### 10.2.2 Working Group on DOTS-Plus for MDR-TB: summary strategic plan, 2006–2015

DOTS-Plus was launched in 1999 to manage multidrug-resistant TB (MDR-TB) with second-line drugs in resource-limited settings. The Stop TB Partnership's Working Group on DOTS-Plus for MDR-TB was established in 2000. It is now clear that DOTS-Plus is an effective, feasible and cost-effective intervention, and the main challenges today are to expand drug-resistance surveillance (DRS) and monitor drug resistance trends worldwide, and to scale-up implementation of DOTS-Plus beyond the pilot phase as an integrated component of DOTS.

#### Strategic vision for 2006–2015

The vision of the Working Group on DOTS-Plus for MDR-TB is to integrate drug resistance surveillance and the management of MDR-TB as routine components of TB control, providing access to diagnosis and treatment for all TB patients and covering all health care providers. This is in line with the comprehensive approach to global TB control expressed in the new Stop TB Strategy, encompassing all TB patients including those with MDR-TB and TB/HIV. As a result, all MDR-TB management measures will be implemented in collaboration with the DEWG and will be in line with the activities of the other Stop TB working groups.

#### Current threat of multidrug-resistant tuberculosis

Along with HIV/AIDS, MDR-TB is the most important threat to TB control. Countries with a high MDR-TB prevalence generally have a history of poor TB control. There are both preventive and restorative strategies to combat resistance – DOTS and DOTS-Plus.

The major barrier to treatment of MDR-TB is the high cost of second-line drugs, which are at least 300 times more expensive than first-line drugs, on the basis of Green Light Committee prices, and between 1000 and 3000 times more expensive in terms of market prices. Additional barriers include the requirement for a sophisticated laboratory to conduct culture and drug susceptibility testing, severe side-effects associated with second-line drugs, and fear of development of resistance to second-line drugs. Consequently, most national TB programmes, other than those in the established market economies and the former Soviet Union, choose to focus on prevention of drug resistance to the exclusion of diagnosis and treatment of MDR-TB. This means that MDR-TB sufferers are left with little or no hope of recovery and that MDR-TB continues to spread.

At the same time, in many countries – including China and India which account for 35% of the global TB caseload – private practitioners and public providers not linked to the NTP diagnose and treat MDR-TB patients. Their treatment practices often fail to meet acceptable standards. The misuse of second-line drugs could lead to the creation of TB strains resistant to all known anti-TB drugs. The control of MDR-TB requires sound implementation of DOTS to prevent the development of new cases, and careful introduction of second-line drugs with adequate laboratory support to stop the amplification and circulation of resistant strains.

#### Priorities and objectives

In May 2005, the World Health Assembly resolution on "Sustainable Financing for TB Prevention and Control" encouraged all Member States "to ensure that all tuberculosis patients have access to the universal standard of care" and requested the Director-General of WHO "to implement and strengthen strategies for the effective control of, and management of persons with, drug-resistant TB".

Currently, less than 2% of the estimated number of culture-positive MDR-TB patients are treated according to WHO recommendations. With the planned expansion of DOTS-Plus, it is envisaged that by 2015, 56% of culture-positive MDR-TB patients will be detected and treated. During the 10-year period of the Global Plan, a cumulative 23% of all culture-positive MDR-TB patients will be treated under DOTS-Plus.

It is estimated that, during the Plan period, 778 000 MDR-TB cases will be treated according to WHO guidelines, 53% of them in the Eastern European Region, 19% in the South-East Asian Region, and 16% in the Western Pacific Region (Figure 33). Of these, 75% or 587 000 will be treated successfully. With the implementation of DOTS and DOTS-Plus, it is expected that the estimated global proportion of re-treatment cases will decrease from 20% in 2005 to 11% in 2015. Most importantly, it is expected that the number of MDR-TB cases will be reduced from an estimated 533 000 in 2005 to 193 000 in 2015, mainly as a result of reduction in incidence and in proportion of re-treatment cases and as a combined effect of all TB control interventions. With the expansion of DOTS-Plus, it is expected that 142 000 deaths from MDR-TB will be averted between 2006 and 2015 (Tables 7 and 8).

*See Figure 33: Number of MDR-TB patients to be treated per year under DOTS-Plus by region, 2006–2015*

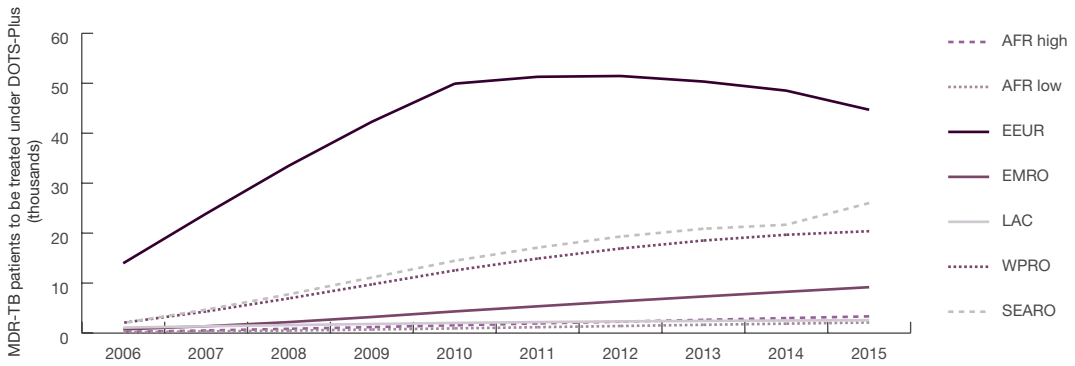
To achieve these goals, the priorities for the next decade are to:

- expand drug resistance surveillance;
- monitor trends and regularly update the global MDR-TB estimates;
- strengthen capacity to perform quality-assured culture and drug susceptibility testing;
- scale up MDR-TB treatment according to WHO guidelines;
- create a healthy and competitive market of quality-assured second-line drugs;
- provide technical and global coordination to accomplish the goals.

Strengthening of health systems and the health workforce to deliver sound diagnostic and treatment services to all MDR-TB patients will be essential to underpin these priorities.

The Green Light Committee mechanism needs to be reformed to meet the increasing demand for quality-assured second-line drugs and technical assistance. One possibility would be to decentralize the functions of reviewing and monitoring DOTS-Plus implementation to WHO regional level. In addition, the GLC

**FIGURE 33:** NUMBER OF MDR-TB PATIENTS TO BE TREATED PER YEAR UNDER DOTS-PLUS BY REGION, 2006–2015




should converge with the Global TB Drug Facility to ensure a reliable and experienced "bundling" mechanism for anti-TB drugs.

The Working Group has five specific objectives for 2015:

**Objective 1:** By 2015, representative and reliable data should be available on the global magnitude of MDR-TB, trends in high MDR-TB prevalence countries, and the relationship between MDR-TB and HIV/AIDS.
Milestones: Drug resistance data should be ready for publication in 2010 for 130 countries with either a high TB burden, expected high MDR-TB prevalence, or high HIV prevalence, with half reporting trend data with three or more data points. Revised estimates of the global MDR-TB burden will be published. In 2015, data should be available for 90% of settings, with 70% of settings reporting trend data with three or more data points.

**Objective 2:** By 2015, all regions should carry out DST for all previously treated TB patients. In the Eastern European Region, DST should also be done for all new TB patients, while in the Latin American, South-East Asian and Western Pacific Regions, DST should be done for 20% of new TB patients, focused on people at increased risk of MDR-TB.
Milestones: By 2010, all countries with a national reference laboratory (NRL) should be performing quality-assured culture and DST, and collaborating with a supranational reference laboratory (SRL). DST will have expanded to cover 92% of all new and previously treated cases in Eastern Europe. All other regions will be providing DST for approximately 60% of targeted previously treated patients, and the Latin American, South-East Asian and Western Pacific Regions will also provide DST for at least 10% of targeted new cases.

**Objective 3:** By 2015, all detected MDR-TB patients should be treated with quality-assured second-line drugs in line with WHO guidelines (17% of the estimated culture-positive MDR-TB cases in 2010 and 56% in 2015).

**Objective 4:** By 2015, the price of second-line drugs will have been further reduced, and quality-assured second-line drugs will be produced by manufacturers based in countries with a high burden of MDR-TB.
Milestone: By 2010, quality-assured production of second-line drugs will have been established in several countries with a high MDR-TB burden, including China, India, the Russian Federation and South Africa.

**Objective 5:** Provide technical direction and strategic planning for the management and coordination of global MDR-TB surveillance and control, in close collaboration with other Stop TB Working Groups including those on new drugs and diagnostics.
Milestones: By 2006, the structure and functions of the Stop TB Working Group on DOTS-Plus for MDR-TB and its subgroups, including the GLC, will be reviewed and adapted to the new challenge of scaling up the diagnosis and treatment of MDR-TB, reaching beyond the initial phase of pilot-testing MDR-TB management. Drug resistance surveillance will be included in the Working Group. By 2008, all WHO regions will have regional GLC mechanisms reviewing applications and ensuring that DOTS-Plus is monitored regularly as part of routine TB control missions. By 2015, all regions and countries will include DRS and MDR-TB management in regular TB courses and workshops.

## Monitoring and evaluation

The global MDR-TB situation is monitored by the WHO/IUATLD global DRS project, and data are published every three years. In addition, MDR-TB estimates have been published and are updated regularly. DOTS-Plus programme performance is currently monitored by WHO and the Green Light Committee. Information will become available on second-line drug use in public and private sectors from an inventory conducted in 2005.

The SRL network was started in conjunction with the WHO/IUATLD global DRS project, and is composed of twenty-three TB laboratories conducting annual proficiency testing. This

network is also responsible for the quality assurance of DST in NRLs worldwide.

A DOTS-Plus recording and reporting system has recently been developed, to allow managers at different levels of NTPs to monitor overall DOTS-Plus programme performance. In the future, elements of this system will also be included in the DOTS recording and reporting system at district level.

As the DOTS strategy evolves to include all TB patients, MDR-TB notifications and treatment outcomes should become part of the annual WHO report (Global tuberculosis control: surveillance, planning and financing).

Monitoring of progress in MDR-TB control will also be undertaken in collaboration with partners and WHO regional and country staff during routine technical missions.

Finally, annual or semi-annual meetings of the Working Group on DOTS-Plus for MDR-TB will take place to review the progress made in global DRS and MDR-TB control, and to give strategic direction for future activities. The Working Group will also monitor funding and expenditure on the global coordination of DOTS-Plus scale-up during the Plan period.

## Key risk factors

The Working Group has identified four major areas of risk which it will seek to address.

- A deterioration in the global MDR-TB situation and continued misuse of second-line drugs.

Unless DOTS-Plus is promoted and scaled up by all health care providers involved in diagnosing and treating MDR-TB (including private practitioners), there is a risk that TB strains resistant to all known anti-TB drugs will emerge and start to circulate. In addition, the potential joint impact of HIV and MDR-TB in resource-limited settings cannot be overstated and requires urgent attention.

Poor quality drugs may favour the emergence of additional drug resistance. Manufacturers of second-line drugs must be mobilized to apply to the WHO prequalification system for second-line drugs, especially as some countries may not be interested in purchasing drugs from the GLC (mainly countries producing second-line drugs). In order to ensure the use of quality-assured drugs, WHO and its partners should advocate for NTPs and funding agencies to purchase drugs from companies on the WHO list of prequalified manufacturers.

- A lack of well functioning laboratory networks providing culture and drug susceptibility testing.

Currently, one of the biggest obstacles to monitoring drug resistance and implementing DOTS-Plus programmes is the lack of well functioning culture and DST laboratories. A massive influx of both technical and financial resources is required to scale up laboratory services, in order to expand DRS and DOTS-Plus globally. The first priority is to have a well equipped, safe, and highly performing central laboratory; services can then be expanded as needed, while maintaining quality. Improvement in laboratory networks would include both the optimal use of existing tools and the development and implementation of new technology. Both the Working Group on New TB Diagnostics and the DEWG laboratory-strengthening subgroup have budgeted for scale-up within the Global Plan.

- Lack of political will.

Lack of national policies on MDR-TB control and of leadership to engage all health care providers present threats to the global MDR-TB situation. Future success will depend on the political commitment and stability of countries, and the commitment of the donor community and technical agencies to scale-up and strengthen DOTS-Plus programmes.

Political commitment is key for any DOTS-Plus programme and must translate into financial and human resources. At country level, financial resources are needed for all aspects of DOTS-Plus implementation. The GFATM now plays a major role in the financing of MDR-TB control, contributing to almost half the current GLC-approved projects. Strengthening the workforce to deliver sound MDR-TB control services is a priority for the next decade, and countries need to have clear plans for human resource development and the financial resources to realize them.

- Lack of global coordination.

At global level, a smooth scale-up of DRS and DOTS-Plus requires resources for monitoring the global MDR-TB epidemic and DOTS-Plus programme performance, as well as continued policy development and dissemination of guidelines. Human resources are needed to provide technical assistance to countries for planning, monitoring, expanding and evaluating DOTS-Plus.

*See Table 20: Expected achievements and costs of DOTS-Plus, 2006–2015, by region.*
*See Table 21: Scale-up of DST and DOTS-Plus by region*

Budget requirements for the Working Group on DOTS-Plus for MDR-TB: 2006–2015

The funding needed for DOTS-Plus implementation at country level for the 10-year period of the Global Plan, 2006–2015, is US$5.8 billion. More than 60% of the funds (US$3.9 billion) are needed for the Eastern European Region.

*See Table 22: Budget requirements for the Working Group on DOTS-Plus for MDR-TB: 2006–2015 (US$ MILLIONS)*

**TABLE 20:** EXPECTED ACHIEVEMENTS AND COSTS OF DOTS-PLUS, 2006–2015, BY REGION.

| | Estimated number of culture-positive MDR-TB cases (thousands) | Number of patients treated under DOTS-Plus (thousands) | Number of patients successfully treated (thousands) | Deaths averted (thousands) | Cost per patient treated under DOTS-Plus (US$) | Total costs (million US$) |
|---|---|---|---|---|---|---|
| Africa – high HIV/AIDS | 147 | 18 | 13 | 3 | 2,273 | 38 |
| Africa – low HIV/AIDS | 58 | 11 | 8 | 2 | 1,979 | 20 |
| Eastern Europe | 858 | 410 | 315 | 72 | 8,196 | 3,450 |
| Eastern Mediterranean | 407 | 48 | 36 | 6 | 3,897 | 180 |
| Latin America | 72 | 20 | 15 | 3 | 5,189 | 103 |
| South-East Asia | 1,021 | 145 | 107 | 31 | 3,908 | 545 |
| Western Pacific | 809 | 126 | 93 | 25 | 5,197 | 644 |
| **TOTAL** | **3,372** | **778** | **587** | **142** | **-** | **4,980** |

**TABLE 21:** SCALE-UP OF DST AND DOTS-PLUS BY REGION

| | DST coverage of new cases (%) | | | DST coverage of previously treated cases (%) | | | DOTS-Plus coverage among detected MDR-TB patients (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2005 | 2010 | 2015 | 2005 | 2010 | 2015 | 2005 | 2010 | 2015 |
| Africa – high HIV/AIDS | 0 | 0 | 0 | 0 | 60 | 100 | 0 | 50 | 100 |
| Africa – low HIV/AIDS | 0 | 0 | 0 | 21 | 60 | 100 | 8 | 54 | 100 |
| Eastern Europe | 83 | 92 | 100 | 83 | 92 | 100 | 5 | 70 | 100 |
| Eastern Mediterranean | 0 | 0 | 0 | 21 | 60 | 100 | 17 | 58 | 100 |
| Latin America | 12 | 16 | 20 | 42 | 71 | 100 | 29 | 65 | 100 |
| South-East Asia | 3 | 12 | 20 | 18 | 59 | 100 | 1 | 43 | 100 |
| Western Pacific | 0 | 10 | 20 | 10 | 55 | 100 | 8 | 54 | 100 |

**TABLE 22:** BUDGET REQUIREMENTS FOR THE WORKING GROUP ON DOTS-PLUS FOR MDR-TB: 2006–2015 (US$ MILLIONS)

| | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | ALL YEARS | % TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **COUNTRY NEEDS** | | | | | | | | | | | | |
| ALL REGIONS | 142 | 258 | 383 | 510 | 634 | 700 | 752 | 788 | 811 | 828 | 5,806 | 100% |
| AFR- HIGH | 1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 45 | 1% |
| AFR LOW | 0 | 1 | 1 | 2 | 2 | 3 | 3 | 4 | 5 | 5 | 26 | 0.4% |
| EEUR | 114 | 202 | 291 | 379 | 461 | 487 | 504 | 508 | 504 | 478 | 3,928 | 68% |
| EMR | 3 | 5 | 9 | 14 | 19 | 24 | 30 | 35 | 41 | 47 | 226 | 4% |
| LAC | 6 | 7 | 9 | 10 | 12 | 13 | 14 | 16 | 16 | 17 | 121 | 2% |
| SEAR | 8 | 19 | 32 | 47 | 64 | 77 | 90 | 100 | 107 | 133 | 678 | 12% |
| WPR | 11 | 23 | 38 | 55 | 73 | 90 | 105 | 118 | 130 | 138 | 782 | 13% |
| **INTERNATIONAL AGENCY NEEDS** | | | | | | | | | | | | |
| TECHNICAL COOPERATION* | - | - | - | - | - | - | - | - | - | - | - | - |
| **WG OPERATIONAL NEEDS** | | | | | | | | | | | | |
| | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 11 | 0.2% |
| **TOTAL** | **143** | **259** | **384** | **511** | **635** | **701** | **753** | **789** | **812** | **829** | **5,817** | |

* Some aspects of technical cooperation will be undertaken jointly for DOTS Expansion, TB/HIV and DOTS-Plus. Since it is difficult to identify what share of these costs applies to each working group, the total is shown in the budget for DOTS Expansion. Annual total cost ranges from US$220 million to US$280 million.