World Health Organization

Stop TB Partnership

MEETING Report

MDR-TB Control Paris, France, October 27 & 28 2013

MDR-TB stakeholders' meeting

Old problems, new solutions

The avant-garde steel, concrete and reflective glass of La Défense provided a soaring backdrop to this discussion of tuberculosis (TB), and its contemporary evolution, multidrug-resistant tuberculosis (MDR-TB).

Stakeholders' meeting Objectives

- ***Discuss methodologies*** *for estimating the burden of MDR-TB and standardised indicators for measuring progress at global, regional and country level*
- ***Share the challenges and best practices*** *from countries in moving towards the targets of universal access to diagnosis and treatment of MDR-TB by 2015*
- ***Identify effective interventions*** *to address the major barriers impeding accelerated scale up of MDR-TB services*
- ***Share the new structure*** *of the reinvigorated Working Group and discuss future key* ***activities.***

The facts of the MDR-TB epidemic are stark: around 450,000 people developed MDR-TB in 2012; 170,000 are thought to have died. Worse, the treatment success rate reported globally is a dismal 48% and extensively drug resistant (XDR) TB had been reported from 92 countries by the end of 2012. Yet, the 21st century provides great promise, with modern diagnostics already resulting in a 42% increase in the number of MDR-TB cases reported to the World Health Organization (WHO) in a single year (from 66,000 in 2011 to 94,000 in 2012). Worrying though, is the gap opening up between diagnosis and treatment: more than 16,000 patients eligible for MDR-TB treatment were not started on treatment and reports of patients on growing waiting lists raises a large red flag.

The 168 participants, squeezing into a meeting room set up for 130, were from affected communities, hard-hit countries, technical agencies, foundations, donors, and academic institutions. Very aware of the challenges required to make a difference to the MDR-TB epidemic, the meeting had standing room only. As discussion and healthy debate took place over the two days, a sense of battle-weariness about slow progress was replaced by an atmosphere of can-do using 'New Solutions' to the familiar 'Old Problems'.

Opening Session

Chair: Karin Weyer, Coordinator responsible for MDR-TB affairs at WHO's Global TB Programme

WHO TB Director: MDR-TB "a public health crisis"

Mario Raviglione, Director of WHO's Global TB Programme (GTB), opened the meeting with a video address. Dr Raviglione summarized the MDR-TB data officially released the week before in the 2013 WHO Global Tuberculosis Report . MDR-TB was, he said, a **public health crisis** requiring innovative solutions.

"I want to take you out of your comfort zones" declared the Executive Secretary of the Stop TB Partnership, Lucica Ditiu. According to her, country progress is much too slow and Ministers and programme managers need know-how and understanding of how to decentralize diagnosis and care for MDR-TB, so that they can produce

"MDR-TB is a global public health crisis" *- Mario Raviglione, GTB Director*

concrete deliverables. She also acknowledged that far too little has been done in advocacy for MDR-TB, leading to complacency and a lack of investment.

Pat Bond was next, a nurse from South Africa and now an advocate with TB Proof (Box 1). Her moving personal account of her struggle with MDR-TB gave the disease a human face. She had a lobe of her lung removed; suffered ongoing nausea and vomiting, joint problems, peripheral neuropathy and depression; and lost her hearing because of one of the medications. She didn't have a choice: "Do you want to be deaf or dead?" asked her doctor. Only later did we learn that Pat's significant hearing loss was permanent.

Pat lost her career as a result of the deafness. Her experience highlights a neglected fact: for many, "successful" treatment of MDR-TB is only the start of a struggle with long-term effects of the disease and the treatment.

Dalene von Delft (Box 1) closed the TB Proof presentation on a hopeful note, showing what a big impact novel treatment options and optimal support structures can have.

Session 2

Chairs: Paula Fujiwara, the Union; Michael Rich, Partners in Health & Harvard Medical School

Country experiences: progress & challenges in scaling up MDR-TB services

Five countries suffering high burdens of MDR-TB gave presentations in this session: China, Indonesia, Nigeria, Pakistan and Uzbekistan. Several common themes emerged. While notifications of MDR-TB cases are going up every year, most of them are still far from treating their full burden of MDR-TB cases. All countries are consistently missing their targets for enrolment and treatment success, and admitted to having diagnosed cases that went untreated, some of whom are known to have died. Reasons ranged from patients refusing treatment, to a lack of drugs, to a lack of human resources, or regulations that mean it's impossible to provide sufficient care.

Above: Pat Bond, nursing sister and TB-PROOF advocate

The proportion of MDR-TB cases is far higher among those previously treated for TB than among new cases; but the absolute numbers of MDR-TB sufferers is higher among new cases – and all countries are struggling to identify those new MDR-TB cases. Largely this was a cost issue, countries saying that they cannot afford to use the new molecular Xpert MTB/RIF assay for all patients thought to have TB, or even MDR-TB. Most have tried out policies that focus on re-treatment cases – some, like Nigeria, still prioritizing the failures of the old Category 2 re-treatment regimen. Pakistan is now starting to test new cases that fail to respond to first-line treatment.

Treatment success varied among the five countries. Pakistan reported a treatment success of 68%. In Indonesia, as cases multiplied from 2009 to 2012, loss to follow-up doubled and treatment success dropped to 55% in 2011. Nigeria reported that 61% of their patients were cured – but this came with a major and serious caveat: the rate was calculated from a total of just 23 patients enrolled on treatment in 2010, while the number of MDR-TB cases among the total notified cases in Nigeria was estimated at 3,400.

From the presentations, it appeared that The Global Fund was funding all second-line drugs in Indonesia, Uzbekistan and Pakistan, and funding the majority of MDR-TB treatments in China and Nigeria. Ejaz Qadeer from Pakistan highlighted that funding after 2015 was his number one challenge once the current Global Fund support is scheduled to end.

In Indonesia, on the other hand, "our greatest challenge is the lack of local level commitment," said Dyah Erti Mustikawati. "We need to find a way of decreasing the fear [of managing MDR-TB], or be faced with endless pilots."

In Nigeria, Gidado Mustafa from KNCV said, the main challenge is "moving samples … and we are still struggling with our data, as we also struggle to integrate PMDT [Programmatic management of Drug resistant TB] into the National TB Programme's activities."

In China, by contrast, Fabio Scano (speaking for China's NTP) said basic TB control was the chief challenge. China still needs more active case-finding to find TB cases in the first place. A further and huge challenge faced by the NTP was ongoing health reform.

Uzbekistan's needs are more basic, according to Prof Mirzagaleb Tillyashaykhov. After the shortage of laboratory equipment comes lack of electrical power, poor logistic capacity (with 40% of the country without transport), and staff afraid to work with MDR-TB patients.

Below: The panel, variously occupied

Box 1: TB Proof

"When will I be able to kiss my husband?"

Dalene von Delft, a young doctor in a South African public hospital, developed a dry cough at the end of 2010. A friend who had had similar symptoms and turned out to have TB suggested she should have a chest X-ray. She did, two days before Christmas. The result: there was no doubt she had TB. But sputum smears were negative. Within a day, a bronchoscopy and line-probe assay showed that she had MDR-TB. Some Christmas present.

Dalene remembers several thoughts coming at her at once – When will I be able to kiss my husband? Will I go deaf with the treatment, and not be able to sing or hear music any more? Dalene was – and is – a keen and competent singer. Will I develop XDR-TB and die? She went home and locked herself into the bathroom to protect her husband from her disease.

Imagine the scene: imagine yourself as Dalene, or her husband Arne – on different sides of a locked door, both in tears, fearing the worst.

Dalene was started on seven different MDR-TB drugs, and developed debilitating side effects from day one: weight loss, diarrhoea, bone pain, liver pain, hypothyroidism, peripheral neuropathy, nausea and vomiting. Her worst fear of irreversible hearing loss was almost realized after just eight weeks of treatment, when regular audiograms started showing progressive high frequency loss. She knew another health worker, a nurse who had been treated for MDR-TB and who lost her hearing totally overnight; for the next two weeks, Dalene listened to music non-stop, not knowing if each song would be her last.

"Deaf or Dead?" It's a recurring, unacceptable "choice" faced by many MDR-TB patients. Dalene was very fortunate to gain access to a third option, substituting the offending injectable drug with bedaquiline as part of a compassionate use programme in South Africa. She was one of the first patients to receive moxifloxacin and bedaquiline together, both known for prolonging the QT interval on ECG, with the risk of ventricular fibrillation and sudden death. But the risk was worth it: she can still hear well enough to practice as a clinician today.

TB Proof

This is the personal story that stimulated the foundation of TB Proof, an advocacy organization set up to raise awareness of occupational TB and to help prevent it from happening.

TB Proof aims to mobilize national and global resources by patient advocacy. They share information on infection control with medical students. Health facility risk assessments are made easier with a specially-developed TB-PROOF Android app.

The name is revealing: as young, fit, well-nourished students they were thought to be "TB Proof" and were encouraged into the wards to care for patients with TB, susceptible or resistant. But it's been known for centuries that some unexposed young people, when infected with TB, are uniquely susceptible to a rapid form of the disease. After all, this is where the word "consumption" came from. Despite this, the fixed false belief that health care workers are somehow immune to becoming sick has been perpetuated, and with it the stigma and discrimination unwittingly aimed at the silent victims.

TB Proof started with Facebook, sharing personal stories and spreading the message that health care workers aren't resistant to TB (or anybody else for that matter). They called for surveillance of health workers. They found that national reporting doesn't capture what hospitals report – not at all.

TB Proof has since moved on to providing education sessions for all kinds of health science students, specifically encouraging the use of "personal protection" and N95 respirators in addition to improving administrative and environmental controls. Originally sponsorship from the manufacturers paid for the N95s. Now the university pays – from student fees.

The Treatment Action Group (TAG) invited Dalene to the Union conference last year. She has met and spoken with the developers of bedaquiline, whom she much admires, and has advocated for more drug development and improved access with other pharma companies. Twice she has lobbied on the Hill, and she's soon going for a third time.

Dalene and her husband passionately want better treatment for MDR-TB, and remain amazed at policy makers' indifference towards TB.

When asked if she sees a life beyond MDR-TB, Dalene looks unsure. Hers is a story of hope, but too many patients still have none.

A video on Dalene's experiences can be found on TAG's website:

http://www.treatmentactiongroup.org/tb/resources

Discussion focused on the need for universal access to MDR-TB diagnosis (Michael Rich) as the bulk of MDR-TB cases was among new patients. He also called for new approaches to treatment and new drugs. Lucica Ditiu pointed out that countries need to show what impact new diagnostic technologies are having in saving lives.

Session 3

Chairs: Salmaan Keshavjee, Partners in Health and Harvard Medical School; Gini Williams, International Council of Nurses

Expanding partner support

Jeroen van Gorkom of KNCV opened the session by describing the work of TBCARE 1. TBCARE 1 and TBCARE 2 (which was covered in the following presentation) are two large consortia of technical agencies supported by the United States Agency for International Development (USAID) to provide TB technical assistance to a range of countries.

TBCARE 1 supports national TB programmes in 16 countries in developing their responses to MDR-TB. This support helps NTPs plan and implement their approaches; assists in scaling up laboratories; and supports improvements to treatment, access to second-line drugs and monitoring and evaluation.

TBCARE 1's work is challenging. Taken as a whole, the 16 countries are only dealing with 33% of their MDR-TB burden right now, though there are isolated success stories – in the Central Asian Republics, for example, 74% of the caseload among the total notified cases was diagnosed in 2012. Overall, in the TBCARE 1 countries, case notification increased 40% between 2010 and 2012.

There are also a number of other challenges. These include issues with the implementation of GeneXpert, ranging from inadequate specimen referral systems; diagnostic algorithms that aren't always followed; gaps between diagnosis and treatment; problematic linkages with culture and DST facilities; a lack of quality assurance; and unreliable maintenance and supplies.

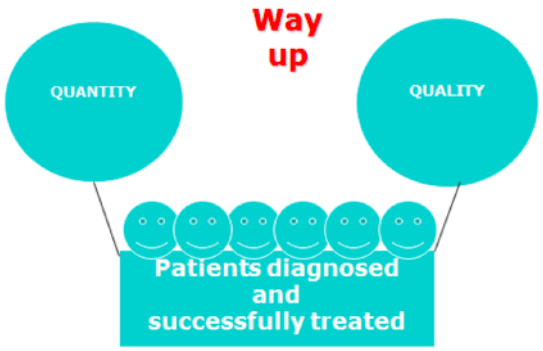
Above: The organising team at work

To meet these challenges TBCARE 1 puts its faith in an acceleration of case-detection focusing on re-treatment patients; boosting ambulatory treatment capacity; strengthening patient-centred approaches and support; and improving M&E with more supervision and data quality checks. In conclusion, Jeroen warned of the need to balance quantity with quality – or face disastrous consequences (Figure 2).

Michael Rich then presented the activities of TBCARE 2, emphasizing the importance of a strong relationship with the NTP. TBCARE 2 focuses mainly on technical resources that can be used by all countries, including the following:

- An online MDR-TB training network , the DR-TB Training Network (https://drtbnetwork.org/) - Fig 3;
- The FAST package for supporting infection control (https://drtbnetwork.org/fast-tb-infection-control-strategy-core-package);
- *The PiH Guide for the Medical Management of MDR-TB (2nd edition)*; and
- *Community-Based Care for*

Figure 2: The quantity:quality balance



USAID TB CARE I

"Countries need to show what impact new technologies are having on saving lives." *- Lucia Ditiu, Executive Secretary, STOP TB Partnership*

Figure 3: DR-TB home page

Drug-Resistant Tuberculosis: A Guide for Implementers. This is a highly relevant reference resource for TB programme managers, policy makers, NGOs, donors, and advocates, which has already been adapted to Malawi and Bangladesh.

TBCARE 2 has also been providing direct country implementation support to Bangladesh. In 2012, 637 cases of MDR-TB were diagnosed in Bangladesh out of the 4,200 estimated among total notified cases. Of these, 549 were put on treatment. Care is being shifted from hospital to community with social support, DOTS provider stipends and cash transfers. As Michael concluded: "accompaniment of implementation is the key to successful country support".

Next, Gini Williams made a strong plea for greater recognition of the role nurses play in PMDT. She countered some of the negativity surrounding staffing problems mentioned in the preceding session, highlighting the many reasons why nurses may find it difficult to provide the quality of care they would like to. These reasons include overwhelming workloads, inadequate infection control, poor deployment decisions, stigma in management and pre-service education, and lack of representation at a strategic levels. Nurses (photo, right) are well-placed to know what needs to be done to address barriers to access and could make a much greater contribution to improving patient and programme outcomes. In her description of the nurses' role in PMDT, she illustrated how nurses provide essential components of successful patient-centred care: discussion and counselling before, during and after diagnosis as well as treatment; home assessments; contact tracing; training of other staff; supervision of infection control; providing guidance on nutrition; record-keeping; maintaining drug supplies; and even going on radio talk shows! The nurse's role is crucial in ensuring that linkages between different parts of the health service, as well as with a variety of voluntary and statutory support services, are made – linkages that are absolutely necessary for good patient-centred MDR-TB care. Gini finished by making a strong plea to keep the case management of both drug susceptible and drug resistant patients unified and not separate them.

The next presentation was by Colleen Daniels, of Treatment Action Group (TAG), who started by showing a really powerful film illustrating the real-life MDR-TB experience of Dalene von Delft and her husband, Arne (Box 1).

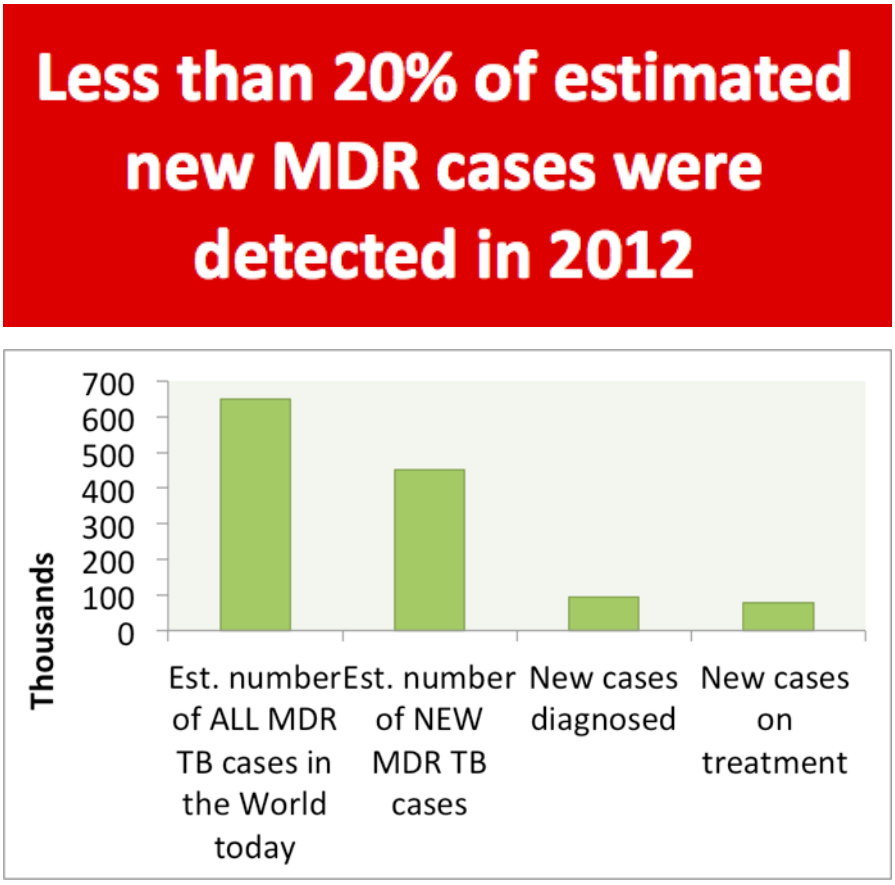
Colleen then summarized the challenges faced in the MDR-TB field (Figure 4, overleaf). She pointed out the failure of MDR-TB treatment programmes to scale up despite the grand international meetings (the Beijing Ministerial Meeting in 2009, for example), and underlined the need for more research and development, "knowing your epidemic", supporting patients as they undergo treatment, and holistic care. Civil society can do more, she said: the big picture lacks a clear idea of how activists are going to help with this list of needs, and what the advocacy messages are that might shake more support from the trees.

Mohammed Yassin of the Global Fund to Fight AIDS, TB and Malaria (GF) then took the floor. His organization, he

Above: Job satisfaction. A TB nurse

"We are collectively failing to respond: we've known what to do for 25 years and we aren't doing it." *- Colleen Daniels, TAG*

Figure 4: MDR-TB case detection



reported, had allocated USD3.8 billion of funding to TB control since its inception; in 2012 the GF provided 75% of all external aid for TB. MDR-TB's slice of the $2.6 billion already accounted for was 14%, but this rose to 25% for the TB allocations made in 2012. Countries might be prioritizing PMDT for support from the GF – not only because these items are very expensive compared to treatment for drug-susceptible disease, but also because people know that the GF is keen to support MDR-TB control. The GF had supported care for 88,000 cases of MDR-TB: 24,000 in the period from mid-2012 to mid-2013 alone.

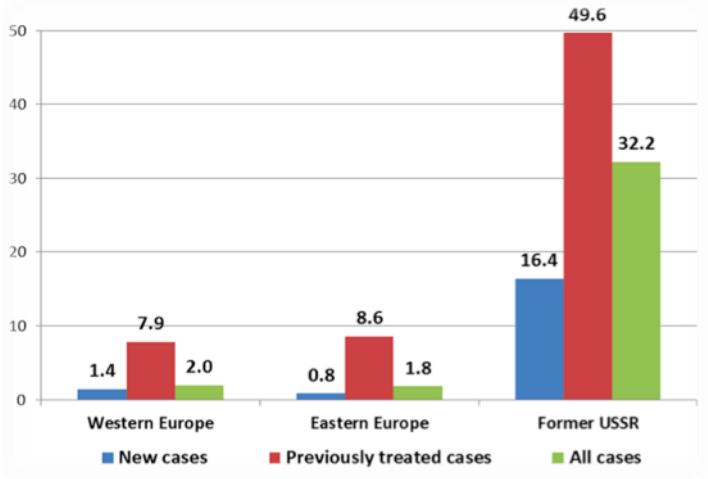
The new funding model will continue to provide support for MDR-TB, and to allow reprogramming of existing grants and prioritization of PMDT in new applications. The Fund expects to see partners' engagement and support in countries, with technical support coordinated by the decentralised regional GLC mechanism.

TB patients in WHO's European Region have the highest burden risk of MDR-TB in the world. The Region will therefore fail to meet the MDG target of halving TB mortality by 2015. It is the countries of the former Soviet Union that face the highest burden (Figure 5): this was the stark message of Andrei Mosneaga, Vice-Chair of the regional Green Light Committee (rGLC), Europe. However, while notifications in the region have increased just 40%, from 27,000 in 2009 to 37,700 in 2012, cases enrolled have more than doubled from 17,000 to 39,700. Alarmingly, the treatment success rate was just 48.8%.

The European Region has prepared a plan to address the MDR-TB crisis , but while some indicators are improving, the proportion of MDR-TB cases among re-treatment cases is very high (close to 50% in the former Soviet Union countries, compared to the 2015 target of 29%). Best practices have been collected and shared with countries , but the new diagnostics require changes to national health systems that the NTPs don't have the authority to make. The excessive hospital capacity of TB beds needs reducing urgently, especially to avoid the risk of further infection in hospitals. The need is running ahead of the demand, in spite of the relative wealth of many of the countries affected.

The Western Pacific Region has seen the most dramatic increases in MDR-TB enrolment, according to Lee Reichman, regional GLC Chair (see Figure 6, overleaf). Despite this, only small proportions of the total burden are being diagnosed (for example just 3% in China in 2012). If in the high burden MDR TB countries of the Western Pacific Region, GeneXpert was to be used to test all individuals presumed to have TB

Figure 5: MDR-TB cases in Western Europe, Eastern Europe and former Soviet Union countries



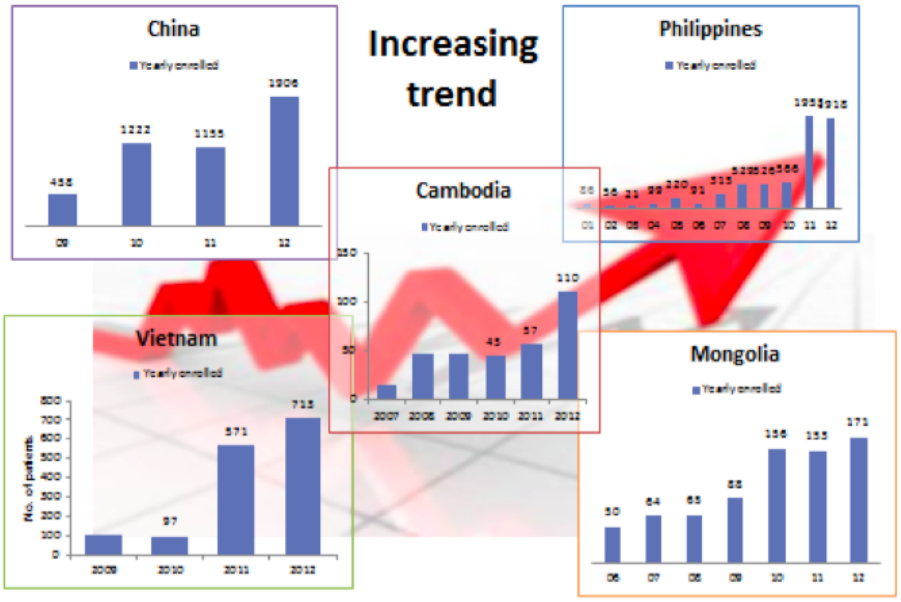


Figure 6: Increasing enrolments of MDR-TB cases in 5 countries of the Western Pacific Region

and all detected cases were then to be treated, the cost would only be around $171 million, said Dr Reichman.

Interestingly, there are opportunities here: the evidence base on how to implement PMDT is increasing; shorter regimens are becoming available, along with new drugs and GeneXpert; laboratory barriers are coming down; in-country capacity to diagnose and treat is increasing, there is less and less dependency on international technical assistance; and the private sector is getting involved. At the same time, though, there are risks. Chief among them is financial sustainability. The GF allocations for TB for the Western Pacific Region countries are insufficient to sustain existing demand, let alone expansion, and countries are therefore hesitant to scale up. Smaller countries have less access to 'impact funding'. In this context, the Western Pacific region would like to see a global advocacy campaign climaxing in a high level conference: perhaps a "Beijing II" meeting, suggested Dr Reichman.

Celine Garfin (pictured), NTP Manager in the Philippines, spoke next, with a focus on the private sector's role in PMDT. Cases on treatment nearly quadrupled from 566 in 2010 to 1,953 in 2011, she said; but sadly the rate of increase wasn't sustained in 2012. In that year only 2,056 were enrolled. Treatment success has varied between 50 and 73% between 1999 and 2009. A significant proportion of care provision comes from the private sector, but the public sector is still by far the largest provider, whether in laboratories or hospitals. In the Philippines, though, it was the private sector that initiated PMDT in the 1990s, and there has been good collaboration with the public sector since then, through the PhilCAT - the Philippines Coalition against TB.

In the discussion, the questions probed the performance of the private sector in the Philippines. Is it cooperation, or competition? Is it doing better or worse than the public sector? Celine's response was that the status quo is more one of cooperation than competition. PhilCAT helps the NTP, and it's in the NTP's interest that the private sector be quality-assured, especially for laboratory services. Business models are needed, though, because some of the private sector providers want to make a profit; they're not doing it for charity, she said.

Paul Nunn then asked whether the real bottlenecks were being addressed in the FSU countries given the problems in drug procurement with overpriced medication, the deportation of undocumented migrants with TB, the failure to encourage initiative in health workers, and the relative wealth of some of these countries compared to their spending on health care. Andrei Mosneaga responded on behalf of the European Region GLC by firstly noting that these problems are not unique to the region, and secondly that there is a growing focus on, and recognition of, the role of hospitals in MDR-TB transmission and the need to cut admissions, which some countries are doing. He pointed out, however, that closing hospitals is politically a difficult thing to do.

A question was also raised about whether or not the current training given to nurses and other front-line health

Below: Dr C Garfin responds to a question during discussion

professionals is adequate. Gini Williams responded that not only was it necessary to train nurses and other health professionals on the technical aspects of treatment and diagnosis, but also that more effort must be made to create the paradigm shift required to make care truly patient-centred. She explained that in order to reduce delays in diagnosis, it was also necessary to think beyond the NTP and increase the knowledge and skills of health care workers in primary and community care settings where people are likely to present with symptoms.

The session concluded on a rather sombre note, with participants acknowledging that despite new ideas and approaches there was a huge amount remaining to be done to rapidly scale up quality services for drug resistant TB patients.

Session 4

Aamir Khan, IRD, Karachi, Pakistan; Chuck Daley, National Jewish Hospital, Denver, Colorado, USA

Innovations and new initiatives in MDR-TB patient care

New diagnostics pipeline

Heidi Albert of the Foundation for Innovative New Diagnostics (FIND) presented the pipeline for new diagnostics for MDR-TB. She started the session by reminding us of the low coverage (5%) of new patients undergoing drug susceptibility testing (DST). We were reminded of Session 2, where it was made clear that the bulk of MDR-TB cases are in this group – and, therefore, that they are mostly undiagnosed.

The TB diagnostics pipeline is fairly full, but mostly with complex assays at early stages of development. Only line-probe assays (LPAs) are in final development stage with submission to WHO planned, and one of these is the Hain Life Sciences second-line LPA. A number of clever portable PCR devices aimed at a point-of-care testing are in development, but these haven't solved the problem of sputum sample preparation.

Conventional phenotypic culture and DST, the current reference standard, is increasingly being challenged on the basis that some phenotypically sensitive strains contain resistance mutations. In other words, phenotypic (growth-based) DST methods may be 'missing' (especially) low-level/ borderline resistance. The clinical outcomes of patients with phenotypically borderline resistant strains are reported to be as poor as those for patients with definitely resistant strains, albeit from small studies. On the other hand, existing molecular tests do not cover all known drug resistance mutations, and for most of the second-line anti-TB drugs the mutations conferring resistance are not all known; neither is the clinical value of many mutations. There is no perfect test, and this will be a conundrum to laboratory experts and clinicians for some time.

Treatment outcome	Bedaquiline/BR N=66	Placebo/BR N=66
Cure	38 (57.6)	21 (31.8)
Failure	5 (7.6)	20 (30.3)
Death	6 (9.1)	1 (1.5)
Transferred out/default	17 (25.8)	24 (34.8)

**3 TMC207/BR subjects and 1 Placebo/BR subject who died during survival follow-up after the 120-week endpoint are counted in this category*

Figure 7: Final data from the bedaquiline study using WHO outcome definitions – modified intention-to-treat

Updated guidance is coming from WHO on how to carry out drug susceptibility testing for all the second-line drugs. But these tests are difficult, so there may be advantages in having commercially developed and standardized test kits. In addition, if on –going trials with new drugs and new TB regimens succeed, these may completely change the requirements for drug susceptibility tests.

New drugs – new policies

Christian Lienhardt of the Global TB Programme of WHO in Geneva described how the interim guidance for the use of bedaquiline (Janssen Infectious Diseases' ATP synthase inhibitor) was developed after the drug was approved in December 2012 by the US Food and Drug Administration for addition to a background regimen in the treatment of MDR-TB. This decision was based on the significant improvement in cure rate (Figure 7).

WHO has reviewed the available data, and concluded in its interim guidance that bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB. This is a conditional recommendation, though, with very low confidence in estimates of effect. And there are clear conditions for bedaquiline use: there should be careful selection of patients (as yet its use in children or pregnant women is not recommended), very close monitoring of the patient, documented patient informed consent, treatment that must be based on WHO recommendations for MDR-TB management, and active pharmacovigilance to pick up any unexpected side-effects. Bedaquiline must not, of course, be added on its own to a failing regimen, and the recommended dose and duration must be strictly observed (400mg daily for the first 2 weeks and 200mg three times weekly for the next 22 weeks, administered with food).

There are, in addition, toxicity concerns with bedaquiline. It can prolong the QT interval, which may lead to potentially fatal ventricular arrhythmias. It's also easily affected by other drugs that alter liver metabolism, and little is known about its drug-drug interactions with anti-retroviral drugs.

A WHO MDR-TB Handbook that is due out in early 2014 will contain more details on how to use bedaquiline.

Mindful of the new TB drugs in the pipeline, and in light of experiences so far with bedaquiline, WHO has produced a strategy for introducing new drugs . The type of evidence and data required by WHO to recommend the use of new drug(s) or regimen(s) for the treatment of TB has been determined, and technical information notes are

available for pharmaceutical developers, regulatory agencies and countries. WHO also has prepared a "Policy Development Framework" that provides recommendations for how new TB drugs or regimens should be introduced into countries, and expert consultations will be held to evaluate new TB drugs or regimens as they emerge from the pipeline. The key is to ensure that new TB drugs or regimens are introduced in such a way as to protect patients from misuse and prevent the emergence of resistance.

Patient-centred care

Ernesto Jaramillo of WHO in Geneva then explored the issue of patient-centred care, pointing out the perceptions that patient-centred care may lead to more work for health workers with loss of power and control over patients, and would only be supported by donor agencies if there was more evidence that it provides value for money.

However, patient-centred care means that "the health system and interventions are designed (and delivered) with respect for the patient's rights, preferences, values and needs […] the patient is treated as a partner rather than just as a recipient" (Massaut S, KNCV). Ernesto presented the expanding body of evidence in favour of patient-centred care in general, and more recent work on MDR-TB specifically (Toczek H, Cox H, du Gros P, Ford N. *Strategies for reducing default in the management of multi-drug resistant tuberculosis: systematic review and meta-analysis*. Int J Tub Lung Dis. 2012; 17, 299-307) . The concept is respected in several recent WHO and Global Fund publications on TB (For example, WHO's *Guidance on ethics of tuberculosis prevention, care and control* (2011); WHO's *Guidance for the programmatic management of drug resistant tuberculosis* (2011 update); and The Global Fund's *Tuberculosis and Human Rights: An information Note*) and also in the draft of the new WHO post-2015 Global TB strategy. These documents refer to "zero-suffering", to the need to protect families from being hit by catastrophic expenditure because of TB, to the need for social protection for patients, and to the incorporation of human rights, ethics and equity. Ernesto asserted that patient-centred care was the main cause of the reduction in treatment delay seen in Khayelitsha in South Africa (Figure 8).

Many specific enablers and incentives designed to encourage adherence to MDR-TB care require more research to prove their utility. Some, like simple human kindness, may be tricky to measure. His main message was that new diagnostic and treatment tools will fail to make the expected impact if they are not matched with approaches that ensure early detection and adherence to treatment, for which patient-centred care is part of the answer.

"Patient-centred care means the patient is treated as a partner rather than just as a recipient." *- Massaut S, KNCV*

Compassionate use

Francis Varaine of Medecins Sans Frontières (MSF) explained that compassionate use of new drugs means "the use of potentially life-saving experimental treatments in patients suffering from a disease for which no satisfactory therapy exists and who cannot enter a clinical trial". Francis presented the experience of a compassionate use programme in Armenia, which had to begin by explaining what compassionate use was as the country had had no concept of it. Though the programme began with bedaquiline in mind, it became clear that to avoid adding a single drug to a failing regimen, linezolid and imipenem/cilastatin would also be needed. MSF and Partners in Health formed a medical committee to review requests and submit them to Janssen: of 37 patients submitted, 28 have been approved and 20 are now on treatment with bedaquiline. All 20 patients are also on linezolid, and most are on imipenem/cilastatin. Three patients died prior to treatment, five were rejected, two refused and some are still pending. Fifteen patients were reported to be smear-negative. The programme has been a long and difficult process, but it provides potentially life-saving treatment - and hope - for patients.

Ethics and human rights

Jerome Singh of the Centre for the AIDS Programme of Research in South Africa (CAPRISA) was up next, informing the meeting that ethics are having increasing impact on global TB policy. This is either explicitly

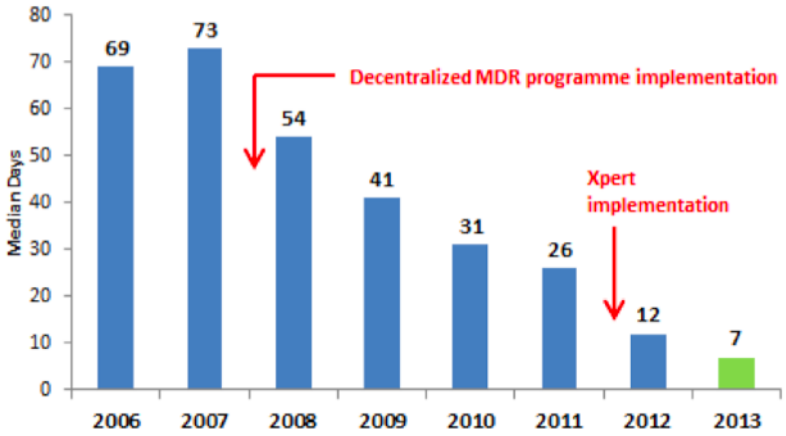


Figure 8: MDR-TB in Khayelitsha (Western Cape, South Africa): Delay to treatment initiation

apparent, such as in WHO's Guidance on ethics in tuberculosis prevention, care and control, or implicitly so – for example, in the free-of-charge provision of the Stop TB Strategy: "anti-TB drugs to all TB patients, both because many patients are poor and may find them difficult to afford, and because treatment has benefits that extend to society as a whole". States have an ethical – and in some cases legal – obligation to make diagnosis and treatment accessible to patients diagnosed with TB, including MDR-TB.

Human rights limit the power of states, and at the same time require them to ensure an environment that enables all people to enjoy their human rights. So, perhaps paradoxically, human rights legislation can oblige states to restrict personal freedoms of individuals if they refuse to take their treatment. Despite this, where states are considering limiting the rights of non-compliant infectious individuals posing a threat to others, they should do so only as a last resort, and these individuals must be offered social support to facilitate treatment adherence. The international community has an ethical obligation to demonstrate meaningful solidarity with high TB and MDR-TB burden countries – for example, by carrying out research to develop new drugs.

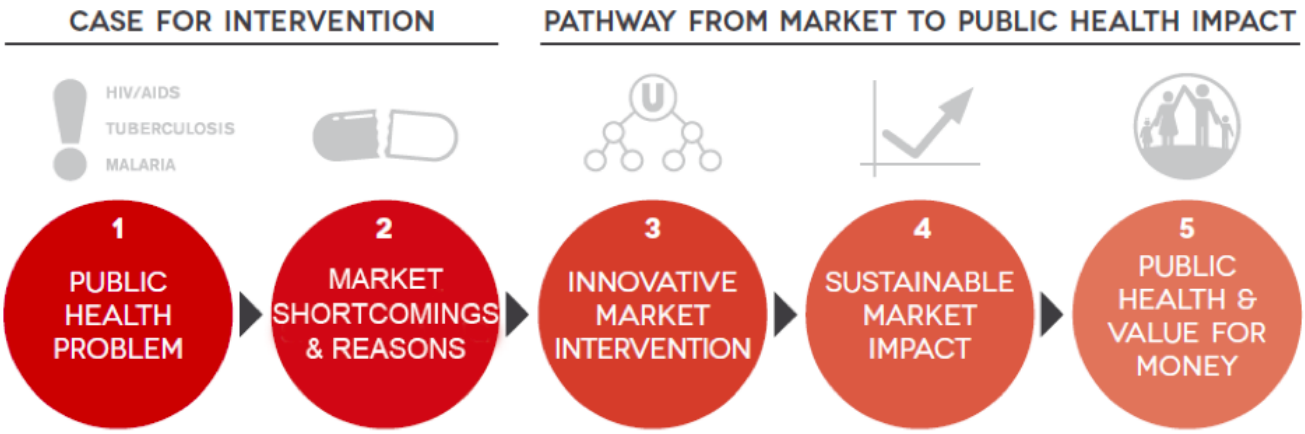
UNITAID and MDR-TB

According to Yamuna Mundade of UNITAID, her organisation is focused on market interventions to increase access to diagnosis and care for TB (Figure 9). UNITAID has so far allocated over US $291 million to TB control in 76 countries. In its early days it supported MDR-TB treatment scale up directly ($56 million), then financed a strategic rotating stockpile ($13m). It has supported the WHO prequalification process of HIV, TB and Malaria products ($53 m), and laboratory capacity building through the EXPAND–TB Project ($87 m). It helped co–finance the 40% reduction in price of the Xpert MTB/RIF cartridge (together with the Bill & Melinda Gates Foundation, or BMGF, and USG); funded a multi-country Xpert MTB/RIF assay rollout via the TBXpert Project ($26 m); and most recently is supporting the development of paediatric anti-TB formulations ($17m). UNITAID's strategic objectives include "increase access to simple, point-of-care (POC) diagnostics for HIV/AIDS, TB, and malaria" and "secure supply of second-line TB medicines, and increase access to emerging medicines and regimens that will improve treatment of both drug-sensitive and multi drug-resistant TB."

The Global Drug Facility (GDF) special adviser, Joel Keravec, then took the floor. He showed that GDF has been key in reducing the costs of the MDR-TB treatment regimen (Figure 10, overleaf), but warned that the second line anti–TB drug (SLD) market is at great risk because of huge concentration in a few countries, such as China and India, that potentially will cease receiving Global Fund support in the coming years, and will almost certainly switch their suppliers to domestic drug sources. The SLD market is already fragmented, with too many products and too few suppliers, and although there have been recent improvements, there is still significant volatility in orders.

In partnership with Systems for Improved Access to Pharmaceuticals and Services (SIAPS), GDF has developed QuanTB, a new tool for quantifying and monitoring TB medicines and an early warning tool for all important actions a manager may need to take. In particular, QuanTB gives advance warning of any impending stock-out. It is free, downloadable for PC and Mac, and can be customized. It will forecast for any type of TB treatment regimens or combination of medicines (including TB/HIV co-medication – see Figure 11, overleaf).

Figure 9: How UNITAID works



Discussion then began. Challenged by Lucy Chesire about what the TB community needs to do in order to receive support from UNITAID, Yamuna Mundade responded that "it needs to think bigger", and unleash better, higher level advocacy based on better data – like prevalence surveys – that illustrates the burden in more countries.

Joel Keravec was then asked by Paul Nunn to clarify a slide in his presentation that implied that GDF aimed to reduce the regulatory burden on drugs. Joel reassured the meeting that this did not refer to prequalification, but rather to the

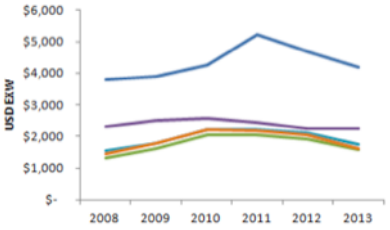


Figure 10: Cost per patient MDR course

registration of drugs in countries. He added that measures such as regional harmonization of regulatory approaches, which the European and Western Pacific regional offices of WHO are pursuing, would certainly help.

Alena Skrahina was concerned that "patient-centred care" might open the door to scenarios where unprepared countries would get new drugs, with the risk of creation of resistance. Jaramillo's response was that if this happened, it should not be viewed as patient-centred care, but rather as a big mistake.

Gini Williams and others were stimulated by the patient-centred care issues to form a break out group on the 2nd day which concluded that they would advocate for GDI to take a patient-centred approach in their ongoing work. The detailed conclusions of the meeting have been circulated.

The session ended with Francis Varaine saying that treatment with the current tools simply takes too long, has so many side effects, and is so difficult that we will never reach a point where we are treating the 450,000 cases annually. Treatment success rates of 48% or less were, he pointed out, disastrous. His conclusion: we must push for more research to develop the new regimens which can cure MDR-TB with a much shorter duration of treatment.

Sessions 5&6

Katherine Floyd and Karin Weyer, WHO, Geneva

Estimating the burden of MDR-TB and monitoring global, regional and country progress

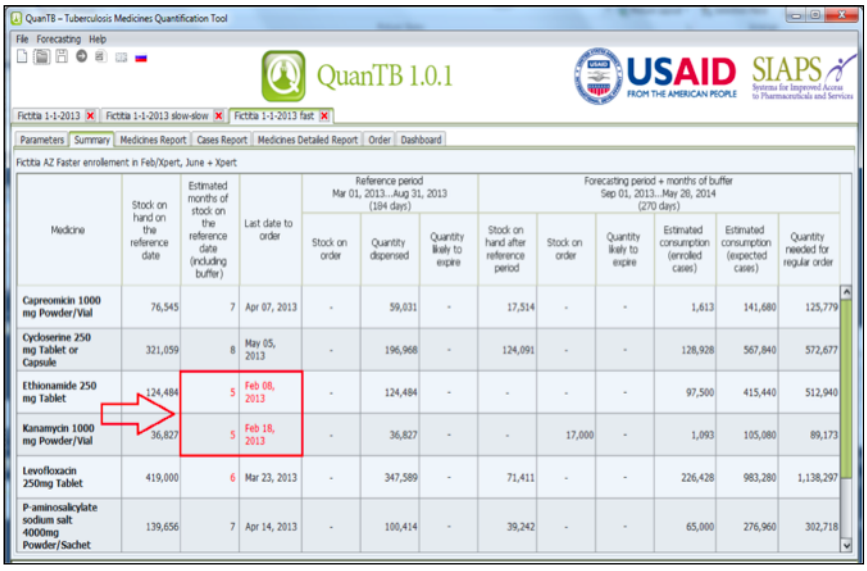
Sessions 5 and 6 were organized following a discussion of MDR-TB burden and programmatic indicators at the June 2013 meeting of the WHO Strategic and Technical Advisory Group for TB (STAG-TB), and agreement that a broader consultation with the MDR-TB community, especially on burden indicators, would be useful. WHO therefore organised these two sessions to discuss the various methods being used to estimate the burden of MDR-TB, and the proposed indicators to monitor progress by national TB control programmes in diagnosing and treating people with MDR-TB.

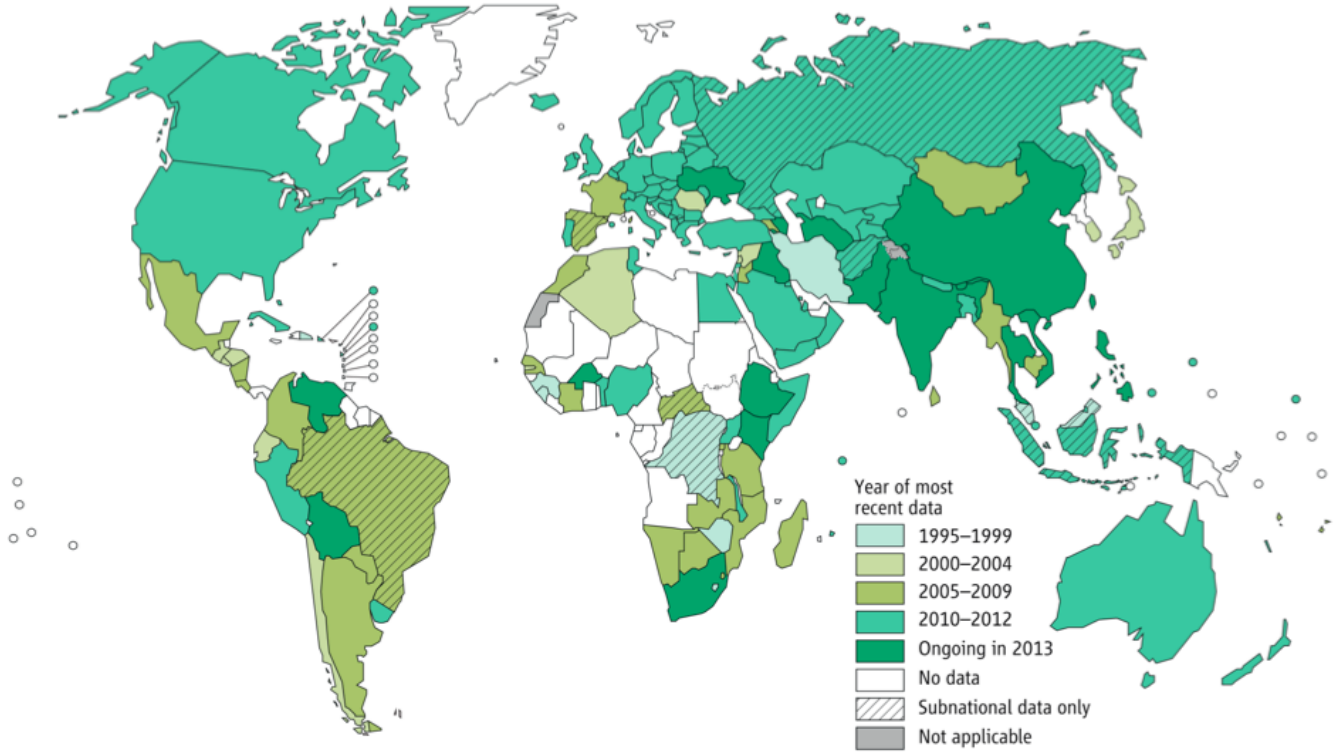
Data on levels of drug resistance among TB patients provide the foundation for estimates of the burden of MDR-TB at global and country levels. Matteo Zignol (WHO Geneva) therefore presented the most recent progress in drug resistance surveillance and the current state of knowledge on levels of drug resistance among notified pulmonary TB patients at the country level. WHO now has surveillance data on levels of drug resistance among new and retreatment cases for 136 out of 194 Member States - 70% - although for 15% of them the data are ten or more years old (see Map 1, overleaf). Of the 136 countries with surveillance data, 70 have continuous surveillance systems (i.e. all TB patients are routinely tested for drug resistance) and 66 rely on special epidemiological surveys of representative samples of patients. Given that periodic surveys are designed to estimate levels of MDR-TB in new cases, countries relying exclusively on periodic surveys to monitor MDR-TB do not have precise estimates of drug resistance in retreatment cases. By the end of 2013, 31 of the 36 high TB and/or high MDR-TB burden countries will have nationally-representative baseline data on levels of drug resistance, while the remaining five (Brazil, Russian Federation, DRC, Afghanistan, and Indonesia) have subnational data. Central and francophone Africa are the "gap on the map".

Time series data are now available for nearly 90 countries, and they indicate a range of patterns. Time trends in drug resistance are clearest in countries with continuous surveillance. Until capacity for continuous surveillance is established, NTPs should plan to repeat drug resistance surveys more regularly, approximately every 3-5 years, to monitor trends.

As far as indicators are concerned, the number of MDR-TB cases detected annually by countries (detection indicator) and the number of detected cases that are started on treatment (enrolment on treatment indicator) are already routinely reported by countries to WHO in the annual

Figure 11: Screenshot of the QuanTB drug forecasting tool, showing a stock-out alert





Map 1: Coverage of anti-TB drug resistance surveillance 1995-2013

rounds of global TB data collection and results are presented in the annual WHO global TB report, (alongside other indicators that are useful for monitoring programme performance, such as the proportion of new and previously treated patients that are tested for drug resistance). This will continue. Indicator definitions are provided in the companion handbook to the 2011 guidelines on PMDT, and an updated edition of the handbook will be issued by WHO in early 2014.

Babis Sismanidis of WHO Geneva then took the floor to present the background to enable the participants to address the question of which indicators could be used to assess the burden of MDR-TB and monitor progress in addressing this burden. Given heated debates whenever the subject is raised, one objective of the meeting was to get input from those passionate about MDR-TB but with different perspectives on what estimates should be produced and the purpose for which they should be used. For each indicator, Babis went through the available and potential data sources and the estimation methods, with their strengths, limitations, and data gaps. It was a superb exposition, making complicated statistical methods comprehensible to participants, and was highly praised by many meeting participants.

Babis described four indicators that could potentially be used for different purposes:

1. The number of MDR cases among notified pulmonary TB cases. This indicator has the strong advantage of depending on directly measured surveillance data (provided a drug resistance survey has been done or routine drug resistance testing has reached a high enough level of coverage). On the other hand, it underestimates the total burden of the disease since MDR-TB cases that exist among TB patients not notified are missed (for example, people treated in the private sector that are not notified to the NTP). Nor does it include chronic cases that are no longer notified and entirely misses cases of MDR-TB among people whose TB has not been diagnosed.

2. MDR-TB incidence, with two possible methods – both of which require indirect estimates and hence make the burden estimates imprecise.

3. MDR-TB mortality, which also requires indirect estimates as very few countries have adequate vital registration systems that report specifically on deaths from M/XDR-TB.

4. MDR-TB prevalence, which can be directly measured in population-based surveys (and provides an estimate of the number of MDR-TB cases in need of MDR treatment at one point in time) – but this is difficult and expensive, and so far only China has done it. Hence indirect estimation is required instead and due to the very low precision of the MDR–TB prevalence estimate in the general population, the burden estimate is highly imprecise.

The presentation sparked a number of questions. Looking for alternative

Above: Q&A during Session 5

methods for estimating MDR-TB, Lara Wolfson (Johnson & Johnson) asked if we could we use triangulation based on the natural history of MDR-TB patients (Answer: it's a priority for future refinement of the estimates). Ejaz Qadeer (National TB programme, Pakistan) wanted to know if inventory studies could be used (Answer: possibly – they would improve the precision of existing estimates of TB incidence and in turn estimates of MDR-TB incidence, specifically). Ed Nardell (Partners in Health) was interested in estimating reinfection as the cause of MDR-TB: this can be done using DNA fingerprinting, but it's an approach that's probably impossible within NTPs, or to summarise MDR-TB burden at the global level. Paul Nunn asked which of the indicators would best capture rapidly developing outbreaks of drug-resistant TB in high HIV prevalence situations such as South Africa. It turns out that most current routine monitoring systems can't capture such events, but there is increasing interest in outbreak detection and investigation for TB. Mirtha Del Granado then wanted to know what happens to MDR-TB patients treated with first- line drugs, and how these outcomes can be reconciled with the high treatment success rates reported globally. Answer: there are differences between regions in treatment success rates, and this partly reflects the occurrence of MDR-TB.

Interestingly the debate turned not to the technical properties of the indicators, but what people wanted to use them for. Nine participants, managers from countries on the one hand and funding and development agencies on the other, had been invited to give their perspectives. Cambodia was the strongest advocate for counting MDR-TB cases only from among notified cases, and was supported in this by India, Vietnam and Kenya. The main reasons given were that this indicator is best suited for planning purposes, and it is also the easiest target to achieve, in what we have seen is a slow moving field. Managers therefore prefer to be held accountable to this indicator, expressing their concern that funding may be jeopardised if progress using more ambitious indicators is judged as being insufficient.

The representatives from the Bill & Melinda Gates Foundation and USAID were clear that they wanted to see "the complete picture and hence big numbers" for advocacy: that is, the incidence or prevalence indicators. They also wanted clarity, and argued that the MDR-cases-only-among-notified-TB-cases indicator is difficult to explain in advocacy settings. Their concern was a desperate situation where TB, with its relatively weak advocacy position, loses out on future funding. However they also understood and acknowledged the need of NTP managers to have a direct measurement for monitoring progress at country level.

KNCV, the Global Fund and a representative of academia could see both sides of the picture, and were acutely aware that underperforming countries risk losing what few resources they currently receive from funding agencies if they can't deliver. These participants urged strengthening of surveillance systems, so that notifications more closely approximate incidence, while conceding that this would take time. "The Global Fund needs ambitious but realistic targets," concluded Mohammed Yassin.

Session chairs Karin Weyer and Katherine Floyd made it clear that WHO is neutral on this issue, and

"The Global Fund needs ambitious but realistic targets." *- Mohammed Yassin*

able to collect and publish whatever statistics are needed.

The chairs then divided the participants into groups for more intensive debate and feedback. The group work focused on discussion of a draft table that clearly described the four major options for MDR-TB burden indicators covered in Dr Sismanidis' presentation (estimated MDR-TB cases among notified pulmonary cases known to NTPs; incidence; prevalence; and mortality) and their potential application for four major purposes (advocacy, planning/allocation of funding, monitoring of programme performance in detection and treatment, and analysis of impact/ trends). Groups were asked to review the table and suggested application of each indicator, and to comment on whether or not they agreed with the content.

The group work was intense and passionate, yet very constructive and productive, with considerable positive feedback from participants. Those concerned about advocacy were anxious to ensure that everyone understood progress on MDR-TB depends on sufficient funds to do the work – and so we all need the strongest case possible for funding agencies. Others stressed that this approach will be a very short-term solution if it is then impossible to make adequate progress against impossibly high targets. The WHO's Global TB Report was a key piece of advocacy: keeping a summary of the MDR-TB situation clear and consistent each year was viewed as vital, as expressed by Michael Kimerling (BMGF). There was also a strong recommendation to include surveillance of the proportion of MDR TB among new patients as an indicator for impact.

In the end, all four groups appeared to agree with most if not all of the proposed applications for each indicator. It was striking that despite some initial reservations about the indicator "estimated MDR-TB cases among notified pulmonary TB patients", all groups ended up by concluding that this was a suitable indicator for measuring country progress in MDR-TB detection and treatment. There was also clear consensus that other indicators such as prevalence and incidence could be used for global advocacy. There was thus clear recognition that different indicators are required for different purposes, and each has strong arguments in their favour, and an emerging consensus about which indicators should be used for what purpose in future.

The first objective of the meeting was therefore achieved. Drs Weyer and Floyd made it clear that in the following weeks WHO would summarize the results of the group work in a format suitable for wider dissemination and share the documentation with meeting participants and additional stakeholders for further comment.

Session 7

Agnes Gebhard, KNCV; Dalene von Delft, TB Proof

Testing new approaches to MDR-TB care

Andrew Nunn of the UK's Medical Research Council (MRC) opened the session with a report on the TB STREAM study. First the background: the observational work of Armand van Deun and colleagues in Bangladesh, which reported an 88% treatment success rate in 206 patients with MDR-TB in 2010 and an 86% success rate from 476 patients at the Union Conference in 2012.

"Are these results reproducible?" That was Prof Nunn's key question. The answer is expected to come from two parallel streams of work: (1) further operational studies in Cameroon, Benin, Niger and some other African countries, as well as Bangladesh; and (2) the TB STREAM trial. TB STREAM is a multi-centre, randomised controlled trial (RCT) to test the non-inferiority of a standardised shorter treatment regimen for MDR-TB patients, currently happening in Ethiopia, South Africa and Vietnam. Mongolia will be added in 2014, but plans to have another arm in India haven't yet come to fruition. The trial is managed by The Union, with the UK MRC responsible for the design; the London School of Hygiene and Tropical Medicine responsible for evaluation; and the Antwerp supranational reference laboratory responsible for the microbiology. USAID and the UK's Department for International Development (DFID) are providing the funding.

So far, 176 patients have been enrolled out of a target of 400. Enrolment should finish by September 2014, with the final analysis expected in July of 2017. The regimen for the trial is similar to the Bangladesh regimen (see Figure 12, overleaf), but with high-dose gatifloxacin replaced by high-dose moxifloxacin given the withdrawal of gatifloxacin from the market after reports of dysglycaemia.

There are concerns, though, about QT prolongation with long-term moxifloxacin treatment, so baseline ECGs are performed at start, during treatment, and after it finishes. Exclusion criteria are pregnancy, resistance to fluoroquinolones, and resistance to 2nd line injectables. Previously treated cases are included, as are those with HIV infection. There is the possibility of future collaboration with Janssen, and the addition of bedaquiline in order to potentially simplify the regimen; or even to replace kanamycin, making it an all oral regimen, which would be a significant advance.

In the discussion it was clear that participants saw TB STREAM as a hugely positive development: at last, a properly conducted RCT of the treatment of MDR-TB cases. There is much hope that the results will lead to a significant change in international recommendations for MDR-TB management-, based on better evidence.

Jennifer Furin (Sentinel) asked about concomitant treatment with antiretroviral drugs (ARVs), especially efavirenz, given that most MDR-TB patients in South Africa are on ARVs. According to Gerry Friedland (Yale University), drug-drug interactions are being looked into.

"WHO's Global TB Report is key for advocacy: keeping a summary of the MDR-TB situation clear and consistent each year is vital." *- Michael Kimerling (Bill & Melinda Gates Foundation)*

Drug	Months	Drug doses by weight group		
		< 33 kg	33 - 50 kg	> 50 kg
Kanamycin*	1-4	15 mg per kilogramme body weight		
Isoniazid (H)	1-4	300mg	400mg	600mg
Prothionamide	1-4	250mg	500mg	750mg
Clofazimine	1-9	50mg	100mg	100mg
Moxifloxacin	1-9	400mg	600mg	800mg
Ethambutol	1-9	800mg	800mg	1200mg
Pyrazinamide	1-9	1000mg	1500mg	2000mg
* Kanamycin 3 times/week in month 4				
** The intensive phase can be extended to 6 months				

Figure 12: The drug regimen being tested in TBSTREAM

Christian Lienhardt asked if the 10% confidence interval accepted by the trial design is too small for detecting a significant difference between the intervention and control groups. Prof Nunn replied that there's a small risk that the study will show non-inferiority of the 9-month regimen when in fact it is inferior. But the assumption was that the need to retreat patients who were treated using the shorter regimen is more than offset by the larger benefit of giving a regimen with a substantially reduced duration (and significantly lower cost) to more patients.

Chen-Yuan Chiang (The Union) then took the floor, giving an upbeat presentation on the latest results of the operational studies of a short treatment regimen for MDR–TB in Benin and Cameroon. Here, prothionamide is given for nine months rather than the four months usually used in Bangladesh. The main exclusion criterion is previous use of second-line drugs. 18% of the 173 participants enrolled to date are HIV-infected. With more than 70% of participants having 2+ or 3+ acid fast bacilli (AFBs) in their sputum, and with four out of six lung zones involved on chest X-ray, most are seriously ill at enrolment on treatment. But despite this, treatment success is 90% to date, with 6% mortality and 3% loss to follow up. Moreover, in the 109 patients followed to 24 months and beyond, there have been no cases of recurrence!

Providing further details on the results from Bangladesh, C-Y Chiang emphasized that the patients recruited between 2005 and 2011 were mostly very sick. On long-term follow up, three quarters remained relapse-free at 24 months. There were no cases of initial resistance to kanamycin, but there was resistance to ofloxacin, which was a risk factor for lower success rates. There has been no evidence of amplification of resistance - in 11 of the failures, four have been cured on re-treatment.

Ekaterina Kurbatova (CDC, US) then presented the final results of the "Preserving Effective TB Treatment Study" – PETTS. In unprecedented detail, this study carried out drug susceptibility testing of second-line drugs at baseline and throughout the treatment and follow up of MDR–TB patients. The interim results have been presented before, but the final clear conclusion presented here was that management in projects conducted according to the international standards of the Green Light Committee (GLC) had significantly better results. The amount of baseline resistance also predicted the poor outcomes of treatment failure, or death – zero initial resistance to second-line drugs was associated with a low likelihood of poor outcomes, while XDR-TB at onset was associated with significantly worse outcomes. Acquired resistance significantly increased the risk of a poor outcome, and was strongly associated with hospital admission.

Jennifer Furin (Sentinel) then described the Sentinel Project on Paediatric Drug-Resistant TB established in 2011: over 300 researchers, caregivers, and advocates from over 50 countries who "share a vision of a world where no child dies from this curable disease".

Network members have been collaborating to raise the visibility of this vulnerable population of children. Children face many particular problems: there are so few estimates of the burden of MDR-TB in this age group; and current diagnostics are ineffective because kids can't produce the sputum they needed, so only a small proportion of children is actually treated. This means there are limited data on the pharmacokinetics of drugs; there are only a few child-friendly formulations; there is a lack of capacity among providers; and there is limited funding.

Sentinel has so far produced a framework to estimate the burden of MDR-TB in children, including those exposed, those in need of prophylaxis and those in need of treatment. It has reached a consensus on research definitions, developed clinical

Above: Dr C-Y Chiang responds to a question to the Panel

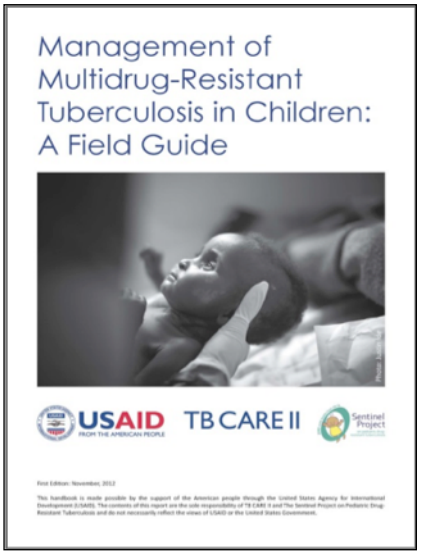


Figure 13: Sentinel Network's *Management of drug-resistant tuberculosis in children: a field guide*

guidelines including a field handbook (Figure 13), 2nd line drug-dosing sheet for kids and other field tools, and conducted capacity building workshops in Chennai, Dhaka, and Paris.

Sentinel continues to seek the inclusion of older children in prevalence surveys (which are currently only conducted in those over 15 years of age), as well as the use of Xpert MTB/RIF® instead of smear microscopy as the primary screening tool in children.

Norbert Ndjeka (Department of Health, South Africa) then stepped up to talk about the decentralization of MDR-TB care in his country. The need is urgent: the number of cases reported as being on MDR–TB treatment by the Department of Health has increased from 3,334 in 2007 to 6,494 in 2012, and treatment success rates fell from 48 to 40% between 2008 and 2010. Previously, patients had to be admitted to a small number of centralized hospitals before treatment was started, and then remain there for several months. This led to life-threatening delays, patients absconding from hospital, and transmission of nosocomial infection. Few such hospitals were implementing infection control as well as they should.

In response, since 2011 the number of treatment sites has been increased from 18 to 52, and patients are only admitted for the first two months of treatment. An array of services is offered at these sites, and early results are positive. In Msinga sub-district (Figure 14) – the site of the famous Tugela Ferry outbreak of XDR-TB in 2006 – notifications of MDR- and XDR-TB have both fallen since these measures were put in place.

In the discussion, the sense of optimism and expectation from the short regimen results, the TBSTREAM study and the clear conclusions of the PETTS study was palpable. The possibility of shorter regimens for the treatment of MDR-TB brought the prospect of relief to the hard-pressed managers present. But some expressed concerns about having to wait so long for trial results, and the sad fact that there are insufficient drugs to protect bedaquiline from the development of resistance.

In light of Sentinel's work, there was a call for TBSTREAM to enroll children, which was positively received by the presenters – who then added that Uzbekistan may also be added to the list of participating countries, thus potentially accelerating progress of the study.

Andrei Zagorski (Management Sciences for Health) warned about the increased risk of fragmentation of the fragile market for second-line drugs if newer drugs and regimens became available; but this risk seems inevitable. Many were worried about moxifloxacin's prolongation of the QT interval, and the possibility that interactions with other drugs known to have similar effects (namely clofazimine and bedaquiline) might increase toxicity. Some, on the other hand, felt that these were the right kind of problems to have – they're the price of progress in drug development.

Session 8

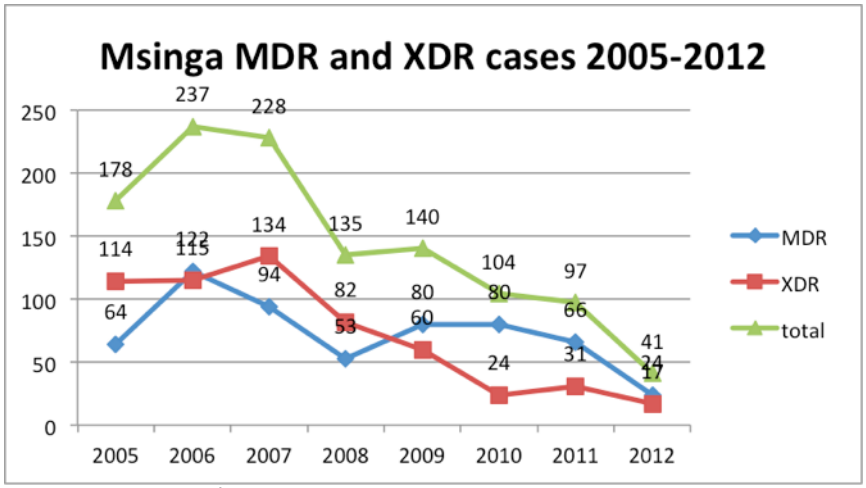
Fraser Wares, WHO, Geneva; Lucy Chesire, TB ACTION Group

Moving forward

The rationale for restructuring the MDR-TB Working Group was presented by Aamir Khan. He was answering a simple question: "Which global coordinating platform might best accelerate national M/XDR-TB control, ensure patient quality of life and get to zero deaths?"

It's clear that a lot of thinking has been done on this issue by members of the global GLC and the Core Group of the MDR-TB Working Group, as well as the Stop TB Partnership (STP) and WHO. The recommendation from all was to merge, formally, and create a new Global Drug–resistant TB Initiative (GDI) - see Figure 15, p.19. This recommendation was endorsed by the STP Coordinating Board and WHO's Strategic and Technical

Figure 14: Notifications of MDR- and XDR-TB in Msinga Sub-District, 2005-2012



Advisory Group (STAG). Box 2 contains the terms of reference.

The next steps, said Dr Khan, were to call for applications to the Core Group (CG); select the CG members and the Chair; and start to identify key strategic priorities. A GDI newsletter and website will hopefully follow soon.

Chuck Daley then proposed a set of strategic priorities (Box 2).

In the discussion on the GDI, some participants wondered if the global structure we've had so far hadn't worked so well because it was too tight – and whether perhaps a looser structure would be more suitable.

Paula Fujiwara (The Union) then asked about the availability of budget; Gini Williams urged that the strategic priorities should be patient-centred; others felt that linkages with other components of the TB effort were important.

The participants proposed several items for inclusion in the strategic priorities: reduction in patient loss to follow-up; a strategy for the introduction of new drugs and regimens; ensure that human resource development is considered in all activities of GDI; coordination with laboratories to ensure alignment of treatment services as diagnostic capacity expands. There was a strong call for an advocacy strategy developed by experts in advocacy and marketing (and not by doctors). Aamir Khan emphasized the importance of WHO in all country level work, then underlined the urgent need to stop the internal discussions so that there can be a renewed focus on the urgent work at hand.

The Minister of Health of Kyrgyzstan, Dr Dinara Saginbayeva, closed the meeting with a short presentation expressing concern that MDR-TB is growing in her country in spite of the government's best efforts and those of international funding and technical agencies. While admitting that her own government had not made TB a high priority, she called on WHO to declare it a public health emergency. She also requested the Global Fund to "change its attitude," and provide more general health systems budget support rather than specific, performance-dependent, funding.

Global Drug-resistant TB Initiative
Accelerating the response

Box 2: GDI terms of reference & strategic priorities

Terms of reference

- Support the dissemination of guidelines and evidence-based policies, norms and standards
- Facilitate coordination of partner support for PMDT expansion through existing mechanisms
- Promote communication and coordination among Stop TB Partnership Working Groups and members, and across WHO Departments, on drug-resistant TB related issues
- Support PMDT expansion through the regional frameworks and recommend strategies based on global and regional analyses on progress in DR-TB scale-up
- Guide ad-hoc, need-derived task groups for knowledge sharing, research, advocacy and other priority areas constituted with different partners as leads for priority thematic areas of work
- Promote DR-TB related TB advocacy activities, resource mapping and coordinated resource mobilization
- Identify and prioritise the research agenda including operational research for introduction and roll-out of new policies, new tools and recently approved drugs for management of DR TB cases.

Proposed strategic priorities for the GDI

1. Promote strategies to facilitate patient access to high-quality DR-TB care through a long-term, in-country capacity building approach
2. Facilitate effective knowledge sharing among partners and harmonise coordination with existing technical assistance mechanisms
3. Facilitate appropriate integration and coordination of efforts to align diagnostic services for patients with access to high-quality care
4. Facilitate strengthening of DR-TB reporting and monitoring systems
5. Strengthen regional frameworks and collaboration with rGLCs for support to country-level PMDT expansion activities
6. Develop targeted advocacy strategies and resource mobilization for DR-TB management scale-up
7. Build global consensus on appropriate management of DR-TB in accordance with international best practices
8. Support prioritization of research to generate evidence for PMDT scale-up.

Closing remarks

To conclude the session, Lucica Ditiu called for more data, more advocacy (by experts), and more deliverables. "We must deliver - or I won't be here next year!" she threatened.

The next steps will be the call for applications for members of the GDI Core Group in the coming month and further consultations on strategic priorities of the GDI prior to the first meeting of the GDI Core Group. Members of the audience were reminded that this was themselves as they all were the initial members of the GDI!

CLOSING REMARKS

Karin Weyer summed up the results of the meeting, and thanked all those involved: participants, presenters and organizers.

Her summary of the meeting's conclusions and what now needs to be done are in Box 3.

Box 3: Chair's summary of the meeting: what now needs to be done

1. **MDR-TB has a human face**. We should applaud the courage of Pat Bond and Dalene von Delft – and applaud TBPROOF and TAG for making such a poignant and personal film. We should also remember that this is happening half a million times a year, usually with less happy outcomes.

2. **Scale-up of MDR-TB efforts needs to be accelerated urgently**. The current doubling time for enrolment on MDR treatment appears to be about 3 years, and ambitious plans seem to be lacking in many countries. Treatment success rates need to be improved. We need more collaboration among partner organizations, donor agencies, advocates and activists. The Global Fund is to be congratulated for providing the lion's share of external funding.

3. **GenXpert is increasing diagnoses significantly**, but a diagnostic/treatment gap – feared and predicted for years – is now a stark reality in many countries.

4. **Bedaquiline is the success story of 2013**. Approved by FDA for use with other drugs, it has potential to save lives. But this could all be blown away by improper use. WHO has set the standard for ways of using new drugs.

5. **Ethics and human rights emphasize the patient-centredness of MDR-TB control**, but we could do more to pressure countries to live up to their obligations to their people. We need more evidence for the enablers, incentives and social support many countries are providing.

6. **Drug resistance surveillance remains vital** in measuring the problem of resistance.

7. **We can now appreciate the pros and cons for the four main MDR indicators**. But two schools of thought are clear, from those in countries who need to plan and are being held to account by their bosses and donors; and from those who want big numbers for advocacy purposes. WHO will complete the consultation on this issue and finalise the outcomes as soon as possible. Different numbers for different purposes seem possible – and a clear communications and advocacy message is essential.

8. **We heard of excellent progress with the "Bangladesh regimen"**. TB STREAM stands to change the treatment paradigm if successful. The PETTS study has produced clear results – doing MDR-TB treatment properly produces better outcomes.

9. **Children are neglected in research on MDR-TB and in care provision**. The Sentinel Project aims to correct this.

10. **We have arrived at a simpler global structure for MDR-TB affairs**. Now, we all should move forward together with the common goal to get the work done for the sake of those individuals suffering from drug resistant TB.

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Figure 15: Schematic of the Global Drug-resistant TB initiative

Figure 16: The new GDI logo, chosen at the meeting by open vote of all participants

Global Drug-resistant TB Initiative

Accelerating the response

World Health Organization

Stop TB Partnership

MDR-TB stakeholders' meeting
La Defense, Paris, 27-28 October 2013




Stop TB Partnership

Global Drug-resistant TB Initiative
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