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Regional Office for the Eastern Mediterranean  
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Bureau régional de la Méditerranée orientale



مَنْظَرَةُ الصَّحَّةِ الْعَالَمِيَّةِ  
المكتب الإقليمي شرق المتوسط

**Regional Committee for the  
Eastern Mediterranean**

**Fifty-sixth Session**

EM/RC56/10  
September 2009

Original: English

**Agenda item 12**

## **A regional response to the emerging threats of multidrug-resistant and extensively drug-resistant tuberculosis**

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## **Executive summary**

There have been major achievements over the past decade in tuberculosis control. Countries of the Eastern Mediterranean Region have addressed successfully the challenge of tuberculosis through implementing the DOTS strategy, with the case detection rate reaching 60% for new smear-positive cases, and an 86% treatment success rate.

However, multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis (M/XDR-TB) pose a threat to global and regional public health security and to efforts to reduce the global and regional burden of tuberculosis. The Beijing Call for Action on Tuberculosis Control and Patient Care and Health Assembly resolution WHA62.15 (2009) on prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis recognize the challenges posed by M/XDR-TB and call for urgent action to address the situation.

The exact burden of multidrug resistance is not known in the Region, as drug resistance surveys have been conducted only in 8 countries of the Region. According to the fourth WHO global report on drug resistance, *Anti-tuberculosis drug resistance in the world*, the prevalence of multidrug resistance is 2.0% among new tuberculosis cases, and 35.3% among re-treated tuberculosis cases in the Region. There are an estimated 25 475 multidrug-resistant tuberculosis cases in the Region annually.

As a response to the challenge of multidrug-resistant and extensively drug resistant tuberculosis, a 5-year regional strategic plan for prevention and control of MDR/XDR-TB is being developed. The goal of the draft plan is to ensure that all countries achieve universal access to diagnosis and treatment for M/XDR-TB cases by 2015.

## 1. Introduction

### 1.1 Regional tuberculosis burden

The Eastern Mediterranean Region contributes to 6% of the estimated and notified tuberculosis cases (all types), and 6% of estimated and 5% of notified smear-positive pulmonary tuberculosis cases worldwide.

In 2007, 383 364 tuberculosis cases (new and relapse) were notified from the countries of the Region. Of these, 155 572 cases were new smear-positive cases. A total of 582 767 tuberculosis cases were estimated in the Region during the same year, with 258 877 new smear-positive cases. The case detection rate for 2007 was 63% for all cases, and 60% for new smear-positive cases. Pakistan and Afghanistan contribute to 58% of the total estimated cases in the Region.

The countries in the Region have been able to successfully address the challenge of tuberculosis control through implementing directly observation of treatment (short course), known as the DOTS strategy, during the past decade in public health facilities, including primary health care centres. During the period 1997–2007, 2 473 111 cases received proper tuberculosis care, with the case detection rate reaching 63% for all cases and 60% for new smear-positive cases, and an 86% treatment success rate.

National tuberculosis programmes are expanding tuberculosis care to cover new elements in the global Stop TB strategy, such as the private–public mix approach, active case finding among high risk groups, and care for multidrug-resistant tuberculosis patients.

However, 37% of tuberculosis cases are still not receiving proper care and contributing to the development of multidrug-resistant tuberculosis, and thousands of multidrug-resistant tuberculosis cases are being left untreated.

### 1.2 Burden of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis

More than half a million new multidrug-resistant tuberculosis cases are estimated to emerge annually as a result of inadequate treatment and subsequent transmission. Extensively drug-resistant tuberculosis, a sub-set of multidrug-resistant tuberculosis caused by strains resistant to second-line drugs, with significantly worse outcomes, is now reported by more than 50 countries. Yet only some 3% of cases of multidrug-resistant tuberculosis are being treated according to WHO standards.

In recognition of the threat to global public health security posed by multidrug resistance, ministers of health of countries with a high burden of tuberculosis met in April 2009 and issued the Beijing Call for Action on Tuberculosis Control and Patient Care. This concern was echoed by Member States at the 62nd World Health Assembly in May 2009, who issued resolution WHA62.15 Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis.

Multidrug resistance is a reflection of mismanagement of tuberculosis cases. The mismanagement includes wrong diagnosis and delay of diagnosis, wrong or interrupted treatment, and misuse of tuberculosis medicines, both first-line and second-line, such as through poor adherence to standardized treatment by private care providers, unregulated sale of anti-tuberculosis medicines and utilization of tuberculosis medicines of unknown quality.

The exact burden of multidrug resistance in the Region is not known, due to the limited number of national drug resistance surveys and surveillance. In the fourth WHO global report on drug resistance, *Anti-tuberculosis drug resistance in the world*, data are reported from 8 countries of

the Region (Egypt, Islamic Republic of Iran, Jordan, Lebanon, Morocco, Oman, Qatar and Yemen). The population-weighted mean of multidrug-resistant tuberculosis based on all countries that have reported in the Region is 2.0% among new cases, 35.3% among previously treated cases, and 5.4% among combined cases.

Lebanon, Morocco and Oman reported low proportions of multidrug resistance among new cases, from 0.5% in Morocco to 1.3% in Oman. Yemen reported a higher proportion of resistance, 2.9%, and Jordan reported 5.4% multidrug resistance among new cases. However, Jordan reports high success rates and a low number of cases requiring re-treatment, suggesting that further evaluation should be done to confirm the high proportion of multidrug-resistant tuberculosis found among new cases.

Jordan, Lebanon, and Oman reported very high proportions of resistance among re-treated cases, however sample sizes were small and the confidence intervals were wide. Trends for multidrug resistance are available only from Oman and Qatar, but they are difficult to interpret because of the small numbers of cases.

The extent of resistance to second-line tuberculosis drugs is also not known. The only available data have been reported from the Islamic Republic of Iran, Pakistan, Qatar, Oman and United Arab Emirates, mainly among extrapulmonary tuberculosis cases. Yemen tested the multidrug-resistant tuberculosis isolates collected during the national drug resistance survey, to check for second-line drug resistance, and none was found. Morocco plans to test multidrug-resistant tuberculosis isolates collected from its nationwide survey for second-line drug resistance.

In summary, countries are implementing the DOTS strategy with good results. The estimated burden of multidrug resistance is moderate in the Region compared to the global burden (25 000 cases out of 500 000). However, the real burden of multidrug resistance is unknown. Moreover, the long treatment period and the high cost of treatment, which is far more than the cost of normal tuberculosis treatment, are also a burden to health systems. It is therefore important to address this challenge and to sustain the achievements. Failure to react by scaling up the regional and country response to multidrug resistance may lead to an epidemic of multidrug-resistant and extensively drug-resistant tuberculosis.

The Stop TB Strategy covers multidrug resistance management, and the Global Plan to Stop TB 2006–2015 addresses the activities, and resources needed for the implementation of proper management of multidrug-resistant tuberculosis. However the response to the challenge of the multidrug resistance is still weak in the Region. This paper highlights the current response, challenges and issues, and the action recommended to scale up the regional response.

## **2. Current response to multidrug-resistant tuberculosis**

### **2.1 Measuring the burden using drug resistance surveys**

As noted above, the burden of multidrug resistance in the Region is not known, due to the limited number of countries that have conducted nationwide anti-tuberculosis drug resistance surveys.

The primary factor limiting the expansion of survey coverage in the Region is the high number of countries currently facing conflict situations. Another limiting factor is the poor laboratory infrastructure in many countries. Currently there is only one supranational reference laboratory in the Region, which is the national reference laboratory of Egypt. The national laboratory in Oman has been nominated as a supranational reference laboratory and is undergoing evaluation. There is a plan to identify another two laboratories in the Region during the coming year.

Currently three countries are planning for a second nationwide drug resistance survey in 2010, namely Egypt, Syrian Arab Republic and Yemen. Saudi Arabia and Sudan have started drug resistance surveys. Libyan Arab Jamahiriya, Pakistan and Somalia are planning to conduct their first nationwide drug resistance surveys during 2010. All the 14 countries eligible for grants from the Global Fund to fight AIDS, Tuberculosis and Malaria have included one or two drug resistance surveys in their 5-year workplans.

## **2.2 Case detection through quality-assured tuberculosis laboratory network**

In all countries of the Region, sputum smear microscopy is the basis for diagnosis of pulmonary tuberculosis and is provided free of charge in all diagnostic centres. Additionally all countries have established a nationwide tuberculosis laboratory network. The main elements of the laboratory network are detailed below.

As of August 2008, 18 countries report laboratory network coverage for direct smear microscopy within the recommended level of one laboratory per 50 000 to 250 000 population. The 4 countries that have lower coverage (i.e. one laboratory for more than 250 000) are Egypt, Iraq, Palestine and Qatar.

A direct smear microscopy network with full (100%) external quality assurance coverage is in place in only 7 countries (Islamic Republic of Iran, Kuwait, Morocco, Oman, Qatar and Yemen). Coverage of external quality assurance is less than 50% in 10 countries (Bahrain, Jordan, Lebanon, Pakistan, Palestine, Saudi Arabia, Somalia, Syrian Arab Republic, Tunisia and United Arab Emirates).

All countries have culture laboratories except Djibouti, Palestine and Somalia. Six countries (Afghanistan, Iraq, Pakistan, Sudan, Syrian Arab Republic and Yemen) have inadequate coverage of culture services, namely only one culture laboratory for a population of more than 5 million. The remaining countries have the WHO-recommended culture laboratory coverage of one laboratory per population of 5 million or less.

All countries have drug sensitivity test laboratories except Afghanistan, Djibouti, Palestine and Somalia. Proficiency testing for drug sensitivity test laboratories is conducted systematically with 100% coverage in 6 countries: Egypt, Islamic Republic of Iran, Morocco, Oman, Qatar and Yemen. Proficiency testing for drug sensitivity test laboratories is partially implemented in Bahrain, Kuwait, Pakistan and Syrian Arab Republic. The remaining eight countries have no proficiency testing for drug sensitivity test laboratories.

All countries have national reference laboratories except Palestine, Saudi Arabia, Somalia and United Arab Emirates. The national reference laboratories in Egypt, Islamic Republic of Iran, Jordan, Lebanon, Morocco, Oman, Qatar, Sudan, Syrian Arab Republic and Tunisia are linked to a supranational reference laboratory. Djibouti, Iraq, Libyan Arab Jamahiriya and Saudi Arabia are in the process of linking their national reference laboratory to a supranational reference laboratory. The remaining countries will be linked to a supranational reference laboratory gradually during 2010–2011. In the majority of countries with culture and drug sensitivity testing laboratories, culture and drug sensitivity testing for first-line drugs is recommended for the cases that fail the normal treatment regimen, in addition to re-treated and chronic cases.

## **2.3 Proper case management of multidrug-resistant tuberculosis cases**

Proper case management includes designing the treatment regimen based on evidence, strict observation of treatment through hospitalization and/or ambulatory treatment with treatment supporters, monitoring adverse effects of treatment, follow-up of the treatment and having trained

human resources. It also includes prevention of transmission of multidrug-resistant tuberculosis by providing adequate infection control measures.

The Stop TB Strategy, in its second component, calls for the control and prevention of multidrug-resistant tuberculosis through increased access to quality-assured second-line anti-tuberculosis drugs and prevention of development of resistance to anti-tuberculosis drugs.

The Green Light Committee (GLC) initiative, together with the Working Group on Multidrug-Resistant Tuberculosis under the Stop TB Partnership, promotes implementation of this strategy in accordance with the Global Plan to Stop TB (2006–2015) and the Global M/XDR-TB response plan (2007–2008).

Established in 2000, the GLC initiative is the mechanism that enables access to affordable, high-quality, second-line anti-tuberculosis drugs for the treatment of multidrug-resistant tuberculosis. GLC is supporting countries in the direct procurement of second-line anti-tuberculosis drugs through qualified suppliers. Support is obtained through application to the GLC describing the national policy to manage multidrug resistance, including treatment regimens and medicines needed.

Currently Egypt, Iraq, Jordan, Lebanon, Morocco, Pakistan, Syrian Arab Republic and Tunisia have GLC-approved projects. Djibouti and Sudan received technical support to develop GLC proposals and have submitted their applications. Iraq and Somalia are in the process of developing proposals for the GLC.

Human resource capacity for multidrug-resistant tuberculosis care in the Region was strengthened through sending experts to attend the international training course in Latvia and regional courses. During 2007–2008, two regional training courses on multidrug-resistant tuberculosis care were supported by the GLC. Study tours were also carried out in some regional centres such as those in Egypt and Jordan.

All countries in the Region with GLC-approved projects have complied with the five components of the multidrug-resistant tuberculosis strategy as shown in Box 1.

**Box 1. Five components of the DOTS strategy as applied to multidrug-resistant tuberculosis**

1. Sustained political commitment
  - Addressing the factors leading to the emergence of multidrug-resistant tuberculosis
  - Long-term investment of staff and resources
  - Coordination of efforts between communities, local governments and international agencies
  - A well-functioning DOTS programme
2. Appropriate case-finding strategy including quality-assured culture and drug susceptibility testing
  - Rational triage of patients into drug susceptibility testing and the drug-resistant tuberculosis control programme
  - Relationship with supranational tuberculosis reference laboratory
3. Appropriate treatment strategies that use second-line drugs under proper case management conditions
  - Rational treatment design (evidence-based)
  - Direct observation of treatment
  - Monitoring and management of adverse effects
  - Properly trained human resources
4. Uninterrupted supply of quality-assured second-line anti-tuberculosis drugs
5. Recording and reporting system designed for drug-resistant tuberculosis control programmes that enable performance monitoring and evaluation of treatment outcomes

Programmes have the following different options for treatment strategies.

*Standardized treatment:* Countries with GLC-approved projects, namely Egypt, Lebanon, Jordan, Morocco, Syrian Arab Republic and Tunisia, have adopted standardized treatment regimens designed on the basis of representative drug resistance survey data of specific treatment categories. However, suspected multidrug-resistant tuberculosis cases should always be confirmed through drug sensitivity testing whenever possible. All patients in a defined group or category receive the same treatment regimen. The treatment period is at least two years, with a 6-month initial phase where patients are hospitalized, and the remaining period (or continuation phase) of treatment provided at home under strict direct supervision.

*Individualized treatment:* Each regimen is designed on the basis of previous history of anti-tuberculosis treatment and individual drug sensitivity test results. Examples of individualized treatment strategies can be seen in Egypt and Pakistan GLC-approved projects and in other countries, but on a very limited scale.

*Standardized treatment with supervision and patient support:* Direct observation of treatment is one of key factors to prevent multidrug resistance through ensuring full adherence to treatment. It also provides an opportunity for better tuberculosis care if it is designed properly. Within the context of multidrug resistance management, it is of extreme importance to ensure that the national tuberculosis control programme is able to provide sustainable direct observation of treatment through both hospitalization and ambulatory phases. This is to ensure patient adherence, which is the key condition for cure.

All countries have reported that direct observation of treatment is in place at least during the intensive phase for all patients in all centres except Jordan, Saudi Arabia, Sudan and Yemen, where direct observation of treatment is not uniformly conducted for all patients. Health workers are the treatment supporters mainly in the primary health cares in Djibouti, Egypt and Morocco. Health workers and family members are the treatment supporters in 8 countries: Iraq, Lebanon, Palestine, Saudi Arabia, Somalia, Sudan, Tunisia and United Arab Emirates. Bahrain has reported that family members are the treatment supporters. In the remaining countries, health workers are the main treatment supporters, in addition to community members and family members. Financial and nutritional support is given to the patients in some countries such as Egypt, Iraq, Syrian Arab Republic, Yemen and member countries of the Gulf Cooperation Council.

#### **2.4 Monitoring and evaluation systems for multidrug-resistant tuberculosis**

The recording and reporting system for multidrug-resistant tuberculosis includes specifically designed forms. Some programmes use electronic forms in addition to the hard copies, such as Egypt and Jordan. Supervision of the management of multidrug-resistant tuberculosis is routinely carried out through the GLC and WHO review missions.

Although improving, the recording and reporting systems for multidrug resistance are not fully in line with WHO guidelines and there is a need to support countries in standardizing their recording and reporting systems for multidrug resistance.

### **3. Strategic issues/challenges**

#### *Limited care capacity*

- The infrastructure of the laboratory network is weak, and includes: weak surveillance systems to monitor laboratory performance and external quality assurance, lack of proper equipment,

lack of standard operating procedures, weak infrastructure in some culture laboratories, weak bio-safety.

- Infection control hazards are common in some countries, indicating the need to give more emphasis to infection control measures in laboratory networks and treatment facilities.

#### *Uncontrolled treatment*

- Treatment of tuberculosis cases (both for drug-sensitive and drug-resistant tuberculosis) is still uncontrolled in the private sector, although with the expansion of the public–private mix approach, more non-public facilities have become engaged in the diagnosis and monitoring of the treatment for tuberculosis cases. Quality of laboratory services in other sectors is not always optimum.
- Anti-tuberculosis medicines (both first-line and second-line) are often available over the counter without prescription.
- Direct observation of treatment is still not regularly done, particularly when treatment is provided only at chest facilities without involving primary health care units. As catchment areas for each chest facility are huge, it is impossible for all patients to come to chest facilities on a daily basis. Non-adherence to direct observation treatment is also found in other sectors.

#### *Limited use of new technology*

- Only a limited number of tuberculosis laboratories are using new technology.
- A limited amount of operational research is conducted in the field of multidrug resistance management, mainly new technology for diagnosis.

#### *Stigma and lack of community support*

- Many countries report high levels of stigma among patients, their families, communities and even among health workers.
- Community participation in providing social support to multidrug resistance cases is still very limited.

#### *Health system weaknesses*

- Health system barriers such as lack of networks of well-established laboratories for diagnosis, lack of hospital inpatient facilities for treatment, and lack of effective drug management systems often impede the implementation and expansion of multidrug-resistant tuberculosis care.
- Multidrug-resistant tuberculosis is a notifiable disease under the International Health Regulations (2005).

#### *Lack of sufficient resources*

- Although some countries, particularly those eligible for Global Fund grants, have obtained support for multidrug-resistant tuberculosis care, many did not anticipate the full costs for multidrug-resistant tuberculosis care, like biosafety level 3 laboratories, infection control, and drug management. Many countries are in need of revising, if not developing, their multidrug-resistant tuberculosis care plan to address the entire range of needs.
- The number of experts in multidrug-resistant tuberculosis care including clinical and laboratory experts is still limited in the Region, although training is being conducted internationally and regionally.

#### **4. Recommended action**

Management of multidrug resistance requires both good diagnosis and treatment services. Diagnosis of multidrug resistance requires a high quality laboratory network supported by national reference laboratories for culture, drug sensitivity testing and external quality assurance with new diagnostics. The quality of culture and drug sensitivity tests should also be verified through proficiency testing usually done by the supranational reference laboratory.

Good treatment requires appropriate regimens based on the drug resistance patterns in the country, high quality drugs for all identified cases, without interruption and according to the guidelines, and proper treatment facilities, either for hospitalization or for ambulatory treatment. Patient care and adherence to supervised treatment are essential, in addition to social and financial support for the patient and the patient's family. Management of adverse reactions to tuberculosis drugs is also very important: this includes follow-up tests and special care for adverse reactions with relevant medicines and consultations. Finally, infection control for both diagnosis and treatment processes is much needed to protect staff, patients and the community and to prevent further infection.

As a response to the challenge of M/XDR-TB, a 5-year regional strategic plan for prevention and control of multidrug-resistant and extensively drug resistant tuberculosis is being developed based on resolution WHA 62.15, the Beijing Call for Action and the global Stop TB strategy. The goal of the plan is to ensure that all countries are receiving the support needed to achieve universal access to diagnosis and treatment of M/XDR-TB by 2015. The specific objectives and expected products are as follows.

##### **Objectives**

1. All countries scale up their response to the challenges of M/XDR-TB by 2010.
2. All countries in the Region establish universal access to quality multidrug-resistant tuberculosis management by 2015.

##### **Products**

- National strategic plans for M/XDR-TB developed, including proposed legislation to rationalize the usage of tuberculosis drugs and ensure notification of all cases to the national tuberculosis control programme for enrollment in treatment.
- Norms for multidrug-resistant tuberculosis care developed, such as guidelines, training materials and handbooks.
- Trainers in multidrug-resistant tuberculosis management available at regional and country level.
- Improved capacity in the fields of diagnosis, tuberculosis laboratory, infection control, treatment, clinical management and drug management, involving all health care providers, as well as advocacy, communication and social mobilization and operational research.
- An electronic nominal recording and reporting system in place to monitor the results of multidrug resistance activities (case finding and treatment outcome).
- A regional network for multidrug-resistant tuberculosis management (consultants and centres of excellence) established, in addition to a regional financial mechanism to support tuberculosis patients.

The strategic plan highlights the activities that need to be carried out by the WHO Regional Office and countries, and takes into consideration the need for multicountry and regional innovations such as centres of excellence. The proposed activities cover the following areas: strengthening national reference laboratories for tuberculosis to ensure proper detection of

multidrug resistance; scaling up clinical capacity to manage multidrug-resistant cases; strengthening drug management for second-line drugs including procurement of quality-assured drugs without interruption and rational use of tuberculosis drugs; expanding the supranational reference laboratory network; strengthening infection control in tuberculosis services; involving the private sector and other public sectors in provision of care to multidrug-resistant cases; and ensuring multidrug resistance is high on the political agenda through advocacy and social mobilization.

## **5. Conclusions**

The global and the regional threat of tuberculosis can be managed only by urgent action through a system-based approach, involving partners across the health system and beyond. Failure to do so may result in a large-scale M/XDR-TB epidemic requiring significantly more investment and efforts.

In the Region, only 2% of estimated multidrug-resistant tuberculosis cases are enrolled under WHO-recommended treatment. The response needs drastic scaling up. This means that policy-makers should provide proper political commitment reflected in securing resources, both financial and human, and in making available a supportive environment for quality management, including legislation to rationalize the usage of tuberculosis drugs and to ensure notification of all cases to the national tuberculosis control programme for enrolment in treatment. The role of other health care providers and the community is critical to ensure wide access to proper care. By addressing all challenges and activities defined in the strategic plan, countries of the Region will be able to meet the global and regional targets and provide universal access to proper care of multidrug-resistant tuberculosis.