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Strengthening TB laboratory capacity to support active case finding

By Theo Smart

Key points

- Improving the rate of TB diagnosis among people living with HIV depends on improving the ability of health facilities to diagnose TB. Faster TB diagnosis will enable people to be treated sooner, reducing the number of TB deaths. It will also reduce the time that infectious people are able to pass on TB.
- To achieve all these outcomes we need screening methods that minimise the time between presentation at the health facility and diagnosis of TB. In particular we need tests that don't miss cases of TB in people (sensitive) and which correctly identify people as having TB rather than another infection (specific).
- Smear microscopy, the current first line of diagnosis, misses many cases of TB in people with HIV; when combined with symptom screening, it produces a lot of TB 'suspects' who turn out not to have TB when tested using TB culture, the next stage of diagnosis.
- Current methods are missing TB cases, but can also result in a large number of unnecessary and expensive lab tests. These methods also involve long delays and multiple visits to the health facility, and many patients get lost during this process.
- A point-of-care test for TB which can diagnose patients while they wait would be a big improvement. So far we don't have a test that can do this which is suitable for use in every health facility.
- However, some new tests are beginning to speed up TB diagnosis.
- The Xpert MTB/Rif test is already being rolled out as the first-line diagnostic test in South Africa. It can provide rapid results, and can also show whether a patient has resistance to rifampicin, a marker for multi-drug resistant TB.
- Evidence from South Africa shows that the test is already increasing the number of TB and MDR-TB cases diagnosed, and its use has resulted in an increase in the number of patients receiving TB treatment.
- It is estimated that the test could reduce the average delay between presentation and treatment down to five days, and substantially reduce the number of TB patients who are lost before completing the diagnostic process.
- Xpert MTB/RIF costs around \$32 per test, so it may not be affordable in all settings. However an economic analysis in South Africa suggests that in smear-negative TB patients Xpert MTB/RIF would prove cheaper than standard diagnostic procedures by the time the rate of loss to follow-up under standard procedures is taken into account.
- Multiple Xpert MTB/RIF tests may be necessary for TB diagnosis in people with advanced HIV disease (very low CD4 cell counts).
- Another cost-effectiveness study using data from a wider range of countries estimated that use of Xpert MTB/RIF as part of the TB diagnostic algorithm would be cost-saving compared to standard practice in settings where liquid culture is expensive and difficult to implement. A diagnostic algorithm employing

liquid culture would identify 10% more TB cases than Xpert MTB/RIF, but was also the most expensive per case diagnosed.

- The up-front costs of introducing the Xpert MTB/RIF test will represent a barrier to implementation, but a number of donors and programmes are already supporting introduction of this technology.
- Growth in use, pressure through advocacy and competition may all play a part in reducing the cost of this test in the future.

This series

This edition of HATIP is kindly supported by the Lilly MDR-TB Partnership. This article forms the second of a three-part series on the implications of new laboratory tests for TB diagnosis. The first part, on active case finding, symptom screening and the use of laboratory tests to support active case finding, was published in [January 2012](#).

The third part of this series on new TB diagnostics will examine the role of two other diagnostics, LAM and fluorescence microscopy, in the improvement of TB diagnosis.

The need for improved diagnostics for TB

If we ever hope to see the sort of profound reductions in the incidence of tuberculosis (TB) that could eventually lead to the 'elimination of TB', health programmes (and not just the TB programme) will have to detect a much higher proportion of the cases of active TB than at present, diagnose all the TB cases and start people on treatment sooner. Finding the undiagnosed active TB cases and shortening the time to diagnosis will reduce the opportunities for TB transmission within the community. But this can only be done by dramatically scaling up active TB case finding strategies such as intensified case finding (ICF) among people living with HIV, and household contact tracing – and by strengthening the TB laboratory capacity to support it.

The programme may depend on confidence in the ability of the laboratory and its capacity to deliver accurate and timely results – healthcare workers may be reluctant to refer for diagnosis if laboratories are unable to keep up with demand. Symptom screening can't increase the rate of TB diagnosis without the laboratory capacity to identify the actual TB cases among people with suspected TB. The more reliable the lab, the better the yield of active case finding activities. The faster the lab returns the results, the better the clinical outcomes should be.

But, at the intermediate and peripheral sites where people typically present, there are limits to how fast and reliable TB diagnostic facilities can become: chiefly, the limitations of acid fast bacilli (AFB) smear microscopy, which has been the first stop for diagnosis for 130 years, virtually unchanged. In addition to being labour-intensive (one lab technician examines stained slides for bacilli, one specimen at a time), microscopy is notoriously insensitive, failing to pick up most active TB cases in people living with HIV or in children.

Despite the shortcomings of microscopy, the household contact tracing strategy used in [the ZAMSTAR active case finding study](#) was still able to significantly reduce TB prevalence at the population level when relying on smear microscopy for diagnosis. However, laboratory strengthening had been a critical component of the ZAMSTAR study. Numerous studies have shown that the basics aren't being done well at many TB laboratories in resource-limited settings, and that some training and additional staff can make a major difference. So, one of ZAMSTAR's goals was to strengthen labs enough that they could handle a greatly increased number of

specimens, and still get the results back to the patient within 48 hours. Not every site was able to reach or maintain that target (especially in South Africa), but lab capacity did improve considerably.

There have also been some improvements to microscopy. "We now have fluorescence microscopy," said Professor Yukari Manabe, of Johns Hopkins University, who is currently working with Makerere University in Uganda. She was speaking as co-chair for the TB diagnostics session at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle in March 2012. "The original fluorescence machines are really unaffordable. But now with light emitting diode [LED] technology we can increase sensitivity on average in meta-analysis about 10% compared with ZN [Ziehl-Neelsen, conventional smears]." (It should be noted however this heightened sensitivity was not observed in one study in people living with HIV, discussed below.)

Because microscopy misses many cases, TB culture has always been the final word in TB diagnosis. Unfortunately, it is technically complex to perform, requiring specific laboratory equipment and appropriate biosafety conditions. Aside from southern Africa, major cities, and centres of excellence, TB culture is not widely accessible in many of the countries with high burdens of TB/HIV – even though normative guidance from the World Health Organization (WHO) stresses that these are just the places where "a substantial investment in culture capacity is required, given the absence of means to diagnose smear-negative TB."¹ In addition, conventional culture on solid media is slow, taking up to six weeks.

Some recent innovations in culturing technique and media have speeded up the culture process. For example, liquid culture using equipment such as the BACTEC can be an automated process with a high throughput (number of specimens per batch processed), delivering a diagnosis within two to three weeks, though again the expense and complexity of the equipment restricts its use to reference laboratories in resource-limited settings.

The limitations of current screening methods: the ACTG 5253 study

Although HATIP has recently given detailed coverage to the use of the WHO 4-symptom screen for TB diagnosis, and its performance in comparison to other screens, or lab tests used as screening tools, a noteworthy study was presented at the TB diagnostics session at CROI which illustrates how much microscopy can limit the potential of a good TB screening strategy.

ACTG Study 5253 was a large simple observational study, originally intended to look at different TB screening/diagnostic approaches among people living with HIV (PLHIV) who were about to start antiretroviral therapy, at sites across the globe where the prevalence and incidence of TB and HIV were vastly different.² Only one of several hundred PLHIV at the Indian/South American sites had a positive culture, so further analysis was restricted to the African sites.

The investigators had hypothesised that a standardised diagnostic evaluation (SDE), which they thought at the time would be an enhanced approach, would improve identification of culture-confirmed TB as compared to what they called the standard of care (SOC) diagnosis. Available specimens from the participants were cultured in solid and liquid media.

The standard of care diagnosis, as they defined it, identified suspects by using a basic symptom screen, which asked if the people living with HIV (PLHIV) had experienced any one of the following symptoms: cough, weight loss, night sweats, fever within

the last month. This screen is quite similar to the WHO 4-symptom screen, except the WHO screen looks for any *current* cough. Suspects would have their sputum smears examined by standard microscopy, and if they were positive, they would be diagnosed with TB. If they were negative, but had a chest X-ray suggestive of TB, or were pregnant, they were treated as having TB.

The standardised diagnostic evaluation involved use of an expanded symptom screen (adding fatigue, chest pain, lymphadenopathy) and gave more attention to symptomatic details, such as duration of cough, whether there was sputum in it and current weight, to see if any of these factors might enhance the screen's predictive value. TB suspects then had their sputum smears examined by fluorescence microscopy, which has previously shown greater sensitivity than standard microscopy.

However, data were collected on each possible predictor from the symptom screen, (as well as each added or expanded symptom in the SDE cohort), together with the chest X-ray and microscopy results *in all of the participants* so that their individual or combined sensitivities, specificities, positive and negative predictive values could be assessed.

The African sites enrolled 445 people, 13% of whom were diagnosed as having culture-positive TB. The performance of some of the individual predictors is listed below.

There were some incongruities between the poster describing the research and what was reported by Dr David Katzenstein of Stanford University, who gave the presentation at CROI on behalf of the study team's lead authors. For instance, he reported that AFB smear microscopy was positive in only 16/54 (30%) of those with culture positive TB – the poster only lists 6 out of 54 (11%) as AFB smear-positive, culture-positive cases. Surprisingly, fluorescence microscopy performed slightly worse, when meta-analysis of other available studies has concluded that it is about 10% more sensitive. This suggests either technical or training deficiencies (such as specimen preparation, technician training or performance), or perhaps the report of increased sensitivity doesn't hold true for specimens from PLHIV with TB in Africa.

Overall, the SOC screening approach had 54% sensitivity (95% CI 40-67%) and 76% specificity (95% CI 72-80%), with positive and negative predictive values of 24% and 92%, respectively. But according to the investigators, for the SDE approach, neither use of fluorescence microscopy nor extended signs and symptoms improved the predictive values of SOC.

That being said, however, the poster does identify some individual or combined predictors that are more sensitive, and do have higher positive or negative predictive values.

Dr Katzenstein drew attention to the symptom screen alone, which had greater sensitivity (90.7%), but only 20.5% specificity; a low positive predictive value (13.7%); but a high negative predictive value of 94.1%. Once smear microscopy is added however, that sensitivity falls to 9%. There are a number of other interesting combinations. For instance, cough and lymphadenopathy seemed to be both more sensitive and more specific than the symptom screen alone (92.6% sensitivity, 24.8 specificity, 14.5% PPV, and 96.0% NPV). Adding any lymphadenopathy to the 4-symptom screen resulted in 96.3% sensitivity, 16.1% specificity, 13.7% PPV, and 96.9% NPV. Another interesting combination was any of the four symptoms and a CD4 cell count below 200, with 98.2% sensitivity, 18.2% specificity, 14.2% PPV and 98.6% NPV.

There were also five patients who had none of the four symptoms but who were culture positive.

Dr Katzenstein concluded that symptom screening “was actually pretty good in terms of the 91% sensitivity that we got; the specificity however as you would imagine is horrible, it’s 21%.”

The poor result for smear microscopy “helps reinforce the notion that it’s bad in HIV-infection,” he said. “And so we’ve become nucleic acid amplification test (NAAT) advocates.”

In conclusion the investigators recommended that, “symptomatic patients should be tested with more sensitive tests, such as culture and/or NAAT.”

The best-known example of the use of a nucleic acid amplification test for TB diagnosis is the much vaunted Xpert MTB/RIF test, the automated, cartridge-based test which simultaneously detects TB and rifampicin resistance (which is being treated as a surrogate for MDR-TB by some programmes, such as South Africa, until confirmatory drug sensitivity tests say otherwise). While the test is profoundly more sensitive than smear microscopy, the equipment and cartridges do not come cheap – though studies are suggesting that even at current pricing, it may be cost-effective in some settings.

But, during the subsequent discussion at CROI, members of the audience made it clear they were worried about the cost implications of the growth in the number of TB suspects identified by the symptom screen, which would result in having to send numbers of specimens for half or two thirds of their patients.

“The challenge is that since the specificity of this screen is so poor, we end up having to do an awful lot of these other expensive tests. How do you think we are going to afford this?” said one audience member.

Given that new tests such as Xpert MTB/RIF are not yet available in many settings, one might first consider different approaches to whittling down the suspect pool. One option might be to leave it to the clinician to judge whether every TB suspect identified by ICF or other active case finding strategies should go through the diagnostic process immediately. But there are not so many expert clinicians available to make these decisions in resource-constrained settings.

HATIP has previously noted that the WHO 4-symptom screen is supposed to rule out TB (to identify those who should be taking isoniazid preventive therapy), and we questioned whether another screen could be developed and applied which is better at ‘ruling in’ active TB. Unfortunately, looking at the incremental yield from combining predictors presented in this study, adding a requirement to refine the screen for an abnormal chest X-ray or positive smear might increase its positive predictive value but would sacrifice a lot of its sensitivity – indeed in most cases, adding any criteria that increased the specificity of the screen seemed to knock sensitivity down to 54% or lower. But the poster presentation clearly did not show every possible combination.

“A very simple and pragmatic strategy to improve specificity, if feasible, is to simply review all symptomatic patients in 1-2 weeks unless symptoms are highly convincing”, Professor Ben Marais told HATIP. “If symptoms persist despite treatment of the most likely alternative cause, then investigate further. In children at least, most of the transient infections caused by viral infections resolve within this time period.”

Such an approach would require good patient support and follow-up mechanisms (such as expert patients and community health workers) to prevent loss to follow-up.

More sensitive diagnostic tools would make things simpler, if they were available.

New diagnostics being introduced – but no simple point-of-care test yet

On the bright side, efforts to stimulate the development of new TB diagnostics have finally begun to deliver some new tools – including the Xpert MTB/RIF assay, which is being rolled out in South Africa to serve as the first-line TB diagnostic test, replacing smear microscopy.

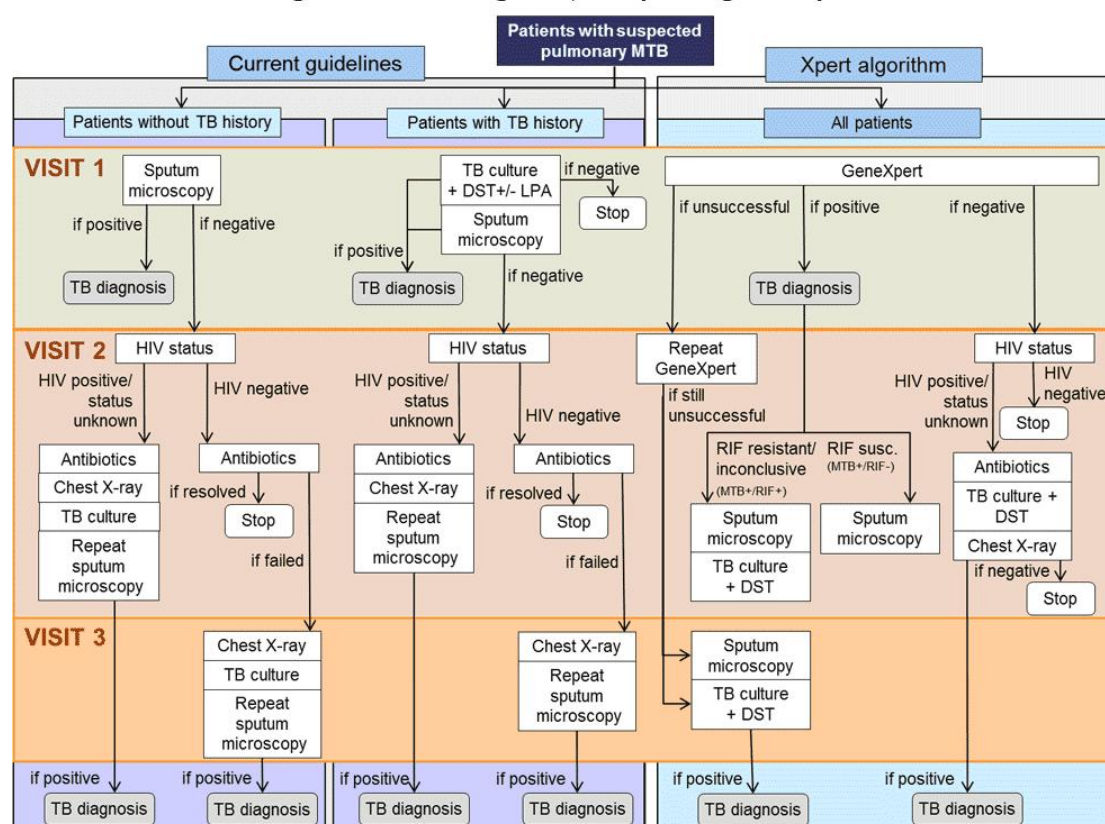
“We’re in probably the most exciting phase for TB diagnostics that any of us have known,” said Dr Helen Ayles of the London School of Hygiene and Tropical Medicine who co-chaired the diagnostics session with Professor Manabe. “But are we where we want to be?”

There were presentations on Xpert MTB/RIF, Hain’s MDRplus line probe assay, an automated AFB microscopy system, and the LAM urine antigen lateral flow assay that day at CROI (see CROI session 46, Thursday for the [slides and webcast](#), or follow [this link for the abstracts](#)). However, as Dr Ayles pointed out, none of these provide what is *most* needed – an inexpensive and simple to administer point-of-care (POC) test that could reliably diagnose a person’s TB within minutes wherever he or she presents for care, making it possible to put them on treatment immediately. Unfortunately, even though it only takes one to two hours to perform, the Xpert MTB/RIF test doesn’t quite reach the level of point-of-care testing that resource-constrained programmes have been hoping for, because cost and other factors limit where and how the Xpert test can be implemented. For instance, in South Africa, the equipment is being installed in microscopy laboratories, rather than in clinics where the patient might present for care.

Without a simple point-of-care TB test, the diagnostic process will remain complicated – one has to consider the health systems issues that could derail the process.

ACTG 5253: Predictors of active TB in people living with HIV

	TB (N=54)	No TB (N=391)	P value	Sensitivity	Specificity	PPV	NPV	LR Positive	LR Negative
AFB smear positive*	6 (11%)	6 (2%)	<0.002	11.32	98.39	50.00	88.62	7.02	0.90
Cough	44 (81%)	237 (61%)	0.003	81.5	39.2	15.7	93.9	1.34	0.47
Fever	23 (43%)	114 (29%)	0.040	43.4	70.8	16.8	90.2	1.49	0.80
Night sweats	26 (48%)	151 (39%)	0.19	48.2	61.4	14.7	89.6	1.25	0.84
Weight loss	30 (60%)	166 (45%)	0.049	60.0	55.4	15.3	91.2	1.34	0.72
BMI < 20	20 (37%)	85 (22%)	0.026	37.0	77.9	19.1	89.8	1.67	0.81
Pulse > 80	35 (65%)	178 (46%)	0.009	64.81	54.5	16.4	91.8	1.42	0.65
Lymphadenopathy	36 (67%)	175 (45%)	0.003	66.7	55.1	17.1	92.3	1.49	0.60
Hepatomegaly	1 (2%)	10 (3%)	>0.99	1.92	97.4	9.1	88.1	0.75	1.01
Splenomegaly	0	2 (1%)	>0.99	0.0	99.5	0.0	88.2	0.0	1.01
CD4 < 200	26 (48%)	121 (31%)	0.020	48.2	69.0	17.7	90.6	1.55	0.75
Haemoglobin < 11	27 (50%)	109 (28%)	0.002	50.0	72.1	19.9	91.3	1.79	0.69
Abnormal chest radiograph compatible with TB	26 (48%)	74 (19%)	<0.001	48.2	81.1	26.0	91.9	2.54	0.64
Fatigue	27 (50%)	157 (40%)	0.19	50.0	59.9	14.7	89.7	1.25	0.84

South Africa's national algorithm for TB diagnosis, incorporating GeneXpert MTB/RIF

Ten steps in the TB diagnostic workflow

Starting from the point at which the person with suspected TB arrives at the health facility, the following steps would be involved before obtaining a diagnosis and putting a person with TB on treatment:

- Collect sputum samples or another biological specimen.
- Collect patient's contact details; get contact details of friends and relatives too, in case the patient is hard to track down.
- Prepare the specimen for transport, send to the lab [if not on site, deal with those logistics]. Document shipment in ledger, to keep track of specimens sent to lab.
- Specimen arrives at lab and undergoes tests (provided the equipment is in good working order, the reagents are in stock, there is a trained technician there, etc).
- Lab enters data/results into system/form. Sends reports back to clinic, using electronic data system, SMS or whatever system is in place to deliver more timely results.
- Back at the clinic, the results need to be collected, reviewed and recorded.
- Contact patient.
- Keep trying to contact patient. Repeat as necessary.
- Patient reached and asked to report to clinic.
- Patient comes to clinic; diagnosis and information given and treatment is initiated.

Tracking the person with TB down and trying to get them to come in for treatment may be the most difficult part of this process, and the step where most people fall through the cracks. Human error can also be counted on to happen at any point. It is not uncommon for shipments to get lost, and efficient communication between the clinic and the lab may not exist.

"There's a real need for an intact health system, in order to have good diagnosis and treatment of patients with tuberculosis," said Professor Yukari Manabe. "Labs need a functional lab space. You need electricity, you need reagents, qualified staff, and as we found with fluorescence microscopy, good quality assurance and control. Then you have to return that result to the patient. And that requires you to be able to get your patient to return to the health centre, an ability to track those patients, to keep good records, and to have a linkage between the lab and the clinic so that you are accurately returning results to the patient."

Aggressively implementing active case finding strategies will require careful co-ordination between clinics and local labs and health programmes using the TB laboratories (not just the TB programme, but the HIV programme, or wherever case finding is happening), as well as the strengthening of the national TB laboratory system. This is especially important when a highly sensitive symptom screen like the WHO 4-symptom screen is being implemented and resulting in a significant increase in numbers of people needing to be tested. Policy makers and programme managers will need to develop plans for laboratory strengthening, which according to the Global Laboratory Initiative must include all the core elements of laboratory infrastructure and maintenance, equipment validation and maintenance, specimen referral and transport mechanisms, a policy framework for implementing new TB diagnostics, hiring and training staff, commodity and supply chain management, laboratory information systems for recording and reporting results, quality assurance systems, and so on.³

The [Global Laboratory Initiative](#) has produced a Roadmap with a stepwise approach to laboratory strengthening as a guide for programmes.⁴ First, policy changes may need to be made at the country level, based on the local epidemiology (TB, HIV, MDR-TB), National TB Control Programme (NTP) priorities for case detection (risk groups to target), the laboratory networks and capacity, the staff resources and skills base, the treatment policies for drug-resistant TB, and financial resources.⁵ Expansion of laboratory service should be based on a tiered system (peripheral, intermediate, or centralised referral lab), what technologies are available; what ancillary lab capacity is needed to manage patient populations also requiring specialised treatments such as antiretroviral treatment, or second-line anti-TB drugs, general microbiology, biochemistry, haematology, etc., adopting an integrated approach.

The third step is the preparation, implementation and impact monitoring of the introduction of new laboratory technology.

Laboratory strengthening

Phase 1: Laboratory preparedness

- Assessment of TB laboratory networks and diagnostic policies
- Upgrade of laboratory infrastructure and biosafety
- Development and implementation of GLP, SOPS, QA, etc.
- Training of core laboratory staff
- Initiation of NTP policy reform on diagnostics

Phase 2: Introduction of new diagnostics

- Integration of new diagnostics into NTP policies and procedures
- Procurement and installation of instruments, reagents, supplies
- Validation of new tools and laboratory performance
- Adjustment of NTP policy based on local data

Phase 3: Impact assessment

- Continued mentoring, technical support and oversight
- Assessment of impact on NTP outcomes

But on top of all that, with new tools becoming available (at a great cost), programmes wishing to strengthen TB laboratory capacity are now faced with difficult resource allocation decisions regarding investment in laboratory infrastructure. Since a real point-of-care test will not be available in the immediate future, it is worth exploring whether any of the new tests could be used to shorten the diagnostic workflow — if, for instance, it would be an advantage if the test could be performed at the site of care. There could be ways to use the new tests in combination, in algorithms or with available tests to improve the chances of getting more accurate diagnoses to people with TB sooner. Some lab-strengthening strategies or algorithms might be more appropriate in one context than another, and for some countries more than others — due to differences in available resources, burden of TB, or rates of TB transmission.

"How should we be moving forward, in countries like South Africa but also in countries like my country Zambia, where we have much less resources but a much more decentralised system at the moment?" Dr Ayles asked the panel and audience.

Moreover, a new diagnostic tool is unlikely to deliver on its promise if the other aspects of laboratory strengthening are not addressed. WHO's STOP TB Department, and the Stop TB Partnership have developed toolkits and other materials to support laboratory strengthening and the introduction of new tools, which can be found [here](#).

This rest of this edition of HATIP describes some of the reports, models, and experiences of scaling up the Xpert MTB/RIF and the other new tools published or presented at conferences over the past year.

Early implementers of Xpert MTB/RIF

South Africa's Health Minister Aaron Motsoaledi knew some drastic steps would have to be taken to manage the TB emergency that he had inherited in South Africa. The usually recommended interventions just wouldn't cut it.

"We have tried all these things. On their own they are very much unlikely to produce the kind of impact needed to match the magnitude of the TB challenge that our country is faced with. That we need bold action is crystal clear, otherwise we will fail in turning the tide against the TB epidemic that is decimating our country," he told an audience of health workers on World TB Day, in 2011.

The first concrete step he announced was the country-wide rollout of the Xpert MTB/RIF test, just a few months after the WHO review gave it a strong recommendation: "The new automated DNA test for TB [Xpert] should be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB." (See algorithm flow chart on page 5 of this edition).

"Over the next 18 months we will roll this out to the length and breadth of the whole country; we will put them in the national health laboratory services facilities. It's an epochal event — it changes everything we've been doing for the last fifty to one hundred years," he said

Indeed, what South Africa was doing was unparalleled — a middle-income country whose health system had been derided just a few years earlier, was attempting an enormous task. The lab specialists and programme managers in South Africa would have to blaze their own trail.

Fortunately, South Africa's parastatal, the National Health Laboratory Services, was up to the task, and documenting what they were doing every step of the way. Their innovative approaches to integrating the diagnostic test into clinical management, and their experience of troubleshooting the introduction of the test at laboratory and facility level will prove extremely useful to other countries who want to follow their lead.

They chose a phased roll-out, starting in all nine provinces with thirty instruments at 25 microscopy sites, equal to about 11% coverage of the national burden. The South African endeavour involves much more than just training technicians and installing the equipment — standard operating procedures have to be rewritten and healthcare workers have to be retrained to handle specimens differently (two smears at diagnosis are being replaced by one Xpert MTB/RIF) and following an adjusted diagnostic algorithm for TB and MDR-TB patients.

"It changes *everything* we do," Professor Wendy Stevens of South Africa's National Health Laboratory Services said at a late breaker presentation at IAS 2011 in Rome.

"We've learned that the algorithm development is complex and time is needed to get consensus," said Prof. Stevens. Switching over to diagnostic platforms meant sweeping changes had to be made to the TB guidelines, request forms, training and resistance reporting.

"Training needs to focus on items like sample preparation and good laboratory practice. We're also running into regulatory issues such as who can do the test, when scope of work is well-defined in South Africa," she said.

The previous algorithms for patients with a prior treatment history and those who were treatment-naïve differed. Now, wherever

Xpert MTB/RIF is implemented at a centralised South African microscopy site, it is the first test given to all TB suspects within that site's catchment area. A positive result is a TB diagnosis, while the course of action if there is a negative result depends upon HIV status (see algorithm). One of the controversies with this algorithm has been that restricting each person to only one Xpert MTB/RIF cartridge would miss a high percentage of people living with HIV who have smear-negative TB. Repeating the test two or three times improves sensitivity, but was judged to be too expensive at the time the algorithm was developed. (Data on the potential cost/benefit of adding a test are discussed below.)

If the test shows rifampicin resistance as well, the results must be confirmed by TB culture and drug sensitivity testing (DST).

If the test fails (due to an error, such as a test fault), the test has to be repeated. In the pilot phase the error rate of about 4% was a cause for concern because it added to the cost of implementation and delayed diagnosis. Some of these errors are well characterised, such as one resulting from putting an insufficient volume of sputum into the cartridge.

But the most common error code being seen in South Africa (#5011) had never been reported before the rollout in that country and involves a signal loss — Cepheid is responding by altering the one of the probes in the test to eliminate this error.

Another operational problem, however, may not be so easily remedied and is likely to be seen more frequently as the test is rolled out in resource-limited settings: the failure of an entire batch of tests if there is a power outage or fluctuations while it is running, or if the machine gets too hot.

All the equipment had to be interfaced with the laboratory information management system (LMIS), and NHLS developed an interface so that it could automatically report the lab number, instrument, cartridge number and whether or not TB was detected, and whether rifampicin resistance was detected, using the Lab-Track Laboratory Information System. This has dramatically improved programme reporting.

There were also some workflow issues with the large instruments (GeneXpert machines come in a range of sizes depending on how many cartridges they can hold and process simultaneously. The largest can house 48 cartridges). They also had to develop their own programme for external quality assurance, and determine how often to run it.

Costing and cost-effectiveness have been studied closely during these early stages of implementation, and extensive modelling has been carried out in order to assess the trade-offs in cost-effectiveness of different algorithms and distributions of diagnostic resources.

The starting point in considering cost is the price of the Xpert MTB/RIF cartridge, which is used once. This equates to the cost of doing one test, but not necessarily achieving one diagnosis, as will be discussed in more detail below.

The cost for the cartridge varies depending on the implementation rate, exchange rates, global volumes, negotiation and freight costs. And even though each test module may technically cost ~US\$17, there are a number of hidden costs including staff costs, the cost of calibrating the equipment, consumables, waste disposal (the cartridges are bulky), transport and logistics, training and quality assurance and overhead.

But there is no question the test is delivering in terms of timely diagnoses. The test has had a profound effect upon the number of TB cases diagnosed, initially increasing the case burden of active TB by two- to three-fold, and detecting three times more rifampicin resistance than planners were expecting. Speaking in July 2011 at

the International AIDS Society conference in Rome, Professor Stevens was unsure whether that figure would prove to be accurate, but subsequent investigation shows that only ~20% of the cases have been found to be false-positive for rifampicin — which suggests that South Africa's MDR-TB problem is much bigger than expected (more on this below).

But the biggest challenge for the country could be the cost of buying and maintaining enough equipment to cover the entire country, which could clearly affect the pace to full implementation. With the first phase of implementation completed as of IAS 2011, the second phase was launched to fully capacitate the high burden districts. Phase 3a/3b will be part of a Gates Foundation-funded, cluster-randomised trial to analyse cost-effectiveness and impact on patient outcome. But the capital expenditures for the equipment alone will be significant, at around US\$21 million for 238 machines (65 G4, 169 G16 and 4 G48s).

This is a huge capital outlay, even for South Africa, which is a relatively wealthy country compared to many of the other countries in sub-Saharan Africa. And on top of that, the cost of the cartridges has yet to fall appreciably. In 2010, South Africa had to test 2 million 'suspects' for active TB. Multiply *that* by US\$32, roughly the cost of the Xpert MTB/RIF test when overhead, labour, and transport are included, according to Kathryn Bistline, a Truman Scholar who works with the Health Economics and Epidemiology Research Office (HE2RO) as well as with Right to Care, a South African HIV/TB prevention, testing, care and treatment NGO.

By the time South Africa has achieved full coverage of GeneXpert, there should probably have been a reduction in price for the cartridge, which currently contributes US\$17 to the US\$32 cost of performing the test. "Once the global volume of 3.7 million cartridges ever procured is obtained we'll have a cartridge price of US\$10.72. When that is reached South Africa will pay closer to US\$25 per test," she said.

Bistline presented some data and modelling on the incremental cost and diagnostic impact of rolling out Xpert MTB/RIF in the public sector of South Africa at the late breaker session at the Union World Conference on Lung Health in Lille, France last October — as well as some additional insight into why South Africa made certain choices in its three-year plan to roll out Xpert MTB/RIF to decentralised labs in the country.⁶

HE2RO was asked by the Ministry of Health to develop costing models on a number of variations on the three-year plan to rollout GeneXpert, comparing it to the smear microscopy-based model, taking into consideration probable health outcomes. One issue with the microscopy model was that the patient would have to visit the facility on more than one occasion in order to get their diagnosis, particularly in cases of smear-negative TB.

"If you're smear-negative, we rely on culture for diagnosis," said Bistline. "The time between the first visit, when you provide a sputum sample for smear; and your second visit when you would get your smear results, is on average five days. And we lose 13% of the TB suspects in this process. But between visit two, when you provide a sputum sample for culture, and visit three which is up six weeks later when you get your culture results — we lose on average 26% of our TB suspects."

In the GeneXpert scenario it is expected that with full GeneXpert coverage, 83% of patients will be diagnosed by visit two, compared to 46% of patients diagnosed by microscopy; another 40% are only diagnosed by microscopy by visit three, which is six weeks later.

This earlier diagnosis drives an increase in TB cases diagnosed and treated. At full GeneXpert coverage, GeneXpert will diagnose

32% more TB cases each year and result in 41% more TB cases initiated onto treatment each year.

The trend is similar for MDR-TB cases — only more dramatic. At full scale, the GeneXpert guidelines will diagnose 77% more MDR-TB cases; and it will do so much earlier.

"At full-scale, we'll be able to diagnose 81% of MDR-TB by visit two. Which also means that we could initiate onto MDR-TB treatment at visit two, *five days after sputum collection*," said Bistline.

(Note, this is not as high as the two-fold or three-fold higher rate of diagnosis reported by Professor Stevens, but the early rollout is likely to mop up a larger proportion of previously long undiagnosed TB, which accumulates when it is not being diagnosed.)

Of course, it will cost the South African National TB Programme more — 59% more for TB diagnosis each year, and 36% more for 'outpatient' TB treatment each year — and 13% more per TB patient treated.

"And it's more per patient treated because we have a greater percentage of MDR-TB patients needing treatment," said Bistline (second-line TB treatment being phenomenally more expensive than the standard TB treatment).

Overall, the total cost of placing GeneXpert technology at decentralised laboratories for the initial diagnosis of pulmonary TB suspects, from 2011 to 2016 in South Africa, will require an additional \$US 327 million for the diagnosis of pulmonary tuberculosis, and an additional \$US 218 million for the treatment of pulmonary tuberculosis. But as a result of that investment, South Africa will be able to increase the number of TB cases diagnosed by 32%; the number of MDR-TB cases identified by 77%; and the number of TB patients put on to TB treatment, by 41%.

"Furthermore, our analysis did not include the impact of appropriate and timely treatment initiation — which should reduce TB transmission and TB morbidity and mortality and which should over time reduce the total cost of the TB Control Programme in South Africa," she said.

So the GeneXpert roll-out is full steam ahead in South Africa, and the country will be purchasing approximately one million Xpert MTB/RIF cartridges in 2012.

Other models for implementing Xpert MTB/RIF: targeting to populations at most risk, algorithms, implementation at the point of care

The irony is that when WHO gave its recommendation to Xpert MTB/RIF, it did not seem to be expecting that the earliest implementer would be moving his entire nation from one diagnostic platform to the new diagnostic platform in the space of three years.

Reading between the lines of the recommendations on GeneXpert, it seemed that WHO was painfully aware that cost was going to make it difficult for many countries to take advantage of what its own review of the evidence showed to be a major advance in TB diagnostics. Consequently, the scope of the recommendation was rather limited.

1) Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB. (Strong recommendation.)

"The selection of individuals to test [with Xpert] would be based on a risk assessment," said Dr Christopher Gilpin of the Global Laboratory Initiative, explaining the policy at the New Diagnostics Working Group Meeting before the Union World Conference on Lung Health last October in Lille. For instance, he said that anyone

diagnosed with, or suspected of having TB, is someone who might be at risk of MDR-TB; or people with symptoms of TB who are known to be HIV-positive, or who are of unknown status in a setting with a high burden of HIV, should also be targeted for GeneXpert testing. And as a secondary consideration, one might also target HIV-negative individuals, not believed to be at risk of MDR-TB but who have either an abnormal chest X-ray, or who are still suspected of having TB despite having a negative sputum smear.

2) Xpert MTB/RIF may be considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens. (Conditional recommendation acknowledging major resource implications.)

In other words, WHO was saying that Xpert MTB/RIF might cost too much to use in every TB suspect as the initial test, and that, unless there was a lot of MDR-TB or HIV, programmes should continue to use microscopy to diagnose the easy smear-positive cases, and then use Xpert MTB/RIF to mop up the rest.

Bistline said this was considered in South Africa, before they chose to offer the test to any TB suspect for reasons of equity.

Another question was whether GeneXpert would be situated within existing laboratory facilities or placed within the facility so that point-of-care testing would be available?

“Currently testing is using a more centralised model, but significant efforts are being invested in appropriate point-of care testing as an extension of the laboratory network,” Sagie Pillay of the NHLS said at the South African AIDS Conference in 2011. But for the GeneXpert to be placed into the health facility, a number of issues would need to be addressed in that context, including:

- Assay validation
- Quality control material and practices
- Patient, clinician acceptance
- LIS (laboratory information system) interface with centralised monitoring
- Simplified standard operating procedures/training
- Biosafety
- Policy
- Reimbursement

Dr Lesley Scott of NHLS presented on the challenges of getting various point-of-care test equipment (including a GeneXpert) to work well together in a primary care clinic, and to report data back to LIS. For example, the machines each required their own dedicated phone line. Achieving a similar level of connectivity between various pieces of equipment and the Laboratory Information System may prove more challenging at primary care facility level.

Because many of the benefits of the GeneXpert technology are driven by its ability to provide rapid diagnosis, Bistline said that South Africa also considered whether the appropriate placement was at the labs or whether it should be at point of treatment.

“Unfortunately now, the point of care is too expensive”, said Bistline. “It would cost three times as much to purchase the instruments. That’s because there’s 3800 health facilities in South Africa that would’ve required a GeneXpert. If we look at an average clinic placement, it would be a tiny GeneXpert 1 with only one module, and the clinic would do less than two tests per day, whereas in a laboratory placement where we’re purchasing GeneXpert 16s, we would do on average 59 tests per day. This lower

volume also drives a higher cost per test. So not only would the initial investment be more for South Africa, but the ongoing cost of doing tests for South Africa would be more expensive.”

Point-of-care Xpert MTB/RIF for smear-negative TB in primary health care

Nevertheless, having a GeneXpert on site offers significant advantages, according to a presentation by Dr Jean Bassett of Witkoppen Health and Welfare Center, a busy primary care clinic in Johannesburg. In particular it may have a role in quickly diagnosing TB in smear-negative cases.

The clinic used a different model than the South African Xpert roll-out. Instead, they followed WHO’s advice, using Xpert MTB/RIF only after two negative smears on microscopy.

Several components were key to their approach. First, expert patient-assistants helped patients to locate the various service points within the clinic. Previously these people had been community volunteers.

Second, to enhance TB infection control, TB sputum was collected in an outside private TB booth, which allowed maximum sunlight and air ventilation. The buffer for the Xpert MTB/RIF was added to the sputum sample outside, and then the test was done on site. This did not require a highly educated health professional, the person who did it for them had completed high school and had no formal training. Then the results were reviewed by a team of clinicians on site.

There were about 200 participants, 72% of whom were HIV-positive, and 69% of those were on ART. They were screened for symptoms of TB (weight loss, fever, night sweats, and cough (in this study for two weeks). Two sputa were collected for smear at the first clinic visit, and the patient was treated with antibiotics. They were sent for chest x-rays if clinically indicated.

Patients were asked to return about five to seven days later, for the smear results — because that’s how long the turnaround time at the microscopy site was at the time. Then, if both smears were negative the patient was enrolled into the study and further sputum was collected: one for microscopy; one sputum for culture; and one for Xpert MTB/RIF.

Seven participants were smear positive, 15 were liquid culture positive, and 16 patients tested positive by Xpert MTB/RIF. Of those patients who were sent for X-ray about half had symptoms and signs suggestive of TB. Note, 65% of the patients had sustained symptoms of TB despite antibiotic treatment.

Twenty out of 21 cases of TB were diagnosed, depending on whether one can have a diagnosis with an Xpert MTB/RIF-positive and culture-negative result.

Out of the 20 or 21 TB cases, 15 or 16 were diagnosed by a single positive Xpert, the remainder by culture. Many of the cultures were contaminated or their results lost. Dr Bassett noticed that the Xpert-positive, culture-negative patients did not respond to the antibiotics, but 2 out of 5 culture-positive, Xpert-negative patients did. But these numbers were too small to be significant.

“Xpert available at point-of-care allowed healthcare workers, at a primary healthcare level, to diagnose TB in smear-negative patients with 76% sensitivity,” said Dr Bassett, who went on to add that even though culture was more sensitive if performed correctly, “there are problems in that turnaround time is long. And in our study 6% of cultures were contaminated, and 13% of results never arrived at the clinic.”

“I would like to suggest that a targeted approach for the use of Xpert at point-of-care should be explored further — especially for highly resource-constrained settings. Specifically we should

consider non-resolution of TB symptoms, after a course of antibiotics; HIV infection; and recent exposure of a patient to TB as reasons to perform an Xpert,” Dr Basset concluded.

How much would a targeted approach cost?

Bistline presented an analysis of the costs of using GeneXpert as a second-line tool to diagnose smear-negative TB.

“We wanted to look at an Xpert algorithm, where we would use Xpert as a second-line diagnosis after smear-microscopy, and our standard practice, which is a third sputum smear-microscopy combined with liquid culture and line-probe assay as needed. In South Africa, if somebody is culture-positive, we identify whether it is m.TB or non-tuberculous mycobacteria by using line-probe assay,” she said.

The study compared the cost of the Xpert practice, to standard practice per outcome – looking at the cost per TB suspect; the cost per TB case diagnosed; and the cost per patient initiated onto TB treatment.

Liquid culture only costs about \$12 a test, so at first it might appear that GeneXpert will be at a disadvantage.

One disadvantage of culture, however, is that if it does turn out positive, patients need to be traced to be provided their results, and to get them on to treatment. Another problem is that 19 of the patients' specimens were contaminated, or missing.

“This means that 19% of the patients did not receive the laboratory diagnosis under the standard practice,” said Bistline.

Another issue was the number of active TB cases who received TB treatment, and when. Fifteen of the 16 Xpert-positive patients started treatment on the same day they received their results, with the remaining patient starting treatment the following day.

On the other hand, of the five patients who were Xpert-negative, but culture-positive, only one started TB treatment within the course of this study.

“That's 20% initiation — or 80% lost to initiation, 80% primary default,” said Bistline. “Is it special to this study? We don't think so. Although our numbers were small we had done a baseline study at the same site. And in the baseline study there was a 72% loss to initiation for smear-negative, culture-positive. It is just a fact that when you have to wait four to six weeks to get your culture results, often times, the patients are not coming back to get onto treatment.”

The cost breakdown:

- Per smear-negative TB suspect, per person tested, the Xpert MTB/RIF is 87% more expensive.
- Per diagnosed patient: Because of the large number of missing and contaminated cultures, standard practice doesn't perform as well, compared to Xpert MTB/RIF — and so the cost per diagnosed patient is only 51% more than the standard practice.
- Per TB case diagnosed: Standard practice and Xpert MTB/RIF algorithm diagnosed very similar numbers of patients, and therefore the costs are similar to just the number of people tested, with Xpert MTB/RIF being 75% more expensive.
- However, considering one of the more important outcomes, the cost per smear-negative TB case initiated on to TB treatment, Xpert MTB/RIF here is 65% less expensive per patient initiated because of the high loss to initiation under the standard practice.

Bistline then drew the audience's attention to the WHO's conditional recommendation to do smears first, in order to reduce the number of Xperts. But, “Only 10% of TB suspects in South Africa are smear-positive – 90% of people are either truly smear-negative i.e. they don't have TB or they have smear-negative TB. So 90% of

the people would come through as smear-microscopy screening, into Xpert,” said Bistline. “Two smears are 80% less expensive than Xpert. So we would save some money by doing smear microscopy first before Xpert. But you're only saving it on 10% of the patients.”

“We also have to look at what it costs to save this money per patient: At what cost to the clinical outcome, and to TB contacts and increased transmission? It shouldn't be, in theory, a large cost because smear doesn't take a very long time to do — we should have a turnaround time of 24 to 72 hours for smear microscopy. But as we heard in the earlier presentation, *the patients aren't coming back*, and we've seen a median time from first smear to Xpert of 16 days, and that was those who *came back*. We didn't trace in this study all those who perhaps had a negative smear but didn't return to the clinic for further testing,” she said.

But as she mentioned earlier, having this expensive equipment at a site doesn't make much sense either. Running just a couple of tests a day was not a very cost-effective way to use this expensive equipment. The higher volume run per day, the cheaper the tests become.

“So it may be that rather than using smear-microscopy as a screening test, if we need to reduce the cost of Xpert MTB/RIF, and we need to look at making sure enough scale and enough volume of tests are performed on these instruments. Then we can actually save the same amount of money, as we would by reducing the number of patients who are using Xpert,” she said.

“But in conclusion, the long provider delays in waiting for culture results means that most smear-negative TB patients are lost to follow-up, prior to TB treatment initiation under standard practice. The Xpert algorithm does have a higher cost than standard practice, per suspect tested. But the Xpert algorithm has a lower cost per TB patient initiated onto treatment,” she concluded.

Modelling the cost-effectiveness of two Xperts in PLHIV with TB symptoms

One way to optimise the volume of the tests run on the equipment at facilities would be to perform a second test in HIV-positive TB suspects who tested negative by Xpert MTB/RIF the first time. Further modelling from HE²RO presented by Dr Sydney Rosen at CROI suggest this may be more cost-effective than the current algorithm in South Africa, which at present only uses one Xpert, and then refers the patient to what was thought to be the cheaper conventional diagnosis via culture.⁷ The findings suggest this may be a false economy.

In one to two hours, an Xpert MTB/Rif test can detect almost as much TB in a sputum specimen as liquid culture can in two or three weeks — although it deserves reiteration that the quality and reliability of liquid culture can vary a lot by lab — contamination is not uncommon, and when that happens, the patient must be tracked down, a sputum sample collected and sent back to the laboratory, which sets back diagnosis by another two or three weeks. That time is doubled in a country where only solid culture is available.

But one Xpert MTB/Rif does not always do that good a job of diagnosing smear-negative TB, especially in people living with advanced HIV. The sensitivity of Xpert MTB/RIF in cases of smear-negative TB has varied according to the population studied.

The pivotal study by Boehme et al published last year in *The Lancet*, which involved over 6600 participants (some with HIV) in six countries, reported that sensitivity of Xpert MTB/RIF for smear-negative, culture-positive cases was 89/124 (71.8%, 95% CI 63.3–78.9).⁸

Cepheid, GeneXpert's manufacturer, puts it slightly higher at around 73.1% and suggests that running the test again increases sensitivity to about 85%, while running three tests on every smear-negative TB suspect achieves a sensitivity of around 90%.

However, smear-negative TB in people living with HIV can be even harder to identify, and Xpert MTB/RIF has shown lower sensitivity in this population. For instance, in a study by Lawn et al, 468 participants living with advanced HIV, with a median CD4 cell count of 171, were able to provide one sputum sample – and 81 were diagnosed with culture-confirmed TB. When their sputum was tested with the Xpert MTB/Rif assay, the sensitivity for smear-positive, culture-positive TB was around 99-100%, but the sensitivity for smear-negative, culture-positive TB in PLHIV with advanced disease was only 43.4%. Sensitivity improved to 62.3% when two samples were tested.⁹

Of course, running a second or third Xpert MTB/Rif on other sputums from the TB suspect living with HIV would double or triple the cost –when the test is already expensive enough. So it is hardly surprising that the current TB diagnostic algorithm in South Africa advises clinic staff to perform only one Xpert in TB suspects living with HIV or with an unknown HIV status (who constitute around 46% of South African TB suspects).

If the Xpert test comes out negative, the algorithm suggests instructing the patients to come back to the clinic, to provide another sputum sample that will be sent out for culturing. In the meantime, the patients is commenced on trial antibiotics and is sent for chest x-ray.

HE2RO proposed an alternative algorithm, where the second sputum sample is sent for a second Xpert test (the X/X algorithm) instead of culture (the X/C algorithm).

The team used the same costing models described above to compare modelled treatment and cost consequences of the two strategies, looking at the implications for case finding and uptake of treatment for the whole country, assuming full scale up of GeneXpert, which was originally anticipated to happen by 2014.

Outcomes and costs for South Africa

At full Xpert scale-up (2014)	Current algorithm (X/C)	Proposed algorithm (X/X)	Difference to X/C
TB cases diagnosed (% of suspects)	447,999 (17.4%)	433,401 (16.8%)	-3% (-3%)
TB cases treated (% of cases diagnosed)	363,318 (81%)	364,443 (84%)	+0.3% (+4%)
Cost per test	Culture: US \$13	Xpert: US \$25	+92%
Cost per suspect	US \$59	US \$53	-1%
Cost per case diagnosed	US \$342	US \$315	-8%
Annual cost of TB diagnostic programme	US \$153 million	US \$136 million	-11%

Results

Since Xpert is less sensitive than culture, it could find fewer cases of TB. However, Dr Rosen noted that based on the results from the pilot test of Xpert in Johannesburg, uptake of treatment

using Xpert is expected to be substantially higher because it's so much faster – the patient gets the results sooner, in fewer visits. In fact, as Bistline pointed out, long provider delays waiting for culture results means that a substantial proportion of smear-negative TB patients are lost to follow-up, prior to TB treatment initiation.

"As a result, we will end up with more cases treated, even though we've identified fewer cases," said Dr Rosen. "So we end up with better health outcomes for the country as a whole under the alternative algorithm."

And even though the cost of the Xpert MTB/Rif test is twice as expensive as the cost of culture, once the costs of the antibiotics, the chest x-ray and extra clinic visits are factored in, the cost per suspect or patient treated using the X/X algorithm is lower than the cost of using the X/C algorithm. Multiplied out to the cases diagnosed and then to the country as a whole, would come to 11% cost savings per year.

"What we have is the potential for a diagnostic algorithm that provides more rapid results to the patients, and is therefore better for the patients; simplifies the diagnostic process at the level of the laboratories and clinics within the country; and potentially generates cost savings [of \$17 million]," said Dr Rosen. "So we're proposing that this alternative algorithm be considered as the Xpert roll-out proceeds."

All this seems to be going in rather a good direction so far for Cepheid's sales, but we should stress that, with the exception of the Boehm study, most of these data come from just one country, South Africa.

More cost-effective than standard practice in many lower-income countries

Building on this work, another modelling study from researchers at the US Centers for Disease Control and recently published online by *JAIDS*, found that both the WHO algorithm with culture or WHO's Xpert algorithm were more cost-effective at reducing early mortality during the first six months of ART in people living with HIV compared to current diagnostic practice in many of the countries in sub-Saharan Africa.¹⁰

What the researchers called the standard practice is essentially the WHO algorithm, without culture, because culture isn't widely accessible in many countries, or not bothered with because of the long wait for results. In other words, it relied on symptom screening, followed by smear microscopy and chest x-ray, and nothing further. This would of course, miss most smear-negative TB cases.

The CDC model used cost inputs derived from South African studies, and outcome data from a Haitian study of PLHIV starting ART where there was little access to culture or chest x-ray.

When considering TB diagnosis, TB treatment, and ART costs, the model found that the current practice cost US\$850 per patient and identified 70 TB cases per 1000 patients starting ART. The Xpert algorithm diagnosed 78 TB cases per 1000 people at a cost of US\$809 per patient. Finally, the WHO algorithm with culture identified the most cases, 86 at a cost of US\$879 per patient.

In the model, the WHO algorithm with culture led to diagnosis in 23% more TB cases compared to the current practice arm and diagnosis of 10% more TB cases compared to the Xpert algorithm. In addition, the model found there would be two less deaths per 100 prevalent TB cases for the algorithm with culture, and one less death per 100 prevalent TB cases with the Xpert algorithm compared with current practice.

"Current practice cost more and averted fewer deaths compared with other strategies," the authors wrote. The algorithm with culture

was not the lowest-cost strategy; although it was the most effective at averting early deaths.”

However, their model didn't include the losses due to contamination, missing specimens and other problems that are common with culture-based diagnosis. But it seems to be understood that it is virtually impossible for many countries to install, implement, and maintain high-throughput liquid culture systems that would be capable of handling the large number of TB suspects that active case finding generates.

The real message here was that Xpert was more cost-effective than what most countries are currently doing (in terms of lives saved). The authors noted that the study didn't take into account the benefits that early detection of MDR-TB could offer.

However, the authors also concede that they did not include any calculations related to the “costs of developing full diagnostic capacity to implement the algorithm with Xpert or the algorithm with culture. There is need for additional information about the costs of establishing (e.g. infrastructure and equipment) and maintaining these capacities (e.g. maintenance, quality assurance, and personnel etc.); these costs are critically important from a program start-up and implementation perspective.”

Barriers and opportunities for GeneXpert

The investment may eventually pay for itself in a country like South Africa, but if a country's health programme hasn't been spending that much money on TB in the first place, it represents a major expenditure.

There could be some algorithms where cheaper tests could reduce costs by reducing some of the need for Xpert in certain populations. For instance, the Determine TB-LAM urinary antigen lateral flow TB test, has comparable sensitivity in one population group (PLHIV with low CD4 cell counts and only costs \$2.50 per test. (This test will be covered in more detail in the third part of this series of articles on laboratory strengthening).

But we are not so fortunate with the Xpert MTB/Rif. According to one of documents that WHO prepared to support implementation, the first year cost of installing and running a small GeneXpert system that reads four cartridges at a time, would be just over \$100,000.¹³ And that might be conservative —remember the \$17 cartridge actually cost \$22 in South Africa due to airfreight, import costs and VAT.

Model inputs: Xpert costs		
Total instrument cost (69 GX4, 192 GX16, 2 GX48): US \$18,649,029		
Cost Item	Cost (2011 USD)	% of total (2014)
Xpert MTB/Rif Cartridge	\$10.72 - \$16.86	42%
Cartridge importation, local transport	\$ 4.27 - \$ 5.10	20%
Overheads	\$2.88	11%
Labour	\$2.90	9%
Transport	\$2.10	8%
Consumables	\$0.62	2%
Training and EQA	\$0.52	2%

Calibration	\$0.72	2%
TOTAL cost per Xpert test	\$24.73 - \$31.70	100%

INDICATIVE COSTS FOR GENE XPRT: SINGLE FACILITY				
Source: Prerequisites to country implementation of Xpert MTB/RIF and key action points at country level (WHO, 2011)				
		Item	Cost	Comment
A	EQUIPMENT	GeneXpert 4 module unit & laptop	17,500 USD	> 60% price reduction compared to US / EU
B		Shipment	1,000 USD	Depends on destination
C		Uninterrupted power source	500 USD	Local purchase; can be supplied by Cepheid on request
D		Printer	200 USD	Local purchase, depends on market
E	MAINTENANCE	Annual calibration	1,800 USD	Done at Cepheid Toulouse
F	CONSUMABLES	Cost per cartridge	16.86 USD	75% reduction compared to EU/US
G		Number of working days per year	250	Dependent on local context
H		Average number of tests per day	15	Dependent on working hours
I		Total tests per unit per year	3750	
J		Losses due to incorrect use (high estimate 10%)	375	
K	HUMAN	Technician salary	5000 USD	Country-specific
L	RESOURCE COSTS	Training and TA	5000 USD	Depends on need
M	INSTALLATION COSTS		19,200 USD	A +B+C+D
N	RUNNING COSTS		71,347 USD	E + F* (I+J)
L	GRAND TOTAL		100,547 USD	N+M+L+K

During the presentation on having a GeneXpert system at the primary health clinic, Dr Bassett said she thought it was quite handy to have around — as a point-of-care TB test. But it would be interesting to know whether it would be her first purchase if her clinic was given \$100,000 tomorrow? Perhaps it would be, but other clinics may have different priorities depending on how resource-limited they are.

This is not trying to pit health system needs against one another (as has so often been done to the HIV world), but funding for health is particularly tight right now, with ceilings being placed on the numbers of people who can go on ART in some countries.

So the cost of GeneXpert tests and the systems are clearly barriers to wider scale-up for countries other than South Africa. Of course, the funding needs to be made available to strengthen TB diagnostic infrastructure, but that requires planning and advocacy.

Securing adequate funding to install and maintain the system is one of the key actions WHO lists in its “[Prerequisites to country implementation of Xpert MTB/RIF and key action points at country level. Checklist](#)” which was developed to help guide countries considering the implementing the Xpert MTB/RIF assay.

GeneXpert systems cannot be installed just anywhere, and at present have some specific requirements for optimal assay performance

“Its need for a stable electric source as well as voltage stabilisation is making it quite limited in terms of the way it can be used at health centre [levels] three and four, in my opinion,” said Prof. Manabe at CROI. If there is loss or even a fluctuation in power, the tests are wasted and must be redone.

According to Dr Catharina Boehme during the diagnostics working group meeting in Lille, there are some systems in operation in clinics that are 'off the grid' — powered by alternative power supplies. For instance, Luwero HC IV, in Uganda, has a somewhat elaborate set-up with four 120 watt solar panels on the roof that charge serially connected batteries, with charge controllers and inverters.

Clearly, the stability of the supply must be determined at each site. According to Dr Gilpin, UPS devices 400V or a battery pack can be used. Cepheid will provide them for approximately US\$500 — it may be better to buy locally. These clearly provide only an interim solution for short power cuts. Whatever power supply is chosen, it needs to last until the tests finish running. Generators may be necessary, but require keeping fuel in stock.

"The need for yearly calibration for the machine to actually go to Europe is another potential drawback," said Prof. Manabe. Indeed, WHO estimates the shipping charges as being over \$1000.

Unless some other arrangement has been worked out, as South Africa has done, each year, programmes must send the GeneXpert machine to Toulouse, France, for maintenance.

According to Dr Boehme, Cepheid is working on a kit that will enable remote calibration. The user will run the calibration software, load the calibration cartridge, data will be sent to Cepheid, which should, in most circumstances enable calibration. This system was still in beta.

"Both the reagents and the machine are quite sensitive to humidity and temperature which may also limit its utility in some countries," said Prof Manabe.

Xpert MTB/Rif results are not reliable if the machine gets above the ambient operating temperature of 30°C — so the room where the equipment is installed must have adequate ventilation and air conditioning. Similarly, adequate space is needed for storage of the cartridges in a recommended temperature range (2-28°C).

According to a presentation that Dr Gilpin made at the Workshop for Early Implementers in 2011, the packages are bulky, and have a maximum shelf-life of 18 months.

WHO stresses that implementing Xpert MTB/RIF doesn't eliminate need for conventional smear, culture, or drug sensitivity testing (DST). If the GeneXpert detects rifampicin resistance, it needs to be confirmed by DST or a line probe assay, as there are false positives. There is some disagreement about how many false positives there are. NHLS claims that about 20% are false positive, but in Dr Steve Lawn's study about half are.

WHO states that microscopy and culture are also still needed to monitor response to treatment, and recommends that those with rifampicin-susceptible TB should be monitored during treatment with microscopy, while those with rifampicin-resistant TB, and placed on MDR-TB treatment should be monitored by sputum smear and culture guidelines.

Countries and programmes should not implement Xpert MTB/Rif without being prepared to offer treatment for MDR-TB should anyone test positive for rifampicin resistance.

WHO also recommend first making sure that the epidemiology justifies implementing Xpert in the region or country. It wouldn't have approved of Dr Bassett's clinic having a unit, because the volume tested each day wasn't high enough: facilities should run at least 10-20 samples a day, or 2000-4000 annually.

Dr Rosen said he thinks that it would be possible to use the tests either at, or very near to, the point of care at a midlevel or district level facility.

"At big sites, if you have high-volume clinics, it might make sense to use it as a point-of-care diagnostic. And that's going to be an

empirical matter — it's just something that has to be worked out in each place," said Dr Rosen. "For example in Zambia you actually could have a successful point-of-care use of Xpert at a big Lusaka clinic where thousands of people are coming through, but absolutely no chance of doing it at a health point in a rural area. So we probably will end up with a combination strategy, that's not just a combination of diagnostics, but different strategies for different parts or different populations within a country."

Prof. Manabe said that in some countries such as Uganda, it might be possible to bus TB suspects to diagnostic hubs for the test. However, Professor Gavin Churchyard said during the discussion at CROI that careful thought should be given to what we want to achieve with the diagnostic.

"How we deploy Xpert is dependant on what we want to achieve. If we are wanting to improve individual benefits in terms of reducing morbidity and mortality, we have to place it in a different place *than* if we want to achieve community-wide population-level effects," he said.

Other early implementers of Xpert MTB/RIF

With all these pre-requisites for running the test, and the high cost, one might think that other countries would wait to see how the public health experiment in South Africa goes before investing in such an expensive technology. However, there are a surprising number of other resource-limited settings that have been purchasing equipment and Xpert MTB/RIF cartridges, albeit not at such an ambitious pace as South Africa.

A number of funders have expressed support; for instance, as of one year ago, TB Reach was planning the procurement of over 100 machines in 25 countries to increase and accelerate case finding; MSF was planning machines in 16 countries; KNCV in three; the International Organization for Migration in 2 countries. Other funders such as PEPFAR (which bought some of South Africa's equipment, TB Care (the USAID initiative), Expand-TB, the World Bank, and, at least until the crisis, the Global Fund, had all expressed interest or were expecting to support scale-up of the Xpert.

As of 31 March, 2012, a total of 611 GeneXpert instruments, including 2,979 modules and 863,790 Xpert MTB/RIF cartridges had been purchased by 61 resource-limited countries, under the concessional pricing worked out by Find and Cepheid (the test's manufacturer).

How they will be using it, or when their implementation may go to scale depends on the country. There are a number of ways the assay could be introduced, and some algorithms for its use may work better, or be more cost-effective for some countries than the full throttle approach that South Africa has taken (as discussed by several of the presentations at the Union World Lung Conference meeting in Lille and CROI in Seattle).

There are several efforts underway to collect this early implementing experience.

WHO's Stop TB Department's Diagnostics and Laboratory Strengthening Unit (TBL) is asking early implementers to share basic information on the ongoing use of their GeneXpert instruments on a quarterly basis. They would like facilities to report the laboratory workload, numbers of tests being performed and results, and main logistical and operational problems being encountered, on a facility basis ([see the website here](#)).

The [Xpert Research Mapping Project](#) is just what it sounds like, a tool for researchers and policy makers to globally map ongoing research activities around the Xpert. It is a collaboration between

the Union, the USAID-funded Treat TB, and WHO. The site currently has listings for 24 research projects in sixteen countries, and the topics, target populations, and level of care where Xpert is being assessed are diverse.

Picking up the gauntlet

“GeneXpert really brings remarkable advantages – and I wonder if there are parallels that could be drawn between access to ARVs, some years ago, and the contemporary problem of access to TB diagnostics,” said Dr Susan Dorman during the discussion. “Clearly civil society played a key role in access to ARVs, and one wonders if there isn’t a real need for bringing in civil society into this problem.”

But, said Mark Harrington of Treatment Action Group, “The comparison between GeneXpert and ARVs is useful but inexact. There are differences in the economics of how companies invest and how much money they make off diagnostics versus drugs. So if you look at the drug companies, they were making billions in the nineties and we were trying to get them to reduce the price, and it wasn’t really until Cipla started making them for hundreds instead of tens of thousands, that they could really be scaleable. I think with Cepheid, which is beginning to make a profit, we can ask them to reduce the price to US \$10.”

However, he did think that it might be a good idea to see whether the Indians could develop a generic diagnostic version of GeneXpert to create competition and lead to lower prices.

But he also noted that part of the success of recent efforts to optimise the antiretroviral market had lain in efforts to improve the supply chain and manufacturing, and to predict market demand. No such processes exists for second-line TB treatment, making it difficult for potential developers to enter the field with confidence.

Yet Xpert MTB/RIF is a central product within a wider second-line TB market that needs to be nursed into existence if the current global MDR-TB burden is ever to be tackled effectively, not least for the utility of the test in defining just how large the scale of the problem might be. But as this edition of HATiP shows, there is still some way to go before the infrastructure that will unleash the surveillance potential of Xpert MTB/RIF is fully developed.

In part three of this series

In part three of this series HATiP will examine the role of the Determine TB-LAM test and how it might be incorporated into diagnostic practice, together with developments in fluorescence microscopy, and the use of combinations of tests to optimise diagnosis.

Part three will also look at the RIF part of the Xpert MTB/RIF assay - its role in surveillance and diagnosis of MDR-TB.

Finally, part three will examine some of the potential point-of-care tests now in development, and assess their potential impact.

References

- [1] WHO. Policy Framework for Implementing New Tuberculosis Diagnostics. Geneva, Prepublication copy, revision June 2011.
- [2] Swindells S et al. Sensitivity and specificity of tuberculosis screening and diagnostics in HIV-Infected individuals: AIDS Clinical Trials Group Protocol A5253. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 927, 2012.
- [3] Weyer K. The Global Laboratory Initiative Roadmap. Global Consultation of the SRL Network, Geneva, 2010.
- [4] The Global Laboratory Initiative, WHO. A Roadmap for Ensuring Quality Tuberculosis Diagnostics Services within National Laboratory Strategic Plans, 2010.
- [5] Weyer K, op cit.
- [6] Bistline K et al. The incremental costs of the national scale-up of laboratory-based Xpert MTB/RIF technology for the diagnosis of pulmonary TB in South Africa. 42nd World Lung Health Conference, Lille, abstract session 34LB, 2011.
- [7] Meyer-Rath G et al. What to do with Xpert negatives? The cost of alternative diagnostic algorithms for TB suspects who are Xpert MTB in a high-burden HIV/MDR-TB Setting. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 923, 2012.
- [8] Boehme CC et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicenter implementation study. *Lancet* 377: 1495–1505, 2011.
- [9] Lawn SD et al. Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study. *PLoS Med* 8(7):e1001067, 2011.
- [10] Abimbola TO et al. Cost-effectiveness of tuberculosis diagnostic strategies to reduce early mortality among persons with advanced HIV infection initiating antiretroviral therapy. *J Acquir Immune Defic Syndr*, published online ahead of print, April 2012.
- [11] WHO. Prerequisites to country implementation of Xpert MTB/RIF and key action points at country level. Checklist. Geneva, 2011.

about HATiP

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The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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