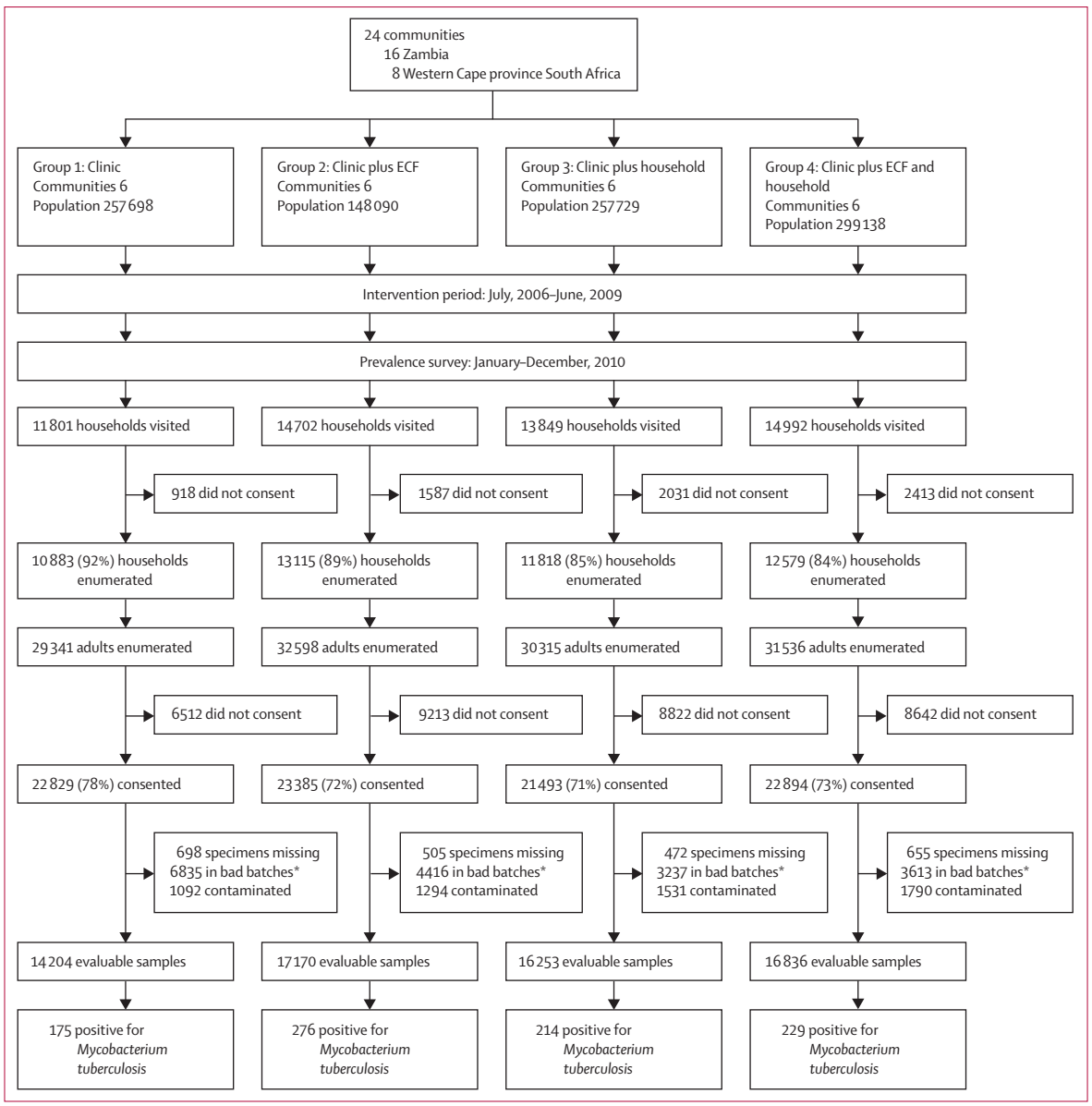

Figure 3: **Study flow diagram for the outcome of prevalent *Mycobacterium tuberculosis* infection**
ECF=enhanced case-finding. *Batches that failed predefined quality assurance criteria (appendix).

The convergence of HIV and tuberculosis has led to an urgent need for an evidence-based public health response to reduce the burden of tuberculosis at the community level. Cluster-randomised trials should provide the gold standard for evidence-based policy making.[26]

A systematic review[27] of published work identified five studies that provided evidence for the effect of interventions on the epidemiology of tuberculosis at community level (panel). Apart from preliminary data from the ZAMSTAR trial, two were randomised trials—the DETECTB[14] trial of enhanced case-finding strategies in Zimbabwe and a trial[15] of a household-level intervention in Brazil. The ZAMSTAR trial is the only study to measure the effect of public health interventions on tuberculosis with a randomised design and direct measurements of the burden of disease as the endpoint. The ZAMSTAR trial covered a population of almost 1 million people and was designed to detect reductions in prevalence of tuberculosis, and incidence of tuberculous infection, of 30%. Our study identified no evidence that the ECF intervention had an effect on the burden of tuberculosis at community level. However, despite not reaching statistical significance, there is plausible evidence that the household intervention did reduce the burden of tuberculosis in these communities.

	Prevalence	Unadjusted analysis		Adjusted analysis*		
	Geometric mean (range)	Prevalence ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Permutation test p value
Group 1: clinic	773 (359–2299)	1	..	1	..	..
Group 2: clinic plus ECF	1011 (380–3103)	1·31 (0·75–2·30)	0·32	1·04 (0·72–1·51)	0·81	..
Group 3: clinic plus household	696 (221–2390)	0·90 (0·51–1·58)	0·69	0·78 (0·54–1·12)	0·16	..
Group 4: clinic plus ECF and household	881 (303–2498)	1·14 (0·65–2·00)	0·62	0·89 (0·62–1·29)	0·51	..
Household: no	884 (359–3103)	1	..	1	..	..
Household: yes	783 (221–2498)	0·89 (0·61–1·29)	0·50	0·82 (0·64–1·04)	0·095	0·063
ECF: no	733 (221–2390)	1	..	1	..	
ECF: yes	944 (303–3103)	1·29 (0·88–1·87)	0·17	1·09 (0·86–1·40)	0·44	0·48

ECF=enhanced case-finding. *Adjusted for prevalence of tuberculous infection in the community in 2005, and HIV prevalence in 2010, as quantitative variables; household socioeconomic position as measured by assets, dwelling structure, water source, and sanitation; age group; sex; education; marital status; and smoking history; adjusted analyses done separately for Zambia and Western Cape communities. These adjustments were specified a priori. Community-level tuberculosis prevalence was positively correlated with community-level HIV prevalence and the prevalence of infection in the community in 2005 (data not shown). In individual-level analysis, the prevalence of tuberculosis decreased with higher household socioeconomic position and better education, was higher in current and ex-smokers than in those who never smoked, and lower in married than non-married individuals (data not shown).

Table 4: **Prevalence of culture-positive *Mycobacterium tuberculosis* in adults (per 100 000 adult population), by trial group, household intervention, and ECF intervention**

The estimates of prevalence used to calculate sample size were, in retrospect, too high for the 16 Zambian sites and too low for the eight South Africa sites; even with the stratified randomisation and analysis, the coefficient of variation was higher than we expected, leading to wide CIs that include unity. Incidence of infection was even more variable amoung communities than the prevalence of tuberculosis.

The data show substantial differences between tuberculosis in the South African communities and the Zambian communities. The Zambian communities were widely distributed and respiratory samples were transported long distances and were cultured in customised containerised laboratories. The quality assurance programme led to a proportion of the Zambian samples being identified as non-evaluable. Although the much lower prevalence of culture positive tuberculosis in the Zambian sites might arise from a lower sensitivity of detection, the findings that the measured incidence of new infection in schoolchildren was also much lower, and that smear positivity was much the same, suggest that these are real differences between the communities in each country. The Western Cape province is known to have a particularly high rate of tuberculosis,[29] and the communities involved in the study were high-density residential areas. Nonetheless, the four-to-five times differences identified in both prevalence of tuberculosis and incidence of new infections emphasise the need for major investment and efforts to control tuberculosis in the Western Cape. The stratification in design and analysis ensure that the differences identified between the countries do not alter the interpretation of the effect of the interventions.

The household intervention builds on traditional psychosocial models of HIV counselling to encourage and support household members to assess their own risks and vulnerabilities to both HIV and tuberculosis and to ease linkage into appropriate diagnosis, care, and prevention either within the home or through existing services. The intervention was successful in finding cases of both HIV and tuberculosis and the household counsellors became resources for the communities in which they worked. This model of household counselling empowers households, and through them neighbours, family, and ultimately communities, to seek care early when symptoms of tuberculosis start. The effect of this intervention is greater than that of ECF because it engages more directly with members of the community and continues beyond the direct period of the intervention. Linkage and retention in care might be important determinants of the success or otherwise of the interventions, and further analysis of routine health data alongside study data is underway to establish whether we can identify differences between the intervention groups that might account for the effects that we recorded.

The failure of the ECF approach to have an effect on the prevalence of tuberculosis is disappointing in view of the clear need to detect more cases and to find and treat them earlier. Many cases were diagnosed through the intervention. However, diagnosis was based on sputum smear microscopy, which is somewhat insensitive as a diagnostic instrument, particularly in the context of high HIV prevalence.[30] To account for local contextual differences between communities, activities within the ECF intervention were developed in consultation with local neighbourhood health committees. The decision to randomise communities to different strategies, though not constraining the specific activities, was influenced by previous successful approaches to alter health behaviours at a community level.[31,32] Many of the individuals who chose to give

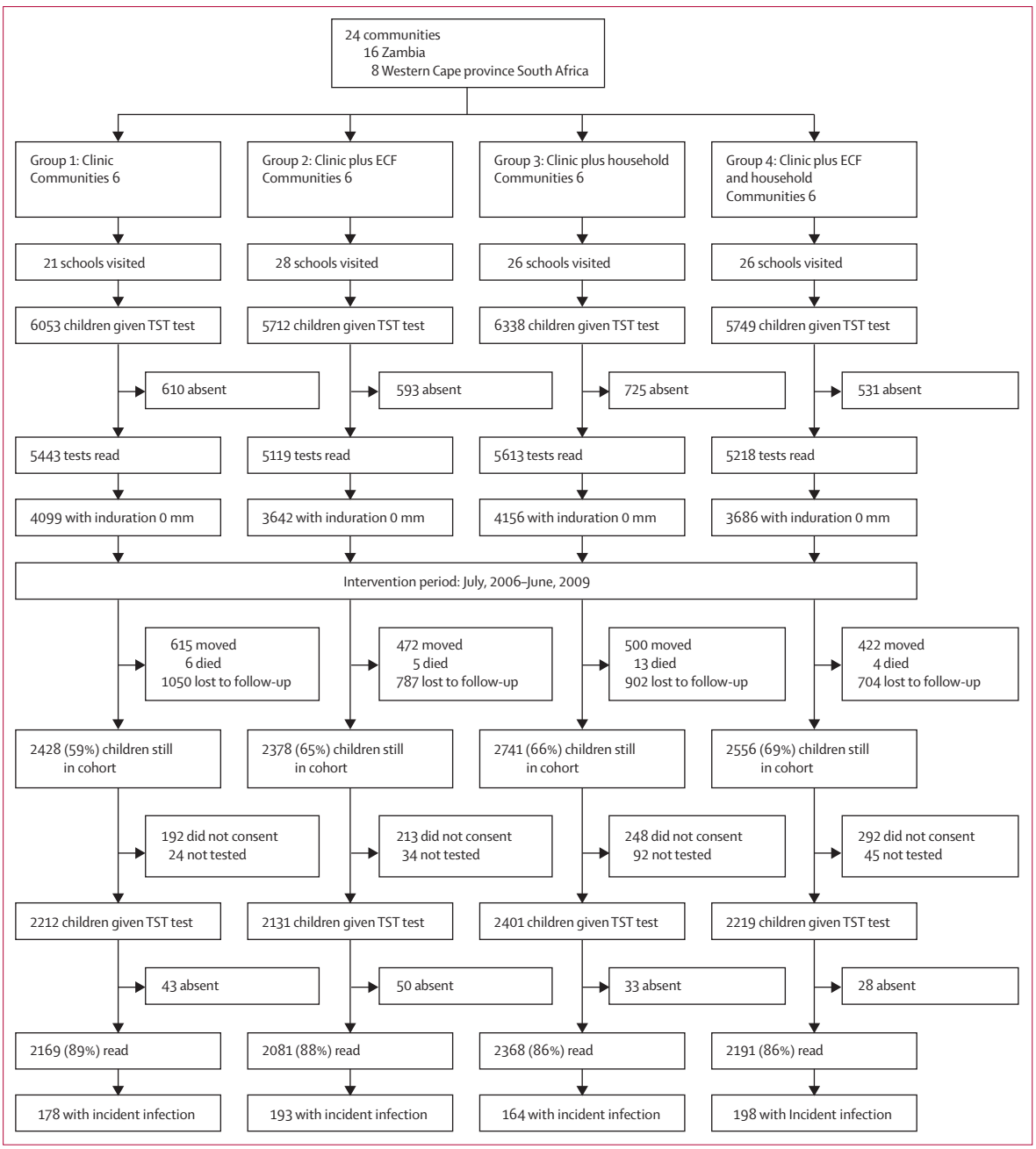

Figure 4: **Study flow diagram for outcome of incidence of tuberculous infection**
ECF=enhanced case-finding. TST=tuberculin skin test. LTFU=lost to follow-up.

sputum through the ECF route had already been coughing for some time and might have already transmitted much of the infection that they would have done even in the absence of the earlier diagnosis. This finding contrasts with the DETECTB trial,[14] which tested two case-finding strategies; one a door-to-door enquiry for people with symptoms to give sputum and the other a mobile van approach. In the DETECTB trial in urban Harare the mobile van was better than the door-to-door enquiry in finding cases of tuberculosis. The strategy that was tested in the ZAMSTAR trial was much the same as the mobile van approach in DETECTB. However, the ZAMSTAR communities were larger than those in DETECTB and overall ZAMSTAR detected a lower proportion of smear-positive cases than did the DETECTB mobile vans. DECTECTB was not powered to be able to measure a difference in prevalence of tuberculosis between the groups of the

	Incidence	Unadjusted analysis		Adjusted analysis*		
	Geometric mean (range)	Rate ratio (95% CI)	p value	Rate ratio (95% CI)	p value	Permutation test p value
Group 1: clinic	1·64 (0·72–4·44)	1	..	1	..	..
Group 2: clinic plus ECF	1·79 (0·26–8·54)	1·09 (0·28–4·24)	0·89	1·18 (0·33–4·22)	0·79	..
Group 3: clinic plus household	0·67 (0·06–4·54)	0·41 (0·11–1·59)	0·18	0·39 (0·11–1·41)	0·14	..
Group 4: clinic plus ECF and household	1·11 (0·06–5·63)	0·68 (0·18–2·63)	0·55	0·62 (0·17–2·21)	0·43	..
Household: no	1·71 (0·26–8·54)	1	..	1	..	..
Household: yes	0·87 (0·06–5·63)	0·51 (0·21–1·24)	0·13	0·45 (0·20–1·05)	0·063	0·10
ECF: no	1·05 (0·06–4·54)	1	..	1	..	..
ECF: yes	1·41 (0·06–8·54)	1·35	0·49	1·36 (0·59–3·14)	0·45	0·55

TST=tuberculin skin test. ECF=enhanced case-finding. *Adjusted for country, prevalence of tuberculous infection in the community in 2005 as a quantitative variable, child age (in years), and sex.

Table 5: **Incidence of TST conversion in schoolchildren (per 100 person-years), by trial group, household intervention, and ECF intervention**

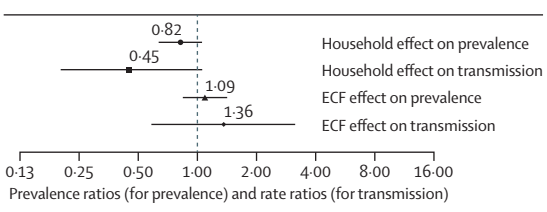

Figure 5: **Summary of effects of trial interventions on culture-positive tuberculosis and transmission of tuberculous infection**
ECF=enhanced case-finding.

Panel: Research in context

Systematic review

A systematic review was done by Kranzer and colleagues.[27] They examined the benefits to communities and individuals of screening for tuberculosis. They identified five studies that provide evidence for whether screening for tuberculosis affects tuberculosis epidemiology in the community, one of them being preliminary data from this study.[28] Two of the other studies were randomised trials—the DETECTB study in Zimbabwe[14] and a study from Brazil.[15] The other two studies identified were observational studies.

Interpretation

As far as we are aware, the ZAMSTAR trial is the only study to have used the prevalence of tuberculosis and the incidence of tuberculous infection, regarded as gold standard measures of the burden of tuberculosis, in a randomised outcome measurement. The results from this study add to the knowledge in this discipline and show that community mobilisation and enhanced case-finding, as done in ZAMSTAR, did not have any effect on the epidemiology of tuberculosis. This finding contrasts with the results of the DETECTB study, which showed an overall reduction in the prevalence of tuberculosis from before to after the intervention.[14] The ZAMSTAR household intervention was closer to the intervention tested in the Brazilian study,[15] which used routine notification data as the endpoint, rather than prevalence of tuberculosis. The Brazilian study showed a decrease in tuberculosis notification rates over the duration of the study when the intervention group was compared with the control group.

trial but did show a substantial reduction in prevalence of tuberculosis with a non-randomised before-and-after design in the whole study area. Although there was no counterfactual for this outcome, further analysis and mathematical modelling might be useful to elucidate reasons for the differences identified.

The two ZAMSTAR interventions are likely to have a direct effect and an indirect effect at community level. The direct effect is on the households of individuals seen by the counsellors, or on individuals who choose to give sputum samples as a result of the ECF activities. The indirect effect might be through the changes in norms and behaviour that could arise from many households in the community being supported, or through individuals who, after sensitisation by the ECF activities, chose to visit their routine health services and thus are not captured in the intervention process data. The advantage of the study design we used was that it captured both the direct and indirect effects of the interventions on the overall burden of disease and transmission in the community within the time period of the study.

A longer period of intervention and observation might be needed to be able to accurately measure an effect. The interventions were designed to reduce transmission of tuberculous infection and are therefore expected to reduce future cases of active disease. Thus the effect on prevalence might be delayed. However, the two interventions also aimed to find undetected cases of smear-positive disease and start these individuals on treatment, which would have some effect on prevalence, although only on reduction of prevalent cases with smear-positive disease.

As with many cluster randomised trials, the number of clusters was quite small and differences existed between the clusters that led to large coefficients of variation with consequent wide CIs.

The substantial losses of evaluable data in the prevalence survey were balanced across the groups and unlikely to have biased the measured effects, although they did decrease the overall power of the study. These losses were mainly attributable to a failure of the

positive mycobacterial control to grow in two of the laboratories. As a result whole batches (of 20 samples) were deemed non-evaluable. The failure of these positive controls to grow was intensively investigated but we concluded that it was probably attributable to a combination of factors, including water quality in specific laboratories. Retention of samples from failed batches in the analysis, even if they were positive, could have biased the results and therefore we decided to exclude the whole batch and all data associated with it from analysis. Losses to follow-up in the incidence cohort were also higher than we planned for, but our study protocol and design dictated that any individual who moved outside of the intervention area of their community was to be censored. Within these communities there was much movement both within and outside of the community. Again these losses were balanced across the groups of the trial and decreased our power to show an effect.

The outcome measurements were chosen to maximise the validity of the randomised trial. Differences in the prevalence of culture positivity between the groups is the gold standard measurement because it is not affected by different diagnostic criteria that might have existed in communities with different interventions, which by their nature could not be delivered in a masked fashion. Similarly, by choosing the most specific criterion for incident tuberculous infection in schoolchildren, the possibility of false-positive cases weakening the measured intervention effect is reduced, but the number of cases of incident infection is also lower and therefore it is harder to show an effect. For both these outcome measurements, the relative difference between communities is the endpoint of the trial, and the absolute measures of prevalence and incidence should be interpreted with caution.

ZAMSTAR was a large study, with almost 1 million people in the study population. Such studies are expensive and take many years to complete because to measure the effect of health system interventions on tuberculosis epidemiology, it is necessary to have sufficiently large units of randomisation to capture tuberculosis transmission. Policy implications therefore have to be drawn on interpretation of the present results despite the weak statistical evidence.

The study showed that although finding additional cases of tuberculosis is important for the individual, we could show no effect at the community level in terms of burden of disease. However, two reliable indicators of tuberculosis epidemiology, measured in two distinct populations, both suggest that a more holistic tuberculosis–HIV intervention at the household level had an important effect on the burden of tuberculosis at community level. This intervention also had additional beneficial effects of increasing HIV counselling and testing and increasing access to antiretroviral therapy. As we move towards universal access for tuberculosis, HIV, and malaria, a combined household approach providing universal HIV testing, tuberculosis screening, malaria prevention, and linkage to diagnosis and care could have major health benefits beyond the individual, or even the household, and provide great health benefits to whole communities.

The ZAMSTAR team

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Contributors

HA, NB, and PG-F were joint principal investigators of this trial. They all contributed to design, management of the trial, supervision of data collection, analysis, and interpretation of results, and writing of this report. MM, EDT, MS, KS, NC, MC, and VB contributed to the management of the trial, supervision of data collection, and interpretation of results. They reviewed and contributed to all drafts of the report. AS, SF, RD, KF, JF, CS, and RJH contributed to the design of the study, the data management and analysis and interpretation of the data. They reviewed and contributed to all drafts of the report. PdH, AJ, and NCGvP contributed to the design of the laboratory aspects of the study. They supervised all laboratory work and analysed and interpreted the laboratory data. They reviewed and contributed to all drafts of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This study was supported by a subcontract from Johns Hopkins University with funds provided by grant number 19790.01 from the Bill & Melinda Gates Foundation. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Bill & Melinda Gates Foundation. We thank the Zambia Ministry of Health, City of Cape Town Health Directorate, the Western Cape Provincial Department of Health, and Zambian and South African National TB Programmes and all the district health managers and health facility staff for allowing us to work in the facilities. We thank the Zambia Ministry of Education, Western Cape Department of Education, and all the principals and teachers at the schools involved in the study. We thank the Community Advisory Boards and the members of the community who participated in the trial. We acknowledge the support and scientific guidance of the CREATE consortium leadership, R Chaisson (principal investigator for CREATE) and L Moulton (Coprincipal investigator for CREATE biostatistics core) and of the ZAMSTAR Study Advisory Group; M Borgdorff, D Enarson, B Chirwa, P Mwaba, Y Mulla, L Mvusi, MPoolman, I Toms, and K Jennings.

References

1 Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect* 1997; **119:** 183–201.

2 Glynn JR, Crampin AC, Yates MD, et al. The importance of recent infection with *Mycobacterium tuberculosis* in an area with high HIV prevalence: a long-term molecular epidemiological study in Northern Malawi. *J Infect Dis* 2005; **192:** 480–87.

3 Godfrey-Faussett P, Sonnenberg P, Shearer SC, et al. Tuberculosis control and molecular epidemiology in a South African gold-mining community. *Lancet* 2000; **356:** 1066–71.

4 Verver S, Warren RM, Munch Z, et al. Transmission of tuberculosis in a high incidence urban community in South Africa. *Int J Epidemiol* 2004; **33:** 351–57.

5 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:** e5602.

6 den Boon S, van Lill SW, Borgdorff MW, et al. High prevalence of tuberculosis in previously treated patients, Cape Town, South Africa. *Emerg Infect Dis* 2007; **13:** 1189–94.

7 van't Hoog AH, Laserson KF, Githui WA, et al. High prevalence of pulmonary tuberculosis and inadequate case finding in rural western Kenya. *Am J Respir Crit Care Med* 2011; **183:** 1245–53.

8 Wood R, Middelkoop K, Myer L, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. *Am J Respir Crit Care Med* 2007; **175:** 87–93.

9 Corbett EL, Bandason T, Cheung YB, et al. Prevalent infectious tuberculosis in Harare, Zimbabwe: burden, risk factors and implications for control. *Int J Tuberc Lung Dis* 2009; **13:** 1231–37.

10 WHO. Global tuberculosis control 2011. Geneva: World Health Organization, 2011.

11 WHO. WHO Policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization, 2012.

12 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.

13 Partnership ST. The global plan to stop TB 2006–2015. Geneva: World Health Organization, 2006.

14 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.

15 Miller AC, Golub JE, Cavalcante SC, et al. Controlled trial of active tuberculosis case finding in a Brazilian favela. *Int J Tuberc Lung Dis* 2010; **14:** 720–26.

16 Shapiro AE, Variava E, Rakgokong MH, et al. Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa. *Am J Respir Crit Care Med* 2012; **185:** 1110–16.

17 Cavalcante SC, Durovni B, Barnes GL, et al. Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2010; **14:** 203–09.

18 Cavalcante SC, Soares EC, Pacheco AG, Chaisson RE, Durovni B. Community DOT for tuberculosis in a Brazilian favela: comparison with a clinic model. *Int J Tuberc Lung Dis* 2007; **11:** 544–49.

19 Flores G, Abreu M, Chaisson CE, et al. A randomized, controlled trial of the effectiveness of community-based case management in insuring uninsured Latino children. *Pediatrics* 2005; **116:** 1433–41.

20 Middelkoop K, Bekker LG, Myer L, et al. Antiretroviral therapy and TB notification rates in a high HIV prevalence South African community. *J Acquir Immune Defic Syndr* 2011; **56:** 263–69.

21 Ayles HM, Sismanidis C, Beyers N, Hayes RJ, Godfrey-Faussett P. ZAMSTAR, the Zambia South Africa TB and HIV reduction study: design of a 2×2 factorial community randomized trial. *Trials* 2008; **9:** 63.

22 Arnadottir T, Rieder HL, Trebucq A, Waaler HT. Guidelines for conducting tuberculin skin test surveys in high prevalence countries. *Tuber Lung Dis* 1996; **77** (suppl 1)**:** 1–19.

23 Shanaube K, Sismanidis C, Ayles H, et al. Annual risk of tuberculous infection using different methods in communities with a high prevalence of TB and HIV in Zambia and South Africa. *PLoS One* 2009; **4:** e7749.

24 Sismanidis C, Moulton LH, Ayles H, et al. Restricted randomization of ZAMSTAR: a 2×2 factorial cluster randomized trial. *Clin Trials* 2008; **5:** 316–27.

25 Hayes R, Moulton LH. Cluster randomised trials. Boca Raton: CRC Press, 2009.

26 Feachem RG. The research imperative: fighting AIDS, TB and malaria. *Trop Med Int Health* 2004; **9:** 1139–41.

27 Kranzer K, Afnan-Holmes H, Tomlin K, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013; **17:** 432–46.

28 Ayles H, and the ZAMSTAR team. A household-based HIV and TB intervention increases HIV testing in households and reduces prevalence of TB at the community level: the ZAMSTAR community randomized trial. *CROI* 2012; 149bLB (abstr).

29 Health Systems Trust. Cape Town TB control—progress report 1997–2003. http://www.hst.org.za/publications/618 (accessed June 25, 2013).

30 Elliott AM, Namaambo K, Allen BW, et al. Negative sputum smear results in HIV-positive patients with pulmonary tuberculosis in Lusaka, Zambia. *Tuber Lung Dis*.1993; **74:** 191–94.

31 Costello A, Azad K, Barnett S. An alternative strategy to reduce maternal mortality. *Lancet* 2006; **368:** 1477–79.

32 Manandhar DS, Osrin D, Shrestha BP, et al. Effect of a participatory intervention with women's groups on birth outcomes in Nepal: cluster-randomised controlled trial. *Lancet* 2004; **364:** 970–79.