BD Global Public Policy Position

Diagnosis and Treatment of Tuberculosis (TB)

for Effective Patient Care and Control of Antibiotic Resistance

ISSUE: Accurate diagnosis of tuberculosis (TB) and identification of clinically appropriate treatment is essential to effectively treat patients, prevent the spread of the disease, and limit the occurrence of drug-resistant strains that threaten public health worldwide.

TB is a highly prevalent and serious infectious disease that affects millions of people worldwide and threatens global health security due to the spread of drug-resistant strains. One in three people in the world is infected with *Mycobacterium tuberculosis*, the organism that causes TB, and TB is the second leading infectious disease killer of adults in the world.\(^1,2\) In 2010 alone, there were an estimated 8.8 million new cases of active TB worldwide.\(^3\) Unfortunately, only a few drugs are effective in treating TB, so as drug-resistant strains spread, it is imperative that TB is diagnosed accurately and drugs are used appropriately. To combat drug-resistant TB, government and non-government organizations (NGOs) should implement TB policies and programs that focus on: 1). effectively treating patients, 2). preventing the further spread of the disease, and 3). limiting the spread of drug resistance over a long-term basis. Appropriate use of complementary diagnostics is an essential component to each of these objectives.

POSITION: Tuberculosis (TB) treatment and control programs should focus on accurate and timely diagnosis, identification of clinically appropriate treatment, and patient monitoring and follow-up. Each of these goals is essential to save lives and reduce the spread of drug-resistant TB. Policies and programs should include the following guiding principles to achieve this:

1. **Focus on controlling TB drug resistance for the patient and for the public.**
   Drug-resistant TB is spreading globally, creating a threat to public health and urgency for accurate diagnosis to ensure proper treatment.
   - If used correctly, drug treatment and diagnostic technologies can have a positive impact in reducing the impact of TB on patients and public health.
   - When diagnostic tests are not used to identify the drugs that are effective against a patient’s strain(s), ineffective treatment may be prescribed, leading to drug resistance which is harmful to the patient and endangers public health.

2. **Use of appropriate and complementary diagnostics based on protocols.**
   TB control programs should use complementary diagnostic technologies, including liquid-based culture and molecular diagnostics, to:
   - Accurately and quickly diagnose patients with active TB
   - Identify drug resistance early

\(^1\) in accordance with WHO and other recognized guidelines
• Identify treatment regimens that are clinically appropriate based on diagnostic testing,
• Monitor patients until they are cured.

TB is a complex disease for which the method of diagnosis, the selection of drug treatment, and the monitoring of the patient during treatment vary depending on the risk status of the patient, the effectiveness of individual drugs on particular strains of TB, and the available resources. There is no single technology that exists today to address all TB diagnostic needs.

Programs should reference well-established and recognized international guidelines and protocols, such as those from the World Health Organization (WHO), that stratify patients based on risk factors. This is particularly important for patients with HIV/TB co-infection and those at risk of drug-resistant TB.

3. **Continued research into new diagnostic technologies and therapies.**
As a result of globalization and greater mobility of people worldwide, the impact of drug resistant strains of TB effects people in nearly every country. To combat this, governments should continue to fund TB control programs and research into new drugs and diagnostics. Public and foundation funding, along with public-private partnerships and collaborations, are critical to these efforts. Stakeholders from various communities play an important role in product development, education, awareness, and access to diagnostics and therapies.

While important innovations in TB diagnosis have been implemented in high-burden countries, (such as liquid-based culture and molecular diagnostics), additional funding and research is needed to develop better and more rapid point-of-care diagnostics that are appropriate for settings with limited resources. Research into new therapies, particularly those for use against resistant strains, is also needed.

4. **Strengthening laboratory capacity to diagnose drug-resistant TB and support drug resistance surveillance.**
Efforts to treat and control TB in many developing countries are hampered by insufficient laboratory capacity to diagnose drug-resistant TB and undertake drug resistance surveillance. Improvements in laboratory and healthcare facilities are needed to ensure the proper continuum of care – including correct and accurate diagnosis and monitoring, ensuring medicines are used appropriately and reach those in need. Infrastructure will vary across health systems and there will remain a need for different technologies appropriate for different healthcare settings.

5. **Evolution of policies and programs as new technologies become available.**
Policies and algorithms for diagnosis, disease monitoring, and treatment should evolve as new technologies become available and as the patterns of TB drug-resistance evolve.
BACKGROUND:

Tuberculosis (TB) is a deadly and infectious disease caused by the bacteria *Mycobacterium tuberculosis*. The disease is spread through airborne transmission of the bacteria from one human to another. Though it primarily affects the lungs, TB can attack any organ in the body.

TB is a serious threat to public health worldwide. TB is:

- the second leading infectious disease killer of adults in the world
- the third leading global cause of death among women aged 15 to 44, and
- the fourth leading killer of young girls in low-income countries.\(^4,5\)

In 2010, an estimated 8.8 million new cases of TB were reported and 1.4 million deaths were attributed to TB worldwide. This represents 3,800 deaths due to TB per day worldwide.

In many countries, there is a strong correlation between TB and HIV/AIDS, and co-infection with both diseases is common. TB is the leading cause of death among people living with HIV/AIDS in the developing world and is responsible for one in four AIDS-related deaths. People with diabetes also appear to be at higher risk for TB, although the reasons for this are not yet completely understood.\(^6\)

While the prevalence of TB is highest in certain regions, the infectious nature of the disease combined with the spread of drug-resistant strains makes it a public health threat to all countries.

In addition to the tremendous impact to human health, TB has a devastating economic impact on families, communities, and countries. TB drains $16 billion from the annual incomes of the world’s poorest countries and will cost these countries an estimated $1 trillion to $3 trillion over the next ten years. In some countries, the loss of productivity attributable to TB approaches 7% of GDP.\(^7\) TB is a disease of poverty that affects mostly young adults in their most productive years. The average TB patient loses three to four months of work time and up to 30% of yearly household earnings. Entire families suffer when one member has the disease. For example, in 2009 an estimated 10 million children were orphaned as a result of parental deaths caused by TB.\(^8\) In India an estimated 300,000 children drop out of school each year to care for relatives with TB.\(^9\)

Investing in the treatment and control of TB is not just a humanitarian imperative, but a sound public health and economic policy. It is essential to reduce the spread of drug-resistant TB, and investments in TB control efforts can reap benefits that equal up to nine times the costs.\(^10\)

Drug resistant TB is a growing threat to global public health.

A particularly alarming aspect of TB is the rise of drug-resistant strains, in which the bacteria have developed a resistance to treatments. There are a limited number of drugs available to treat TB, but this arsenal is even more limited with a growing number of cases that are resistant to many or all of the available therapies. All cases of TB are challenging to treat, but drug-resistant cases are even more difficult to treat, are more costly, and have lower success rates. While the overall rate of new TB cases has shown a slight decline in recent years, the WHO has determined that diagnosis and appropriate treatment of drug-resistant TB continues to be a serious threat to public health.

It is believed that the majority of multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) cases are undiagnosed. This means patients are not receiving adequate treatment, which contributes to the spread of drug-resistant TB. The WHO estimates that only 16 percent of the
estimated number of MDR-TB cases are treated according to internationally recognized standards.\textsuperscript{11} This extensive gap in diagnosis and proper treatment is contributing to the spread of drug-resistant TB. Therefore, accurate diagnosis of TB and identification of the appropriate therapeutic regimen is an imperative for the health of individual patients, the effective use of scarce health resources in high-burden countries, and global public health security.

Some alarming statistics on drug-resistant TB include:

- XDR-TB cases have been confirmed in 58 countries and in all continents except Antarctica.\textsuperscript{12}
- The WHO estimates that in 2010 there were 650,000 prevalent cases of MDR-TB globally.\textsuperscript{13}
- Among all incident TB cases worldwide, 4% are estimated to have MDR-TB, but there is a large range across regions. The proportion of MDR-TB among new and previously treated cases is reported as high as 28% and 62%, respectively, in some regions.\textsuperscript{14}
- The mortality of MDR-TB and XDR-TB is extremely high. In the United States, the Centers for Disease Control (CDC) reported that 25% of XDR-TB and 19% of MDR-TB patients died within one year of diagnosis.\textsuperscript{15} Mortality rates in developing countries are much higher, with one study showing mortality in South Africa from MDR-TB and XDR-TB 71% and 83%, respectively.\textsuperscript{16}
- The true magnitude of drug-resistant infections is unknown due to a lack of surveillance. Reliable data on patterns of drug resistance are not available for 41% of countries, so global estimates have to be based on models rather than accurate surveillance data.\textsuperscript{17}

Complementary diagnostics are essential for effective TB treatment and control.

TB treatment and control begins with the accurate diagnosis of infected patients and their placement on the treatment regimen appropriate for the drug-sensitivity of the infecting strain. It is critical that patients are placed on the most appropriate regimen early after diagnosis to ensure the best chance of patient recovery and to control drug-resistant TB. Inaccurate diagnosis and incorrect or incomplete treatment regimens can result in patients not being helped and drug resistance spreading. Therefore, it is essential that policies directed to TB treatment and control incorporate the appropriate use of diagnostic technologies to ensure:

1. Accurate and timely diagnosis of patients.
3. Identification of clinically appropriate therapeutic regimens.

No single diagnostic technology available today can accomplish all of this. The WHO recognizes the need to use complementary diagnostic technologies and states,

“none of the existing TB diagnostic tools are mutually exclusive and they can be implemented in various combinations in country screening and diagnostic algorithms, which are highly setting and resource specific.”\textsuperscript{18}

To guide policymakers as they incorporate the different diagnostic technologies into their policies and programs to treat and control TB, the WHO and other bodies have developed algorithms for the use of diagnostics. Many high-burden settings use diagnostics appropriately and in a manner consistent with
Effective treatment and control of TB and the spread of drug-resistance requires complementary diagnostics because the each diagnostic available today has limitations. The WHO and other bodies have developed algorithms to guide the use of diagnostics. Some of the factors that must be considered in determining which diagnostic technology to use at a given time include:19,20

- Ability to guide treatment decisions, including drug sensitivity testing (DST) to identify drug-resistant strains
- Ability to detect both pulmonary and extra-pulmonary TB, the latter of which accounts for an estimated 10–20% of active TB cases
- Utility in monitoring patients’ response to treatment after initial diagnosis
- Resource setting and position in the tiered health system
- Risk status of the patient for HIV or MDR-TB
- Time required for results of diagnosis
- Age of patient

Culture diagnostics are essential to monitor antibiotic treatment and reduce drug resistance.
It is important to identify treatment failures accurately and quickly in order to effectively treat patients and reduce transmission of drug-resistant TB to others. Liquid culture provides results weeks faster than solid culture and has superior sensitivity.

After the initial diagnosis and identification of the appropriate treatment regimen, patients need to be monitored to ensure the treatments are working and the regimens are adjusted as needed. Monitoring will also ensure compliance to therapeutic regimens. This is a critical step in TB treatment and control. Inappropriate use of therapies that are not effective in a specific patient promotes further drug resistance. This has a direct impact on the individual patient as well as global public health.

Some diagnostic technologies that may be useful in providing an initial diagnosis do not provide information needed for monitoring patients over the course of treatment. Presently, culture diagnostics are necessary for the effective monitoring of patients. Rapid molecular diagnostics that may provide an initial diagnosis are not capable of distinguishing between the presence of viable and non-viable *M. tuberculosis* in patients.

Patients must be monitored to ensure compliance with regimens and to ensure treatment regimens are working, and adjust them as needed. Lack of effective monitoring promotes the spread of drug-resistant TB. Presently, culture diagnostics are required to effectively monitor drug-resistant patients. It is critical to identify treatment failures and adjust regimens quickly in order to control the further spread of drug-resistant strains.
Research into new diagnostics and therapies is needed. There are a number of tools available for the diagnosis, treatment, and prevention of TB, and it is essential that policymakers make the best use of these available technologies. Liquid-based culture and molecular diagnostics are two important innovations that are available for the diagnosis of TB. While they have been implemented in many high-burden settings, additional use, consistent with recommended algorithms and protocols, is needed to control this disease. However, there is also a strong need for additional research and development of diagnostic solutions that are efficient and sustainable for resource-limited settings. Two examples of areas for further development are research into biomarkers and the development of more rapid point-of-care diagnostics.

Research and development of new therapeutics, particularly those for use against resistant strains, is also needed. The treatments available today require long, complicated and toxic regimens that are prone to lapses in adherence. The arsenal of drugs available against MDR-TB and XDR-TB is extremely limited. A more effective vaccine that can be implemented in the developing world is another current critical gap in effective TB prevention and control.

The increase in drug resistance in today’s mobile society impacts all countries, and developed countries should continue to prioritize policies and resources to control the spread of TB. The research and development that is needed will require collaboration among governments, NGOs, and industry. Public and foundation funding, along with public-private partnerships and collaborations, are critical to adequately support the needed research and product development. Stakeholders from different communities play an important role in product development, education, awareness, and ensuring access to diagnostics and therapies.

Lab strengthening is critical for effective TB treatment and control. Laboratories play a central role in patient care and surveillance. Unfortunately, the capacity of labs to deliver the quality-assured diagnostic services needed for effective treatment of control of TB – and particularly the growing threat of drug-resistant TB – is severely limited. The WHO reported in 2009 that “arguably the weakest component of health systems, laboratory services have historically been grossly neglected and underfunded.” Strengthening of quality lab infrastructure is essential to ensure that the most appropriate diagnostics, including liquid culture and rapid diagnostics as outlined in treatment algorithms, can be implemented into TB treatment and control programs. This is a prudent investment because the strengthening of quality laboratory capacity could have benefits well beyond improved TB diagnosis. With strong planning and careful integration, these investments could be made in a way that bolsters overall lab capacity for many infectious and chronic diseases in resource-poor settings.
Everyday, TB is Becoming More Drug-Resistant

There are two ways in which drug-resistant TB occurs and spreads. The first is when a strain of TB that was susceptible to drugs develops resistance during the course of treatment. This can occur if the patient takes the medication inconsistently, if drugs become unavailable during treatment, or if clinicians fail to prescribe an effective treatment regimen. The second way drug resistance spreads is when a patient infected with drug-resistant TB directly infects another person. Both of these paths demonstrate the urgency of accurate diagnosis, identification of appropriate treatment regimens, and patient monitoring.

The scourge of drug-resistant TB, caused by improper diagnosis and treatment

**Drug-susceptible TB:** The two most powerful first-line TB drugs are isoniazid and rifampin. TB that is sensitive to these drugs can be effectively treated by them, in conjunction with other drugs, although the regimen can take six months. Patients must be monitored for effectiveness of and adherence to treatment.

**Multidrug-resistant TB (MDR-TB):** MDR-TB is a form of TB that is resistant to the two most powerful first-line TB drugs: isoniazid and rifampin. Treatment for MDR-TB requires drugs that are more toxic and cost 50 to 200 times more than standard TB medicines. They must also be taken for 18 to 24 months. Unfortunately, the availability of these drugs is often limited in resource-poor countries.

**Extensively drug-resistant TB (XDR-TB):** XDR-TB is resistant to almost all drugs, including the two main first-line drugs, the best second-line drugs (fluoroquinolones), as well as at least one of three injectable drugs (amikacin, kanamycin, or capreomycin). XDR-TB develops when MDR-TB is not adequately treated and second-line drugs are misused or mismanaged. It can also be directly transmitted from person to person, which frequently occurs in HIV+ patients. The treatment options for XDR-TB are extremely limited and involve toxic and expensive drugs that must be taken for 18 to 24 months. A single case of XDR-TB can cost $600,000 or more to treat, and even then a cure is not guaranteed.
Complementary Diagnostics are Required for TB Control and Treatment

Although there have been significant advances in TB diagnostics, the most widely used diagnostic for active TB is still one that developed over 100 years ago. In this test, known as direct sputum smear microscopy for acid-fast bacilli (AFB smear), a patient’s sputum is collected and then analyzed under a microscope. If *M. tuberculosis* is detected in the patient’s sputum using this methodology, he or she has active TB and is infectious. However, the test has poor sensitivity and an accurate positive result from an infected patient requires that the patient produces a significant amount of bacilli in his or her sputum. Therefore, patients who may actually have an active TB infection may receive a false negative from the smear test. Overall, smear microscopy can at best detect around 45–60% of people who have active TB.

Smear microscopy has severe limitations in accurately diagnosing TB

*Overall, smear microscopy – a test developed over 100 years ago – can at best detect 45–60% of cases of active TB. The effectiveness of is even more limited in patients co-infected with HIV and TB, with the test failing to detect as many as 80 percent of all HIV-associated TB cases.* This test is also usually unable to detect extrapulmonary TB (TB infection outside of the lungs), which is more common among HIV-infected patients and represents an estimated 10 to 20 percent of all TB cases. The accurate detection rates in children are even lower – estimated to be only 5% – because children aren’t able to cough up sputum samples with detectable levels of bacteria. Significantly, the smear test cannot distinguish between drug-susceptible TB and drug-resistant TB.

There are advanced diagnostic technologies available, such as liquid culture and some types of molecular testing that are regarded as the current international gold standard for TB diagnosis. These technologies each provide important and different advantages over the smear test for diagnosis. Of extreme importance to both individual patients and global public health, liquid culture can detect and distinguish drug sensitivity, and it is an essential tool for accurately diagnosing MDR-TB and XDR-TB.

Liquid culture is a critical tool in accurately diagnosing TB and identifying MDR-TB and XDR-TB

*Liquid culture provides several significant improvements in TB diagnosis over the use of the smear test alone. Liquid culture provides a higher degree of sensitivity than the smear test, so many patients that may receive a false-negative through a smear test, including HIV/TB co-infected patients and children, can more accurately be diagnosed through the use of liquid culture.* Of extreme importance to both individual patients and global public health, liquid culture can detect and distinguish drug sensitivity, and it is an essential tool for accurately diagnosing MDR-TB and XDR-TB. It is particularly valuable in determining which drugs can be used to effectively treat these patients. Liquid culture can also detect extra-pulmonary TB.

Molecular tests can be used in high-risk populations to provide a rapid screening of patients with suspected pulmonary cases of MDR-TB or co-infection of HIV/TB. These tests can often be conducted at the district or sub-district level, which provides an opportunity to move TB diagnostic technology lower down the health system tier. Because these tests can provide results within a few hours, they enable patients that fit the criteria above to be diagnosed and, if the diagnosis indicates drug-sensitive TB, placed on the appropriate regimen during one visit to a healthcare clinic.
However, molecular tests also have limitations. Importantly, molecular tests do not provide a complete analysis of drug resistance. None of the available molecular tests today can detect XDR-TB, and the newest rapid test can detect resistance to one – but not both – of the first-line drugs. (Resistance to rifampicin can be detected; resistance to isoniazid cannot.) Reflex testing by culture is required to obtain the full critical information of drug resistance to ensure a patient is placed on the appropriate, effective regimen.
References:

7 http://www.gbchealth.org/our-work/health_focus_areas/tuberculosis/
18 WHO....

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