# A Costed Framework for the Global Drug Resistant TB Initiative (GDI), 2017-2018

Global Drug-resistant TB Initiative

Accelerating the response

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# A. Introduction

## 1. Background

Multidrug-resistant TB (MDR-TB) and its variant, extensively drug-resistant TB (XDR−TB), are forms of TB that threaten progress towards achieving global control of tuberculosis (TB) because they are much more difficult and costly to diagnose and treat successfully than drug-susceptible TB. Worldwide in 2014, about 480,000 people developed MDR-TB and approximately 190,000 deaths were caused by it, according to the World Health Organization (WHO).

For the past decade there have been steady annual increases in the number of patients diagnosed and treated for MDR-TB, but these increases have been insufficient, and, overall, progress against MDR-TB has been frustratingly slow. The Green Light Committee (GLC) was set up in 2000 to enable countries to expand treatment of MDR-TB, but at the same time assuage concerns by members of the TB community that such efforts would not worsen the drug resistance situation. As its name suggests, its activities largely focused on approving country plans for treating MDR-TB, and ensuring they would not create further drug resistance. The GLC was not designed to expand MDR-TB management to all those in need of it. Drug resistance became an integral component of the global TB control strategy with the publication of the WHO's Stop TB strategy in 2006, although several WHO staff at HQ and in the European Region had been working in the area since the end of the 1990s. Since the early 2000s, drug resistance has gradually become a central element of the efforts of the two major funding agencies working in TB, the Global Fund and USAID. UNITAID, the global health initiative that addresses commodity supply issues, has worked on MDR-TB almost since its inception in 2006. MDR-TB was addressed by the Gates Foundation in its grant to Partners in Health for work in Peru in the early 2000s. However, it only became a major element of the Foundation's work in 2008, in the lead up to a major international conference on the topic in Beijing that the Foundation, together with WHO and the Chinese Ministry of Health held in 2009.

Drug resistance was not, therefore, a major activity area for National TB Control Programmes in middle and low-income countries, with the notable exception of some former Soviet Union states, until after 2006. Since then, countries have struggled with this complex problem and the GDI was established in 2013 to coordinate the global response and provide support to countries, by merging the MDR-TB Working Group of WHO and the Stop TB Partnership, and the GLC.

## 2. What is the GDI?

The Global Drug−resistant TB Initiative (GDI), as currently constituted, is a Working Group for issues surrounding drug−resistant TB (DR-TB). It replaced the previous MDR-TB Working Group and the global Green Light Committee. The GDI is a multi-institutional, multi-disciplinary platform, which aims to organize and coordinate the efforts of stakeholders to help countries address drug resistant TB in both their public and private sectors. Ultimately, the aim is to achieve universal access to care and appropriate treatment for all DR−TB patients.

## 3. The purpose of this paper

The intention of the GDI is to undertake activities to ensure a holistic, quality-assured, patient-centred approach for all DR-TB patients, through innovative partnerships in priority countries – and to mobilize resources to achieve this. To assist in mobilizing resources for the GDI, a 2−year "costed framework document" was requested by the GDI secretariat, which was to include a high-level strategic plan for GDI to support countries in addressing MDR-TB. The paper therefore addresses the current progress at the global level in addressing MDR-TB; the global policy environment; the current major global streams of work on MDR-TB; an assessment of what GDI has achieved so far, and, through a limited SWOT analysis, a definition of its comparative advantage within the MDR-TB

space. Finally, a budgeted proposal for GDI's work over the next two years is presented, with an outline of the costs and their justification.

## 4. Progress in addressing MDR globally

An estimated 3.3% of new cases and 20% of previously treated cases have MDR-TB and these levels appear unchanged in recent years. Among patients notified with TB in 2014, WHO estimates 300,000 have MDR-TB - more than half of these patients were in India, China and Russia. Globally, 12% of new bacteriologically confirmed cases, and 58% of previously treated TB patients were tested for drug resistance in 2014, which is a significant increase on 2013 that also highlights the challenge to get more new patients tested. The overall detection of cases of MDR-TB has increased from 29,000 in 2008 to about 123,000 in 2014, but remained fairly static between 2013 and 2014 as countries focused on ensuring that the cases diagnosed received treatment. The number of cases initiating treatment therefore rose from around 97,000 in 2013 to 111,000 in 2014 – equivalent to just 25.6% of the total estimated cases of MDR-TB. The proportion of cases detected, but not treated, fell from 29% in 2013 to 10% in 2014. Worldwide, only 50% of MDR-TB cases were successfully treated in 2014, although some mid and low-income countries achieved success rates of over 75%.

Despite this important progress in the scale-up of MDR-TB services and care, the current pace is too slow for a treatable and curable condition. It will not lead to achievement of the targets set out in resolution WHA62.15, nor of the targets of the End TB Strategy. Achieving universal access to treatment as envisaged in these two documents requires a bold and concerted drive on many fronts of TB care. This document considers the role that GDI should play in scaling up MDR-TB services and improving their impact.

## 5. Obstacles to a faster pace

- Quality of DS-TB management is not adequate in many setting therefore contributing to expanding DR-TB burden;
- Many high burden countries, e.g. China, Russia, India are failing to address the problem of drug-resistant TB and its prevention. They have not made adequately bold and supportive policies that address the problem nationwide;
- As a result, countries are failing to introduce the guidance recommended by WHO that would enable the use of modern diagnostic tests, universal DST and appropriate drug regimens, and introduction of the new drugs against MDR-TB[1]. Old, out-dated policies persist, such as compulsory admission to hospital for MDR-TB cases. There is lack of investment in sufficiently trained staff and infrastructure, adequately equipped laboratories, and commodities;
- Capacity to initiate treatment and provide appropriate clinical management for all identified patients remains limited in countries, and patients receive insufficient support to the completion of therapy.
- Financial support for technical assistance to countries from funding agencies is insufficient to support expansion of the capacity to manage patients with MDR-TB;
- In spite of recent reductions in the price of second-line drugs, the costs of management of MDR-TB cases remain high;
- The success rates for treatment of MDR-TB are low and appropriate models of care have not yet been established, resulting in a high proportion of loss-to-follow-up.;

[1] MSF. Out of Step 2015. TB Policies in 24 countries. A survey of diagnostic and treatment practices.

- The economic costs that countries will face later, if they fail to address MDR-TB, have not been clearly laid out, aside of analysis performed in European region[2];
- For the most part, countries have not yet realised that there is a window of opportunity to address the gap between the diagnosed and the incident cases, while there is still a manageable sized problem.

The global TB community will need to address many, if not all of these bottlenecks if a faster pace of addressing the DR-TB problem is to be achieved.

## 6. Technical opportunities to accelerate provision of care for MDR-TB

There are several reasons to be optimistic about the technical aspects of expanding MDR-TB care:

- A point-of-care platform providing rapid and precise diagnosis of TB and drug resistance will likely be approved for use in 2017;
- A significantly shorter and lower cost regimen for treatment of MDR-TB is recommended for use in countries or areas with known low risk of resistance to fluoroquinolones and injectables, or in RR-TB patients shown to be sensitive to these drugs;
- The two recently approved drugs for treatment of MDR-TB, bedaquiline and delamanid, are being steadily investigated to work out their appropriate role in treatment regimens;
- There is already greater availability of fourth generation fluoroquinolones with less cross-resistance with earlier generations than was previously thought;
- New drug development, beyond these two recently approved drugs is continuing, and new routes of administration are being actively researched; all-oral regimens are in clinical trials already;
- Mobile phone apps are being developed to help reduce delay in starting treatment for MDR-TB, and for maintaining patients on treatment once they have started.

## 7. The End TB Strategy

The End TB Strategy marks a critical shift from controlling TB to ending the epidemic by 2035, and includes clear and ambitious targets to coordinate the global response. It also makes clear demands on those responsible for progress on MDR-TB. To reduce the number of TB deaths by 95% by 2035, and bring TB incidence down to less than 10 cases per 100,000 demands significantly more effective approaches to MDR-TB than countries currently use. The 2020 milestone of eliminating catastrophic costs is also aimed at MDR-TB, since it is the families of MDR-TB cases that bear the brunt of such high expenditure. This goal also illustrates the degree to which provision of care for MDR-TB needs to be linked with the wider strategies of universal health care (UHC) and the provision of social protection.

In **Pillar 1** of the End TB Strategy – integrated patient-centred care and prevention - provision of universal drug susceptibility testing[3] (DST) and the monitoring and management of drug safety, particularly of any newly introduced drugs, are key to provision of care for MDR-TB. Universal DST is only practicable with the new rapid molecular diagnostic tests, illustrating the key importance of expanding availability of these tests, down to the point of care (POC).

[2] Jakab, Z., Acosta, C.D., Kluge, H.H., Dara, M., 2015. Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis in the WHO European Region 2011–2015: Cost-effectiveness analysis. Tuberculosis, Supplement issue: Tuberculosis in Evolution 95, Supplement 1, S212–S216. doi:10.1016/j.tube.2015.02.027

[3] Universal access to DST is currently defined as DST for at least rifampicin among all patients with bacteriologically confirmed TB, and further DST for at least fluoroquinolones and second-line injectable agents among all TB patients with rifampicin resistance.

Implementing **Pillar 2** – bold policies and supportive systems aimed at ending the TB epidemic – requires that those working on MDR-TB need to join forces with the TB community as a whole to engage in discussions with policy makers in the wider health sector, and in the social welfare and social protection sectors. Alliances made through engagement with civil society and affected communities will be crucial to provide the necessary protection and support to MDR-TB cases to avoid catastrophic costs and achieve a cure. Work to strengthen the regulatory frameworks on notification, vital registration, quality assurance, rational use of drugs and infection control are all key areas of interest for MDR-TB.

**Pillar 3** – intensified research and innovation – is as important for ending MDR-TB as it is for TB in general. New diagnostics, drugs and vaccines are all needed, beyond those developed in the last four years, as well as new approaches for implementing them. All this creates a demand for operational or implementation research at country level, to show the most effective ways of using the new tools and approaches and to demonstrate the impact that they have.

## B. Main activities and funding streams within the current MDR-TB space

### 1. Status of global funding for MDR-TB

Of the USD 8 billion required, according to WHO, for a full response to the global TB epidemic in 2015, USD 1.6 billion is required for MDR-TB and USD 0.6 billion for laboratory strengthening including provision of new molecular tests, much of which is necessary to improve detection of MDR-TB. About USD 6.6 billion was allocated to TB in 2015, leaving a gap of USD 1.4 billion, when measured against the WHO requirements. When countries measure their gaps, though, they are less ambitious than the WHO, and the national level gap for MDR-TB activities was only about USD 0.14 billion. This is probably because MDR-TB is mostly found in the middle-income countries rather than the lowest income countries, but it also reflects the lack of ambition in countries.

### 2. Main MDR-TB activities

The major activities addressing MDR-TB globally are listed and briefly described in Annex 2. In summary, a significant amount of funds is being invested into MDR-TB. The Global Fund and USAID are, by a long way, the largest suppliers of external financial assistance to countries' MDR-TB work. WHO clearly takes the lead in drug resistance surveillance, monitoring and evaluation of national TB programmes' efforts, policy formulation for addressing drug-resistant TB, including guidance for TB laboratories, and organisation of the provision of technical assistance. New drug regimens are being tested by UNITAID's end TB project, by the Union and other research consortia. The GDF is procuring internationally quality-assured drugs and supplying them to countries. DR-TB STAT is bringing together those working on the introduction of new drugs into countries and identifying and resolving obstacles.

## C. Stakeholder analysis within the MDR-TB field

Stakeholders were interviewed between 12th December 2015 and January 6, 2016. Those interviewed are listed in Annex 1, and their actual quotations or annotated statements from those interviews are in Annex 2. The gist of these interviews is summarised here.

### 1. GDI as a network for exchange of ideas and information

All but one of the stakeholders interviewed expressed that the provision of a network for exchange of ideas and information was a useful and valuable function of GDI and wished to see it continue, even expand. However, to maximise the value needs an increased sense of mutual accountability and more discussion of how partners can support each other. There is room for greater collaboration between members of the GDI – "collective action is more effective than multiple

individual actions". More collaboration on the production of "technical advocacy", i.e. papers describing the successes of PMDT would be valuable and useful.

### 2. Technical assistance (TA)

Almost all interviewees supported the GDI facilitating more, and better quality, TA in support of countries' implementing all aspects of PMDT, including the introduction of new drugs. A better understanding is needed, according to one observer, of what the gaps are, where they are and how they should be addressed. Mapping of countries' needs and current status of MDR-TB efforts would be critical to this discussion, akin to the analyses of countries carried out by WHO for the USAID priority countries. GDI partners could both advocate to countries to introduce the new approaches and policies, and provide TA to assist them to do so and support implementation. TA funding, some stakeholders felt, could be better directed to where it is needed and where it would work best.

### 3. Implementation of PMDT

Many stakeholders expressed concern about the quality of implementation, and the low treatment success rate – WHO, many said, should do more to improve it, especially by addressing the quality of the work of the rGLCs outside EURO and WPRO. There needs to be more advocacy at country level to increase the level of demand for quality MDR-TB services. The private sector seems hardly to be addressed at all.

### 4. Analytical work

Many stakeholders asserted that there is no clear, effective strategy to address MDR-TB – that what we have may be the best that we can do with existing tools, but there is nothing akin to the old DOTS strategy for drug-susceptible TB. Until there is, according to those involved with the end TB Project, funds need to be spent on developing new tools, new regimens and new approaches. Technical arguments in support of PMDT need to be strengthened. More work is required on the cost-effectiveness of PMDT. Different scenarios should be modelled for countries and the economic and financial costs that would need to be paid in future, if there is no action now, made very clear.

## D. GDI and its environment

### 1. Structures, governance, funding, and functions of GDI

The GDI is, in principle, a matrix structure with both WHO and the Stop TB Partnership sharing jurisdiction over its elements and workings. In practice, however, the GDI is managed by WHO which provides the Secretariat for the Core Group and the GDI as a whole. The Core Group was formed in 2013 as a merger of the global GLC and the Core Group of the old MDR-TB Working Group. It meets twice yearly. At the same time main mechanism for the provision of technical assistance to countries on MDR-TB was decentralised to the rGLCs that are all based in WHO Regional Offices.

The Global Fund and USAID are the sole financiers of the GDI and rGLC mechanisms: in 2015, WHO, GTB, Geneva, received a total of USD 394,000 for the GDI work, and the Regional Offices received USD 1.6 million for the operations of the rGLCs and in-country activities. Funding for the rGLCs comes from the Global Fund through a "levy" on countries' Global Fund grants (if they address MDR-TB which most TB grants do). Part of the funding for the GDI comes through a central component from the Fund's Geneva office. USAID complements funding for technical assistance through USAID/PEPFAR-WHO GLC related grant. In return, WHO provides TA to the USAID specified countries and maintains the human resources in Geneva to support the GDI Secretariat. Part of the funds to support the GDI work are sourced from the USAID grant directed to the Working Groups of the Stop TB Partnership channelled through the Partnership.

The overall strategic priority is to "Build global consensus on appropriate management of DR-TB for patient centred care delivery in accordance with international best practices." GDI is intended to provide the necessary umbrella structure to facilitate integration, partnership building, and coordination of activities directed against MDR-TB. GDI's functions are to:

a. Develop a strategic agenda, including relevant research areas, a work plan and an estimate of resource needs for activities in priority areas in the framework of the Partnership;
b. Provide a coordination mechanism for the implementation of activities agreed by the Partnership and approved by the Coordinating Board through a core group (CG) (the constitution and functions of the Core Group are described in section VI);
c. Act as a consensus-building mechanism in support of the development of new technical standards where appropriate and advise on development of overarching strategies that involve multiple sectors and partners;
d. Serve as a mechanism for developing broad global consensus, unifying strategies, objectives and priorities and monitoring global PMDT efforts based on the reports generated by the Global TB Programme of WHO, research activities as well as country specific feedback from TB program managers and partners received during meetings and workshops;
e. Participate in developing and implementing approaches to communications, resource mobilization and advocacy for PMDT;
f. Report to the Partnership Coordinating Board on plans and progress towards reaching PMDT targets.

## 2. GDI activities

GDI's activities include an annual meeting for some 100 participants at which the main streams of activity in MDR-TB control are presented and discussed. When budget can afford, many country managers and decision-makers are invited in order for them to take part first-hand in these presentations and discussions. A LIST-SERV of some 300 members has been set up so that members can receive regular mailshots of relevant MDR-TB material.

The GDI core group convenes activity- or project specific, time-limited task forces to undertake specific tasks. The DR-TB Research Task Force has prepared an updated research agenda, which was published. Members of GDI have published a generic protocol for country level introduction of the shorter MDR-TB regimen in a framework of operational research. The DR-TB STAT Task Force is a recent group formed of MDR-TB experts that provides technical assistance through regular video and telephone conferences aimed at facilitating the introduction of the new drugs into countries. In the process, it finds itself trouble-shooting on other bottlenecks in the provision of MDR-TB care. The Advocacy Task Force produced a number of videos mainly of MDR-TB patient experiences, but together with the Patient-Centred Care Task Force ceased operations through lack of funds.

The regional GLCs are committees that review progress in MDR-TB management expansion in the regions. The rGLC s are driven by the WHO Regional Offices and their secretariats organise and manage technical assistance to countries through identification of experts, liaison with countries, preparation of objectives, logistics of missions, and monitoring of the effectiveness of the missions and countries' performance. Results of missions and regional progress are discussed at the rGLC meetings. The general opinion of the rGLCs is that they work reasonably well in EURO and WPRO, and there have been notable improvements in AFRO in recent months, but elsewhere further progress is needed. In EURO and WPRO, the rGLCs are cooperative bodies that mostly use partner agencies and individuals to carry out country missions. AFRO, on the other hand, uses largely WHO staff. Effectiveness seems to depend on competent, pro-active secretariats that have the resources in terms of time and money to carry out the work and maintain good links with funding agencies and WHO, Geneva. However, because the funding arrangements with the Global Fund were set up when the GLC was essentially a monitoring body rather than an MDR-TB treatment expansion body, the funding available for TA missions is insufficient to do much more than monitor activities and make

recommendations. The rGLC mechanism lacks enough resources to apply the lessons learnt by the highly successful UNITAID supported EXPAND-TB Project (Annex 2.3) which aimed at provision of TA of sufficient duration to be able to train up laboratory staff and build national capacity.

In summary, the GDI has a platform for information exchange, which is viewed as useful by almost all of the stakeholders consulted, but it has lacked the financial resources to hold it annually. The GDI does not yet benefit from a high level of engaged support from its members, probably because it is a young organisation, and its chief platform meetings has only been held twice. The Task Forces have produced valuable products useful for expanding MDR-TB management, but they lack mainly financial resources to do more. Improvement is needed in the rGLC mechanism. There are new ideas, energy and enthusiasm in abundance in the TB drug resistance space, but partners are largely pursuing their own goals. There is a real opportunity for greater coordination and collaboration in expanded provision of MDR-TB care, prevention and treatment, which GDI is well-positioned to supply.

## E. Analysis – what is needed now and in the next 3 years to promote PMDT in countries

### 1. Technical assistance (TA)

There is general agreement in the TB community that a major rate-limiting step is "the capacity of staff at country level to get and keep patients on treatment". Agreement extends to the idea that TA is the solution to this problem, but it needs to be country focused, with emphasis on training of local staff, and a definitive shift away from the monitoring style of the rGLC, towards longer durations of TA. Current levels of support for TA are dependent on the Global Fund and USAID, and there are signs that, without a clear improvement in the quality and the model of the TA, the current level of support may not be maintained beyond 2016. This is a serious threat which the rGLC mechanism needs to address with urgency.

More rapid expansion of MDR-TB services requires stronger mechanisms to provide more and better TA. These include greater engagement of countries in thinking through the demand driven approach; they need to budget more for TA for PMDT, and receive more of it, especially long-term TA, based in the country. Countries should express these needs more explicitly in the National Strategic Plans (often they do not). They should include more clinical training, especially for new drugs, and for better-structured and planned TA. Consultants who assist with NSP preparation should be brought on board. Countries need to be reminded of the TA need at meetings such as the WHO's End-TB Summits that are intended to be held each year in association with the Union Conference. We need a stronger mechanism to follow up on monitoring recommendations.

Improving the current levels of treatment success is a priority – for the patients concerned primarily - but also to bolster the arguments in support of advocacy for more MDR-TB management. This emphasizes the need for TA to focus on clinical management, as well as on the programmatic management that is necessary for disseminating better clinical practices. The world lacks focused training materials that are appropriate and adapted to country conditions. These need to be rapidly developed to support expansion of TA.

DR-TB STAT has shown the way in how to address country-level bottlenecks in the provision of the new drugs for MDR-TB. A similar approach could be used to address other bottlenecks through a system of regular telephone and videoconference calls between countries and a roster of dedicated experts in all aspects of MDR-TB service provision. This could be done either by expanding existing DR-TB STAT operations, if the group is willing, or setting up an additional group.

Infection control remains a major issue for TB control and management in developing countries, especially in facilities providing MDR-TB services. To prevent transmission in these facilities a range of products is required including training packages, resource centres for facility designs and managerial expertise, linked with other national or local airborne infection control efforts.

As new drugs become available at country level, operational guidelines are needed to lay out how they are to be introduced in the country, and how their adverse effects are to be monitored. Generic guidelines produced at the global level could speed up the development of appropriate guidelines at national level.

### 2. Advocacy at country level

WHO has set the pace in the development of global policies and has responded well to the arrival of the new diagnostic tests and to the new drugs effective against MDR-TB. Countries, however, are generally slow to adopt these policies, and even slower to implement them. Once policies are published, efforts to approach countries rapidly and directly, and advocate for their rapid introduction, are too few. When countries backslide after the ending of external funding, little or no action is taken. For example, the acute reduction in recruitment and treatment for MDR-TB that took place at the end of Quarter 2 of 2014 in China, because of the end of the Global Fund support, has gone more or less unchallenged. Countries currently are generally unwilling to invest in MDR-TB, but no agency of any size or global weight is effectively confronting them for this failure. Even MSF, in its recent "Out of Step" report, focused on a rather restricted and technical review of policy implementation at country level.

Globally, interest in anti-microbial resistance (AMR) is growing strongly. The tuberculosis community has more experience in this area than most, and the various AMR forums (WHO, UK Government etc.) that are being set up offer the possibility of collaboration with anti TB DR efforts.

Monitoring the implementation of policies is done, to some extent, by WHO's annual Global TB Report, and special surveys are sometimes required to follow up on the extent of policy take up. However, neither of these is being much used to shed light on countries' inactivity. They are not properly exploited for advocacy purposes.

The new UN Special Envoy (SE) for Tuberculosis, Ambassador Dr Eric Goosby, has opened up new possibilities for advocacy at country level to support the expansion of PMDT. The SE has access to higher levels of the political landscape than either the Stop TB Partnership Executive Secretary or the WHO GTB Director. MDR-TB is concentrated in relatively few key countries, notably India, China, Russia, Pakistan, Ukraine and South Africa. Of these, India and China are key at present. There are possibilities in Pakistan and South Africa. It is essential that India is encouraged to keep up and even increase its currently impressive level of MDR-TB diagnosis and treatment. Advocacy is required to ensure that India funds its own NSP to the levels it needs – as clearly stated by the India JMM in April 2015. China's level of diagnosis and treatment for MDR-TB fell precipitously after June 2014 when the Global Fund support ended. The global response to this drop has been very muted, even though it threatens the achievements of the new End TB Strategy. The Chinese are responsible stewards of their health care system and very likely open to sensitive, diplomatic discussions on the needs of patients with MDR-TB, as long as those undertaking that discussion are properly briefed and sensitive to the major constraints faced by the Chinese Government and Ministry of Health.

One reason for the inaction described above is that the arguments that should underpin good advocacy have not been adequately assembled. The cost-effectiveness of PMDT using the current tools has not been strongly enough illustrated in different country contexts. Admittedly, the low levels of treatment success reported from countries is a problem in constructing these arguments (see next section). However, much more could be done to model different scenarios for countries,

and to illustrate the economic and financial costs that would need to be paid in future, if DR-TB continues to be inadequately addressed now.

Therefore, a strong, coordinated, advocacy effort, aimed at specific priority countries, is needed at global level involving multiple partners including the GDI and its secretariat, the Stop TB Partnership, WHO HQ and regions, the UN SE, The Union and other partners.

### 3. Platform for information exchange, collaboration and partnerships

To stimulate TA and promote stronger advocacy (the essential needs according to conclusions of the two sections above) an annual forum for exchange of information and experience is essential – and viewed positively by all but one of the stakeholders consulted. The annual forum would also greatly facilitate the collaborations and partnerships needed to expand MDR-TB services.

The End TB Strategy has included drug resistant TB as well as drug susceptible TB in its Pillar 1, which integrates patient-centred care and prevention. The new policies on the short regimen for MDR-TB treatment should provide many advocacy opportunities to promote the new policy and put pressure on countries to introduce it rapidly. Advocacy also has a role to play in pushing for new, low cost sources of production of drugs such as clofazimine, which will be needed in larger quantities once the new shorter regimens are adopted. Further interactions with the pharmaceutical industry could help to support availability of the new drugs for MDR-TB. Advocates for MDR-TB should link with others in the TB community to hold discussions with policy makers in the wider health sector, and in the social welfare and social protection areas, and address collaboratively the issue of avoiding catastrophic costs from MDR-TB. Alliances made through engagement with civil society and affected communities will be crucial in order to make progress in this area – and the menace of drug resistance should assist in making these linkages. Collaborations thus made should not only address direct improvements to susceptible or resistant TB care, prevention and treatment, but could also, by greater engagement of communities, serve to strengthen the regulatory frameworks on notification, vital registration, quality assurance, rational use of drugs and infection control – all areas that indirectly support better management of MDR-TB.

A number of stakeholders in GDI have expressed their interest in addressing MDR-TB at the sub-national level, rather than the national level, because of the greater chance of having an impact at a smaller scale. Linking national level activities with successful projects on MDR-TB at city (e.g. Karachi in Pakistan), oblast (e.g. Orel, Tomsk in Russia), or district level (e.g. Achham district in Nepal) might also serve to stimulate national level activity. If the rGLCs could become places where those working in MDR-TB could bring their local or national bottlenecks, discuss them, and address them directly – and have them resolved, they would more likely attract financial support.

With the notable exception of the work of IRD and the NTP in Pakistan, MDR-TB in the private sector is a major gap. It has taken a very long time, but in drug susceptible TB, major advances have recently been made in public-private collaborations, e.g. in India, that have noticeably increased national case finding. MDR-TB needs to be a part of those collaborations, and similar efforts are needed in a range of countries where the private sector is often the preferred supplier.

## F. Budget estimates

The GDI aims to make a greater impact on the control of MDR-TB through expanding its activities in the following areas:

### 1. Tools to support countries

a) Coordination of the preparation of modern, focused training materials for improved management of MDR-TB, patient support that includes electronic tools/mobile technologies

to implement the positive results that are coming out of operational research on new technologies such as video observed treatment (VOT), etc. Distance learning approaches will also be incorporated;

b) The GDI looks to expand the activities of DR-TB STAT to address a wider range of bottlenecks at country level beyond those obstructing the introduction of the new SLDs;

### 2. Advocacy

To address the current gaps in advocacy aimed at addressing MDR-TB specifically, the GDI aims to:

a) Facilitate development of specific country-level advocacy approaches that start with five of the top high MDR-TB burden countries e.g. India, China, Pakistan, Philippines, Indonesia.
b) Provide technical support to high level approaches by the UN SE;
c) Develop global coordination links with AMR activities;
d) Develop sound technical papers detailing the cost-effectiveness of PMDT in different settings;
e) Develop a high quality paper illustrating the costs of failure to act now against MDR-TB;
f) Videos and other materials describing impact of MDR-TB on patients and health workers;
g) Twice-yearly GDI newsletter.

### 3. Platform for information exchange, collaboration and partnerships

In its crucial aim of linking stakeholders in MDR-TB prevention, care and treatment, and sharing information and experiences, the GDI aims to:

a) Hold a wide-ranging annual forum that includes civil society, community groups, TB managers and decision-makers from high MDR-TB burden countries as well as academics, representatives of pharmaceutical companies, international NGOs, foundations and development agencies;
b) Create links with TB community efforts on health insurance, social protection, social welfare; development of approaches to the private sector to improve its management of MDR-TB;
c) Develop a strategic approach to improve the management of MDR-TB in the private sector.

**Table 1. GDI proposed budget overview, 2017-2018**

| Item | | Costs (USD) | | |
|---|---|---|---|---|
| | | 2017 | 2018 | Total |
| ***Tools to support countries*** | | | | |
| | Expanded support to overcome bottlenecks in countries | 50,000.00 | 50,000.00 | 100,000.00 |
| | DR-TB STAT Task Force activities | 202,500.00 | 202,500.00 | 405,000.00 |
| | Other Task Force activities | 100,000.00 | 100,000.00 | 200,000.00 |
| Subtotal | | 150,000.00 | 150,000.00 | 300,000.00 |
| ***Advocacy*** | | | | |
| | Technical support to UN SE | 25,000.00 | 25,000.00 | 50,000.00 |
| | Coordination activities with AMR etc. | 25,000.00 | 25,000.00 | 50,000.00 |
| | Videos on the impact of MDR-TB on patients and h/workers | 10,000.00 | 10,000.00 | 20,000.00 |
| | Paper on cost-effectiveness | 20,000.00 | 20,000.00 | 40,000.00 |
| | Paper on consequences of failing to address MDR-TB | 20,000.00 | 20,000.00 | 40,000.00 |
| | GDI newsletter | 10,000.00 | 10,000.00 | 20,000.00 |
| Subtotal | | 110,000.00 | 110,000.00 | 220,000.00 |
| ***Platform for information exchange, collaboration and partnerships*** | | | | |
| | Annual GDI Forum | 100,000.00 | 100,000.00 | 200,000.00 |
| | Core Group meetings (x2 per year) | 80,000.00 | 80,000.00 | 160,000.00 |
| Subtotal | | 180,000.00 | 180,000.00 | 360,000.00 |
| ***Staff*** | | | | |
| | WHO-HQ Secretariat: 1 P4 FTE | 270,000.00 | 270,000.00 | 540,000.00 |
| | WHO-HQ admin support 0.25 FTE | 30,000.00 | 30,000.00 | 60,000.00 |
| | Advocacy and communication specialist in the TBP | 250,000.00 | 250,000.00 | 500,000.00 |
| | DR-TB STAT coordinator (partial funding) | 60,000.00 | 60,000.00 | 120,000.00 |
| | DR-TB STAT admin support | 20,000.00 | 20,000.00 | 40,000.00 |
| | Other Task Force admin support | 20,000.00 | 20,000.00 | 40,000.00 |
| Subtotal | | 650,000.00 | 650,000.00 | 1,300,000.00 |
| **Total** | | 1,090,000.00 | 1,090,000.00 | 2,180,000.00 |

# Annexes

## Annex 1. List of people interviewed

Ernesto Jaramillo, WHO
Christian Lienhardt, WHO
Fuad Mirzayev, WHO
Mario Raviglione, WHO
Fraser Wares, WHO,
Karin Weyer, WHO
Maarten van Cleeff, KNCV
Jane Coyne, Office of the UN Special Envoy for TB
Jennifer Furin, MSF, South Africa
Janet Ginnard, Unitaid
Alex Golubkov, USAID
Salmaan Keshavjee, Partners in Health
Michael Rich, Partners in Health
Mukadi Ya Diul, USAID
Mohammed Yassin, Global Fund

## Annex 2. Main activities in the MDR-TB space

### 1. The Global Fund

The Global Fund supports many countries to carry out PMDT at a cost that is very approximately equal to their support for drug sensitive TB – something in the region of USD 250 million annually. The Fund's target is 260,000 cases treated in the 5 years, 2012-2016, and this is on track, with a recent exponential increase. According to GF staff, progress is slow in countries because case-finding is low, mainly because of a lack of capacity in countries. The tools and the financial resources available at country level, they feel, are sufficient to achieve their targets.

### 2. Challenge TB – USAID and KNCV

Like its USAID-supported predecessors, TBCARE, TBCAP and TBCTA, Challenge TB is addressing MDR-TB. Currently, unlike with GLI at its inception, Challenge TB does not have access to the same level of funding for "Core" projects as its predecessors. Therefore, less money is available for initiatives such as GDI, although one project is coordinated with GDI, the bedaquiline starting project that coordinates technical assistance for pharmacovigilance, drug supplies, country level guidelines and support to centres of excellence. Most of the MDR-TB funding, however, comes from country grants. Challenge TB supports MDR-TB activities in SIAPS and with pharmaceutical companies, as well as taking part in DR-TB STAT (see below).

### 3. Unitaid

Unitaid, under its current management, sees itself playing a more catalytic role than previously, between the upstream players of the Gates Foundation, its PPPs and academia, WHO and its policy development function, and the more downstream agencies such as the Global Fund and USAID that support countries in implementation. They see themselves in the future working closely with WHO on the how tools should be developed and used, and, for example, found the target product profiles produce by WHO for new diagnostic tools extremely useful. They look to the Partnership to understand patients' needs, to carry out advocacy and increase awareness. Unitaid now looks to align itself very well with all these partners and try to be more systematic and focus on areas where they can intervene positively. They are clear of their roles in Hepatitis C and HIV, but are re-doing their disease narratives for TB and malaria.

*Availability of SLDs*

For over a decade, though, Unitaid has been supporting MDR-TB control efforts through the direct supply of commodities, and making them cheaper through changes to the market. The **Strategic Rotating Stockpile (SRS**) **($8 million, GDF and Stop TB Partnership**) consists of medicines sufficient for 5,800 MDR-TB treatments which can be accessed by countries at short notice. It has been in action since 2008, and was the first global effort of its kind. The SRS permits emergency orders to be serviced rapidly, and reduces lead times. It also facilitates the consolidation of market demand and encourages generic manufactures with SNRA approval or WHO Prequalification to stay in the market by providing a source of regular orders for their quality products. The second-line TB drugs market is low-volume, high-price – a volatile combination and SRS helps to increase demand and lower volatility, and to some extent helps to lower the price of the SLDs.

**End TB – 2015-2019. $60.4 million, PiH with IRD and MSF**

Approved in principle in 2012/13, Board changes at Unitaid in 2014 and the technical difficulties of such a programme, delayed the start to 2015. There are two streams of work. The first is the promotion of the introduction of new drugs (delamanid and bedaquiline, plus others in Group 5, namely clofazimine, linezolid and imipenem, into 15 countries), with guidelines, import assistance, funds, and whatever it takes to remove barriers, including an observational study on the removal of barriers. The second is a controlled clinical trial of new shorter, oral regimens, with 5 arms and "adaptive randomisation" to decrease the numbers needed in each arm. Results are not expected until 2020 – indeed recruitment is only anticipated to begin in 2016-17.

*Availability of Diagnostics*

Diagnosing MDR-TB is extremely difficult in resource-poor settings, where access to laboratories with sophisticated equipment can be limited. Most countries have little or no diagnostic capacity for MDR-TB. Instead, many countries rely on traditional testing methods for MDR-TB which typically take up to four months. The arrival of new, particularly molecular, rapid diagnostic technologies opened up the possibility of revolutionising TB laboratory work in developing countries. Unitaid responded with two large scale projects, EXPAND-TB and TB Xpert.

**EXPAND TB 2009-2015, $89.6 million GLI, GDF, FIND, WHO[4]**

Through EXPAND TB, twenty seven low-income and high-burden TB countries now have fully functioning laboratories, equipped with a number of new diagnostic tests, including the "line probe assay" and Xpert MTB Rif. By 2012 the number of MDR-TB cases being notified in the same countries had tripled to over 35,000 cases, compared to 2008. In 2009 alone, the contribution of the EXPAND-TB project to MDR-TB case finding was 14% of the cases diagnosed in the 27 countries and by 2012 the figure had reached 69%. EXPAND-TB has also achieved price reductions of up to 80% for diagnostic equipment and supplies through special negotiations and competitive tenders. EXPAND-TB has also provided training to more than 3000 staff to integrate the new technologies into national programmes and improve MDR-TB case detection. A hundred and one of the planned 103 state of the art Central or Reference laboratories have been established and over 100,000 MDR-TB cases were detected by the end of 2014.

[4] The EXPAND TB Project countries are: Azerbaijan, Bangladesh, Belarus, Cameroon, Cote d'Ivoire, Djibouti, Ethiopia, Georgia, Haiti, India, Indonesia, Kazakhstan, Kenya, Kyrgyz republic, Lesotho, Mozambique, Myanmar, Peru, Republic of Moldova, Rwanda, Senegal, Swaziland, Tajikistan, Uganda, UR Tanzania, Uzbekistan, Viet Nam. Currently this Project is transitioning: 13 countries have transitioned out at the end of 2014 and the remaining 14 countries will transition out at the end of 2015

**TB Xpert (2013-2015) – $25.9 m, GTB of WHO, with GDF + TB REACH**

The TBXpert Project will scale up access to Xpert MTB/RIF in 21 countries and reduce the cost of its use. Two external implementers will roll out the activities via the non-governmental and private sector. Together with the Gates Foundation and USAID, UNITAID achieved a 40 percent price reduction for the Cepheid MTB/RIF cartridges. The project will assist in timely procurement of 225 GeneXpert instruments in project sites in 21 low- and middle-income countries, utilising over 1.4 million Xpert MTB/RIF tests in 2013-2015. Through an agreement led by UNITAID, the United States Government and the Bill & Melinda Gates Foundation, the manufacturer of Xpert, Cepheid, had significantly reduced the price of diagnostic cartridges from $17 to less than $10. This price reduction allowed an accelerated roll-out of the test.

**Associated Initiatives**

Interactive Research and Design, UAE under TB REACH of the Stop TB Partnership is implementing a special private sector Social-Business model in the three countries: Bangladesh, Indonesia and Pakistan where at the respective urban centres in Dhaka, Jakarta and Karachi, patients accessing private providers will be tested using MTB/RIF. The African Society for Laboratory Medicine, Ethiopia is providing Technical Assistance to Laboratory capacity building and uptake of TBXpert Technology in 5 African countries.

### 4. GDF

The StopTB/GDF is the largest global supplier of the internationally quality assured TB medicines (first line drugs, second line drugs and paediatric forms) in the public sector and sole supplier of SLD for TB programs supported through the Global Fund mechanism. Between 2007 and 2015 GDF delivered 198,000 MDR-TB treatment courses with the estimated value of 565 million USD[5]. The GDF is also a provider of new TB medicines and products, including bedaquiline through the USAID-Janssen donation program, and delamanid, new TB paediatric and latent TB infection treatment medicines through negotiated prices and agreements with the suppliers. TB diagnostics products and equipment are also available to countries via the GDF. The GDF is a unique facility that provides procurement services to countries and programs along with technical assistance, capacity strengthening, and innovative tools for managing procurement and supply, monitoring access to medicines (Early Warning Systems), and developing rational phase-in plans for the introduction of new TB medicines and regimens.

### 5. DR-TB STAT

DR-TB STAT, an officially recognized task force of the Global Drug-Resistance Initiative (GDI) since July, 2015, continues to host monthly meetings to facilitate the introduction of bedaquiline and delamanid under program conditions. The group, which was formed in response to the "Call to Action" on new drug introduction, began meeting in May of 2015 and has reviewed the progress of new drug introduction in key countries, including South Africa, India, Indonesia, Georgia, the Philippines, Lesotho, Kenya, Swaziland, Peru and Vietnam. Multiple stakeholders have come together during the calls to help troubleshoot issues in new drug introduction. The group also produces a global "snapshot" on progress of new drug introduction.

### 6. The UNION

The Union draws from the best scientific evidence and expertise to advance solutions to public health challenges affecting people living in poverty and has a significant focus on TB among other lung diseases. The UNION managed STREAM trial compares, in a non-inferiority design, the efficacy

[5] Figures provided by the GDF manager in August 2016.

and safety of a shorter MDR-TB regimen with the locally used conventional regimen for MDR-TB in its stage 1 and a shorter, all oral, shorter MDR-TB regimens including bedaquiline in its stage 2.

### 7. WHO

WHO is clearly responsible for global policy development for MDR-TB and related laboratory policies, for monitoring and evaluation, drug resistance surveillance, and the rGLCs. There is general appreciation across the stakeholders interviewed for WHO's work in these areas, with the exception of the four rGLCS that are felt to be less effective. The reasons why two are perceived to be effective relates mostly to the individual members of the secretariat who in EURO and WPRO appear to have the energy and the time to carry out the tasks successfully.

### Other research

Several controlled clinical trials are underway to test new drugs and new regimens. Research into new diagnostic tests has expanded in recent years. Vaccine research remains difficult and complex, while there are still no clear ways of identifying potential effective vaccines prior to testing them in costly and time-consuming clinical trials.

## Annex 3. Stakeholder analysis within the MDR-TB field

The following are actual quotations, or annotated statements from the stakeholders interviewed by the consultant between 12th December, 2015 and January 6, 2016, arranged in the form of a SWOT analysis.

**Strengths**

- Networks are necessary and appreciated by a number of stakeholders. "Our work would go even better if GDI was bigger." A network like GDI is definitely needed. It certainly shouldn't fold up.
- "Can GDI relieve obstacles (at country level)?" The answer is "Yes", since that is what DR-TB STAT has achieved. But there are few other examples.

**Weaknesses**

- MDR-TB is in crisis. We have no underlying global plan that's convincing for MDR-TB. "The TB community is not enthusiastic enough and moves too slowly."
- Expansion of DR treatment programmes is not conducted with sufficient quality, and this is extremely worrying. WHO could do much more to ensure quality of programmes.
- It is staff ability and drive that is limiting progress. Treatment success is low and gives rise to the question from managers, "Why invest in such a low success?" Advocacy is needed to change the mind-set of programme staff, technical assistance is essential for increasing rates of diagnosis and treatment, through planning, better implementation, monitoring, and should be tailored for countries' needs.
- The same vigour we saw in the introduction of Xpert MTB/RIF to countries is missing in GDI. But Xpert MTB/RIF was a simpler problem. Perhaps MDR-TB is just too indigestible.
- The rGLC mechanism needs to change to become more demand-based, and more supportive to expansion, rather than simply monitoring progress since the last mission. Quality of TA is low at present – there is insufficient follow-up from the rGLC missions, which have too little impact. With some exceptions in EURO and WPRO, rGLC performance is generally low, and value for money is not being achieved. The nature of TA needs to change. Stronger mechanisms are needed but countries are insufficiently engaged in thinking through the demand driven approach. We need a stronger mechanism to follow up on monitoring recommendations; more clinical training is needed, especially for new drugs, and needs to be better structured and planned. Countries are not budgeting enough for TA for PMDT and are not getting sufficient TA.

These needs should be in NSPs, but often are not. rGLCs need to be stronger – an active secretariat is the key – and improve their planning and selection of the committees.

- There is confusion about the identity of GDI and of WHO. When WHO acts, is it acting as part of GDI or as WHO? Opinions are divided as to whether the rGLCs are a part of GDI, although the large funding agencies, the Global Fund and USAID, certainly think they are.
- Very little is happening with the private sector (even though GDI's mandate is clear that it should be engaging with the private sector to promote MDR-TB care and treatment). NTPs seem very scared of working with private sectors – WHO needs to do more to push them. You can't imagine the HIV world would accept countries not introducing life-saving new drugs.
- The GeneXpert is still too complicated and countries are reluctant to use it even though it is essential if they are to reach their targets.

**Threats**

- The GLC mechanism is at risk because the GF/WHO agreement needs revision at the end of 2016. The GF will certainly focus thereafter on higher burden countries and ignore countries with tiny numbers of MDRTB patients. Performance based payments are likely. If TA in general, and the GLC mechanism in particular, cannot be improved, there is a risk of reduction in support from the Global Fund.
- It takes time to lay the foundations for MDR-TB management at country level. It is easier to diagnose than to treat MDR-TB. There are concerns that management in the community may not work –with 31% case fatality in community treatment in South Africa (HIV may be the main cause). 50% treatment success is not good enough and is not sufficient to attract funds. There are insufficient treatment sites and access by patients is difficult for them.

**Opportunities**

- WHO should be stronger with the rGLCs, and push them more strongly to get existing policies implemented. Whatever GDI does, WHO needs to back it strongly.
- GDI could provide a change of direction by discussing what TA works and what does not; how TA can and should change (improving quality of TA and making GLC support more demand driven and focused on support rather than simply monitoring) and developing a mechanism for how the quality can be improved (BAU will not work). TA for PMDT needs to be aligned with support for TB in general. Peer review of consultant reports would help improve quality. The GF is willing to support regional training of consultants.
- GDI could do much more to push the introduction of new drugs at country level.
- The world needs leader countries that show good results with MDR-TB treatment, perhaps through establishment of centres of excellence. It is clinical capacity that is mostly lacking and this could be addressed by increasing TA, just as was done for laboratories through Expand TB and TB Expert. Even more support is needed for PMDT because it is so difficult. Donors, rightly, want consultants trained in countries, and therefore the TA would be for local training. Generic training modules would be helpful.