



A challenge to science and policy



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July 2009



“As soon as we relax the control of TB, the disease is back. We should be much more proactive and develop new treatment and prevention to fight TB where it exists.”

Huanming Yang BGI



New tools for tuberculosis

July 2009

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by Robert Walgate, reporting for [EAGLES](#) and [RealHealthNews](#)

Summary

In 2009, the usual method for the diagnosis of tuberculosis (TB) in the developing world is to take a smear of sputum from the patient on a slide, and to stare at it through a microscope to identify a few TB bacilli, *Mycobacterium tuberculosis*, in the smear.

This awkward and insensitive technique is the same as that used by Robert Koch to discover this bacillus, in 1882 - more than a century ago.

In 2009, the only vaccine in use against TB is BCG - *Bacille Calmette Guérin* - prepared from a strain of the weakened live cow tuberculosis bacillus, *Mycobacterium bovis*.

This only partially protective vaccine was developed and first introduced in 1921 - 88 years ago.

In 2009, the standard "short" course treatment for tuberculosis (TB) is isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, then isoniazid and rifampicin alone for a further four months.

But isoniazid was first isolated at the beginning of last century, and was first used against TB in 1952. Pyrazinamide was introduced to the treatment in 1954, ethambutol in 1962, and rifampicin in 1963 - so the most recent drug in the standard therapy is nearly half a century old.

These are the tools in use *now*, against a virulent and fatal disease, which is increasing its resistance to the existing drugs.

So in this report EAGLES interviews the leading experts on TB and TB research into new drugs, diagnostics, and vaccines, to discover where the world stands - and what Europe should be doing - to improve our defences against this disease, both in Europe and worldwide; and we report from the TB frontiers in Assam, India and Malawi, Africa.



Introduction

According to the World Health Organization (WHO), 1.6 million people died from tuberculosis (TB) in 2005, the most recent year with reliable statistics. South-East Asia accounted for one third of incident cases globally, but the estimated incidence (number of new cases) in sub-Saharan Africa is nearly twice that of South-East Asia, at nearly 350 cases per 100 000 population, in part as a result of the HIV/AIDS epidemic, in which TB is a major opportunistic infection.

HIV and TB form a lethal combination, says WHO. Each speeds the other's progress. Someone who is HIV-positive and infected with TB bacilli is many times more likely to become sick with TB than someone infected with TB bacilli that is HIV-negative. In Africa, HIV is the single most important factor contributing to the massive increase in TB incidence and mortality since 1990 - a tripling to quadrupling of the problem - says WHO.

Drug resistance is also increasingly common, as a result of inconsistent or partial treatment. Strains of the TB bacillus resistant to a single drug have been found in every country surveyed; and strains of TB resistant to all major anti-TB drugs, MDR- and XDR-TB have emerged.

EAGLES held a meeting on the challenges of TB in Shenzhen, China, in November 2008 at which these issues were debated. China, reported Daniel Chin of WHO's office in Beijing, has 16% of the world's TB cases - but 25% of the world's MDR-TB cases, giving it the largest MDR-TB epidemic in the world. It is concentrated in a few provinces where good management of TB treatment arrived late, said Chin.

Europe's TB researchers brilliant - but funding needs to double for clinical trials of their products

Perhaps it's the brilliance of Europe's TB researchers, but most of the good ideas in TB vaccine research are coming from Europe, according to Jerry Sadoff, the Chief Executive Officer of Aeras, the world's centre for TB vaccine development and trials, (see below). And the European and Developing Country Clinical Trials Programme, EDCTP, is proving a good partner under its new director Charles Mgone, we hear from Sadoff - and from Mel Spiegelman, the Director of Research and Development for the Global TB Alliance, the world's coordinating centre for the development of new drugs for TB (see below).

But these are ideas - what about the funding to turn them into reality, the 'development' in 'research and development'? Research for TB drugs is hitting a brick wall in the funding for clinical trials, which are very expensive, Spiegelman tells us, and vaccine research also needs to scale up that work with some 51 candidates on stream.

Clinical trials are fundamental to TB product development. Because the disease is so lengthy and complex, and the human immune system is still not fully understood, much of the experimentation to produce useful new tools will come from trials 'in the field', we learn from our interviewees.

So for this rounder view, closer to the patients and the global challenge of TB, what does the Executive Director of the StopTB coalition of over 900 TB organizations worldwide, Mario Raviglione, based in WHO, Geneva, tell us about European support for this



research? It's far from sufficient, he says. And for TB control, it's vanishing.

"TB is everywhere, and TB doesn't stop at borders. Europe has the worst MDR-TB and XDR-TB in the world right next door and in fact coming in, from neighbouring countries in Eastern Europe".

"And immigration is coming from all over the world, so it's not just Eastern Europe we need to be concerned about. Italy just recently had an outbreak in Rome, affecting dozens of children. They were found to be positive after having been exposed to a teacher from another country... And so on and so forth. This is happening everywhere in Europe".

"And yet the European Community and the member states of the Community are making extremely limited investments in TB research - both compared to the real needs, and compared the investments of others, especially the US National Institutes of Health (NIH) and American private foundations like the Bill and Melinda Gates Foundation", Mario Raviglione told EAGLES.

"In Europe the British Medical Research Council is best placed, but they are still spending small amounts. There is a huge difference in spending on TB research between on the one side the NIH and the Gates Foundation, and on the other, the rest, right? But then after that you find fairly little. After the UK, if you look at Germany, if you look at Italy, if you look at France, if you look at Spain, at all of these other economically fairly powerful countries, they are investing practically nothing on TB research."

"So it's clear that the headline is that Europe needs to invest more. And they need to invest strategically."

What are the research priorities?

So what research and development do we need most, from the perspective of TB control?

"Obviously the pipelines for the three key types of tool - diagnostics, drug treatments, and vaccines - need to be bigger", Mario Raviglione told EAGLES.

"There are even global agreements, consensus, about what new diagnostics need to be developed, for example. What we need at the point of care is a simple diagnostic tool that will allow a person to go there with a cough, and immediately a little test says TB.

"That's really the final, ultimate solution to the TB problem - at least prior to the magic bullet: a one shot vaccine given in childhood that would protect for life - but that dream looks a long way off" said Raviglione.

However, the researchers interviewed by EAGLES (see below) claim that a new vaccine regimen could be ready by 2016 - and a diagnostic tool as simple to use as a microscope, that can even detect MDT-TB, is already available: but it costs \$15 000 - a huge investment in the hardest-hit countries whose health budget is often only a few dollars per year for each person.



TB vaccines “within the decade”

EAGLES interviewed Jerry Sadoff, the President and Chief Executive Officer of Aeras, the key global centre for the development of new TB vaccines - who was decidedly upbeat about the promise for vaccines. And most of the good ideas are coming from Europe, he said.

Jerry Sadoff, of Aeras TB vaccines - would you make a prediction? We're going to have a TB vaccine in what shall we say, a decade? "Oh at least... We're hoping to get maybe by 2016 or so a new TB vaccine regimen. We should be able to do that within the decade."

>EAGLES: Jerry Sadoff, one vaccine at Aeras has been giving some striking results - the AERAS-402/Crucell Ad35 vaccine.

JS: Yes - we have very good data in South Africa; we get very good responses from CD8s [a key component of the T-cell element of the immune system, and considered very important for TB vaccines]. They're the best we've seen against TB vaccine and some of the highest we've seen against any vaccine. And we also get CD4s [another T-cell component] that look good.

Then we did a study in St Louis, Missouri. The people in South Africa had had BCG vaccination at birth [the classical, only partially effective vaccine developed from bovine TB and first used in humans in 1921].

We had done a study previously in Lenexa, Kansas, where we saw just modest responses against the vaccine in people that were naïve [has been exposed to neither BCG nor TB]. So we went back and took naïve people in St

Louis and gave them BCG - and then we 'boosted' them with our vaccine.

What we found was that after two boosts with the 402 we got consistently very high responses; it looks very good.

We look at the naïve people as an indication of what might happen in infants. We couldn't tell in South Africa if people had had BCG. So this was a very important experiment - we learned that naïves given BCG would have a good response. So we've just started vaccinating infants along those lines in South Africa. And I'm pretty confident that we'll get similar results.

The European and Developing Countries Clinical Trials Partnership (EDCTP) have funded us to test that more widely, in Mozambique, Kenya and Uganda. We've had a just marvellous relationship in the last couple of years with Charles Mgone and the EDCTP. They've really got their act together; at least as far as TB vaccines go.

>EAGLES: How many infants will be included?

JS: The problem with TB is that we don't really have a 'marker' - we don't definitely know what immune response might predict that a vaccine will be protective [against disease]. And we don't really know how the animal models of TB compare with human responses. It's the same in HIV. We are making progress but until now we don't really know what our animal models mean.



StopTB lists 51 TB vaccine candidates going into clinical trials. The trials are essential experiments: "there are lots of questions that we have to answer and unfortunately we can't answer them in animals because we don't know if those animals reflect what goes on in humans" says Jerry Sadoff, Aeras

>EAGLES: Frankly, there are an amazing number of candidates for TB vaccines! A document from Stop TB for example from September 2008 lists 10 vaccine 'priming' candidates [like BCG in the AERAS402 trials] in Phase One by the end of 2009, another five by 2010 or later; in booster vaccines [like AERAS402] the figures were 12 and 11, and vaccines for immunotherapy eight and five. So altogether for the different approaches, it's 51 candidates.

JS: But they're including a lot of pre-clinical stuff that's not going to make it.

>EAGLES: That's certainly true but the question I was leading to is this: to what extent do you think the candidates are based on a scientific understanding of the immune system, and especially on understanding the complex immunology of TB? It's a pretty clever organism. I wonder how well we understand it, or even the immune system, and even more their interaction?

So to what extent are these clinical trials actually real experiments that will teach us more - and at the same time, if we're lucky, create a vaccine?

JS: I think you've captured it pretty well. I think that there are several problems. One, we don't know exactly what type of immunity we need. Second, we don't yet know which of the antigens [components of the bacillus

that stimulate the immune system] should go into the vaccine. And third, we're not exactly clear *where* immunity has to be; do we need a highly specific response in the lung, or will a systemic immunity be good enough? Those are the questions, and we have tentative theoretical answers to each of those questions.

In fact I think we need *all* arms of the immune system to work and that's difficult. So we need CD4s and CD8s and probably antibodies [produced by B-cells] to some extent. We need at least the CD4s and CD8s. And what kinds of antigens do we need? I think we need antigens from each of the phases of the TB bug in its life cycle in the human. So we need the antigens it expresses while it's initially getting into the body, and then the ones it may make when it becomes latent, and the ones it may make when it gets out of the latent state, becomes active and gets back into the lung, where it might cause disease.

>EAGLES: So you want to attack everything?

JS: I want to attack everything! I also believe that we probably need a very good immunity in the lung and also one systemically. The bug is very clever as you said; it's lived with us for at least 50,000 to 60,000 years if not longer. So it's also learned to live in an organ, the lung, which is kind of sensitive to inflammation.

When you get pneumonia, like viral pneumonia, it's not because it's killing cells; it's the inflammation [a localised immune response] that kills you. And the TB bug knows that or has learnt that, from an evolutionary point of view. So it can't create too much inflammation in the lung because that's



fatal to the human. That gives the bug sort of a niche to live in.

Like you just said, there are lots of questions that we have to answer and unfortunately we can't answer them in animals because we don't know if those animals reflect what goes on in humans.

To some extent we're trying vaccines with different antigens in them and being able to induce different kinds of immunity in different locations is the sort of rational, logical approach. So we try and put as many of those components into a vaccine as we can and learn if those things are enough or not.

>EAGLES: But if a vaccine created inflammation in the lung that could be a danger situation.

JS: The other problem we have in TB is that we need to vaccinate *everybody*, kids and adults. We're sure we'll vaccinate people that have latent TB [where the bacillus sits quietly in the lung]; in fact we want to do that because we want to make sure that the vaccine will prevent those with latent infection from developing real disease. That's probably the key to controlling things. So therefore just like you said, if they have the organism in their lung already, we want to make sure the vaccine doesn't cause inflammation against it - that would be serious.

And that's why for the 402 vaccine right now, we're testing at the Lung Institute in Cape Town, in people that have or recently had TB, so that we can show that it's safe, and we're showing that. That's a very important component.

It's moving along, it's not as fast as we'd like because there are so many people dying of TB all the time. But we're trying to be careful in going

forward, just as fast as we can, to show that these vaccines have some potential.

Vaccines turned into extremely fine mist or dust can be breathed in - and going deep into the fine tubes of the lung produce "extraordinary" immune responses in monkeys, 100-1000 times those created by injections. This could be turned into a 10-cent device and avoid the problems of needles, says Jerry Sadoff of Aeras.

JS: One of the other things I should mention to you is that we've learnt something very interesting in the last two years. We took our 402 candidate and we made it into very tiny particles, either with an aerosoliser that has laser-drilled holes and a filter that makes a very very fine mist, or with a device that makes an extremely fine dry powder. And when we gave that to monkeys in the lung, they get extraordinarily high levels of CD8s and CD4s in their lung.

We think that's because when you make it small like that it's breathed deep into the lung, into the tiny alveoli, as opposed to getting stuck up in the trachea and the walls.

>EAGLES: I see - as fine particles the vaccine goes deeper.

JS: It goes where the air goes. The lung is sort of a big filter to keep *out* dust. So everything that's big sticks to the walls of the tubing that goes down into the bottom of the lung. But then if you make the particles small enough, they just float with the air and don't stick to the walls, and so they get down deep. And when it gets down deep then it interacts with the macrophages and other immune cells



that are down there, making very powerful immune responses, at least 100 to 1,000 times higher in the lung than we get there if we give that very same vaccine as an injection into the arm.

>EAGLES: It looks to me as if the whole field is getting very promising. We're going to have a TB vaccine in what shall we say, a decade?

JS: Oh at least, we might get the recombinant BCG licence by 2013 because we can fast track on that. We're hoping to get maybe by 2016 or so a new TB vaccine regimen. We should be able to do within the decade, yes.

It's very exciting for us because when we started five years ago there were hardly anything in the clinic. And now we've got at least four different candidates in the clinic right now. There are others that we're not sponsoring. And then of course we're putting two more in.

>EAGLES: Let me finish up with one question on relations with Europe. You've already expressed that they're very good with EDCTP. Anything you'd like to see improve?

"Most of the really promising candidates for TB vaccines are coming out of Europe" - Jerry Sadoff, Aeras

JS: One thing I'd like to say about Europe is that while there's a lot of US NIH support, most of the candidates that are really promising candidates for TB vaccines are coming out of Europe!

>EAGLES: How do you explain that?

JS: BCG vaccine was developed and used in Europe while it wasn't used in

the US. And the US has put a lot more emphasis on basic research. I think European research has focused on research that could lead into vaccines and making early vaccine candidates.

So we've had a very good relationship with the Europeans because that's where the candidates are coming from! We really like the idea that the European Commission has supported basic research that leads towards vaccines. That's been very helpful to us because we've had good relations with those groups.

TB drugs

EAGLES interviewed Mel Spiegelman, the Director of Research and Development for the Global TB Alliance, which is the world's major focus for the development of new drugs for TB:

>EAGLES: Mel Spiegelman, what's your deep strategy at the Global Alliance for TB drug development?

MS: Well our main job is to put ourselves out of business! That's our strategy. And I say that only somewhat facetiously. I think the really important part of our strategy is that we do research and development and work on getting new drugs, new TB regimens, to the people that need them.

"Our main job is to put ourselves out of business!" - Mel Spiegelman, Global Alliance for TB drug development

But our really unique strategy is leverage: taking full advantage of whatever resources are being devoted to TB drug development, wherever they are, across the globe.



A lot of organisations are trying to develop or do things with new TB drugs. And that's great. Every single one of them should be applauded. It's really fantastic; we don't have enough.

But TB is a unique disease. Other than latent infection, which I'm going to put off to the side a minute because that's a separate entity, everybody knows that TB has to be treated with combinations of drugs. And not only does it have to be treated with combinations of drugs, the testing process for a new drug can only really be done beyond two weeks without combinations.

>EAGLES: Why is that?

MS: Because we know new TB drugs will generate resistance, and usually do it pretty quickly. If you have a new drug, the last thing in the world you want to do with that new drug is use it by itself, because you're almost assured that you'll ruin the drug.

So, the reality is if the global assault on TB is going to make the sort of progress that's needed, our progress will ultimately depend on not just coming up with the drug, but coming up with a markedly more effective regimen of a number of drugs. And probably almost all of that regimen will be new drugs.

We'll almost certainly need combinations of new drugs, "What that means is that we've got to be in a position to take advantage of everybody's contributions... Now we're looking at about 12 drugs" - Mel Spiegelman, TB Alliance

What that means is that we've got to be in a position to take advantage of *everybody's* contributions, not just say moxyfloxacin and PA-824 because they happen to be in our portfolio, but really

working with every single drugs sponsor that's out there.

We are now looking at about 12 drugs. We talk to, and try to collaborate with, every single company that's out there. We have contractual agreements with Glaxo, with Bayer, with Novartis. We're in active discussions with virtually with every other company that's doing TB work.

The goal is to make sure that we truly leverage everybody's contribution so that we can make really tremendous progress as quickly as possible and not just small incremental progress.

The goal is to make sure that we truly leverage everybody's contribution so that we can make really tremendous progress as quickly as possible, and not just small incremental progress... we aim to get treatment down from eight months to two months, and with MDR- and XDR- TB from two years to a few months - Mel Spiegelman

MS: That's what we're shooting for; that's what we've begun to test in the laboratory already. With all the new drugs, we're testing them to see which combination really can get treatment times down [from the current 6-8 months for drug sensitive TB], not just to four months, which hopefully moxyfloxacin can do, but down to two months.

And this is the part that's really exciting. If the combinations that we find are novel drugs for which there's no resistance out there, there's every reason to believe that even in MDR- and XDR-TB, with such a combination we can go from two years treatment times down to a few months. Inherently MDR-TB is the same disease as drug sensitive



TB. It just happens that the organism is resistant to some of the present drugs. It's nothing to do with its resistance to new drugs.

Inherently MDR-TB is the same disease as drug sensitive TB. It just happens that the organism is resistant to some of the present drugs. It's nothing to do with its resistance to new drugs - Mel Spiegelman

>EAGLES: Because the new ones are all in very different classes.

MS: That's right, with different mechanisms of action. Not that the disease is any different. If we have a new combination that can bring the treatment duration for drug sensitive disease down to two months, one can say that the benefit for drug sensitive is going to go from six to two. The benefit in drug resistant TB will go from two years to two months. So, that's where by working together we can have tremendous leverage and benefit across the board.

But the amount of funding that's presently available to do the TB work that's necessary to make this progress is woefully inadequate.

>EAGLES: You're talking about the cost of field trials?

MS: That's where we're really running into the roadblock. The research components are expensive and we need more. There's no question about it. But that is really a fraction of the cost of the field trials that are necessary in TB.

>EAGLES: Just walk me through why field trials are so expensive.

MS: First of all, just to put it in perspective, it's true across the board.

Whenever you set up clinical trials, you run into the cost of clinical trials, especially trials that have to run for a long period of time. You're supporting a lot of people. You're supporting a very big infrastructure around the trials, to ensure that the trials are being done the right way, according to good clinical practice. And especially in TB where there's a very heavy laboratory component to all the clinical trials, you have to pay for that too.

>EAGLES: You say we have woefully inadequate funding for that. By what factor?

MS: We need billions of dollars. It's a little staggering the mountain we have to climb in terms of getting the financial support.

We need billions of dollars for field trials. It's a little staggering the mountain we have to climb in terms of getting the financial support... but meanwhile, we're going to see the numbers of TB cases in the EU grow dramatically - Mel Spiegelman

>EAGLES: So what does that mean? Who's in a position to provide that form of financial support?

MS: Realistically, one of the big places we have to look is to governments. And realistically, a big part will have to be played by governments within the European Union, simply because those governments are still some of the richest in the world, leaving aside today's financial crisis.

And now we're also entering a new era, the expansion of the EU. With that, we're now going to see the numbers of TB cases in the EU grows dramatically.



>EAGLES: So, that's the case you'd put, for example, to European parliamentarians, or to the Commission or to the European Council of Ministers - that they actually need to take care of this issue because they're exposed.

MS: Right. First there's the moral obligation that applies to every country in the world. It's a global problem. I think the moral obligation would rest on what I would call charitable giving. Then there's also enlightened self-interest that in fact this is not only on the EU's doorstep, but already inside the house. It's a problem that's growing in the globalized world, in the globalized economies. There's the saying that TB is only a flight away.

>EAGLES: The European Commission has its own European and Developing Countries' Clinical Trials Partnership, the EDCTP. Has that been of value to you?

MS: Yes, it has. Especially now under Charles Mgone's leadership, the EDCTP has really done a great job within the confines of what they've been given.

>EAGLES: They have been criticised in the past. Are you saying they've upped their game a bit?

MS: I think they had a rocky beginning, let me put it that way. But clearly, I think they're now functioning much better.

>EAGLES: That's interesting. We heard the same from Jerry Sadoff, the Director of Aeras, which is developing TB vaccines, as you know.

>EAGLES: To talk about specific drugs, I understand that PA-824 was far more effective than you expected.

MS: Yes, and the next study that we would like to do is actually going down

in dose even lower than 200 milligrams. That has a lot of benefit down the road. Clearly, the biggest benefit is if the drug works. But then, the fewer drugs you have to give, the less costly it is to make. And the fewer drugs you have to give, usually the fewer side effects you ultimately see with the drug.

And another thing that's also important in the field of TB is that a small dose makes it easier to use in what are called fixed-dose combinations. They're very helpful in poor communities in developing countries - the drugs to be combined are actually given in one pill. That helps with compliance, and so it slows the development of resistance, etc.

>EAGLES: From what you're saying it sounds to me rather as if we can expect a gradual improvement in the treatment regimens. They're going to get shorter; they're going to get a little bit more effective. But perhaps there isn't a sudden, dramatic magic bullet.

I would say if we could get the treatment of drug resistant and drug sensitive disease down to being able to cure 95% of everybody in two weeks or so, that's a magic bullet. We can get there. The issue is how long is it going to take? And that's directly related to how much funding we can get - Mel Spiegelman

MS: I think the key here is we should expect that there will be improvement. I fully expect that. The question is how fast can we see that improvement, and how fast can we get to a magic bullet? I would say if we could get the treatment of drug resistant and drug sensitive disease down to being able to cure 95% of everybody in two weeks or so, that's a magic bullet. We can get there. The issue is how long is it going to take?



And that's directly related to how much funding we can get.

>EAGLES: So, the limitation is not in the number of candidates that are coming along. There are plenty of candidates and plenty of ideas. You just need to test them.

MS: I would say right now, the rate-limiting factor that we have is the resources. We always could use more candidates, but right now we don't have the resources to adequately test even the candidates that we've got.

I think the relationships with China are also very crucial... China has the second highest TB burden in the world... and excellent science. We're working with them to discover natural products against TB - Mel Spiegelman

I think the relationships with China are also very crucial.

It didn't make that much press, but we already have one ongoing project with an institute in China that's going very well. We are planning to do clinical trials with moxyfloxacin in China later this year. We have this new project that will start up with a new institute in China. We see China as being a very important country. China has the second highest TB burden in the world in terms of numbers of patients. And where we can make a dent on the problem, China clearly is important. China does have excellent science. China has resources now. I think it may have been lost in our announcements, but through the Academy of Sciences the project that we're doing is being co-funded, 50-50, between the Alliance and China. That's extremely important because China's government is now engaging in putting its own resources behind the problem.

>EAGLES: Also interesting is the fact that they're looking, with you, at natural products for treating TB. As you know, artemisinin [now the key drug for malaria] is an example of a Chinese natural product that turned out to be extremely useful to the world.

MS: Yes, and the best drug for TB these days, rifampicin, is also a natural product.

We made a strategic assessment internally over a year ago. We wanted to get more involved with natural products. We scoured around the world to look at where's the best place to go to. Obviously, we've got limited resources that to invest in any single endeavour. But it was really out of that initiative that we ultimately identified the Institute of Microbiology in China. We think that's where we get the biggest so-called 'bang for our buck' in terms of pursuing the whole field of natural products for TB. It was a strategic decision we made, and then it really took a year or so to get to the point where we identified the partner that we felt was the best to go with. And it was in China.

TB diagnostics

EAGLES interviewed Mark Perkins, the Chief Scientific Officer of FIND, the Foundation for Innovative New Diagnostics, the world's leading centre for developing TB diagnostics:

>EAGLES: Mark Perkins, TB diagnostics is a very complex area, because the disease itself is complex, it has dormant and active phases, the duration of infection can be very long, and the exact need for diagnostics is different in different situations and stages of the disease. But let's try to



simplify this issue with a simple question. What is FIND most proud of?

Mark Perkins: There are two things that I think we should be proud of. One is that we've conceptualised the exact *need* for diagnostics in a much more refined way than has ever been done before.

We've worked out exactly what kinds of TB tests are needed, where, to be used by whom, to accomplish what - that's something people haven't been thinking about... in the kind of detail that we've now achieved... This has really helped us a lot in getting the types of diagnostics placed in the places where they're needed and for the right people - Mark Perkins

That is, we've worked out exactly what kind of tests are needed, where, to be used by whom, to accomplish what? That's something people haven't been thinking about. I've had meetings of 50 to 100 experts at a time over the last decade, and not reached the kind of detail that we've now achieved.

We've identified at each level of the health system the kind of test we need there, what kind of patient would be arriving there, and what kind of speed and sensitivity would be most appropriate.

We've even considered how do the results need to be delivered, whether printed, written or hand scrawled, whether it should include drug susceptibility data and so on.

This has really helped us a lot in getting the types of diagnostics placed in the places where they're needed and for the right people.

>EAGLES: That's interesting. You've said before that a lot of tests have fallen by the wayside, because they haven't taken that kind of thing into account.

MP: An interesting example of this is that civil society, quite rightly I think, is agitating for a 'point of care' test. But we can't be naive about this. The kind of test that people are imagining for TB, are there precedents? Are there tests of that kind for any other disease in use in the world? In fact there's no community level testing for anything other than malaria, and that's only because you can treat it on the spot with ACTs [artemisinin combination therapies].

With HIV for example you need to do counselling. That means that we place the tests at a higher level of the health system. And TB is a disease that requires six months therapy.

So the point of care for TB is also at a higher level than the village. It is at the health centre. So that has been one of our internal priorities - to get technology that can be used at health centre level.

The message I meant to send is that one needs to think carefully about how you describe the health system, and what information we would gain, and who would use it for what.

That being said, the opposite force in action is that most patients, quite obviously, seek their first care as close to their house as they can. So that is the village healer, or the pharmacist, or eventually by some interaction with the public health system, in what is probably a primary care clinic. And everything beyond that requires weeks of percolating through the health system.



A poor citizen in Bangalore walks to his chest clinic past the Xerox manufacturing plant, past the Microsoft factory, past the cell phone tower - and when he gets to a clinic and they say the only technology we have to offer you to help understand what's wrong with you is a microscope! - Mark Perkins

And it's different for every individual patient. So many people in Brazil, for example, live in large urban areas, not the countryside. And we can't ignore the fact that a poor citizen in Bangalore walks to his chest clinic past the Xerox manufacturing plant, past the Microsoft factory, past the cell phone tower - and when he gets to a clinic and they say the only technology we have to offer you to help understand what's wrong with you is a microscope!

Yet he or she is in the centre of modern technology, as a lot of city dwellers are! So in developing diagnostics we can't ignore the fact that in many places in the world patients are not in a rural Chinese or Mozambican village.

So we have to somewhat complexify our images of diagnostics. But that being said, for people who do live outside urban areas, and there are many, they perhaps see the longest delays in finding out what's wrong with them. We do need some way to accelerate their path towards therapy.

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I was in conversation with Bill Gates recently; he finally latched on to this concept that if you had a dipstick for TB, it would encourage people to move to get therapy. It would not mean immediate treatment at the place where the diagnosis was being made.

So the concept of point of [diagnostic] interaction, *and* a possibly different point of treatment, instead of 'point of care', has taken hold.

>EAGLES: TB is a disease with stigma, a bit like HIV. So perhaps diagnosis needs to be at a level where stigma can be cared for to a certain extent.

In India I was in villages where patients would tell me that they would go to the health centre in the next village over, because they didn't want to anyone to know that they had TB - Mark Perkins

MP: In India I was in villages where patients would tell me that they would go to the health centre in the next village over, because they didn't want to anyone to know that they had TB.

But the second thing that I think we should be proud of is, I'm a little bit ashamed to be so specific, but it's a new molecular test for TB that we've just launched, and CE marked [meaning that the data has been submitted to the European Union, and registered for sale in Europe, legitimising it for world use] that has quite dramatic performance.

MP: It's a 90 minute assay that we've developed with Cepheid in the US, with no work for the helper other than pouring some reagent into the sputum pot, to kill all the TB bacilli, and letting it sit until the bacilli are dead - which takes 15 minutes; and then simply



taking a pipette and depositing some of the sputum into a cartridge; and then closing the lid and pushing start on the machine. That's it.

>EAGLES: And what's the result?

[With our new \$15 000 machine] there's a screen, and it says TB, or no TB. And if it's TB it says whether it is multidrug resistant. It's very simple to use, requiring the same or even fewer skills than microscopy. With global funds it's really simplicity of use, not cost, that should determine placement in the health system - Mark Perkins

MP: Then there's a screen, and it says TB, or no TB. And if it's TB it says whether it is multidrug resistant.

>EAGLES: That's amazing.

MP: So that has been 3-4 years in development, and has just finished a multicentre clinical trial in five sites worldwide.

>EAGLES: However StopTB says its costs for equipment and consumables are high.

MP: It is expensive. The machine costs about a third as much as an automated culture machine, but that still is US\$15,000. That's production costs; the market costs are considerably higher. Then there are the running costs. I'm not sure that they are that big a deal, but running costs are significant. Our original target was under US\$10 per test, but we're now at around US\$20.

>EAGLES: So this has to be used at a high level in the health system.

MP: No. The point is, that cost doesn't really decide where you are in the health system.

>EAGLES: Could you explain?

MP: In a health system that is able to get global funds, then it's really simplicity of use - not cost - that determines placement. It is true that at the higher levels of health system there's more political power and people probably tend to hold on to technology close to where they work, but in a real sense it's not the cost that counts.

>EAGLES: You mean somebody will pay for it if it really works?

MP: Well yes.

>EAGLES: That's your view.

MP: We have a couple of thoughts on this. One is that you should think about cost, based on what something does for you, not just on calling it 'a TB test'. So if you currently do culture of the bacilli followed by drug susceptibility testing, it takes you on average 100 days - and it costs US\$40-60 per test plus lots of technician time. On top of that it's dangerous, because you're growing multidrug-resistant organisms in the laboratory. So if you can replace that with something that does it while the patient is waiting in the clinic, with high accuracy, this has extraordinary value. So the fact that it's half the cost, we should be pleased about!

>EAGLES: So where do you think this will go in the health system?

MP: This will depend on countries. In general, this will go as low in the health system as health systems are capable of dealing with the information it generates.



Let me give you an example. Our thinking has been like this. In general, we tend to break the health system down into a national reference laboratory, referral centres, district hospitals, health centres, and primary health care clinics.

And to be simpler still, we can take the microscopy centres, of which there are some 30 000 in countries, is where most TB patients currently get a definition of whether or not they have TB.

So we've called this test a microscopy centre test because it requires essentially the same or even fewer skills than microscopy.

But it can be different in the countryside. We were in Uganda recently to do demonstration projects for this technology, and we drove an hour from Kampala - you may have done this yourself - and you go to the health post and it's quite depressing. They've run out of drugs.

>EAGLES: Sure, the pharmacy's often empty.

MP: So they couldn't respond to a positive result if you gave it to them! This will turn into our major challenge. We've been shouting for a test to diagnose TB quickly and when we have one, we'll find out that in many places it doesn't matter - there are no drugs!

The test costs currently around US\$20, but it's not even for sale in our market yet so you can't really quote a cost at point of sale. It'll depend on volumes; it'll depend on shipping costs. One of the expensive things to do is to ship the reagent that kills the TB bacilli, because it's considered a toxin by shipping standards, and shipping toxic goods costs a lot of money. So we may end up

having this manufactured locally. Certainly, costs will fall in the first year or two. It's possible that with local manufacture of these reagents the cost will fall dramatically and we'll reach close to our US\$10 price point.

>EAGLES: Is it conceivable that you could get local manufacture of the equipment itself?

MP: It is. I've spent a lot of time in the manufacturing plant. It is an incredibly complex process. That being said, the company has just set up subsidiary manufacturing in Sweden and that means a team of engineers and all the plans moved in six months to Sweden and building the auto robotics. It's not impossible to do that in China or India, of course. They can build Philips' digital X-ray machines. And there's no jingoism here, it's just that it's a complex process. Plus, [there may be an export problem because] this assay was developed with US government money to detect Anthrax, out of the Homeland Security funding early on. We'll to look at the exportability of the processes.

>EAGLES: You've been talking about placing this test in the microscopy centre. But if you compare it with a microscope you're comparing something enormously cheaper, in capital cost.

MP: Yes. So it means bringing the capacity and the cost of culture level testing to microscopy centres. That means we now have a question of political will.

With the microscope, maybe ten million people a year were sent home with wrong diagnosis. Now we have an effective assay so what shall we do?



With the microscope, maybe ten million people a year were sent home with wrong diagnosis. Now we have an effective assay so what shall we do? - Mark Perkins

I think there are no denying that this is expensive, and this one of the challenges. We've come to realise that point of care testing, something where something that you put a jiggle of sputum or blood on and you've got a result, is as dramatic a challenge as getting a malaria vaccine or TB vaccine. It's not simple.

We've come to realise that putting a jiggle of sputum or blood on [a test strip] and you've got a result, is as dramatic a challenge as getting a malaria vaccine or TB vaccine. It's not simple - Mark Perkins

So that was one of our strategic decision points about three or four years ago. Georgio Roscigno [the Chief Executive Officer of FIND] and I were discussing what our plan should be, and I made the decision at the time that whatever its shape and whatever its complexity and whatever its cost, we should start with developing a test that does what we want tests to do. Then we should work on simplifying costing, etc... Because if you haven't even got an example, if you've not shown that it can even happen and you're ten years down the road, where are you?

>EAGLES: What about simply improving microscopy?

MP: Well the microscopy that most people are using is not very different from that of Robert Koch [the man who showed that the tuberculosis bacillus caused TB in 1882], but huge events in microscopy have taken place since then

and there have been a lot of interesting simplifications.

One of the most striking possibilities is to convert cell phone cameras into microscopes - Mark Perkins

MP: Well one of the most striking possibilities is to convert cell phone cameras into microscopes. It turns out with a fairly simple bit of engineering and a couple of lenses you can get cell phone cameras to do microscopy work for almost pennies.

One area of development that should be as easy as falling off a log is to get the software engineers to figure how this can be automated. One issue is auto-focussing, because you need the lens to know when it's in focus and when it's not

>EAGLES: and the bacilli are not hard-edged objects.

MP: Exactly. There are some simple ways around this; we could add something to sputum, some little crystals that a cell phone microscope would focus on. So there are some approaches there.

The second thing that software needs to do is basically recognise shapes that would identify the TB bacillus. But it should be possible.

But we don't currently have technologies that are really easy to use, like a dipstick, which can detect extremely low quantities of material. This is a huge technology goal. I think we'll get there.

The question I have internally for myself is; will we get there in three years and everyone will say, bravo, or will we get there in 30 years and everyone will say,



why did we ever fund researchers to do this work?

And I don't mean FIND, I mean the world. It's a major challenge. Fortunately, there are few diseases of wealthy countries - heart attacks and others - where there are relevant human proteins that are present in low quantities, so there's a bit of a scramble in the industry to try to develop such tests, anyway. So we get to piggyback on that.

>EAGLES: Can I ask you one last question? Is there enough money in this field?

MP: I don't think there's any field of human endeavour where the answer is there's plenty of it. In a sense, it's not a fair question. There's more money in the field than there has been for a long time. We can be very pleased about this.

But there's more money needed, and there is some coordination needed. Vast sums are being spent on basic research and also on technology transfer for the development of detectors for things like bio-weapons, and we are spending a fair amount of time trolling through what the bio-weapons billions are covering, to see if we could spend a few million to turn this or that into a TB diagnostic. It just makes sense. But it's relatively unfocussed work, bio-weapons spending - so it's not been a highly productive zone.

The work, then, requires as much care as it does money, let's put it that way. If you replicated funding five times at five other organisations you certainly wouldn't get fivefold more work done. I'm sure you would get about twice as much work done.

I think that what is needed, and civil society rightly urges this too, is open, transparent and communicative interactions that allow people to know what's going on [in each field of research]. Civil society urges that because they want to know what's happening.

We need to have a critical mass of people communicating frequently with each other and investigating the area. Whether they're all in one organisation or in multiple organisations doesn't really matter, but the structure needs to be such that they're not competitive agencies each trying to get the limelight.



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StopTB Partnership <http://www.stoptb.org/>

The TB Alliance - the Global Alliance for TB Drug Development
<http://www.tballiance.org/home/home.php>

Aeras Global TB Vaccine Foundation <http://www.aeras.org/home/home.php>

FIND, The Foundation for Innovative New Diagnostics
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