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HIV and TB in Practice: Going beyond the clinic to eliminate TB and TB/HIV; *by Theo Smart* *page 9*

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An intensive household counselling intervention reduces the burden of TB in ZAMSTAR study

By Theo Smart

ZAMSTAR

An intensive 'household counselling' intervention (involving TB contact tracing, multiple home visits, TB and HIV counselling and screening with linkages to care) reduced the prevalence of culture-positive tuberculosis (TB) by 22% within randomised communities in Zambia and the Western Cape of South Africa, according to the results of ZAMSTAR, a long-awaited, large-scale trial, which were released on October 30th at the 42nd Union World Conference on Lung Health in Lille, France.

"In the era of HIV, this is the first community-randomised trial of a public health intervention to be shown to have an impact on the epidemiology of TB at community-level," said Professor Peter Godfrey-Faussett of the London School of Hygiene and Tropical Medicine (LSHTM), one of three ZAMSTAR principal investigators.

However, another study intervention did not have a positive effect on TB prevalence. This intervention was called enhanced case finding (ECF) – ***but it is very important not to confuse this with intensified case finding (ICF) which involves actively screening people for TB***. ECF, as defined by this study, involved a number of activities to make a TB diagnosis easier to access and encourage people with symptoms to seek out diagnosis, but essentially continued to be dependent on a person's own health-seeking behaviour (more below).

ZAMSTAR was the largest study ever conducted to study methods of reducing TB prevalence at community level. Consequently, an entire conference symposium was dedicated to discussing the results, some aspects of which were surprising. These data will probably continue to be analysed for years to come. This article will only touch on some of the key findings from the study, and subsequent articles will present further analysis, and expert opinion on the trial's ramifications.

Background to ZAMSTAR

The communities in which the ZAMSTAR study took place all had an extremely high burden of TB and HIV, much of it undiagnosed.

Prof. Godfrey-Faussett noted that most people with culture positive TB have symptoms (90% overall, and 95% of the HIV-infected) – but not everyone complains of cough. Most did not meet the formal definition of 'TB suspect' at the time (cough for two or three weeks), "and might have been missed by routine services even if they had presented," he said.

"More alarmingly, perhaps, is that even those people who did meet the definition of 'TB suspect' when they went to the clinic, were not asked for a sputum specimen, because of the barriers involved in giving sputum and of registering and going through the process of getting a diagnosis made," said Prof. Godfrey-Faussett. "So there are many opportunities being missed for TB control. The ZAMSTAR philosophy has been that we do need to go beyond the clinic, if we are going to make a difference."

Consequently, the ZAMSTAR team sought to evaluate, in a rigorous manner, two ways in which to increase TB diagnosis and treatment and interrupt the transmission of TB in communities with a high burden of both TB and HIV (the home counselling intervention and ECF, described in more detail below).

Prevalence of TB in the ZAMSTAR sites (from the outcome portion of the ZAMSTAR study)

Zambian sites	Prevalence 542/100,000 adults (Stand Deviation (SD) 263)	Community range 221-10,967/100,000
South African sites	Prevalence 2319/100,000 (SD 487)	Community range 1489-3054/100,000

The study was carried out by a consortium of three institutions, Zambia AIDS Related TB (ZAMBART) Project, Desmond Tutu TB Centre (DTTC) at Stellenbosch University (in the Western Cape province of South Africa) and the London School of Hygiene and Tropical Medicine (LSHTM), as one of three large studies within the Consortium to Respond Effectively to the AIDS and TB Epidemics (CREATE), which received major funding from the Bill and Melinda Gates Foundation to do the sort of research which could produce policy-changing results.

Study design

ZAMSTAR randomised communities – not people (though the outcomes were measured in individuals). Thus, though the total population covered was 962,655, the trial had a total sample size of 24 communities: 16 were spread throughout Zambia – and 8 in the Western Cape province of South Africa.

The community, for this purpose, was defined as the population attending one TB diagnostic centre.

To participate in the trial, the communities had to have a minimum population of 25,000, a TB notification rate of more than 400 cases per 100,000 inhabitants per year and what was considered to be a high HIV prevalence rate.

Randomisation was stratified by country (since they were quite different) and by high and low tuberculin skin test (TST) baseline prevalence in the communities (see below).

It is very important to note that *all* the communities involved in the study received extra support – including additional dedicated staff – to improve TB and HIV care and service integration over the course of the study. This third non-randomised intervention may be important for understanding some of the study's more anomalous results.

Communities were randomised into four arms, six communities per arm.

- Group 1 served as the control since the communities in this arm received neither of the two interventions – though as Dr Helen Ayles, also one of the principal investigators, based in Zambia, said: "we don't like to call it a control arm", because of the additional staff. (Population included: 257,698.)
- Group 2: Enhanced case finding (ECF). (Population included: 148,090.)
- Group 3: The household intervention (HH). Population included: 257,729.)
- Group 4: Both ECF and HH. (Population included: 299,138.)

The primary endpoint was the prevalence of tuberculosis in the communities (compared by intervention) – in other words, ECF vs no ECF; and HH versus no HH.

The secondary endpoints, compared in the same way, included the incidence of TB infection at the community level (which was measured by TST conversions in children, indicating TB transmission); and at the household level: difference in TB outcomes, TB incidence, and HIV incidence were measured.

Study interventions

The intervention phase of the trial lasted three years (2006 to 2009) carried out by field staff and trained community members – with rigorous monitoring and evaluation and quality assurance.

Enhanced case finding (ECF)

ECF consisted of community mobilisation efforts to encourage community members to seek a TB diagnosis, combined with efforts to improve access to a timely TB diagnosis.

Community mobilisation activities could be drama, using megaphones, leafleting, football matches, fashion shows, beauty pageants and "whatever worked for that community," said Dr Ayles. In addition, there was a school intervention with TB/HIV education activities for children who, it was hoped, would then take the message of TB and HIV home to their families, and encourage household members to seek diagnosis whenever they had symptoms of TB.

To increase TB diagnostic access, sputum collection points were set up in the community, and at community mobilisation events. Also, open access or fast track points were set up at the community's TB clinic, so that individuals coming to the clinic with a cough could immediately go and give a sputum sample, and get the result back there without having to sit and wait and go through the normal clinic process.

The guiding principles for ECF were that each person should be able to give a sputum sample within a 30-minute walk of their home; and they should be able to get their sputum smear microscopy results within 48 hours.

Household intervention (HH)

The household intervention (HH) involved contact tracing of a TB patient, "who served as the gateway to a household at risk from TB and HIV," said Dr Ayles. It consisted of three visits by a trained household counsellor – one at the beginning of a TB patient's treatment, one at two months, and one at the end of TB treatment.

During these visits, the whole household was educated about TB and HIV and each household member was screened for TB using a symptom screen and smear microscopy. HIV counselling and testing was also offered for all members of the household, either to the group as a whole, the couple or individually. Then the household received ongoing counselling and referral for care for HIV and TB as necessary.

Process results

ECF did appear to attract at least some TB suspects, with 20,630 people submitting a sputum sample. Overall, 4.6% of the residents in the communities gave a sputum sample through ECF. Out of the samples submitted, 1699 (8.2%) were found to be smear-positive. This translated into an overall case rate of 277/100,000 (211/100,000 for Zambia, and 561/100,000 in South Africa), accounting for 24% of all the smear-positive diagnoses being made in the community. The cost for the intervention was (US) $17,137-24,455 per ECF site, per year, for a total cost of $0.37-0.71 per person, per annum.

Dr Ayles noted that getting the microscopy result back to the patient within 48 hours proved challenging. She said, "We only achieved our target in just under 50% of the time in Zambia," where diagnosis was decentralised. In South Africa's centralised system, a result in under 48 hours was obtained in less than 25% of the specimens.

HH reached 9353 households containing 36,751 people, though only 84% (27,074) were reached by all three household visits. This amounted to 5.8% of the population in the HH communities (though, again, some of the individuals at highest risk of TB and HIV). The intervention, if spread across the community cost US $24,126-34,661 per site per year, or $0.48-0.80 per person per annum.

Dr Ayles did not present the number or rate of TB cases identified by contact screening but a large number of HIV cases were identified. 99.3% of the adults (over 18,000 individuals) in each household received HIV education and counselling, of whom 12,000 (66.5%) accepted HIV testing, and 7021 (37.9%) were HIV-positive (the proportion of those who actually tested who were positive was much higher). Around 4000 are accessing ART and cotrimoxazole, but the uptake of isoniazid preventive therapy has been very low in these communities.

Study outcomes

After the intervention period, adults in the community were sampled at random to determine the prevalence of TB.

55,450 households were visited – though a number of households (or individuals) refused to offer consent to participate in the survey. 90,601 consenting individuals answered a questionnaire, submitted a respiratory sample (inoculated into two liquid culture tubes), and were offered HIV testing. Blood sugar testing was also offered due to the strong association between diabetes and tuberculosis. One batch involving 16,710 specimens was rejected due to quality assurance problems and 9461 specimens were rejected due to contamination.

Out of the remaining 64,430 evaluable cultures, 884 were found to have TB.

Upon analysis, only the HH intervention appeared to reduce TB prevalence in the community, but ECF had no effect (see table below).

A longitudinal study was performed to evaluate TB transmission in the community, as measured by TST conversions among children who were negative at baseline. The baseline survey was conducted in 98 schools in 24 communities, involving 21,393 children in grades 1-3. At baseline, 16.5% were TST positive (with an induration of ≥ 10 mm) in Zambia (95% CI 12-21.1, and 30.5% in South Africa (95% CI: 22.9-38.2). There was little difference seen between children with a BCG scar and those without.

8809 children who were negative at baseline were seen during the second survey roughly four years later – 733 had converted to TST positive. The HH intervention arm appeared to reduce conversions by 55%, though this was not quite statistically significant. However, the ECF intervention arm did not appear to reduce incidence at all.

The analysis of the secondary outcomes relied on a cohort survey (SOCS), in which TB index cases who were involved in the HH invention were enrolled for follow-up throughout the intervention period, to see whether there were changes in TB outcomes or incidence and HIV incidence in the home. None could really be

found partly because TB outcomes were generally good once diagnosed, and the incidence of HIV was already high. The SOCS visits may also have diluted the intervention effects.

"TB is sometimes seen as an unavoidable part of life in poor communities. We need to improve and strengthen our health services, we need better methods to diagnose TB in clinics and we need people affected by TB, usually in poor communities, to demand that things change," said Dr Godfrey-Faussett.

Effects of the interventions at the community level

	HH	ECF
TB prevalence in intervention communities	746/100,000	927/100,000
TB prevalence in non-intervention communities	883/100,000	711/100,000
Adjusted risk ratio (95% confidence interval)	0.78 (0.61-1.00) (significant)	1.11 (0.87-1.42) (NS)
TB incidence in intervention communities	0.87/100 years	1.41/100 years
TB incidence in non-intervention communities	1.71/100 years	1.05/100 years
Adjusted risk ratio (95% confidence interval)	0.45 (0.20-1.05)	1.36 (0.59-3.14)

The implications of ZAMSTAR for research and policy

By Theo Smart

The intervention that worked

So what was the primary take-home message of this complex study, the one that policy makers and funders need to take to heart?

Sending out counsellors to repeatedly make home visits for TB contact tracing (coupled with TB screening, home HIV counselling and testing (HCT) with effective linkages to care) reduced the prevalence of TB in a community with a high burden of TB and HIV by 22%. It also markedly reduced the risk of children in the home becoming latently infected, though this finding did not reach statistical significance (perhaps difficult given the relatively small number of communities in this study).

As implemented in this study, the enhanced case-finding intervention did not reduce the prevalence of TB in the communities (see below).

But contact tracing? Old news. Doing it well with HCT and making sure all TB/HIV cases get into care? Common sense really. It needs to be done.

Even so Professor Beyers recommended caution in generalising the results of the study to other settings.

"I think we have to point out that what we presented – especially from South Africa, were communities in the Western Cape province– and we need to be careful extrapolating, throughout our country," she said. "We still need interventions to reduce TB and HIV – especially in my country."

But while it's true that the Western Cape has a very high prevalence of TB, and a very high rate of TB transmission in the peri-urban communities around Cape Town (and also fairly good cure rates), it would be ludicrous if after all the time and money spent, the study's positive findings could not be used to inform policy in the region. We can't run a study like this asking the same question in every province.

As Dr Haileyesus Getahun of the World Health Organization's Stop TB department, who co-chaired the session, pointed out that "what we see in the southern part of the continent is different." He said that national TB prevalence surveys run by WHO and being presented concurrently in another symposium, show incidence dropping in parts of the world, including Ethiopia. "Something different is going on in southern Africa, which is the epicentre of the TB and HIV epidemic," he said.

Additional interventions are desperately needed targetting communities with a high burden of TB and HIV. Zamstar's data demonstrating that the intensified home counselling intervention has such a substantial impact must be used to force programmes and donors to really put these programmes in place.

"We had a discussion two weeks ago with the Global Fund directors and UNAIDS about reprogramming things that are working — and TB/HIV is the low-hanging fruit. But how can we push countries to implement TB/HIV activities that are having an impact?" asked Dr Lucica Ditiu, the Executive Secretary of the Stop TB Partnership. "We have to use these data, it should become routine in how we work."

Some audience members asked about the cost effectiveness of the intervention, and whether it could be taken to scale outside of a clinical trial.

"How scale-able is it?" said Professor Helen Ayles, another one of the study's principal investigators. "In Zambia, after the intervention finished in 2009, this was taken up by the communities and we've now trained several hundred household counsellors who are home-based carers, community-based organisations, so they are continuing household counselling — and it can be done with lay counsellors, so it can be done at scale."

"People keep saying that Zamstar was a huge study and an expensive study. The expense is in the measurement, in the rigorous evaluation," said Principal Investigator Professor Peter Godfrey-Faussett of the London School of Hygiene & Tropical Medicine. "This is four household counsellors per community, and these are people who aren't paid anything like as much as me, I'm afraid. These are local people, lay counsellors, recruited to work in the community, from the community in which they work. These are not massive interventions."

Indeed, according to Dr Yogan Pillay, the deputy director general of HIV/AIDS, TB in maternal, child and women health in the South African Department of Health, the intensified household intervention is very close to what is already being rolled out in South Africa.

"One of the implications for South Africa is that we have a high TB burden, together with a high HIV burden. So we need to do something dramatic about it. And I'm pleased to say that we have already started.We didn't wait for the results of the study. I'm particularly glad that Zamstar found some effect, otherwise all of our interventions are going to be inefficient and cost-ineffective."

The South African programme started in February of this year, just before World TB Day, with intensified case-finding at home level. Between February 2011 and March 2012, the goal is to visit 200,000 households of index cases, to screen all the household members for TB and offer them HIV counselling and testing (HCT).

The teams will also look to see if there are children in the household that are not fully immunised, or pregnant women who are not enrolled in antenatal classes. Dr Pillay said the country was well on the way to reaching this number, having visited over 100,000 households to date.

"We are following the example, in practice, and we are hoping to go to scale," he said, and emphasised that this was being done within the context of primary healthcare re-engineering.

"We have already started with implementing a ward-based primary healthcare outreach team approach, which will focus really on three things: HIV; TB; and maternal and child health — in the first two years. To help facilitate this, we are retraining 5,000 community healthcare workers and deploying them in specific geographic areas, with an emphasis on TB/HIV and maternal child health," said Dr Pillay.

This part of the programme began in October and Dr Pillay said that they hope to have data on how it is doing within the year. In addition health services in the school system are to be improved and dedicated specialists will be appointed– specifically paediatricians and obstetricians; and neonatal and paediatric nurses and midwives in each of the 48 health districts.

Dr Pillay said he had taken home some key lessons from the success of the household intervention:

"What the study pointed out to me is that we need to pay specific attention to:

1 The link between households and communities and clinics, and how to strengthen the referral systems.
2 How to ensure that the outreach teams perform to the necessary quality standards;
3 How do we better link the lab system with the outreach teams?;
4 How to ensure that the impact of what we do can be measured.

A point that was raised by several of the experts in the audience was that a large part of the benefit in the household intervention was related to the early HIV diagnosis and subsequent linkages into care. Dr Godfrey-Faussett sees the household intervention as complementing a number of developments in HIV care and management

"As for where all of this is going, if you think about integration between TB and HIV services: getting out into the households, and [so] moving more towards test and treat strategies. There's no doubt, at the individual level, that the risk of TB is lowered when people take ARVs but there hasn't been a controlled study showing that ARVs lower the risk of TB at the community level. But here's something, a TB intervention that does have an effect at the community level that we can now tie in with better HIV integration [with these test and treat strategies in the household]. Hopefully that's something that the next study we will do at the Zamstar sites can look at," Dr Godfrey-Faussett told HATIP.

The intervention that didn't work

As already noted, the more novel enhanced case-finding (ECF) strategy didn't have any impact at all on TB prevalence. Enhanced case-finding scaled up community-wide efforts to identify TB cases. with activities to increase access to a timely diagnosis for smear-positive TB, and a host of interventions to get people to seek out an early diagnosis so that they would get on treatment earlier and consequently would be less likely to spread TB. In fact, the communities randomised to that intervention did a little worse, though it wasn't a statistically significant finding.

"I'm sure the team will spend many hours trying to figure out why the community-based interventions did not work; and why the incidence really didn't come down as much as I think we would all have liked to see it come down," said Dr Pillay.

"They're not exactly the results that we'd hoped for," Prof. Peter Godfrey-Faussett of the London School Hygiene & Tropical Medicine, told HATIP. "We'd all hoped that ECF would show an effect. And yet we are very proud that our study has shown that an intervention, intensified household counselling, can reduce the prevalence of TB at the community level, the first RCT to do this in the era of HIV."

But what had attracted most people's attention about the ZAMSTAR study was its testing of an enhanced case-finding model that promised to involve communities. It was colourful and exciting: there was the innovation of sputum collection posts being installed in rural communities and informal settlements, the creativity in the social mobilisation campaigns with drama, radio and other media. And there were projects in elementary schools in which children were trained to look out for symptoms of TB in their family members, and then haul, push or pull their loved one to the sputum collection post if necessary.

But perhaps what was most engaging was the sense that ECF was empowering communities to take charge of their own health. So in some ways, the failure of ECF was a bit of a moral defeat. It also raises the stakes for other studies to demonstrate that increasing case detection will have an impact on the TB epidemic.

"I'm gutted," Dr Liz Corbett of the London School Hygiene & Tropical Medicine told HATIP, when asked how she felt about the results. "I'm so disappointed that the enhanced case finding in such a major study didn't show an effect."

Dr Corbett was hopeful that Zamstar would support the case for scaling up more aggressive case finding interventions that she believes are needed to reduce the burden of TB in communities.

Dr Corbett was not involved in ZAMSTAR, but has been very involved in researching different approaches to case finding and TB prevention in the community. At the Union Conference two years ago, she reported the results of DetecTB, which evaluated two periodic case finding interventions (a week every six months), providing TB diagnostic services with either a mobile van visiting the neighbourhood, or via door-to-door screening. The mobile van appeared to find a higher yield of TB cases, but together both interventions diagnosed about 41% of the TB cases in the community during the study period, presumably earlier than the cases would have been diagnosed otherwise. Consequently, this was followed by a substantial reduction in the prevalence of TB at the population level within a few years — with a more marked reduction seen in the HIV-negative than HIV-positive members of the community.

Dr Corbett did wonder whether there weren't too many differences between the urban sites in the Western Cape with exceptionally high burdens of TB and Zambia's sites, noting that "one size does not fit all when it comes to case finding". Differences between community structure and local transport could serve as more of a barrier to health services in one setting than another.

In addition, ECF couldn't really be standardised across the communities, as Dr Beyers noted during the Zamstar symposia.

"ECF was done locally by the local community, and while everything was carefully documented, it was heterogeneous. It was easier to standardise the household intervention," she said.

But it is also possible, that for one reason or another, the Zamstar ECF intervention may not have been aggressive enough, only contributing to about a quarter of the smear positive diagnoses in the community. There is little information, as yet, about how well

the enhanced case-finding intervention succeeded in getting people diagnosed and onto treatment *earlier*.

It is also worth pointing out that ECF relied on smear microscopy aiming for a 48-hour diagnosis, and smear microscopy misses a lot of cases, especially among people living with HIV who are far more likely to have smear-negative TB. The prevalence survey at the end of the study screened for culture-positive TB, which would include smear-negative cases that might have been more likely to go undiagnosed in the ECF arm.

One member of the audience drew attention to the fact that communities randomised to ECF actually had a higher TB prevalence than those without it. Had any of the investigators considered whether the intervention had a harmful effect?

Prof. Godfrey-Faussett pointed out that the confidence interval on that observation crosses 1, so this could well have been chance. But he also said that they had thought about it, and hadn't yet come up with any plausible way for the ECF intervention to do harm. However, they had only had the results for about a week at the time, and with more time to look at the data (it would be interesting to see a comparison of each arm of the study for instance), and analyses, someone may come up with at least a partial possible explanation.

It might be useful to consider exactly who was using those sputum collection centres in the ECF communities. Some of those cases were indeed the people investigators were hoping for, with highly infectious smear-positive TB presenting earlier, and being put on treatment sooner than they would otherwise. If that was all that was happening in the community, one would certainly think it should reduce the burden of TB, with the magnitude of the effect depending on how much earlier and how many more of the cases in the community they were picking up.

But that wasn't the only thing going on in these communities. Most of the people leaving specimens at the sputum collection centre didn't have smear-positive TB, yet they were leaving their specimens anyway, which must have increased the workload for the smear microscopist. That would have meant processing more specimens and more time looking at slides through the microscope, which could have delayed timely diagnosis, and the turnaround of results of cases likely to be positive. Studies have found that the efficiency and accuracy of smear microscopists falls with larger volumes of slides (their eyes get tired reading slide after slide after slide, day in, day out). But the microscopists in the communities without ECF may have had a lighter workload. So laboratory-related delays in diagnosis are one potential problem that could reduce the impact of ECF.

In addition to possibly flooding the lab with specimens, what else was going on with these other people who left their specimens at the drop off centre? What was their story? Obviously, they must have had a cough or some symptoms, or they wouldn't have done it.

Many of them could in fact have had smear-negative TB, especially if they were HIV-positive. (In fact, it seems likely that the household intervention with its prolonged contact and linkage to health services may have resulted in smear-negative cases being diagnosed sooner). Many of the TB suspects could have had some other respiratory infection, or condition, and again might be HIV-positive. Some of them could have been quite ill with other HIV-related complications.

So what would have happened to these people? If everything goes according to protocol, they should know in a few days that they don't have TB. In practice, Prof Ayles noted that they had trouble turning around results that quickly, succeeding only 50% of the time in Zambia, and only 25% of the time in the Western Cape.

But once sick people know that they don't have TB, what do they do? One would hope that they would eventually present to the clinic and receive diagnosis and care. But believing that they don't have TB, will going to the clinic to get a diagnosis seem to be as pressing, or will they try to self-medicate, or visit their sangoma instead? Could getting that negative TB result actually reduce further health-seeking behaviour, and delay diagnosis?

Many probably never make their way to the health services, so the sputum collection centre might have been their one effort to get diagnosed by Western medicine.

Those who do present to heath facilities may go later than they would have otherwise. For these people, sputum drop off/collection centres could have actually introduced another step before presenting for care. In settings where the drop-off centres weren't available, it is possible that more people would have gone to the clinic for diagnosis, possibly sooner if still motivated by fear that they have TB. Given the improving standard of care, there is a good chance that, they would have also received provider-initiated testing and counselling in the clinic, and gotten their HIV diagnosed. And once the HIV diagnosis was made, they should have received a more thorough examination, and had their other conditions, potentially smear-negative TB, diagnosed as well. On top of that, a proportion of the people who test HIV positive would hopefully have been put on ART, which would in turn decrease their risk of TB over the long run.

By not providing this opportunity for HIV diagnosis, ECF and the sputum collection centres may not do as good a job of getting people living with HIV into care and reducing their TB risk, as health facilities that offered more than just a TB diagnosis. Consequently, communities randomised to ECF could have had a larger pool of the very people who are most susceptible to TB, which could have undermined TB control in that district, possibly leading to a higher prevalence of TB. Which is just what the study found (though it was not statistically significant). That's compared to the arm that had no intervention, other than general health system and laboratory strengthening.

For the communities that had the enhanced household counselling intervention on top of standard clinical care, there would have been an even smaller pool of people at high risk of TB. One thing that the counselling intervention excelled at was finding large numbers of individuals with HIV in the index case's household, even though it did not appear to reduce the burden of TB within the households at the time point when this was assessed. Households receiving some continuity in care could have been more likely to receive early and effective treatment, and less likely to spread TB within the broader community.

This is supposition and the evidence in fact may turn out not to support it — nevertheless, in complex systems, interventions can have unintended consequences. There could be a danger with ECF approaches that are too narrowly focused primarily on smear-positive TB as though that is the primary problem in the communities. The DOTS strategy that successfully contained TB in the rest of the world ran into the same problem — even the best performing DOTS programmes in Southern Africa failed in the context of HIV. And even with the higher case detection rates that ECF may deliver, focussing on smear- positive TB alone, without increasing HIV case detection and treatment, may not be enough in a setting with a high burden of HIV.

In fact, in a recently published paper in the *South African Medical Journal* by Wood et al describe how TB control policy based on passive case detection and the DOTS strategy has failed in the region, partly because of HIV.

"Passive case-finding is detection of active TB disease among symptomatic patients presenting to medical services, and is promoted in developing countries as part of the WHO-recommended DOTS strategy," they wrote, but, "The DOTS strategy is insufficient in high HIV-burdened settings. In high transmission settings where effective contact numbers are high, lower case-finding rates and delays in diagnosis and initiation of chemotherapy result in ongoing transmission."

Wood et al call for a new more aggressive approach to go into the worst affected communities, using new diagnostic technologies and intensified case finding. Despite the the efforts to encourage case detection using enhanced case-finding in this setting, it remains passive. A number of other studies at the conference generated more promising results to increase case finding — though none of these have looked at population level impacts as yet. These are described in a separate article.

More from Zamstar to come?

Finally, Zamstar was one of the largest, most complex studies ever performed in communities with a high burden of both TB and HIV, and simply conducting the study was transformative for many involved.

Some of the study's benefits are ancillary. For instance, Dr Nathan Kapatha, the National TB programme manager in Zambia, said Zamstar opened his mind to a certain TB/HIV intervention.

"We learned that we can actually implement IPT. We implemented it within the Zamstar sites, and if we could do it in the Zamstar sites, why can't we do it in our programme? It gives me strength and confidence that we can implement what we should implement," he said.

And the data on the primary outcomes are only the tip of the iceberg. This study will be data mined for years to come.

"We still have lots more work to do," said Dr Beyers. "Lots of analyses need to happen; and we have a very strong social science team and there's an enormous amount of data available on risk factors for tuberculosis. So watch this space."

NAM publishes a wide range of publications on treatment for HIV. For details contact:

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HIV and TB in Practice: Going beyond the clinic to eliminate TB and TB/HIV

By Theo Smart

Key points

- **The ZAMSTAR study has shown that an intensive programme of contact tracing, home visits by community health workers, TB screening, HIV counselling and testing, TB treatment and linkage to HIV care reduced TB prevalence by 22% in communities that received the intervention in Zambia and the Western Cape province of South Africa.**
- **Active TB case-finding is a strategy designed to identify TB cases earlier in the course of infection. If TB cases are found sooner, they can begin treatment sooner, and so pass on TB to fewer people.**
- **The more people with undiagnosed TB in the community, the greater the chance that people will be exposed to TB repeatedly.**
- **Current `passive` case detection strategies largely rely on people coming to the clinic when they feel ill. This approach misses large numbers of people in the early stages of TB, and those who never make it to the clinic.**
- **More aggressive approaches to finding TB cases are needed, many experts believe.**
- **Household screening approaches which go out into the community to look for new cases have great potential. Several studies have shown a very high yield of new TB cases among the household contacts of TB patients.**
- **More research is needed to identify whether different types of communities need different approaches to active case-finding, and to assess the impact of large programmes of active case-finding on TB prevalence.**
- **Intensive household contact tracing could be delivered by trained lay counsellors at relatively low cost.**
- **Community health care workers will need training and supervision to manage their new responsibilities and changes in their roles where active case-finding is employed.**

Clarification: IPT and ART

A line was accidentally omitted from the key points of HATIP 183 on ART and TB prevention, which could make the point misleading.

Isoniazid preventive therapy can prevent TB in people with high CD4 counts *and* low CD4 cell counts, when there are signs of immune response to TB, as measured by a positive tuberculin skin test (TST). TSTs can be difficult to perform in some settings and given the high risk of TB in people living with HIV, WHO guidelines emphasise that TSTs are not a requirement for initiating IPT

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Improving the ways in which case finding is carried out was a major theme at the World Lung Health conference in Lille, France in October. This article reviews some of the key presentations on the subject and recent data that support more active approaches to case-finding. It also reviews some of the operational issues that arise when active case-finding approaches are implemented.

The move towards active case finding

"Do we need to go beyond the clinic?' The results of Zamstar show, unequivocally, yes, that we need to go beyond the clinic," said Dr Yogan Pillay, Deputy Director-General of the Health Department in South Africa, speaking at the 42nd Union World Lung Health Conference.

"Do we have a choice? Clearly, no. Why? Because TB lives in communities and in households. We need to find people with TB, diagnose them accurately and treat them completely. If we don't, we'll wind up with more of what we have in our country – MDR and XDR-TB," Dr Pillay told the audience.

The need to dramatically increase TB case detection is linked to a growing consensus among some experts that the TB response needs a radical makeover. There have been calls for the TB world to become far more ambitious in the targets it sets — such as the recent call from Keshavjee et al for zero deaths from tuberculosis in *The Lancet*[1]— and to no longer be satisfied with incremental improvement in indicators. New strategies and tools must be aggressively evaluated and, if efficacious scaled up.

One of the first things that must change is the dependency of TB control programmes on passive case finding (waiting for people with TB symptoms to present to the clinic for diagnosis and treatment), a half measure that leaves too many TB cases untreated in the community, where they perpetuate the epidemic. The goal should rather be to identify the case early and keep the patient on treatment until they are cured, interrupting the spread of the disease, and decreasing the incidence of new cases until the

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disease becomes more and more uncommon in the population and ultimately TB is eradicated.

The problem with passive case detection

The rationale for improved or active case finding is simply to find more of the cases of TB earlier.

"If we do that we will hopefully initiate therapy earlier, and thus reduce morbidity and mortality on an individual level but also reduce transmission to the population at risk; and one hopes in the end, to reduce TB incidence and prevalence," said Professor Jonathan Golub, of the Center for Tuberculosis Research at Johns Hopkins University at a symposia on active case finding that ran concurrently with the Zamstar symposia.

However, while WHO recommends intensified case-finding in HIV-infected patients, the current case detection policy for everyone else is a passive case detection policy. According to Professor Golub, this is based on a number of old assumptions: that smear is the best and only diagnostic available; that smear negative patients have been considered to not be very infectious; smear-negative patients will eventually become smear-positive; most patients seek care when symptomatic; health system strengthening *will* work; and active case-finding is too resource-intensive.

Research diagnostic advances and research on costing (discussed below) and other study findings suggest many of these assumptions have become untrue.

"Smear-negative patients are infectious – we've known that for several years now, said Prof. Golub. "Smear-negative patients will often *die* before becoming smear positive – and if we don't find them earlier, then we lose our chance of diagnosing them. Patients do *not* often seek care on their own – and therefore active case finding may be necessary to go find these patients. Health systems strengthening has been shown not to be adequate, in detecting TB cases at a rate that we would like to detect them."

As Dr Pillay suggested, failing to look for TB in the community or home could be at least part of the reason for the unrelenting TB epidemic and growing drug-resistant TB epidemics in southern Africa, clearly fuelled by the HIV epidemic and poverty. With passive case detection, a substantial proportion of the people who get TB will remain undiagnosed and untreated, typically for months, all the while unaware that they are spreading the infection to their family members and community.

According to a recent paper from researchers at the Desmond Tutu HIV Centre and the University of Cape Town, the more untreated TB cases there are in a community, the greater the chance that people will be exposed to TB repeatedly, leading to more infections and more TB activation — and this level of exposure and transmission to TB will sustain the shockingly high incidence of TB in Southern Africa indefinitely — unless something is done to reduce the number of people with undiagnosed TB in the communities.[2]

This will require a more aggressive TB control strategy, which the researchers suggest could include targeted prevention interventions, active case-finding approaches should be reconsidered supported by new diagnostic tools such as GeneXpert to get more people with TB on treatment sooner and reduce transmission. The strategy would be something, the paper's authors note, akin to the test-and-treat ART 4 prevention strategies that some HIV programmes are moving towards.

But southern Africa, is, after all, something of a 'special situation' — or more like the worst-case scenario. Is this reappraisal of TB control strategy really necessary in the rest of the world where most countries are reporting gains in the fight against TB?

Yes, because the improvement is nowhere near enough.

"Incidence is going down, but slowly, and we have seen for the first time absolute cases going down, but slowly," said Dr Knut Lönnroth of WHO's STOP TB Department during one symposium. "We need to become much more aggressive."

"Despite improving trends, the numbers speak for themselves," said Dr Lucica Ditiu, Executive Director of the Stop TB Partnership, who gave an impassioned plea for the TB community to be less complacent with the status quo of TB management during the conference's first morning plenary

"Each year, 1.4 million men, women and children continue to die from a curable disease. We ought to be outraged!" she said. "In the hour that we are talking now, 160 people will die from TB... We need to be shaking with a sense of urgency about the people suffering with TB. Treatment only costs $30 dollars. This is 2011 and we can't get treatments to people? Where is the anger?"

Part of the problem, she suggested is that people have been too complacent about the case detection rate.

"We are stagnating in our case detection rate, at around 65% this year," she said. "Where are the remaining 35%?! We really don't know very well, but that number is huge. Where are they?"

In fact, 3 million people with TB are estimated to go undiagnosed and untreated each year, and contribute to the spread of the infection. But in a number of ways, passive case detection also short-changes those who do get a diagnosis.

"Those who are eventually being reached and are receiving quality care usually had a long delay behind them," said Dr Lönnroth, "Many would have had experienced a lot of ill health and catastrophic health expenditure, and were spreading the disease to others during that delay."

"We are stuck around 65% case detection because we are taking the low-hanging fruit, just diagnosing those people that come to our hospitals and clinics, the people who can negotiate the health system, people more like us," said Dr Ditiu. "We need to shift towards those people that are not on our radar. Most of these people come from poor or vulnerable groups, people we may not be as comfortable with. And we'll never change the figures dramatically unless we scale up, working with and empowering the people suffering, civil society and the communities," she said.

"We in the TB control world have somehow got stuck," said Dr Lönnroth, explaining that TB diagnosis and treatment, according to the basic DOTS strategy, which relied on passive case finding focused on smear positive cases, had been acknowledged as one of the most cost-effective public health interventions, in the same league as vaccinating against childhood infections.

"Of course it is all still true. You invest one dollar, you get one dollar back. Now the problem has been or might be that everything that has evolved since has been compared to this benchmark," said Dr Lönnroth. "And when new interesting effective interventions come along, people all say well, this is good, interesting, this is effective — but it looks very expensive and not that much more effective than the basic stuff that we're already doing."

The cost-effectiveness of passive case detection is a large part of the reason why it has remained the case detection policy at WHO for so long, but as Prof. Golub said, nowadays "there is a new reality. Smear is not necessarily the best technology available – we've seen in recent years a lot of new technologies that are being developed. And there is some new and some old evidence that suggests that active case finding is not too resource intensive".

WHO is currently developing policy guideline's on active case detection — in fact, Prof. Golub's talk described a comprehensive literature review including all the active case finding reviews (so far just in English) published over the last 70 years, Some of the key findings of the review, including specific contexts in which active case finding may be more cost effective, are described later in this article.

Dr Lönnroth had a somewhat different take on the cost-efficiency of active case finding and other elements needed to increase the number of cases diagnosed and treated. His talk opened a symposia organised by TB Reach, which is a funding initiative to support innovative approaches to early and increased TB case detection, especially targetting the poor and vulnerable and other people with limited access to care.

"The first thing we need to transform is our mindset about cost, cost effectiveness and affordability," said Dr Lönnroth. "Now, when we are at the cross roads, we need to decide whether we are going to go for universal access to TB diagnosis and treatment, detecting everyone, and eventually go for TB elimination... if that is the case, then we need to make another type of comparison when we talk about affordability and cost effectiveness."

He described two ways of looking at this:

1) **Opportunity cost:** What would be the outcome, 10 or 20 years from now, and the cost of the lost opportunity, of not doing everything we can with the current technology to reach those who are most difficult to reach? What is the cost of leaving this amount of untreated TB in the community (considered in terms of the cumulative cost of treating all the active disease that would develop and be detected over the years as a result of leaving these people with TB unreached, undiagnosed and untreated in the community) compared to the cost of identifying and treating the index cases now?

"I'm convinced that being aggressive when stepping up case detection is going to be cost effective, and beyond that, it's going to save costs, for the individual, in the immediate, and for communities and for health systems as well in the long term," said Dr Lönnroth.

Clearly, this is similar to models of the cost-effectiveness of universal HIV test and treat, which could theoretically reduce transmission, become cost-effective over time, and eventually lead to the end of AIDS."

2) **Value for money in resource allocation:** The other comparison is to compare the cost of improving case detection with the costs of other interventions being implemented in the health systems, and justify the investment in the TB-related intervention in light of less essential activities. "Some expensive health interventions have very limited public health impact, there's also quite a lot of unnecessary and indeed expensive and harmful stuff happening in the health sector. So if we start comparing this with other things that are going on in the health services, we can find a much better argument for the needful investments," he said.

"So step up the advocacy and fundraising," he added.

Changes and innovations that may improve case detection

Dr Lönnroth listed five programmatic elements — including some specific tools, approaches and interventions — where transformation could increase the provision of TB diagnostic services and treatment to those who are most difficult to reach. This list serves as the framework for listing a number of related studies and innovations described at the conference.

Diagnostics

As Prof. Golub noted, there have been a host of diagnostic advances, including high-quality culture, liquid culture, drug-sensitivity testing and line-probe assays that could improve access to more timely treatment for many of the people with smear-negative, extrapulmonary and drug-resistant TB.

Clearly, the most transformative diagnostic test so far is the Gene Xpert MTB/RIF assay, which can diagnose TB within hours, faster and more reliably than smear-microscopy, though clearly it is much more expensive and introducing it into many countries will put a strain on resources for health.

GeneXpert is recommended to detect possible cases of MDR-TB (potentially useful in algorithms with drug susceptibility testing, that would have a better chance of getting the patient on an effective treatment regimen sooner). It is also recommended by WHO for first-line diagnosis of people living with HIV, and is much more likely to identify smear negative cases, especially if more than one specimen is run in these patients). However, if its use is limited just to the detection of possible MDR-TB or for diagnosis of TB in people living with HIV, it won't benefit the vast majority of people living with TB (85% of estimated TB is neither MDR, nor HIV-related). In South Africa, it is being scaled up as the first-level diagnostic test for all TB suspects, but this is a massive and expensive undertaking. Several presentations were made on the implementation and real world costs of the test — along with complaints that it is diagnosing much more MDR-TB than South Africa has hospital beds for, in settings where there aren't enough decentralised teams to deliver MDR-TB treatment.

Although the GeneXpert assay can produce a result in record time, its expense limits the number of reader units that countries can afford to have installed, and most facilities will have to ship specimens to the centralised labs, adding transport delays to the time it takes to get a diagnosis.

"It's a big jump from the microscope to GeneXpert, it is a really useful test. But we are not yet at the point of care," said Dr Ditiu.

The conference reports on diagnostics and the operational aspects of introducing Gene Xpert into clinical practice, will be discussed in a forthcoming edition of HATIP.

Dr Lönnruth also believes that chest x-ray remains an important screening tool that could help improve access to timely diagnosis for some patients.

"X-ray has been rightfully vilified as a diagnostic tool because it has poor specificity and the inter-operator variability is huge," he said, referring to the problem that different specialists reading chest x-rays have been shown to interpret them differently. "But a number of studies have recently shown that as a screening tool it can be highly useful in many prevalence surveys.

There were a number of studies on intensified case finding at the conference that reported that adding chest-x-ray increased the likelihood of identifying culture positive TB in people living with HIV who would not have otherwise been detected by screening algorithms or smear microscopy.

There have also been some recent advances in technology and practice that make chest x-rays easier to use, according to Dr Lönnroth. These include quality assured equipment and reading, digital X-ray and telemedicine. "You can send the picture off to a call centre in Hyderabad, where there is a radiologist and you'll have the results in 5 minutes," he said. There have also been advances in automated reading (Computer Aided Diagnostics – CAD) that he said could allow chest x-ray to be used as a screening tool, where a

positive result would need to be verified by a proper diagnostic test, such as GeneXpert.

"Finally, better diagnostics for latent TB infection are needed. This needs to go hand in hand with better treatments and more feasible treatments," he said.

Transform Public-Private mixes from projects to national scale up

In many countries, people seek and access care for TB outside the public health system, for instance, from private doctors, pharmacists or non-governmental organisations.

Public-private mix (PPM) is a comprehensive approach for systematic involvement of all the relevant health care providers in TB which tries to make certain that they all adhere to International Standards for TB Care and help the country achieve national and global TB control targets. PPM encompasses a range of diverse collaborative strategies, and there are many PPM pilot projects. Regardless, according to the recent Global TB report, non-public health providers typically contribute 20-40% of the TB cases notified in areas where they exist. So clearly PPM is important to fully scale up to maintain a high quality of service, and improve the reach of TB diagnosis and effective TB treatment.

"We need to step out of the project thinking, and really think of this as something that should be mainstreamed into all programme planning and scaled up on a national scale" he said. He referred to one CIDA-funded project on intensified case finding being conducted in five countries. One significant element of the programme was the inclusion of both public and private hospitals. This was "showing a dramatic contribution by the hospital sector, and a significant increase in case notification when you do so. This kind of intervention needs to be scaled up rapidly," said Dr Lönnroth.

Community and civil society engagement

The thinking around community and civil society engagement must also evolve. NGOs/CSOs are a critical vehicle to effectively scale up community-based TB activities. Study after study at the conference illustrated the benefits of this engagement, showing that CSOs/CBOs and expert patients can dramatically increase the reach and quality of TB services including diagnosis, linkage to treatment and retention in care.

"We are going to remain stuck at our current levels of programme performance, unless we start scaling up and engaging the civil society," Dr Ditiu said in the talk early during the conference.

WHO is currently holding a series of consultations to develop normative guidance to facilitate this scale-up, with constructive engagement between civil society organisations and the TB programme. This has already identified a number of key issues such as the need for clarity and simplicity in community-based TB activities. Quality indicators to measure engagement need to be developed, and innovation and use of modern technology is required.

The process is being spearheaded by Dr Haileyesus Getahun of the STOP TB Department of WHO, who moderated a conference symposium introducing the issue, that sought input from CBOs and the government health sector to better define the core elements that need to be addressed in the normative guidance WHO is developing. Essentially, the process seeks to make the interaction a little formal, so that the partnership between programme and civil society organisations can move forward in a more structured and productive way.

Transform the health systems

Many lessons have been learned in the recent expansion of health services, in resource-limited settings. To provide universal access, all diagnosis and treatment, services must be free of charge, *including new technologies*, throughout the health system.

In addition, the implementation of HIV and TB collaboration and integration of essential services have provided a model for exploiting synergisms across other programmes (NCDs, Maternal and Child Health, etc), and underscore the need for a strengthened PHC that can provide high quality services close to where the patient lives.

"We need to more actively promote Full Universal Health Coverage: including Social support and protection," said Dr Lönnroth, "to make health services more accessible, to make it easier to stay on treatment, and to make it more attractive to come forward and seek healthcare.

Outreach campaigns and programmes may also benefit from integration and collaboration to develop platforms addressing multiple diseases and risk factor for screening, combined with broad health promotion.

"If we are thinking about scaling up mass community screenings for TB, we cannot do this in a vertical manner, we need to link up with other health programmes that are thinking about screening for other risk factors, in particular non-communicable disease and HIV," said Dr Lönnruth. In additional to the financial and logistical benefits, some interventions may amplify the effect of the other. For instance, in the Zamstar study results, one of the strengths of the contact tracing intervention was that it provided increased access to HIV counselling and testing while the enhanced case finding intervention did not.

Transform our thinking about early detection

All of these elements ultimately support strategies that improve early detection.

For example, decentralisation of TB diagnostic services to points closer to the patient can reduce barriers that delay access to diagnosis.

Novel approaches and innovative technologies could shorten the time spent undiagnosed, such as innovations for outreach, campaigns, mobile diagnostics, health education, and e-health innovations. The TB Reach portfolio is rich with examples.

But the primary way to find cases earlier is through TB screening (active, enhanced, intensified case finding and contact tracing), especially when targetted at groups at risk of TB. Depending on the diagnostic tools, when screening is aggressive, it may identify cases at an extremely early stage in the course of disease, while they have no or vague symptoms. These may make up the majority of those who go undiagnosed.

TB screening of groups at risk may be performed to reach vulnerable groups with poor health access. Many face stigma and discrimination and are afraid to go to health services, or as Dr Ditiu said, "may not understand their rights."

Dr Lönnroth suggested that risk group screening should start with the most feasible-to-reach groups with high TB prevalence — these include all respiratory and obstructive pulmonary disease and in-patients where there is a high prevalence of undetected TB, HIV, perhaps diabetics in high TB burden settings, TB contacts (such as home-based, and prisoners). These are the low-hanging fruit where screening would be most cost-effective.

Of course, improving access to early diagnosis and life-saving treatment for marginalised populations is its own justification —

however, if the goal of active case-finding is to reduce TB prevalence, other factors, such as who is screened, and what proportion of the local cases are due to recent infections are critical determinants of the epidemiological impact of screening, according to Dr Corbett, so screening strategies must weigh other considerations in addition to picking the low hanging fruit (see below).

Fruit were the prevailing euphemism for TB cases in these studies, probably because Prof. Golub and colleagues had chosen to display the findings of the review, involving 30,000 abstracts on case finding, on the branches of case-finding trees, with fruit representing cases from different populations, hanging on different branches of the tree, depending on how easy they are to reach, as well as what sort of tools (type of active case-finding strategy) was best suited to harvest (or find) such cases.

He divided the studies by type (community, risk group, contact tracing) and risk group, and using weighted study data, determined how many people would have to be screened to detect one case in each group, in different settings, and with which tools. For instance, when looking at HIV-positive people, "what really stands out here is that when we look at and consider culture in a diagnosis – when we're screening for HIV-infected patients – we see that the number needed to screen (to detect a TB case) drops down considerably. This is really a reflection of the fact that many HIV-positive patients are smear-negative, culture-positive. Culture is extremely important in capturing the TB in that population," he said.

"How we conceptualise a case-finding tree is looking at the tree-tops: These are the populations that may be the hardest to reach, may require a ladder and require more work to get to. In this population, to find these cases requires community-wide, or door-to-door mobile units. The mid-range branches are where we classify people known to be living with HIV/AIDS. As we've mentioned, many of these are smear-negative and may need a culture. So this adds a little bit of complexity to the accessibility and the yield in these populations. Low-hanging branches – diabetics –are populations that are relatively ripe for screening and we need to get to them. Low hanging fruit – we refer to as the 'contacts'. The fallen fruit – those who are just really waiting to be screened are the prison population and the PMTCT clinics," he said.

But Prof. Golub further explained that these risks shift markedly based on whether someone lives in a low, medium or high incidence country. For instance in South Africa case yields among people living with HIV and general outpatient settings are particularly high (the fruit on the ground or low hanging). In medium and high incidence countries, people who use drugs or alcohol or the elderly are at higher risk.

Outreach to marginalised groups can yield significant rates for case-finding. According to Dr Ditiu, "in the TB Reach projects, after three quarters the number of cases detected and treated increased by 20%, which shows that if you have people focusing on the unreachable people with the tools you have, looking for the cases among the poor and vulnerable or sex workers, we can increase case detection."

Community population-wide screening is a much more ambitious and expensive undertaking, though the total yield and total impact is large. Reaching out to vulnerable communities where TB prevalence is high, such as poor neighbourhoods, urban slums, requires more resources and is very difficult to implement without involving others, including other healthcare providers (or programmes, such as the HIV programme people) as well as communities, civil societies and social services.

However, Dr Liz Corbett believes community screening exercises are absolutely essential to interrupt the cycle of transmission.

"With case-finding, one has to recognise that most TB disease is due to recent TB transmission, to casual contact. So, if you're doing profiling and trying to identify high-risk people, then you're going to miss most people with active disease in the community," she said. "Many of these people don't actually have much by the way of symptoms. If you look in the facility, you see an overwhelming predominance of sick HIV-positive people, but out in the community, some of the HIV-negatives especially, can be very healthy with their disease. So you find these people with your active case-finding intervention and by doing so, prevent disease in the quite near future, in both HIV-positives and negatives – that's the principle of case finding."

Major meta-analysis confirm high yields for household contact tracing

While the manner in which ZAMSTAR implemented its intensive household contact tracing intervention (with HIV counselling and testing, and repeated visits linking cases to HIV or TB care and support), may have had something to do with the magnitude of the intervention's impact upon TB prevalence in the community, a number of other studies presented at the conference, including Prof. Golub's meta-analysis, lent support to the importance of household contact tracing-based interventions as a TB case-finding strategy. However, the effectiveness of the intervention could be dependent on the training and support provided for the caregivers making home visits, according to one programme operating in KwaZulu Natal.

According to Professor Golub's review, which included 71 studies of household contact tracing, whether in low, moderate, medium, or high incidence countries, the number of household contacts needed to screen to find an active case was low — around 35 in high incidence countries.

"Contact tracing can be a very easy way to find TB," he said. "Many people here already recognise that contact tracing is not done in many areas, especially with high incidence and medium incidence where TB control does not have the resources available to screen contacts of TB cases, even though this is a population that's quite ripe for screening," he said.

Likewise, although the data on children were a little more difficult to disaggregate, and risks vary somewhat with background prevalence, the number needed to screen is very low for children who are household contacts, community contacts or living with HIV.

Another systematic review and meta-analysis in low and middle-income countries several years ago reached a similar conclusion.[3] Using the data from forty-one eligible studies of household contact tracing, the researchers found that about 4.5% of household contacts of TB cases in the studies were found to have TB. That is an extremely high yield for screening, though the reviews do not assess whether this form of active case finding could reduce the burden of TB in a population.

DOTS plus household contact tracing reduced incidence in Rio de Janeiro.

However, there may be supportive findings from another cluster–randomised trial published last year, which reported a modest reduction in TB incidence in Rio de Janeiro associated with a household contact tracing intervention that was somewhat similar to what was provided in ZAMSTAR.[4] Communities in the study were randomised to standard DOTS-support for people with TB, or to the intervention (DOTS-A) in which DOTS-supporters also performed household contact tracing for active TB and performing tuberculin

skin tests to screen for latent TB. TB suspects were referred for diagnosis, and diagnosed cases were linked to care, while isoniazid preventive therapy (IPT) was provided to those with latent TB.

Over the study period of four years, in the DOTS-A arm, 26 (4%) cases of active TB were diagnosed and treated among the household contacts, along with 429 (61.3%) cases of LTBI detected, 258 (60.1%) of whom started IPT. It should now be noted that only about 30% of the TB cases in communities randomised to the DOTS-A group, actually participated in the study. Despite this, TB incidence increased by 5% in DOTS communities and decreased by 10% in DOTS-A communities, for a difference of 15% after 5 years (P = 0.04). It's possible that IPT could have contributed to this effect especially if a substantial number of household members had HIV (most were untested). However, the investigators concluded that the early identification and treatment of active TB among the household contacts could have reduced TB transmission to the community.

Household contact-tracing for TB and HIV in South Africa and Ethiopia

An even higher proportion of TB cases were detected among household contacts in a study in the Northwest Province of South Africa (although many of the cases were only identified by use of culture.

"The active case-finding that we conducted with household contact tracing found a dramatic prevalence of undetected TB in household contacts – over 6000 per 100,000," said Dr Adrienne Shapiro of Johns Hopkin's University. "We also found a high rate of undetected HIV among household contacts.... So despite the purported high cost of contact tracing, this kind of a yield suggests that contact tracing may be a good way to identify high risk patients in settings where passive case-finding is not succeeding in controlling the epidemic."

Dr Shapiro presented two studies that were performed in the Matlosana Municipality in the Northwest Province, a semi-rural and mining and farming area, with residential township areas that are served by separate clinics. The first study assessed active case-finding in households (ACF-HH) targetting household contacts of 725 known TB patients for TB and HIV screening. In the second study, random-HH, 312 households were selected at random in the district, (using an aerial Google Earth map of the township, and excluding households involved in the contact tracing intervention). Staff were given GPS with the homes' coordinates, and invited the occupants to participate in the study.

Although the study household member selection was different in the two groups ,the subsequent study procedures were the same. A study team consisting of a nurse and two lay counsellors would visit each house, at least three times, in order to enrol as many members as possible. Each occupant was interviewed to complete a symptom screen questionnaire and was asked to provide a single sputum specimen, offered HIV counselling and testing, and anyone who tested positive for HIV had a CD4 cell count test. At the time the study took place anyone with a CD4 cell count below 250 qualified for antiretroviral therapy (ART). Sputum specimens were tested with smear microscopy and TB culture at the government reference laboratories in the local tertiary hospital. Culture was not the practice in the district but was included to assess the accuracy of the symptom screen and to determine how much smear-negative TB might be missed. The household teams returned the results to the households and provided referrals into the local healthcare system for treatment.

At baseline, the TB patients were more likely to be unemployed, have had prior TB and to have received an HIV-positive diagnosis at the time of enrolment than their contacts. Overall the groups were similar between the contacts and the random household members, although there was some suggestion of lower socio-economic status in the contact houses.

Results

In the household contact tracing study, 2% of contacts already had TB at the time of household visit. Three-quarters of the contacts gave sputum specimens, of which nearly 8% were positive for TB. Using the entire study population as a dominator, the prevalence of TB in the households was 6016/100,000 (95% CI 4839-7193/100,000).

In the random household study, a similar fraction of participants gave sputum specimens but only four TB cases were found; less than 1% of people screened for a TB prevalence of 405/100,000 (95% CI 0-982/100,000.

Although all the random household patients initiated TB treatment within a month, only 56% of newly diagnosed TB patients in the ACF-HH arm initiated treatment within a month. Anyone who was diagnosed with TB and had not initiated, received further follow-up visits from study staff in order to encourage them getting treatment.

As for HIV, in the ACF-HH group, 7% of household contacts had a pre-existing HIV diagnosis, 55% of contacts were willing to test, and 11% were newly diagnosed with HIV. Nearly 20% of these had a baseline CD4 of less than 200. In the random households, about 5% previously knew they were HIV-positive; 53% were willing to test, and of those about 14% were HIV-positive. Again, the study found a very high proportion of HIV-positives with a CD4 cell count of less than 250 at the time of diagnosis. Very few of those who qualified for treatment were reported to have started ART (only 2 out of 32 in the ACF-HH, and 6 out of 19 in the random households).

But some aspects of the study raise questions. 93% of the contacts were diagnosed solely on the basis of TB culture. A second sputum specimen might have led to more cases being diagnosed by smear, but it seems unlikely to have made a profound difference. In addition to being smear-negative, the contacts were largely asymptomatic – only 11% had any symptoms. Also worth noting, TB diagnosed in contacts in this study was much less likely to be in HIV-infected people than the index cases.

Dr Shapiro and colleagues then tried to determine how much earlier TB and HIV were diagnosed by active case-finding in the household than if the health system had waited for passive case detection. They found the CD4 cell count was about 219 cells higher among the people who tested HIV-positive in their study when compared to the CD4 cell counts at diagnosis of people presenting at a local clinic — which they believe suggests that they are identifying these individuals 3 to 7 years earlier than the norm. She noted that this might provide another way to find people earlier in the course of HIV disease, as programmes move towards earlier ART.

As for TB, the median duration of symptoms before diagnosis of the index cases was 4 weeks (which actually seems somewhat shorter than the norm to this writer), while the median duration of symptoms in the contact cases was zero days. It is not clear how long it would have taken for these cases to become symptomatic.

"It's probably much more than 4 weeks earlier that we're finding people when they're asymptomatic, because it will be even longer before they go on to develop symptoms," Dr Shapiro said, which she suggested would reduce the risk of transmission as they will receive

treatment before they have a chance to transmit the infection. She suggested active case finding/household contact tracing might also facilitate TB infection control. "By screening people in households you prevent people who have TB from going into clinical settings where they may be exposing immunosuppressed people to TB," she said.

However, there may be some who might disagree with some of Dr Shapiro's conclusions about some of the study's other policy implications regarding the use of culture for screening. Except for the diagnostic technique, implementation of the study was fairly simple.

"Participation was very good suggesting that this approach to case detection is feasible in the community setting," she said. "And also of note, the study staff had skills very comparable to existing counsellors and nursing staff at the local clinic, suggesting that the transfer of these activities to the local clinics might be possible within the setting of the national programmes."

Household contact tracing by health extension workers dramatically increased TB case finding in southern Ethiopia

Health extension workers, part of Ethiopia's health services already embedded and providing comprehensive care in local communities, can also perform contact tracing during home visits. They substantially increased case detection in their communities, particularly of women who were previously less likely to receive a TB diagnosis, according a study in Southern Ethiopia presented as a late breaker presentation by Dr Mohammed Yassin of Liverpool School of Tropical Medicine.

"Tuberculosis is one of the biggest problems in Ethiopia, and the country reports more than 140,000 TB patients per year," said Dr Yassin. But despite the expansion of the DOTS strategy to virtually every health facility in the country, the programme is challenged by a low case notification rate. "Because the gap between an estimated incidence and case notification rate is still wide, there are many cases that are not yet diagnosed and patients not yet receiving treatment in the communities."

Access to TB diagnostic and treatment services are limited by the uneven distribution of health facilities, with more in the urban areas, and by socio economic barriers hindering access for women, children, the elderly, and people with disabilities. There is limited awareness about the disease or the availability of the free diagnosis and treatment, but there is TB-related stigma. There are also some discrepancies and problems related with recording and reporting in the national TB Control programme.

However, Ethiopia has embarked upon a progressive response to its human resources for health shortage, by training new cadres of health workers to deliver essential care throughout the country. The country has implemented a 16-package Health Extension Programme and deployed over 30,000 Health Extension Workers (HEWs) to communities to provide comprehensive health services. Health Extension Workers, almost all of whom are women, according to Dr Yassin, work for the Ministry of Health and live within the communities.

What if these HEWs, who are already living among the rural population, could deliver community-based DOTs to support adherence and improve outcomes, and at the same time perform contact tracing in the homes to increase case detection [like the DOTS A arm in the study in Rio] and also improve the routine recording and reporting systems?

With support from TB Reach, the Canadian-funded initiative that supports the development of novel strategies and projects to promote early and increased TB case detection, and the Stop TB Partnership, Dr Yassin and colleagues developed a project including a number of community-based interventions to support enhanced case finding in the Sidama Zone, home to three million people in Southern Ethiopia.

The project involved the establishment of a field coordinating team and project office, hiring supervisors in each of the 19 districts throughout the zone, who were provided with motorbikes to support TB control activities. Community-based DOTS was introduced by engaging HEWs, who performed TB diagnosis and treatment support activities. There were extensive ACSM activities to increase awareness about TB and availability of services within the villages and communities. The routine recording and reporting system also had to be strengthened in order to monitor and supervise the programme.

There were some basic ACSM activities including awareness creation workshops conducted at all levels and attended by over 1200 political, community, religious leaders, stakeholders, health personnel & ex-TB patients. ACSM activities were also conducted in schools, social and religious gatherings and through local radio.

What clearly was crucial was training the project staff – HEWs from 524 kebeles (the smallest administrative unit in the country), 300 health centre staff, TB focal persons and the 19 supervisors. In addition, the district labs were upgraded somewhat with the purchase of 20 LED fluorescent microscopes and lab technicians were trained.

As part of the community DOTS programme, in the course of their daily business, HEWs visited homes to provide treatment and support, and screened for symptoms of TB. HEWs identified TB "suspects," collected their sputum samples, and prepared the smears on slides for microscopy and phoned their supervisors to collect the smears. (They all have mobile phones to keep in contact with the supervisor). The supervisors would pick up the slides, take them to the lab technicians, who examined the smears, and reported results to supervisors (keeping slides for EDA). The supervisor would get the results, and make certain that treatment was initiated by smear-positive cases in their residences, screened household contacts and initiated IPT for children who were asymptomatic. Treatment support was provided by HEWs who reported the outcomes and follows smear-negative cases within the communities.

Case finding between October 2010 and September 2011

A total of 33,510 (60% females) TB suspects were identified and screened by HEWs, 1473 (4.4%) were diagnosed as smear-positive and initiated treatment (54% females). Over 15,000 contacts of smear-positive cases were visited: 1150 were symptomatic and 48 who had TB were treated, and 659 asymptomatic children under the age of five received IPT. 2283 (45% female) patients with smear-positive TB and 1420 (44% females) with smear-negative TB, were diagnosed and initiated treatment in health facilities.

What is important is that the smear-positive case notification rate doubled during the first year of the project, from 68 to 132 per 100,000 population. A similar phenomenon was not observed in a similar zone which didn't implement the project and served as a control.

In addition, the new community-based approach resulted in a higher proportion of females and children being screened and treated for TB. Women are now being screened and treated in more or less equal numbers as men.

"Our approach brings services closer to communities and has almost doubled the TB notification rate," said Dr Yassin. "Decentralization of diagnostic and treatment services and

involvement of HEWs in TB control is feasible and key for improved and more equitable TB control program in Ethiopia. However, implementation of this community-based approach requires proper planning, capacity building and collaboration with stakeholders and engagement of communities."

Dr Yassin says the intervention achieves a high impact and relatively little cost.

"The HEW are already part of the MOH programme providing comprehensive health services, so we are not paying them anything extra, other than reimbursing the money for the mobile phone airtime. We did buy motor bikes for each of the 19 supervisors and paid for fuel so the supervisors could get around and transport the specimens," he said. "But considering the value of this project, which yielded a case detection rate that doubled within one year, the investment of this project is really minimum. So we are now discussing scaling up within the national programme, and already other zones are already planning to initiate the same activities. We need to maximize this type of high impact intervention with high value for the minimum money activities.

Study in KZN suggests it may be time to 'upscale' community health workers to deliver active TB case-finding interventions

Community health workers perform home visits and could provide similar screening services in many places with high burdens of HIV and TB, but a study presented by Jeanine Uwimana of the University of the Western Cape found that existing community health workers could be under-utilised, under-trained and likely to miss critical opportunities to provide TB screening, household contact tracing, and other essential TB/HIV activities.

"We know that provision of TB and HIV integrated services needs to go beyond the facility fences, and that we'll have to see how we can provide that at a community level," she said. "But first we have to see what is currently happening at the community level."

KwaZulu-Natal is one of the provinces with a good, strong community health worker programme. So Uwimana and colleagues performed a study todetermine the level of provision of TB/HIV integrated services at community level in four sub-districts in Sisonke district, in KwaZulu Natal with an estimated sample size of 3,000 households, including adults aged 18 years and above, using a cellphone system to collect the data.

4,488 household members were interviewed. Most of the participants were women, with a high level of unemployment (90%); with 46% of participants earning between R500.00 to R1000.00 per month (less than 50 to 100 Euros per month).

Out of the 3870 household members, 6% were currently diagnosed and on TB treatment. But among the 3481 females – 4.5% were pregnant, and of the women who were currently pregnant, 7% were HIV-positive and 10% were diagnosed with TB and on TB treatment (illustrating the particularly high risk of TB/HIV in pregnant women). When this survey was performed, in 2008, only 56% of the participants had been tested for HIV, 22% were HIV positive.

A total of 3,012 (78%) of households said that they had been visited by community health workers, but few were being offered critical TB- and HIV-related interventions, such as TB symptom screening, which was performed in only 21% of the households. Home-based HIV counselling and testing was offered to 17%. Only 7% of the TB patients were provided with adherence support and ART adherence support, was offered to only 2% of those who needed it. Likewise, only 2% of the women who became pregnant were counselled about Prevention of Parent to Child Transmission. (PPTCT)

"The findings of this study suggest that key services such as TB symptom screening, TB contact tracing, and treatment adherence support for TB, ART and PMTCT clients that community-based caregivers are believed to be providing are inadequate. There is an urgent need to see how we can scale up or enhance the provision of TB and HIV integrated services at the community level," she said. "There is need as well for task shifting and upscaling of community care workers to provide comprehensive care."

This led to an intervention that Uwimana described in a separate presentation on the following day, with a study comparing standard community health worker to a new cadre of community health workers she and her colleagues at the TB/HIV Care Association and the Sisonke Health District trained in essential TB/HIV activities.

She and her colleagues had observed that multiple cadres of community health workers exist in South Africa, each performing somewhat different duties. People in the community routinely received multiple home visits from different types of care workers. In an effort to streamline this process, Uwimana and her colleagues at TB/HIV Care Association and the Sisonke Health District, decided to take home based caregivers and community health workers, and train them together as one cadre: community care workers.

The comparison was something of a foregone conclusion, as the community care workers provided a wider variety of TB/HIV services. When compared to the standard community health worker, the community care workers intervention cluster performed much better in terms of TB symptom screening, STI screening, and household contact tracing, with a statistically significant difference.

However, while these may be relative low-cost interventions, Dr Uwimana made it clear that programmes shouldn't jump to conclusions about how easy it will be to implement.

"We had enormous challenges in implementing this intervention," she said, listing familiar problems tracking down patients. Other challenges related to lack of supervisory capacity. "In some areas we had such a large number of community care workers with only one supervisor/community health facilitator, placed at the community level who was in charge. According to the norm it's one community health facilitator to 25 community care workers, but in some areas there were more to control – that was a big challenge for supervision; Lack of transport was a main problem; and then the quality of supervision was one of the challenges that *ultimately* affected the results of our study. Without proper supervision of these community care workers, we cannot be successful."

But will these programmatic elements really get us to TB eradication?

Active screening and other interventions to increase case detection and detect cases sooner should reduce the burden of illness in the people who receive diagnosis and treatment (especially ICF in people living with HIV). That alone is reason enough to scale up these interventions in risk groups and household contacts. But how well do the community-wide interventions (the most expensive approach), actually reduce the incidence of TB in the community? There aren't enough data to say.

"So far from within this systematic review, we have noticed that what is missing in the literature, is really hard outcomes," said Professor Golub. "The reason we're doing active case finding is to try to change the epidemiological situation in a population, and we really need to do studies that are showing a change in TB incidence,

a change in prevalence, a change in mortality after a case finding strategy has been implemented. It's relatively easy to report how many cases you have found from doing case detection, but you want to report how many cases you have averted and hopefully show a change in the epidemiological situation. We hope it will result in a drop in diagnostic delays, and finding people earlier. But we want to see studies doing a head-to-head comparison of different strategies to see which ones are most effective at different populations, and operational research is quite important to include in these studies, determining specifically the cost-effectiveness of different strategies in different settings."

That's a very tall order, and Dr Corbett seemed somewhat pessimistic about the ability to standardise case-finding interventions well enough to be able to draw these sort of conclusions from studies. After describing her positive experience with the case finding study in Harare, she described her follow-up study in Blantyre, Malawi.

"Unfortunately as we are getting more and more knowledge about case-finding, it seems that there's no real 'one-size fits all' approach. So, the mobile testing van that we use so successfully in Harare is actually quite difficult in Blantyre – the road access is poor; you can't penetrate communities in the same way that you can in Harare" she said. She added that the Zamstar study shows "really we don't understand well enough how to work with communities, they're much more difficult to standardize and interact with than facilities. "

Based on some mathematical models she believes that there will also be very big differences between communities, based upon the characteristics of transmission in that setting. "What matters is how well you are doing in terms of detecting, but also very critically, how much of your active TB is due to recent TB infection? If you're in these high HIV-prevalence areas in Africa, where about 80% is due to recent infection – you'll get a big impact. If you're down to about 40%, as you would be in parts of South-East Asia then you can anticipate a much lower impact. But the modelling also shows the potential to be cost saving in high TB transmission settings," she said.

"Community-level interventions have potential for rapid gains, and we should really be focusing on them because of that," she said. There's much to learn still about case finding and demonstrating hard outcomes, and eventually, they will need to study the impact of these campaigns with a long-term intervention using enhanced monitoring and evaluation to measure TB incidence outcomes – which would require robust and stable routine systems.

"But we have to accept that one size did not fit all communities. I'm adopting an approach where you set targets, you titrate your effort [in] the community mobilisation component until you reach something that you're happy with," she said.

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