MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS IN THE AFRICAN REGION

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Tuberculosis remains a high-priority communicable disease in the African Region. With approximately 12% of the world's population, the region accounted for 30% of all notified TB cases in 2010. Of the cases notified, approximately 55% tested positive for HIV, making HIV the most important risk factor for TB incidence. Despite significant progress in implementing internationally recommended directly observed treatment, short-course (DOTS) based programmes, TB control in the region faces a number of challenges, notably poor programme performance indicators, limited access to health services, poor health infrastructure, inadequate laboratory testing facilities, weak surveillance systems, inadequate infection control measures and for drug-resistant TB, inadequate availability of second-line medicines and poor capacity to manage drug-resistant TB. National programmes are also constrained by inadequate resources for scaling up control interventions.

Since 2006, drug-resistant TB has emerged as a new threat. To date, multidrug-resistant TB (MDR-TB) has been reported in 42 of the 46 countries, 8 of which have also reported extensively drug-resistant TB (XDR-TB) cases. Ministers of Health from four MDR-TB countries in the Region (Democratic Republic of Congo, Ethiopia, Nigeria and South Africa) were party to the Beijing Call for Action against drug-resistant TB that was adopted in April 2009 and several global health initiatives, including the Global Fund, are in place to support TB control in the Region. The key actions to combat the drug-resistant TB problem in the Region include developing and scaling up programmatic management of drug-resistant TB, establishing laboratory-based surveillance systems for drug-resistant TB, improving the supply of second-line medicines, implementing TB infection control measures and expanding regional networks to diagnose and monitor multidrug-resistant and extensively drug-resistant TB.

RÉSUMÉ

La tuberculose reste une maladie transmissible hautement prioritaire dans la Région africaine. Avec environ 12 % de la population mondiale, la Région a enregistré 30 % de tous les cas de tuberculose notifiés dans le monde en 2010. Environ 55 % des cas notifiés de tuberculose étaient VIH-positifs, ce qui fait du VIH le facteur de risque le plus important de la tuberculose. En dépit des progrès importants réalisés dans la mise en œuvre des programmes de traitement de brève durée sous surveillance directe (DOTS) recommandé sur le plan international, la lutte contre la tuberculose pose de nombreux défis dans la Région, notamment la faiblesse des indicateurs de performance de programme, un accès limité aux services de santé, l'inadéquation de l'infrastructure sanitaire et des structures d'expérimentation en laboratoire, la faiblesse des systèmes de surveillance, l'inadaptation des mesures de lutte contre les infections et la tuberculose pharmacorésistante, la disponibilité limitée des médicaments de deuxième intention et la capacité insuffisante de prise en charge de la tuberculose pharmacorésistante. Les programmes nationaux font également face à des contraintes liées à l'insuffisance de ressources humaines et financières pour porter à l'échelle les interventions de lutte.

Depuis 2006, la tuberculose pharmacorésistante se pose comme une nouvelle entrave à la lutte antituberculeuse dans la Région. Des cas de tuberculose multirésistante (TB-MR) ont été notifiés dans 42 pays sur 46 et des cas de tuberculose ultrarésistante (TB-UR) dans 8 pays. Les ministères de la Santé de quatre pays de la Région à prévalence de TB-MR (République démocratique du Congo, Éthiopie, Nigeria et Afrique du Sud) ont soutenu l'Appel à l'action de Pékin contre la tuberculose pharmacorésistante, qui a été adopté en avril 2009, et plusieurs initiatives mondiales en faveur de la santé, dont celle du Fonds mondial, sont en place pour soutenir la lutte antituberculeuse dans la Région africaine. Les principales actions visant à surmonter le problème de la tuberculose pharmacorésistante dans la Région comprennent le développement et la mise à l'échelle d'une prise en charge programmatique de la tuberculose pharmacorésistante, l'établissement de systèmes de surveillance en laboratoire de la tuberculose pharmacorésistante, l'amélioration de la fourniture de médicaments de deuxième intention, la mise en œuvre de mesures de lutte antituberculeuse et l'extension des réseaux régionaux de diagnostic et suivi de la TB-MR et de la TB-UR.

SUMÁRIO

A tuberculose continua a ser uma doença transmissível de alta prioridade na Região Africana. Com aproximadamente 12% da população mundial, a Região representa 30% de todos os casos notificados de TB em 2010. Dos casos notificados, aproximadamente 55% apresentaram teste positivo de VIH, tornando o VIH no factor de risco mais importante para a incidência da TB. Apesar dos progressos significativos na implementação de programas internacionalmente recomendados baseados notratamento por Observação Directa de Curta Duração (DOTS), o controlo da TB na região enfrenta uma série de desafios, nomeadamente indicadores de desempenho do programa fracos, acesso limitado aos serviços de saúde, fracas infra-estruturas de saúde, instalações laboratoriais inadequadas, fracos sistemas de vigilância, medidas inadequadas de controlo da infecção e da TB resistente, disponibilidade inadequada de medicamentos de segunda linha e fraca capacidade de gerir a TB resistente. Os programas nacionais também são condicionados por recursos humanos e financeiros inadequados para intensificar as intervenções de controlo.

A TB resistente aos medicamentos surgiu como uma nova ameaça ao controlo da doença na Região a partir de 2006. Até à data, a TB multirresistente (TB-MR) foi notificada em 42 dos 46 países, em 8 dos quais também notificaram casos de TB ultra-resistente (TB-UR). Os ministros da saúde de quatro países com TB-MR na Região (África do Sul, Etiópia, Nigéria e República Democrática do Congo) foram Partes signatárias do Apelo à Acção de Pequim contra a TB resistente aos medicamentos, que foi adoptado em Abril de 2009, e de várias outras iniciativas a nível mundial, incluindo o Fundo Mundial, e que estão implementadas para apoiar o controlo de TB na Região. As principais acções para combater o problema da TB resistente aos medicamentos na Região incluem o desenvolvimento e intensificação da gestão programática da TB resistente aos medicamentos, a criação de sistemas de vigilância laboratorial para a TB resistente aos medicamentos, melhoria do abastecimento de medicamentos de segunda linha, implementação de medidas de controlo da infecção da TB e expansão de redes regionais para diagnosticar e controlar a tuberculose multirresistente e ultra-resistente.

BACKGROUND

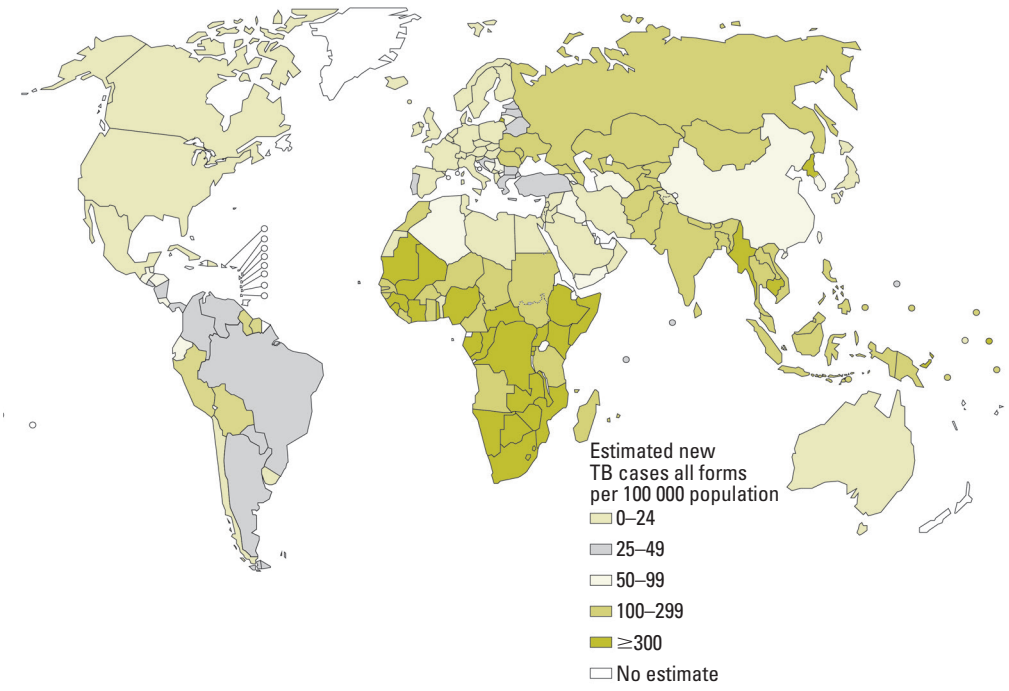
Tuberculosis is a high-priority communicable disease in the WHO Africa Region. Latest available information (2010 Global TB Control Report),[1] indicates that the African Region has the highest TB incidence rates (Figure 1) and with only 12% of the world population contributed 30% of notified TB cases in 2009. Case notification rates have increased from 82 per 100 000 in 1990 to 170 per 100 000 in 2009. At the same time, 55% of TB patients tested in the same year were HIV-positive, making HIV infection the single most important risk factor for TB incidence in the Region. This trend needs to be reversed for the Region to meet the Millennium Development Goals (MDG) targets for TB control.

Recognizing the threat posed by the TB epidemic, the WHO Regional Committee for Africa at its 53rd session in 2003 adopted Resolution AFR/RC53/R6 calling for scaling up of interventions against HIV/AIDS, TB and malaria in all Member States. Subsequently, at its 55th session in Maputo, Mozambique, in 2005, the Regional Committee declared TB an emergency in the African Region[2] calling upon Member States to implement urgent and extraordinary actions to quickly bring the epidemic under control.

Notwithstanding, subsequent to this resolution, the region has been experiencing an increasing magnitude of multi-drug resistant TB forms, and reported the first ever outbreak of extensively drug-resistant TB in 2006. While initially thought to be a rare occurrence, more and more countries in all subregions have since begun to identify and set up treatment programmes for M/XDR-TB control (Table 2). The need for accelerated action is vital.

This paper seeks to chronicle the emergence of drug-resistant TB forms in the Region and actions proposed for its urgent control.

Figure 1. Estimated TB incidence rates (2009)



EMERGENCE OF DRUG-RESISTANT TB FORMS IN THE REGION

SITUATION ANALYSIS

Since 2006, the Region has witnessed the increasing emergence of multidrug-resistant TB and extensively drug-resistant TB cases defined respectively as TB caused by organisms that are resistant to at least isoniazid and rifampicin, and MDR-TB organisms that are also resistant to any one of the fluoroquinolone family of anti-TB medicines and to at least one of four injectable second-line drugs (amikacin, capreomycin, kanamycin and viomycin). Between January 2004 and December 2011 (tentative

Table 1. Reported MDR-TB cases in the African Region 2004–2011

Country	2004	2005	2006	2007	2008	2009	2010	2011	Total to date	Percentage of notifications
Algeria	0	74	0	0	0	0	56		130	0.2
Angola	0	0	0	2	0	0	3		5	0.0
Benin	15	28	21	11	4	14	15	3	111	0.2
Botswana	0	12	0	139	126	101	106	31	515	1.0
Burkina Faso	0	3	6	31	16	19	31		106	0.2
Burundi	10	0	0	28	17	0	24		79	0.1
Cameroon	0	0	0	0	24	0	35	28	87	0.2
Cape Verde	0	0	0	5	0	0	0		5	0.0
Central African Republic	0	0	0	0	12	7	9		28	0.1
Chad	0	0	0	0	0	0	3		3	0.0
Comoros	0	0	0	0	2	0	0		2	0.0
Congo	0	0	0	21	0	0	0		21	0.0
Côte d'Ivoire	36	47	0	0	24	43	50		200	0.4
Democratic Republic of the Congo	0	0	1	15	128	91	87		322	0.6
Equatorial Guinea	2	0	0	0	5	0	0		7	0.0
Eritrea	0	0	0	0	0	0	0	11	11	0.0
Ethiopia	0	0	0	145	130	233	140		648	1.2
Gabon	0	0	0	0	0	0	0		0	0.0
Gambia	0	0	1	0	0	0	0		1	0.0
Ghana	2	1	0	7	2	0	4		16	0.0
Guinea	1	20	25	36	72	69	31		254	0.5
Guinea-Bissau	0	0	0	0	0	0	0		0	0.0
Kenya	36	44	89	82	102	150	112		615	1.1
Lesotho	4	0	0	46	0	0	527		577	1.1
Liberia	0	0	0	0	2	0	0		2	0.0
Madagascar	10	0	2	5	6	3	3		29	0.1
Malawi	0	9	0	12	25	6	40	19	111	0.2
Mali	8	2	0	11	7	22	12	8	70	0.1
Mauritania	0	11	7	14	6	0	35		73	0.1
Mauritius	0	0	2	0	1	1	2		6	0.0
Mozambique	75	115	129	163	181	140	165		968	1.8
Namibia	0	0	0	291	221	301	214	94	1121	2.1
Niger	0	0	0	2	52	24	39		117	0.2
Nigeria	0	0	0	45	23	28	21	70	187	0.3
Rwanda	0	35	0	105	79	78	90	27	414	0.8
Sao Tome and Principe	0	0	0	1	0	0	0		1	0.0
Senegal	20	0	0	10	7	11	38		86	0.2
Seychelles	0	0	0	0	0	0	0		0	0.0
Sierra Leone	0	0	0	0	0	0	0		0	0.0
South Africa	3219	4120	5774	7429	8198	9070	7386		45196	84.0
Swaziland	3	0	0	110	170	0	326		609	1.1
Togo	2	0	0	1	2	4	2	3	14	0.0
Uganda	17	46	0	67	26	57	93	71	377	0.7
United Republic of Tanzania	4	10	13	169	24	24	34	20	298	0.6
Zambia	37	0	50	27	56	29	0		199	0.4
Zimbabwe	0	0	0	1	1	29	28	118	177	0.3
Total	**3501**	**4577**	**6120**	**9031**	**9751**	**12 563**	**11 771**	**2514**	**53 798**	**100**

Table 2. Extensively drug-resistant TB cases in the African Region 2006–2010

Country	2004	2005	2006	2007	2008	2009	2010	Total to date	Percentage of notifications
Botswana			-	3	2	1		6	0.2
Burkina Faso			-	0	1	1		2	0.1
Kenya			-	1	1	-		2	0.1
Lesotho				1	20	17		38	1.2
Mozambique			-	2	-	-		2	0.1
Namibia			-	8	20	17		45	1.4
South Africa	85	298	464	458	488	594	741	3128	96.8
Swaziland			-	5	2	-		7	0.2
Total	**85**	**298**	**464**	**478**	**534**	**630**	**741**	**3230**	**100**

data), a total of 53 798 MDR-TB cases were reported by 42 countries (Table 1). At the same time, 3231 XDR-TB cases were reported from 8 countries,[3] 84% and 96.8% of them respectively from South Africa alone.

While 42 countries have ever notified cases of MDR- and or XDR-TB, only 28 of these are known to have structured treatment programmes in place.[4] Even where treatment programmes exist, not all confirmed cases are receiving treatment mostly due to the unavailability of adequate supplies of second-line anti-TB medicines.

RESPONSE ANALYSIS

The Stop TB Strategy, launched in 2006, addresses among others the global threat of drug-resistant TB. Responding to this launch, the Regional Office published a framework for the control of drug-resistant TB in 2007 that was complemented by the 2008 emergency update of the Global Guidelines for Programmatic Management of Drug-Resistant TB. To respond to new developments especially in the area of diagnostics, WHO published a revised version of the Global Guidelines for Programmatic Management of Drug Resistant TB (PMDR-TB) in 2011[5] which is now being implemented by Member States alongside the 2008 emergency update.

In April 2009, 27 MDR-TB high-burden countries including the Democratic Republic of the Congo, Ethiopia, Nigeria and South Africa met in Beijing, China, where they issued a Call for Action against drug-resistant TB.[6]

At its 62nd session, in May 2009, the World Health Assembly adopted Resolution WHA62.15 on Prevention and Control of multidrug-resistant TB and extensively drug-resistant TB which was then adopted in the WHO Africa Region.[7] Several global health initiatives including the Global Fund are in place to support TB control in the Region.

Given the importance of the emergence and spread of drug-resistant TB, this paper seeks to highlight the issues and challenges, and proposes the way forward in the prevention and control of MDR-TB and XDR-TB in the WHO African Region.

ISSUES AND CHALLENGES

Despite universal adoption by Member States of the internationally recommended (DOTS) Strategy, the African Region has some of the highest TB notification rates on record, and the highest TB/HIV co-infection rates leading to unprecedented increases in TB incidence over the past two decades.

Even though rising over time, the TB treatment success rate for new smear positive cases in the Region stands at only 80% compared with the 87% global target, mostly due to very high rates of preventable unfavourable outcomes such as patient default, transfer out and proportion of patients not evaluated at the end of treatment (see Figure 2).

The recent emergence of drug-resistant TB forms has further complicated TB control efforts in the Region, especially in the presence of high TB/HIV co-infection and general lack of infection control measures in communities and health facilities, increasing the likelihood of cross infection with TB including drug-resistant forms.

In most national TB control programmes, control policies, manuals and guidelines have not been updated to include prevention and management of drug-resistant TB. National MDR-TB guidelines are also not universally available due to the little attention that drug-resistant TB received in national programmes until the emergence of XDR-TB in the Region in 2006.

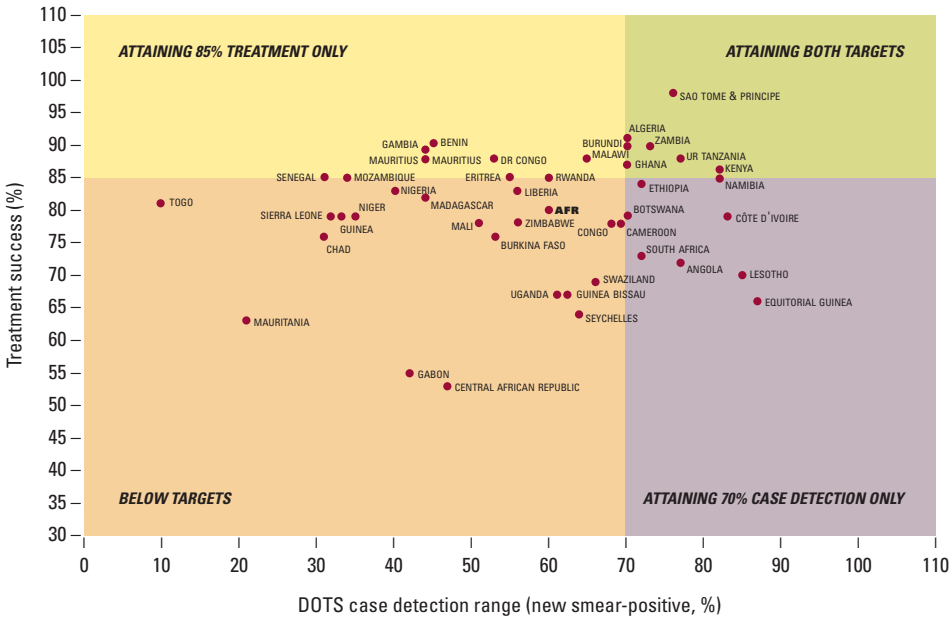
In addition, health system challenges such as poor health infrastructure, poor access to diagnostic and treatment services, inadequate human resources for health and weak-to-ineffective systems of patient follow-up during treatment significantly hamper efforts to identify and effectively treat drug-resistant TB cases. Inaction in establishing strong TB programmes with sound policies for drug-resistant TB may lead to a new epidemic with serious consequences for public health.

Diagnosis of drug-resistant TB is primarily bacteriological requiring the existence of laboratory technologies and a network for TB bacterial culture, antigenic or molecular analysis, and anti-TB drug susceptibility testing. Notwithstanding, provision of quality-assured laboratory services poses a major challenge to many countries in our Region. By the end of 2010, there were at least 12 countries in the Region[8] that had no local capacity to perform TB culture and susceptibility testing to first-line anti-TB medicines for confirmation of MDR-TB. Even worse, only Algeria and South Africa have local laboratory capability to conduct susceptibility testing of second-line anti-TB medicines to exclude XDR-TB.

The true magnitude of drug-resistant TB in the Region remains unknown due to lack of reliable data collection systems for drug-resistant TB cases in the majority of Member States. Surveillance and public awareness of drug-resistant TB are generally lacking, and only Botswana has routinely and regularly undertaken repeat representative countrywide surveys to determine the profile of drug-resistant TB over time. Between 2007 and 2010, ten countries carried out representative countrywide TB drug-resistance surveys[9] as well as XDR-TB surveys.

Considering the airborne nature of TB transmission including MDR-TB and XDR-TB, it is important to ensure early diagnosis and containment of infectious cases while adhering

Figure 2. DOTS status in the WHO African Region 2010



Note: Information relates to cohort which completed treatment in 2009, patients detected in 2010 and data compiled in 2011.

to the best possible standards of care and infection control. Isolation facilities are generally lacking in health facilities and communities, hampering the containment of MDR-TB and XDR-TB cases and the reduction of facility-based and community-based transmission of infection. Inadequate administrative controls and poor ventilation in crowded health care facilities coupled with general inadequacy of personal protection and other infection control measures increase the risk of nosocomial transmission of TB infection including drug-resistant TB.

Unlike first-line medicines, second-line medicines for the treatment of MDR-TB and XDRTB are not adequately available in the majority of countries in the Region. Second-line medicines are also not as effective as first-line medicines and tend to be associated with increased and severe adverse effects, making treatment compliance more difficult for patients. In addition, there is limited global supply of quality assured second-line medicines due to the limited number of international suppliers of these medicines. As a result, available country surveillance data indicate that a significant number of confirmed MDR-TB cases remain untreated. This is partly due to the high cost of second-line anti-TB medicines as well as lack of budget line items in TB control budgets for procurement of these medicines.

Even when second-line TB medicines are available for treatment of MDR-TB and XDRTB, the very lengthy duration of treatment (at least 24 months) and the need to treat patients near their families as much as possible pose major challenges.[11] There is therefore need for operational research to determine how best to treat MDR-TB and XDR-TB in the communities.[10]

ACTIONS PROPOSED

The aim and objectives for drug-resistant TB control in the region is to promote and support actions to prevent, identify and effectively treat drug-resistant TB through universal adoption and scale up of Programmatic Management of Drug-Resistant TB (PMDR-TB) in all Member States in the Region. Given that most of the issues and challenges associated with prevention and control of TB drug resistance revolve around the health system (e.g. limited access to general TB services, weak medicines procurement and supply management systems, weak TB laboratory infrastructure, inadequate funding, inadequate human resources for health, poor transport and communication systems, and weak strategic information and logistic systems) the actions proposed below are framed in the context of strengthening the overall health system.

Preventing the generation of drug-resistant TB forms – actions to close the tap: Countries should improve programme performance indicators for pan-susceptible TB, especially TB treatment success rates. This can be achieved by improving treatment compliance and completion rates through reducing patient default and transfer out rates and minimizing the proportion of patients not evaluated at the end of treatment. To this end, countries should identify and remove barriers to care for poor and other vulnerable communities and mobilize resources to support community-level partnerships and local initiatives.

Developing and scaling up programmatic management of drug-resistant TB: Countries should update their policies by adapting WHO guidelines for programmatic management of drug-resistant TB in DOTS programmes.[12] Furthermore, national programmes should ensure uninterrupted supply of second-line anti-TB medicines, their rational use, pharmacovigilance, and establish or strengthen drug resistance monitoring systems and infection control. Countries should also

update their human resource plans to ensure adequate human resource capacity to combat MDR-TB and XDR-TB as well as addressing staffing, motivation, retention and support PMDR-TB also entails training of teams of health care workers in order to build capacity for identification and management of confirmed cases. Collaboration with non-governmental structures, including the private sector, should be embraced to accelerate coverage and access to service points. In areas with high HIV prevalence collaborative engagement of AIDS control programmes is essential to reduce the dual burdens of TB and HIV/AIDS. Likewise, systems for patient follow up and psychosocial support must be developed and monitored. These should include advocacy, communication and social mobilization strategies.

Establishing and sustaining national drug-resistant TB surveillance systems: Countries should establish routine laboratory-based surveillance of resistance to first- and second-line TB medicines among previously treated cases and other high risk TB patients and groups. They should also conduct regular periodic representative drug resistance surveys and establish standardized recording and reporting systems for drug-resistant TB as a logical extension of the regular TB recording and reporting system.

In order to strengthen cross-border surveillance, countries should work with partners and strive to set up electronic surveillance systems and incorporate TB programmes in International Health Regulation committees in countries to minimize transmission within and outside borders while ensuring that all cases of MDR-TB and XDR-TB are notified.

Strengthening procurement and supply management systems for second-line anti-TB medicines: Countries should review the essential drug list to include second-line anti-TB medicines and strengthen their procurement and supply chain management to ensure uninterrupted availability of good quality, affordable second-line medicines and related commodities. In this respect, countries are encouraged to apply for concessionary-priced, quality-assured second-line anti-TB medicines through the Global Drug Facility (GDF) system while accessing technical support from the evolving Regional Green Light Committee system (rGLC).

Developing and implementing TB infection control measures: National programmes should incorporate TB infection control strategies within existing national infection control policies

and guidelines, and implement administrative, environmental and personal protection infection control measures for MDR-TB and XDR-TB in all health facilities. Infection control should be taken into account in the design of health facilities, especially in the context of HIV/AIDS to avoid cross-infections, especially in HIV high prevalent settings. The dangers of cross-infection between HIV and TB should be clearly elaborated and health staff concerned should be fully briefed on control measures. Furthermore, in collaboration with relevant government departments, TB programmes should support the development, implementation and monitoring of infection control plans in all health facilities.

Mobilizing financial resources for supporting implementation of the recommended actions: In the context of overall health system strengthening, countries should allocate sufficient funds from the national budgets for control of TB including MDR-TB and XDR-TB. Countries should also mobilize additional resources from global and regional initiatives to complement their national resources. Under the new GLC framework, all countries can have access to low-priced second-line anti-TB medicines from the GDF which can be bought with resources from various global health initiatives. The use of such initiatives should go a long way to strengthen the overall health system.

Expanding regional networks for diagnosis of MDR-TB and XDR-TB: WHO and other technical partners should work with national governments to establish quality assured networks of TB laboratory services including evaluation and scale up of new rapid diagnostic technologies for pan-susceptible and drug-resistant TB such as the line probe assay and GeneXpert technology platform as they become available. National governments should also be supported to through strengthening of sub regional capacity to perform supranational TB reference laboratory functions including the establishment of additional regional laboratories capable of identifying strains resistant to second-line anti-TB medicines in order to identify XDR-TB among confirmed MDR-TB cases.

Undertaking operational research: The capacity to conduct clinical trials for new diagnostics and drugs should be improved in the Region. Countries with support of partners should perform operational research for example to determine how best to treat MDR/XDR-TB in the communities while taking appropriate infection control measures to reduce transmission.

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