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Diagnosing Inaccuracy: New WHO Policy Shift to End Ineffective TB Practices

An Interview with Dr. Mario Raviglione

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On July 20, 2011, the World Health Organization (WHO) announced a recommendation to ban active tuberculosis (TB) blood tests. This policy statement marked the first time that the WHO has urged an end to a commonly used practice in TB diagnosis.

NBR spoke with Dr. Mario Raviglione, Director of WHO Stop TB Department, to learn more about the reasons behind this recommendation and the state of TB in the world today. Dr. Raviglione was a delegate to the 2009 Pacific Health Summit on multidrug-resistant tuberculosis (MDR-TB), for which NBR continues to be the Secretariat. This interview is part of a series of Expert Interviews that NBR is conducting on past Summit themes and was published on the NBR website: www.nbr.org.

As Director of the WHO Stop TB Department, Dr. Mario Raviglione oversees global and country-specific strategies for TB diagnosis, treatment, and monitoring. A respected and influential leader in the epidemiology and research of TB, he has established and overseen numerous TB surveillance projects worldwide. Dr. Raviglione is a physician with specialties in internal medicine and infectious diseases.

Two types of tests are used to help diagnose active TB infection—a skin test and a blood test. The WHO's July 20, 2011 recommendation to end active TB blood tests marks the first time that the WHO has instituted a "negative" policy recommendation in the TB field. Can you explain this momentous recommendation and the reasoning behind the WHO's timing, as well as what catalyzed the study on the effectiveness of TB blood tests in the first place?

Indeed this was an extraordinary normative decision. We at the WHO have been aware since the mid-2000s of the use of serological [blood] tests for *active* TB disease in some highly endemic countries—note that we are not talking here about the blood tests for *latent* infection, known as IGRAs [Interferon-Gamma Release Assays].[1] More recently, reports in India indicated, for instance, that over one million such blood tests for active TB were being used annually. The literature on these tests has always been rather controversial. Thus, also considering data from other reviews that appeared in 2007, we decided it was time for the WHO to examine the issue in detail.

We commissioned a systematic review of all literature related to some 18 serological tests produced in countries such as Australia, France, Germany, Italy, the UK, and the U.S., as well as India and China. The

[1] People with latent TB do not manifest symptoms of the disease. They are carriers of TB but cannot infect others. For more information, see "The Difference between Latent TB Infection and Active TB Disease," http://www.cdc.gov/tb/publications/factsheets/general/LTBIandActiveTB.htm.

review revealed that these blood tests, often not even approved for use by national authorities in their countries of manufacturing origin, are on the whole inaccurate and a true waste of time—in one out of two cases, they have been shown to produce false results. These tests may not be able to detect TB when a patient has an active disease, or they may tell you that there is TB present when in fact there is not.

The unreliability of these tests is a serious risk for any person subjected to them, as the result is that some people will not be treated for TB when they need it while others may receive treatment when they do not. In addition, we are aware that these tests are used mainly in countries' private sectors; no national program that we know of recommends them. Essentially, this means that poor people are asked to pay USD $10-30 for a useless test.

At WHO, we considered the full evidence, assessed all of these points, exposed the results of the assessment to our advisory committees, got the recommendation to make them public for the sake of the poor people affected by TB, and informed the world that it is time to abandon the use of these inaccurate tests for TB.

According to the WHO, TB blood tests are often found in countries with "weak regulatory mechanisms for diagnostics."[2] Where specifically are blood tests for active TB most commonly used? In light of the recommendation, what do you see as implications for on-the-ground diagnostic and treatment practices, particularly in Asia, where 55% of the world's estimated TB cases occurred in 2009?[3]

The WHO will soon publish a study on the countries in which we know these inaccurate tests are used. They include India, as well as 17 of the 22 highest TB burden countries worldwide. The Indian Government, via its Ministry of Health and Family Welfare and the Revised National TB Control Program that directs the country's national TB program, has already informed doctors and practitioners in its system about the WHO recommendations through an unprecedented circular message. In order to stop this malpractice, it is also necessary for professional associations to help with the dissemination of the information among their members. It will also require, in some cases, a decisive move by the governments officially banning the use of these tests.

I want to make sure that people understand that this is not an action against the biological and diagnostics research industry. Rather, it is our moral responsibility to ensure that the people with TB around the world can receive the best practice of care. We would like to appeal to the companies producing these tests to stop selling inaccurate diagnostics. Ultimately, this is a good opportunity to continue investing in research for better and reliable tests that everyone will want.

Regarding on-the-ground practices, I think that international WHO-approved recommendations on both the diagnosis and treatment for TB are clear. National programs have adopted them virtually everywhere; the challenge remains that of engaging private practitioners in such a way that bad practices end while international standards of care—ones that exist and are published—are adopted universally.

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[2] "WHO warns against the use of inaccurate blood tests for active tuberculosis," World Health Organization, Press Release, July 20, 2011.

[3] Global Tuberculosis Control 2010, World Health Organization, 7, http://www.who.int/tb/publications/global_report/2010/gtbr10_main.pdf.

Southeast Asia carries one-third of the global burden of TB and is the only region of the world where the TB incidence rate is not falling.[4] Why is TB prevalence so high in Asia, and what practical issues impair prevention? What policies or actions might help reverse this trend?

Southeast Asia has an incidence curve that remains flat. It has remained that way for many years. Other regions, however, including Africa, are nowadays showing a slight decline in incidence. Like you noted, TB is still rampant in Asia, with millions of new TB cases yearly. The underlying reasons for the continuing high TB incidence on the Asian continent are linked to the classical factors and determinants, all under the poverty umbrella: poor nutrition, inadequate housing, poor access to health services, the cost of care, and then smoking, HIV infection, growing rates of chronic diseases like diabetes, etc.

At the WHO, we recommend that TB be fought on four fronts. First, countries must have effective TB programs that are capable of preventing transmission by detecting cases as early as possible, so that contagiousness is minimized, and treating cases properly. The quality of programs varies by country.

Second, without a proper health system and good accessible services, no TB program will ever function well. For instance, if we charge the poorest people for diagnosis or, worse, treatment, we cannot pretend to save the world from TB. The poorest among the poor who get TB do not have the financial resources to take on the expenditures linked to diagnostics, and the subsequent treatment—the drugs, transport to the clinic or hospital, home care visits by a doctor, etc. In fact, in some countries, mainly in Africa, the cost of diagnosis exceeds the annual income of an entire family. Additionally, without a system of laboratories able to use the most modern rapid technology and without proper infection control practices in public settings and community clinics, we will always have problems with TB.

Fourth, the social and economic factors that cause ill health and TB must be alleviated: This is a big picture issue as it entails interventions for poverty, bad housing, nutrition, education, etc., that are beyond the reach of the health community alone.

As for the rest of the world, we need to continue supporting and investing in research for new more effective tools to prevent, diagnose, and treat TB.

As you know, the 2009 Pacific Health Summit addressed focused on Multidrug-Resistant TB (MDR-TB)[5]. What progress or new developments have you seen since the Summit for both TB and MDR-TB?

I would say that the 2009 Summit did a great deal to help define the big research agenda for TB and MDR-TB. One of the outcomes, I believe, was the creation of the proper basis for discussions among pharma companies that resulted in the establishment of the visionary project called CPTR, which stands

[4] "TB in Southeast Asia," Regional Office for Southeast Asia, World Health Organization, http://www.searo.who.int/en/Section10/Section2097/Section2100_10639.htm.

[5] Multi-drug resistant tuberculosis (MDR-TB) is a strain of TB that does not respond to first-line treatment of the disease; thus it is resistant to certain TB drugs.

for Critical Path for TB Treatment Regimens.[6] If this project succeeds, we may have not only new drugs, but brand new regimens ready to go into clinical use within years rather than decades.

In addition, the 2009 Summit definitely called attention to the big issue of MDR-TB. Unfortunately, we have too few such high-level events on TB, and attention tends to wane without them. In many countries, we have seen some progress, but we are far from a satisfactory level of care for the nearly half a million MDR-TB cases that we estimate emerge annually.

The best development we have seen in the past few years is the appearance of a new rapid molecular test for TB, the one called Xpert, which can detect TB and rifampicin[7] resistance, as a proxy for MDR-TB, within 100 minutes. We are now supporting country efforts to introduce this new technology and we predict that some 35 countries may have it before the end of this year.

Treatment for MDR-TB is much more difficult and costly than for standard TB. India and China are among the world's top five countries where MDR-TB cases occur.[8] What strategies or policies are currently being deployed to control and treat MDR-TB in these settings? How significant of a threat is MDR-TB compared to standard TB?

India and China alone may account for some 40% of the global burden of MDR-TB. Both countries are moving to address this issue, but not fast enough to face the roughly 100,000 cases that emerge every year in each. Their governments must move faster in all fronts, or else the response globally will be slow. MDR-TB is difficult to diagnose, and even more difficult to treat, requiring expensive, toxic, less potent, and rare drugs. The treatment we have today itself lasts a minimum of 18 months. The care threat is therefore huge: it is difficult enough to treat normal TB within six months, and one can imagine how much more difficult it must be to deal with MDR-TB.

All countries should adopt, as quickly as possible, modern rapid diagnostics that allow immediate detection of MDR-TB and therefore facilitate immediate proper treatment regimens. Without rapid tests, there will be little progress.

Drugs also remain a challenge. Some are still rare agents, expensive, and often not in sufficient quantity worldwide. If this year we could detect all of the cases that we estimate exist, instead of the only 10-15% that are normally detected, then we would be in serious trouble to treat them, as the production of second-line drugs for MDR-TB is simply insufficient. I think we have not yet succeeded in convincing manufacturers to produce them in sufficiently large quantity. This is a vicious cycle, as the manufacturers' response is that today there is no market, in view of the insufficient detection of MDR-TB cases. Thus, we truly need to diagnose more patients, create the market, and insist on the increased production of quality drugs. The challenges then are those I mentioned already: a response depends on the health system and the services available, and success depends in large part on free services to the poor. The alternative is failure.

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[6] For more information on CPTR, see http://www.c-path.org/CPTR.cfm.

[7] Rifampicin is an antibiotic also known by its drug name Rifampin. Taken in pill form, Rifampin destroys TB bacteria within the body. For more information, see http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682403.html.

[8] "2009 Update: Tuberculosis Facts," Stop TB Partnership and the World Health Organization, http://www.stoptb.org/assets/documents/resources/factsheets/tbfactsheet_2009update_one_page.pdf.

Looking ahead five to ten years, do you think a new TB vaccine is finally within our reach? What changes might we see regarding management and treatment models of TB? How has the UN Millennium Development Goal (MDG) that calls for halting the spread of TB by 2015 impacted the field?[9]

With regard to the MDGs, the un-ambitious goal of reducing TB incidence was already reached as of a few years ago, and incidence has been declining worldwide since 2004. The problem is that incidence is falling at a rate of less than 1% per year, which means that a century from now, there will be a pretty flat line in our period of time, rather than one that represents a significant decline.

In all frankness, I do believe that our basic understanding of the pathogenesis and immunology of TB is still insufficient to guarantee that we will really have an effective vaccine at hand in five to ten years. At the moment, there are about 12 vaccines in the pipeline for development, some in advanced trial phases. However, most are just better BCGs[10]—the relatively ineffective vaccine for TB that is used today. I find it hard to believe that we will have an effective new vaccine that truly allows elimination within a decade. In order to get a more effective vaccine, we need to revolutionize our knowledge on the immunological response to TB. This is why we need to invest even more on research and vaccinology if we want to succeed.

At the same time, the more feasible solution to TB, at this point, is still an effective diagnostic: simple, rapid, and applicable at the bedside, at the point of care. If we could screen all coughers and detect TB within a minute, we would surely be more effective in cutting transmission and reducing contagion. This step will be the first one towards elimination, as we will spare young generations from latent infection, i.e., being a carrier, and therefore save them from future active disease.

Once we have a case diagnosed, then a shorter treatment period will surely help, and this time reduction requires new drugs and new regimens. I am concerned when I hear from the pharma industry that the new MDR-TB drugs that might appear in the market in the next few years may not be tested as drugs for normal TB. Doing so requires investments in clinical trials, and not many are willing to pay.

I am also concerned when I hear some saying that the golden decade for a resurrection of TB research has come to an end. We are not yet there. We still do not have a point-of-care test. We still do not have a new drug out there, let alone a vaccine. If efforts are not consolidated, we would have wasted another opportunity for a resolute attack on TB.

[9] "Goal 6: Combat AIDS, malaria and other infectious diseases," Millennium Development Goals, United Nations, http://www.un.org/millenniumgoals/aids.shtml.

[10] For more information, see "Facts about Bacille Calmette Guerin (BCG) Vaccine," Seattle and King County Public Health, http://www.kingcounty.gov/healthservices/health/communicable/TB/bcgvaccine.aspx.