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World Health
Organization



TIME BOMB: *Multidrug-resistant tuberculosis*

Stop tuberculosis (TB) - easier said than done, of course. But although the task is massive, the aim is perfectly feasible. If patients have access to appropriate TB treatment, and if those patients stick to it, then standard tuberculosis can be cured in more than nine out of ten cases.

Unfortunately, that's a pretty big "if".

Because when a TB patient does not receive and complete proper treatment, he can end up in a worse state than when he started. And in some parts of the world, that's precisely what is happening. Consequently, a far nastier, cleverer TB genie is out of the bottle ... and we are all at risk.

Multidrug-resistant TB (MDR-TB) is a form of TB that is far more difficult, and far more expensive to cure than the common, "drug-susceptible" form of the disease.

MDR-TB is so called because it is resistant to at least isoniazid and rifampicin (two of the first-line drugs used for the treatment of TB). Resistance occurs when the bacilli develop the ability to withstand antibiotic attack and relay that ability to their progeny. Since that entire strain of bacteria inherits this capacity to resist the effects of the various treatments, resistance can spread from one person to another. And fast. Before he dies, the average MDR-TB patient may infect a further 15 to 20 people.

Yet it didn't have to be this way. Unlike standard TB, the drug-resistant variety is a purely man-made phenomenon, born of human error. In areas that conform to World Health Organization (WHO) guidelines governing the treatment of TB, there is minimal or no MDR-TB.

Successful treatment of TB depends on close cooperation between the patient and doctor and other health care workers. It also requires proper funding. If patients don't take all their medicines in the precise way and at the precise time their doctor tells them - or if a sick person stops taking his medicines because he is already feeling better, or if treatment is inadequate to begin with - he can become sick again. This is because the TB bacteria learn to outwit the TB antibiotics, and soon those medications no longer work against the disease. Then the illness returns with a vengeance. When this happens, the person now has resistant TB disease.

That's when the real problems start.

In developed nations, between 60 and 80 percent of patients with MDR-TB are cured. In developing nations, nearly all patients are condemned to die because effective treatment is often impossible to afford - it costs 100 times more to cure MDR-TB than drug-susceptible TB.

So far, more than 70 countries and territories have reported such cases. In some places, MDR-TB is still a time bomb waiting to explode. In Africa, for example, where the rates of TB drug resistance are relatively low at the moment, there is potential for a huge increase because of the growing burden of HIV, which weakens a person's immune system, and therefore renders the individual more susceptible to other forms of the disease like MDR-TB. Elsewhere, in places such as China, the Islamic Republic of Iran and the former Soviet Union, the bomb has already long since exploded. Estonia, for instance, reports that around 40 percent of new cases of TB are resistant to at least one tuberculosis drug.

But wait - it doesn't end there. You can't shut out the problem by throwing away your newspaper or turning off the television. MDR-TB is not simply one more scourge that afflicts remote areas of the atlas. Sure, this plague is as deadly as others that torment swathes of the developing world. Unlike those diseases, however, MDR-TB is airborne ... and it doesn't only travel on the wings of a cough or a sneeze. In these days of globalization, mass migration and cheap air travel, MDR-TB is just a plane ride away.

In the USA, MDR-TB has been reported in most states. New York struggled with an outbreak 12 years ago which cost US\$ 110 million over four years to bring under control. Countries such as Israel and the UK have seen recent increases in MDR-TB due mainly to immigration.

In other words, none of us is safe. We are facing a worldwide public health emergency. And we might as well start dealing with it now.

To find out how, read on ...

J.W. Lee
Director
Stop TB

The Stop TB Partnership is a global movement with more than 200 member organizations (including the World Health Organization) that are engaged in TB control efforts. The Stop TB Partnership Secretariat is hosted by the World Health Organization in Geneva, and coordinates the activities of the Partnership.

DOTS-PLUS: DEFUSING THE THREAT

New enemy - new tactics

The WHO recommended strategy for curing “ordinary” TB (known as “DOTS” - see accompanying sidebar) is a proven success. But in those places in which MDR-TB is already common and increasing, it can be like shutting the stable door after the horse has bolted.

“DOTS does what it’s designed for - it cures ordinary TB,” agrees Stop TB scientist Rajesh Gupta. “But trying to treat MDR-TB requires going beyond ordinary methods - you need something extraordinary.”

So in 1998 WHO and several of its partner organizations around the world conceived DOTS-Plus, a strategy that is still under continuous development and testing, for the management of MDR-TB.

DOTS-Plus works as a supplement to standard DOTS-based TB programmes already in place. “It is not intended as a ‘catch-all’ strategy,” emphasizes Thelma Tupasi, director of the Philippine Coalition Against Tuberculosis (PCAT), a nongovernmental organization and Stop TB’s partner in the Philippines. “DOTS-Plus is meant for areas with significant incidences of MDR-TB ... but within those areas, standard TB cases continue to be treated with standard DOTS procedures, and those procedures must be followed through to the finish - how else can we stop more drug-resistant TB occurring?”

At present, Stop TB’s partners around the world choose between two variants of DOTS-Plus:

- Some countries can afford to devise individualized treatment regimens for patients according to case-by-case drug-susceptibility patterns.

- For areas with less access to funding and equipment, a more standardized DOTS-Plus treatment regimen might be appropriate. If patients failing DOTS are presumed to have MDR-TB, and if drug-susceptibility testing is limited, they might be placed on an empirical treatment regimen consisting of second-line TB drugs.

Whichever approach is favoured, however, identifying and thoroughly training partners in both the private and public health sectors is crucial, since DOTS-Plus requires diagnostic methods that are more expensive and sophisticated than those followed by standard DOTS treatment. “Countries that have always

competently controlled ordinary TB - such as Benin, Chile, Cuba, Botswana, Kenya and Uruguay - don’t have a problem with drug resistance in the first place,” points out Stop TB’s Gupta. “But if a country hasn’t got DOTS right then how can they be expected to get DOTS-Plus right?”

That’s a fair point. For the DOTS-Plus approach entails an even more sophisticated combination of

“carrot and stick.” MDR-TB patients often already have severe lung damage after failing for years on previous regimens. Under DOTS-Plus, they must endure an additional two years of daily, observed combination therapy, including injectable antibiotics, which can produce unpleasant side-effects.

“It is tough: left to himself, a patient might simply say ‘to hell with this. This is too awful,’” PCAT’s Thelma Tupasi grins wryly. “But we can and must keep them on track - if people drop out of DOTS-Plus before they’ve finished their treatment, then their friends, neighbours - and ultimately, their whole community - is at risk for MDR-TB or worse.”



The WHO internationally recommended strategy for TB treatment is called “DOTS.” It has five key components. These are: government commitment to sustained TB control; case detection by sputum microscopy; standardized treatment of six to eight months; a regular supply of essential TB drugs; and a standardized reporting system.



A six-month supply of drugs from DOTS costs less than US\$ 10 in some parts of the world. The World Bank has ranked the DOTS strategy as one of the “most cost-effective of all health interventions.”

Countries that employ DOTS have been able to prevent drug resistance from increasing. Some countries using DOTS, such as Cuba and Nepal, have even begun to see declining levels of drug resistance.

THE PARTNERSHIP PRINCIPLE

Ganging up on MDR-TB

04

As of July 2002, the Green Light Committee (GLC) had approved seven pilot projects (*see following pages*) to implement the DOTS-Plus strategy, and is currently reviewing five further applications. Preliminary results from those programmes already under way show percentages of culture negativization to be between 46 and 79 percent. Continued support for these projects - together with the implementation of new programmes in other countries - will contribute to the building of a sound policy for the control of MDR-TB.



DOTS-Plus is all very well in theory, but unless it is carefully introduced and monitored, it can cause more problems than it solves.

So a year after hitting on the DOTS-Plus concept, WHO set up a Working Group (which later become “The Stop TB Working Group on DOTS-Plus for MDR-TB”) to set out guidelines to approve, advise and oversee pilot DOTS-Plus projects.

The Working Group comprises representatives of governments, academic institutions, civil society organizations and bilateral donors. “It’s very much a team effort,” insists Stop TB’s Drug Resistance Task Manager Marcos Espinal. “We can’t do it without our local and international partners’ input, and they can’t achieve much locally and internationally without WHO co-ordinating technical and financial support from the global community.”

Espinal and his colleagues on the Working Group concede that their DOTS-Plus strategy is still in the pilot stage. Even so, the body’s “Green Light Committee,” which meets regularly to consider proposals for establishing pilot projects, requires that these proposals address certain basic criteria.

“Sometimes a potential partner is accepted straight away,” says Ernesto Jaramillo, Stop TB’s GLC coordinator. “Sometimes, they’ll come to us with a proposal, we’ll look at it, and say, ‘Congratulations on a wonderful presentation. There are one or two things that need further fine-tuning - and the Working Group members will help you fix that. Once that’s done, I’m sure your project will be successful.’”

On many aspects of strategic policy, though, the committee is perfectly open to suggestions.

For example, the GLC recognizes that it is difficult for some patients to travel to receive their daily treatment, and at the same time earn enough money to stay alive.

One way around the problem is the use of incentives and enablers - such as public transport vouchers or food coupons - which patients receive each time they appear for directly observed therapy.

“It’s all about flexibility: we know better than the people in Geneva what kind of incentives will persuade patients to turn up for therapy,” says Kai Vink, head of Estonia’s TB Control Programme. “There are other things, like drugs, that we rely on them for.”

In fact, the irregular supply of MDR-TB medicines was almost the first item on the Working Group’s agenda when it was founded in 1999. The Working Group has since made arrangements with the pharmaceutical industry to provide concessionally priced second-line drugs to officially approved DOTS-Plus pilot projects (*see next page*).

“We can’t physically stop people buying expensive drugs from unlicensed pharmacies or whatever,” explains Myriam Hekens, International Medical Coordinator for Stop TB partner Médecins sans Frontières (MSF), who led the drive to procure the cut-rate anti-MDR-TB drugs. “But by going through the Green Light Committee, and thus qualifying for these medicines which they can then pass on for free, programmes can appeal to patients’ wallets, as well as their lungs.”



DRUG PRICES SLASHED!

... but Stop TB's global drugstore is "members only"



Once upon a time, there were some TB specialists who actually argued against treating MDR-TB in "resource-poor settings." Drug-susceptibility testing and the second-line drugs required to treat MDR-TB, they maintained, were hopelessly cost-ineffective and unsustainable.

Actually, they were right ... kind of.

"Demand from individual projects for second-line drugs is both irregular and relatively small," explains Myriam Hekens of Médecins sans Frontières. "So if all those projects try to negotiate individually, then of course they end up having to pay top price."

But by negotiating collectively and ordering in bulk, the Working Group members reasoned, it should be possible to bring drug prices down.

So that's precisely what they did. Working together, WHO, MSF, Harvard Medical School and other partners have won price reductions of up to 99 percent for high quality MDR-TB medicines.

Acting as a negotiator for all parties, MSF defined the market, consolidated the various sources of demand, negotiated prices, provided advance funds for bulk purchases and assisted with technical support. "They did a great job - a great job," confirms Patrizia Carlevaro, head of the International Aid Unit at Eli Lilly Export, the Geneva branch

of Indiana-based drug company Eli Lilly & Co. "As a company, we have always been aware that we sometimes have to think less about business and more about simply doing the right thing. But we couldn't just throw drugs out of the window and hope they got to the right people. The logistical and technical side of things has to be just right. And now it is."

In some cases, the Working Group even had to dampen drugs companies' spirit of generosity: "Some of them actually said 'here, take them: we'll give you these drugs for free,'" recalls Mario Raviglione, Stop TB's Coordinator of Tuberculosis Strategy and Operations. "But we wanted to get generic players in the market, because no single company can possibly satisfy world demand on its own. So we came across a price that would stimulate competition, and so bring other companies into the game."

A key factor in persuading the drugs companies to cooperate was the built-in safeguard provided by the Green Light Committee - indeed, Eli Lilly and other suppliers have made it clear they will pull out of the scheme if they ever discover their drugs are being used inappropriately or irresponsibly.

"Our cooperation depends on our being satisfied that rational approaches to MDR-TB control are in place," warns Laura Jacobus, founder of Jacobus Pharmaceuticals of New Jersey, USA, which is supplying one of the drugs. "The Green Light Committee's involvement provides that reassurance. In fact, without the GLC's input and continued presence, I doubt this arrangement could have come to fruition in the first place."



Public health officials estimate that US\$ 1 billion a year will be needed to treat patients and control the TB epidemic in the 22 countries that now account for 80 percent of the world's TB burden. Surprisingly, WHO has found that the governments of these 22 low-income nations are already paying 70 percent of the cost of TB treatment and control. Even so, this still leaves a gap of US\$ 330 million a year.

HARVESTING THE SOVIET STORM

Fixing the communist legacy

06

In areas of minimal or no drug resistance, “standard” DOTS has achieved cure rates of up to 95 percent.

China provides the most striking example of the effectiveness of DOTS in preventing the emergence of MDR-TB. Drug resistance is three times lower in regions using DOTS than in regions not using the strategy.

In those parts of China that adhere to DOTS, doctors report cure rates of 96 percent among new cases.

Poor old Estonia. According to WHO statistics, nearly 35 percent of new TB cases in this tiny Baltic republic are resistant to at least one tuberculosis drug; while some 14 percent of cases are multidrug-resistant.

That’s the highest prevalence of MDR-TB in the world ... officially, at least.

But in a way, Estonia is almost a victim of its own success. Because those worrying figures wouldn’t even have come to light in the first place had it not been for the efforts of Estonia’s DOTS-Plus pilot programme.

“We know how much MDR-TB there is around because we are conscientious about diagnosis and we keep good records,” points out Kai Vink, director of Estonia’s countrywide DOTS-Plus programme. “If people don’t keep proper records and don’t test for MDR-TB properly in the first place, then who is to say what their real MDR-TB levels are?”

She has a point.

It was only during the second half of the 1990s that surveys organized by WHO and the Paris-based International Union Against Tuberculosis and Lung Disease (IUATLD) confirmed the existence of MDR-TB.

Countries and settings with worrying rates of drug resistance included the Islamic Republic of Iran, the Henan and Zhanjiang provinces of China and Tamil Nadu state in India.



But the real horror story, investigators discovered, lurked in the countries of the former USSR.

The Soviet health care system had kept tuberculosis - a major killer in the 19th and early 20th centuries - at bay by relying on mandatory mass screenings and X-ray diagnosis, and by isolating patients in sanatoria for years.

PILOT PROJECT

Estonia

Estonia’s country-wide DOTS-Plus programme began in March 2001, and allows for the enrolment of 200 patients over a two-year period. Preliminary results show a sputum negativization of 46 percent of patients after six months of treatment. The pilot project has become a leverage tool to promote the expansion of the DOTS strategy in Estonia. To support the DOTS-Plus project, the Estonian National Tuberculosis Programme is building an infrastructure to provide hospital-based treatment during the first months of therapy. However, there are still substantial difficulties in tackling the problems created by the high level of alcoholism among the enrolled patients. Technical assistance in conducting cost-effectiveness analysis is also needed.



“Traditionally, tuberculosis was considered to be a disease of socioeconomic deprivation, so the early communist leaders had an ideological interest in keeping it under control,” explains Peter Cegielski, a medical epidemiologist with the Atlanta, U.S. Centers for Disease Control & Prevention (CDC), which is running four DOTS projects in the Russian Federation. “But as the military rivalry between the USA and the Soviet Union began to increase in the 1960s, less and less money went towards TB control.”

The supply of money all but petered out completely with the fall of communism and the breakup of the Soviet Union in 1991. Throughout the former Soviet republics, public health services collapsed, while levels of poverty, homelessness, migration and intravenous drug use soared.

Tuberculosis is most rife in Russian jails, whose overcrowded, poorly ventilated cells provide the perfect MDR-TB breeding ground. Prison doctors estimate that of the nearly one million-strong prison population, 100,000 inmates have TB, while perhaps almost 30 percent are infected with drug-resistant strains. And with some 50,000 prisoners released into society every year, the primary source of MDR-TB infection is constantly expanding, since there is normally no “handover” routine between penitentiary and civil hospital authorities to ensure that ex-prisoners adhere to their treatment protocols.

“Prisoners are a prime example of an unmotivated population,” remarks Malgorzata Grzemska, Stop TB’s Medical Officer for Europe. “Many of them have nowhere to go when they are released. They have no job, no money, no prospects – so it’s not surprising that continuing with their treatment usually comes pretty low in their priorities. Their main worry is staying alive from day to day.”

The Russian MDR-TB epidemic is in part due to an extended delay in full implementation of DOTS. That failure is in turn often down to lack of funding: Although the Russian government recently increased spending on TB programmes, many regional hospitals and clinics still don’t follow WHO internationally recommended guidelines for TB control. And while several international organizations have offered to fund TB efforts, many Russian officials have – through a mixture of motives – been reluctant to accept outside help.

“That’s bad – you see, the longer they leave it, the more trouble they’re storing up,” points out Estonian programme manager Vink. “Just look at the sheer geographical size of the Russian Federation and look at little Estonia and then tell me who has the bigger problem. To tell you the truth, I’d say I’m actually quite optimistic – at least we’ve made a start.”

The Russian Federation, by contrast, has a much, much longer way to go.

MDR-TB has been a particular concern among HIV-infected persons. Some of the factors that have contributed to the number of cases of MDR-TB, both in general and among HIV patients, include:

- delayed diagnosis and delayed determination of drug susceptibility, which may take several weeks,
- susceptibility of immunosuppressed individuals for not only acquiring MDR-TB but for rapid disease progression, which may result in rapid transmission of the disease to other immunosuppressed patients,
- inadequate respiratory isolation procedures and other environmental safety conditions, especially in confined areas such as prisons.

Latvia began to implement DOTS fully in 1997. However, poor case management in the past and the overcrowded conditions of TB wards still helped to make Latvia the country with the second highest MDR-TB rate in the world. The proportion of MDR-TB among new TB patients in this country is 9.5 percent. On February 2001, the GLC approved a countrywide DOTS-Plus pilot project. Some 350 patients were approved for enrolment from both the civil and prison sectors. Of those, 266 have been already recruited. Culture negativization is around 65 percent and the default rate is 10 percent. Sustained drug procurement has been the main difficulty faced by the National Tuberculosis Programme. This is due to delays in the flow of funds to purchase second-line TB drugs.



PILOT PROJECT

Latvia

PERU FIGHTS BACK

... with a little help from its friends

08

Exporting the DOTS-Plus model to the rest of the world will require solid amounts of extra cash.

Indeed, just finishing the job in Peru will require significantly more funding.

“We can’t do it alone,” Peru National Tuberculosis Programme manager Eduardo Ticona states bluntly. “We are committed, we have devoted as much of our resources as possible, and we will continue to meet our responsibility. But the international community has to meet its responsibility also. There is no way that TB and MDR-TB control is a one-way responsibility.”

A lot of TB experts are eating humble pie these days. And they’re quite happy to admit it.

Until very recently, the high cost of second-line TB drugs made MDR-TB untreatable in areas of great poverty. “In developing countries people with multidrug-resistant TB usually die,” a 1996 WHO report stated bluntly.

We’ve come a long way since then.

First came the adoption of the DOTS-Plus strategy. Then there was the Working Group’s landmark attainment of a reliable supply of high quality, cut-price drugs. Next, the Green Light Committee’s creation of an efficient drug supply line – direct from manufacturer to DOTS-Plus programmes – and its efforts to ensure those drugs are prescribed and administered properly.

Now, with the arrival of heartening news from Peru, comes confirmation that all the pieces in the MDR-TB puzzle are starting to fall into place.

Peru’s current status as “model pupil” marks a complete turnaround for TB’s one-time “bad boy.” Peru has seen the efficacy of its TB control improve markedly since it instituted DOTS 12 years ago. Nevertheless, poor TB control before the 1990s – in particular, low cure rates – has left behind a tangible legacy: endemic tuberculous drug resistance.



“The case of Peru, which now has one of the best TB control programmes in the world, clearly illustrates how the epidemiology of ‘ordinary’ TB and drug-resistant TB cannot be viewed separately,” remarks Stop TB’s Rajesh Gupta. “In such settings, careful tailoring of TB treatment programme strategies is critical.”

To their credit, the Peruvians were among the first to absorb the implications of the first MDR-TB surveys in the mid-1990s. The government-sponsored Peruvian National TB Control Programme (NTP) has tackled the scourge since 1997, when it implemented a nationwide programme to manage failure cases of first-line drugs with second-line drugs using a standardized treatment regime. “The programme has been shown to be feasible and affordable at a cost of US\$ 200 per life saved,” remarks Stop TB’s Marcos Espinal. “In fact, our findings in Peru could well form the basis of a standard model for middle-income countries.”

A SURVIVOR'S STORY

LIMA, 1999 – Take a look at this family snapshot. All in all, a pretty standard portrait of domestic contentment, right?

Wrong. She doesn’t know it yet, but the young woman on the left is riddled with bone-rotting, lung-destroying MDR-TB.

“The trouble with MDR-TB is you can’t always tell who has it just by looking,” mourns Cesar Bonilla, Head of TB at Lima’s Carrion Hospital. “That’s what makes it so dangerous: drug-resistant TB can be transmitted from person to person – it’s not only caused by people not taking all their drugs.”

Luckily, Gisela Bejar sought help in time.



Actually, the Peruvian government's approach in many ways sets an example for both developed *and* developing worlds. MDR-TB is most common in areas where wealth and poverty are mingled and where the poor tend to receive some therapy but not enough - places such as New York City, post-Soviet Russia ... and Peru.

Despite the plaudits that their efforts attracted, the Peruvians were determined to keep building on their early successes. Three years after entering the struggle against MDR-TB, they struck a further blow against the scourge when they teamed up with the Harvard University-based Partners in Health (PIH) who, together with PIH's Peruvian chapter *Socios en Salud*, set up a second DOTS-Plus pilot project in the capital, Lima. The PIH programme provides individualized treatment regimens to patients who have failed the NTP's standardized DOTS-Plus.

The Lima programme opened in May 2000 in three poor districts of Northern Lima, and now extends to the rest of the city. The Stop TB Working Group's Green Light Committee has approved 800 patients for enrolment every year for the past two years. Over the past 24 months, the programme has achieved treatment-success rates of 79 percent - significantly higher than those previously reported in the USA, and at a significantly lower cost - as little as US\$ 800 per patient compared to as much as US\$ 100,000.



With figures like those to boast about, it's hard for those involved to hide a sense of triumph. Nevertheless, without the "can do" ethos and the spirit of true partnership, none of them believe Peru could have traveled quite so far, quite so quickly. "We were told the second-line drugs for DOTS-Plus were too expensive - we made them cheap. Then we were told that there was no guarantee these drugs would be used properly - so we created the Green Light Committee" recounts Stop TB's Mario Raviglione. "Well, all I can say is if anyone still has any doubts about what is possible, they can go to Peru and see for themselves."

The Peruvian project likely wouldn't even have gotten this far if it hadn't been the generosity of a certain business icon.

In July 2000, to help stem the growing MDR-TB crisis, the Bill and Melinda Gates Foundation awarded a US\$ 44.7 million, five-year grant to Harvard Medical School for the creation of a collaborative partnership that will develop a replicable model for controlling MDR-TB.

In addition to Partners in Health and the Peruvian National Tuberculosis Programme, the Peruvian team also includes: Harvard Medical School's Department of Social Medicine; the Massachusetts State Laboratory Institute; the Task Force for Child Survival and Development in Atlanta, Georgia; the U.S. Centers for Disease Control and Prevention; and WHO.

In April 1999, Mrs Bejar, from the poor Lima suburb of Callao, visited Carrion complaining of the classic symptoms: weight loss, lack of appetite, a persistent cough, back pain, fever and night sweats. Bonilla diagnosed her with tuberculosis and placed her on a course of first-line TB drugs.

Five months later, by now coughing blood, Mrs Bejar was still testing positive and entered hospital. Although her condition subsequently saw a slight improvement, she remained smear-positive (i.e. the TB bacillus was still present in the sputum she was coughing up).

In August 2000 having finally been diagnosed with MDR-TB, Mrs Bejar embarked on standardized DOTS-Plus treatment. After only four months, sputum tests showed she was bacteriologically negative (and therefore non-infectious). By February 2002, Mrs Bejar having completed her course of treatment, doctors declared her free of the disease.

Today, now aged 25, Gisela Bejar has everything to live for. "I feel great - the fever's gone, my weight has jumped from 46 to 70 kilos ..." she smiles happily. "Best of all, I know my three children are safe - all the time I was ill, I was terrified I might have infected them. I didn't, but if Dr Bonilla hadn't been there for me, who knows if any of my family would still be alive today?"

PLUGGING THE DAM

A call to arms from the DOTS-Plus generals

10

Do you know the old Dutch proverb about a little boy living by the ocean who comes across a hole in a local sea defense wall? The hole is tiny, and is only leaking a little water, but the lad knows that the hole will soon grow bigger and bigger. Eventually, if the damage is ignored for long enough, the dam will collapse, the water will come rushing in, and everyone will drown.

So instead of heading home for his supper, the boy decides to stick his finger in the hole and wait until someone comes along to fix it.

That, in essence, is the attitude of the Working Group and its Green Light Committee.

Strengthening MDR-TB control *now* through DOTS-Plus will help to reduce morbidity, mortality and transmission due to MDR-TB. By directing MDR-TB patients to effective treatment protocols *now*, we are saving direct costs. And by controlling the primary cycle of MDR-TB transmission *now*, we are saving future funds and indirect costs that would otherwise have to be diverted into treatment for both sick individuals and those that they infect.

So much for keeping our finger in the hole. But if we want to fix the problem for good, more work needs to be done – particularly in the field of research.

Now that the complete genome sequence of *Mycobacterium tuberculosis* has been uncovered, scientists have fundamental information about each

of the possible targets for new TB drugs. (Indeed, those scientists can now even determine precisely which drugs a MDR-TB patient is resistant to by looking at his DNA strands.)

Meantime, the research community is looking at better, less traumatic ways of administering those drugs. For example, Harvard Medical School is testing a method that would dispense some MDR-TB drugs in aerosol form, direct to the lungs. If successful, this form of deeply penetrative treatment could pre-empt the kind of severe gastric side-effects associated with drugs that are ingested in the traditional way.

Yet vaccine and drug development is still hampered by the continued reluctance of some big pharmaceutical companies to invest more in the development of new TB cures. The assumption persists that treating MDR-TB will not generate sufficient revenue, and that labeling a new antibiotic as an TB drug will taint it in other markets. For instance, there are mainstream drugs which are currently undergoing testing – or have already been passed for use in the developed world – against illnesses like pneumonia. These drugs could also prove to be useful components of the DOTS-Plus regimen. However, the makers of these drugs fear that their longer-term use over a two-year DOTS-Plus programme could lead to regulations that restricted their application exclusively to the treatment of tuberculosis. And so they refuse to consider their deployment in the fight against MDR-TB.

PILOT PROJECT

The Philippines

The private sector diagnoses and treats up to 50 percent of all TB patients in the Philippines. Engaging the private sector in TB control remains one of the most important challenges facing the country's National Tuberculosis Programme. The Makati Medical Center, a private care facility in Manila, has successfully introduced the DOTS strategy in close collaboration with the local public health authorities. Makati's DOTS-Plus pilot project was approved by the GLC to enrol up to 200 patients over two years. After the first six months, 65 percent of patients were culture negative. However, the lack of guaranteed funds to support the purchase of second-line TB drugs and the inadequacy of infection control measures continue to trouble managers.



The reasons for such reluctance may often be quite understandable. Nevertheless, for the sake of global health and the greater good, we need to build on the ties which the Green Light Committee has already forged with the pharmaceuticals industry to create an even deeper level of trust and cooperation.

That said, we must be realistic. Companies such as Ely Lilly and Jacobus don't have to help us at all. Essentially, they've already chosen to supply us with high-quality second-line TB drugs at concessional prices not because they're looking to make easy money, but because they feel it's the right thing to do.

But we have to recognize that not everyone can afford to be so generous. Accordingly, we can't always be too sniffy about whom we choose as our partners. The three lynchpins of the DOTS-Plus strategy are: detection, therapy and compliance. What we desperately need at a local level are more truly motivated medical practitioners who can be trained and trusted to operate complex diagnostic equipment, maintain regular case histories, compile and collate data, and relentlessly complete the task of providing care. If that means sometimes enlisting the support of the private, "for profit" medical sector, then so be it. Indeed, in view of the deficiencies of many public health care systems, and given the fact that half the patients with MDR-TB seek out the services of private health service providers anyway, it would be foolish of us not to.

Not so long ago, issues like these were bitterly contested within the TB community. Today, after trial and error and much discussion, there's broad consensus. Yet paradoxically, the further we inch forward, and the more we understand about the nature of MDR-TB, the greater the danger of shooting ourselves in the foot. For instance, it's all very well bringing in generic drug makers to increase the flow of second-line TB drugs for DOTS-Plus. But at the same time, we have to be doubly certain that those generic producers will supply our programmes with fully potent medicines. If they don't, then consumption of poor-quality, sub-standard drugs will only breed further resistance to the "real thing."

That's why the monitoring and regulatory role of the Working Group and the Green Light Committee is so crucial. As we enlist more pilot projects and spread our net wider, we can't afford a single slip. DOTS-Plus is our last chance. If we mess this up, then we won't just have multidrug-resistant TB to worry about. It'll be *super*-multidrug-resistant TB.

And if that happens, then we might just as well take our finger out of the hole and go home.

Frightening, isn't it?

Jim Yong Kim

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(Chair of the Stop TB Working Group on DOTS-Plus for MDR-TB)*

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This central Russian region implemented DOTS in 1994, and expanded the strategy to the prison population four years later. Unfortunately, treatment outcomes were compromised due to the high rate of MDR-TB, particularly in the prison sector. In March 2001, the GLC approved a DOTS-Plus pilot project conducted by Harvard University's Partners in Health, in collaboration with the Tomsk TB control programme. The project covers both the prison and the civilian population and has so far recruited around a third of the 630 patients approved for enrolment within the next two years. Culture negativization rates of 71 percent have been achieved, and managers report excellent coordination between the civilian and prison sectors.



PILOT PROJECT

**Tomsk,
Russian
Federation**



The Meeting of the Working Group on DOTS-Plus for MDR-TB took place April 10-12 in Tallinn, Estonia, 2002. In attendance were 152 Working Group members from 32 countries, plus a variety of partner agencies.

The agenda included the following policy points: progress of the Working Group; progress of the DOTS-Plus pilot projects in the seven countries approved so far by the Green Light Committee; convergence between the GLC and the Global Drug Facility (GDF), clinical/epidemiological aspects of MDR-TB; methods of monitoring MDR-TB patient treatment; and research priorities. The most important conclusions and recommendations included the following:

The Working Group shall continue to implement projects in different settings in order to define more clearly strategies for proper management of MDR-TB cases.

In the meantime, treatment/monitoring policy should be finalized as soon as possible to allow international comparison and homogenous assessment of results. To this end, a prioritized research agenda should now be finalized through a consultative process.

The current second-line TB drugs are likely to be used for the next several years. Therefore, we should redouble our efforts to ensure wider production of good-quality products by assisting the transfer of their production technology to generic companies. WHO should continue to encourage generic manufacturers and the research-based industry to engage in serious discussions about entering this segment of the market.

A Core Group composed of seven members was established via a process of nominations and consensus approval. Membership includes: WHO, Chair of the Working Group, and Chair of the Green Light Committee on a fixed basis; and two country representatives (Philippines and Estonia), one agency (University of Alabama) and one donor (USAID) to sit on a rotational basis. This core group will be responsible for: assisting with the preparatory work for the Working Group meetings; assisting in faster decision-making related to Working Group activities; helping with the preparation of the Working Group's work plan; communicating and coordinating with the members of the Working Group; liaising with the GLC, helping countries to implement the GLC's recommendations; and interacting with other Stop TB bodies to ensure full coordination of activities.

The next meeting of the Working Group will be held in 2003.

The full report of the meeting is available from Stop TB.

Applying for Green Light Committee Support

It is the GLC's task to review applications for WHO support from potential DOTS-Plus pilot projects and to determine whether or not they incorporate the principles of the "Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB." To read this document, go to: <http://www.who.int/gtb/publications/dotspiluspilot-2000-279/english/index.htm>

Before contacting WHO, project managers interested in submitting proposals should review the document "Instructions for Applying to the Green Light Committee for Access to Second-line Anti-Tuberculosis Drugs" at: <http://www.who.int/gtb/policyrd/DOTSpilush.htm>

Sample protocols are available to design standardized or individualized treatment regimens with second-line TB drugs to be used in DOTS-Plus projects. These may be found at:

<http://www.who.int/gtb/publications/mdrtb/PDF/who.tb.99.260.pdf>

Specific instructions regarding the application process are available at:

http://www.who.int/gtb/policyrd/pdf/glc_application_instructions.pdf

or by emailing the DOTS-Plus secretariat at: dotsplus@who.int

The GLC will meet twice more in 2002 - on 11 October and 20 December - to consider applications. Proposals for pilot projects must be submitted by 20 September and 20 November, respectively.

Further to recommendations at the April 2002 Tallinn meeting (*see above*), WHO Geneva will host a two-day training workshop 13-15 November 2002.

Various partners, representatives and principal investigators from each of the pilot projects worldwide will meet to compare and contrast experiences, and further refine various training issues related to the implementation of DOTS-Plus treatment.

Delegates will assess training material, job aids and guidelines developed to date in each of the pilot projects.

"We want to be doubly sure that all the partner projects are thoroughly training their staff regarding the management and follow-up of MDR-TB," explains Stop TB's Marcos Espinal. "Although many aspects of DOTS-Plus are 'setting specific,' there are certain training issues that should be standardized. A workshop is a good way of comparing experiences and results, and thus coming up with a generic set of guidelines that are still flexible enough to meet very different sets of working conditions."