Summary of the Sixteenth Meeting of the
International Task Force for Disease Eradication (II)
January 12, 2010

The Sixteenth Meeting of the International Task Force for Disease Eradication (ITFDE) was convened at The Carter Center from 8:30am to 3:30pm on January 12, 2010 to discuss tuberculosis. The Task Force Members are: Sir George Alleyne, Johns Hopkins University; Mr. Ekkehard Betsch, The World Bank; Dr. Stephen Blount, Centers for Disease Control and Prevention (CDC); Dr. Mickey Chopra, UNICEF; Dr. Donald Hopkins, The Carter Center (Chair); Dr. Adetokunbo Lucas, Harvard University; Professor David Molyneux, Liverpool School of Tropical Medicine (Rtd.); Dr. Mark Rosenberg, Task Force for Global Health; Dr. Lorenzo Savioli, World Health Organization (WHO); Dr. Harrison Spencer, Association of Schools of Public Health; Dr. Dyann Wirth, Harvard School of Public Health; and Dr. Yoichi Yamagata, Japan International Cooperation Agency (JICA). Eight Task Force members (Alleyne, Betsch, Blount, Hopkins, Lucas, Rosenberg, Spencer, Wirth) attended this meeting, and one was represented by an alternate (Dr. Mario Raviglione for Savioli).

The presenters on tuberculosis were Dr. Jose Becerra and Dr. Kevin Cain of the Centers for Disease Control and Prevention, Dr. Megan Murray of the Harvard School of Public Health, and Dr. Mario Raviglione of the World Health Organization. A representative from the Foundation for Innovative New Diagnostics (FIND) was unable to attend.

Tuberculosis

In 2008, there were an estimated 9.4 million cases of tuberculosis globally, including 1.4 million cases of HIV-associated tuberculosis, and 1.8 million deaths, including 0.52 million deaths in HIV-infected patients. In the same year, there were an estimated 0.5 million cases of multidrug-resistant tuberculosis (MDR-TB: strains resistant to, at least, the two most important first-line drugs isoniazid and rifampicin) with at least 0.15 million associated deaths, as well as about 50,000 cases of extensively drug-resistant tuberculosis (XDR-TB: resistant to first- and second-line drugs) and at least 30,000 associated deaths. Drug-resistant tuberculosis strains, including XDR-TB, have been found in every country where they have been sought.

Approximately 85% of all tuberculosis cases are located in the South East Asian (34%), African (31%) and Western Pacific (20%) Regions of WHO, with the remainder in the Eastern Mediterranean (7%), European (5%) and American (3%) Regions. Cases of MDR-TB are especially numerous in nations of the former Soviet Union, India and China, while 80% of TB/HIV cases are found in Africa, especially in southern and southeastern Africa.

The DOTS strategy, launched by WHO in 1995, calls for government commitment to tuberculosis control; bacteriological diagnosis of cases detected among symptomatic

patients; use of standard short-course chemotherapy regimen under supervision in all patients; assurance of a regular supply of drugs; and a system for surveillance and monitoring of the program performance. Specific targets were set by the World Health Assembly in 1991: to detect at least 70% of estimated cases and cure at least 85% of those detected. The Stop TB Strategy, launched by WHO in 2006, calls for enhancing the DOTS strategy to address new challenges and to expand access to the most vulnerable populations. It targets achievement of the TB-related Millennium Development Goal 6, target 6c: "to have halted by 2015 and begun to reverse the incidence of tuberculosis". Other elements of the Stop TB Strategy require addressing TB/HIV, MDR-TB and the needs of the poor and vulnerable; contributing to strengthening health systems; engaging all healthcare providers; empowering people with tuberculosis and their communities; and promoting research. The Stop TB Partnership, established in 2001 and housed by WHO, defined the goals of reducing overall prevalence and deaths from tuberculosis by 50% by 2015 (compared to 1990), and achieving elimination (defined as an incidence of <1 case per million population) by 2050 (global incidence is about 1,400 per million population now).

Major achievements between 1995 and 2008 include 36 million patients cured, more than 6 million deaths averted compared to non-DOTS treatment, reduction of case fatality rate from 7.6% to 4%, and attainment of highest-ever cure rates of 87% in 2007-8. Incidence rates are declining globally and in all sub-regions except in certain African countries since 2004, but not as rapidly as predicted (less than 1% per year) or as necessary in order to reach the program's quantitative targets. However, the absolute number of cases is still increasing, due to population growth off-setting per capita rate reductions, and limited reduction in transmission. Funding for tuberculosis programs has increased substantially in recent years, from US$2.7 billion in 2006 to US$4.1 billion in 2010, including near doubling of government funding to almost US$2.5 billion. However, the funding gap remains substantial compared to funding needs estimated by the Global Plan to Stop TB.

Overall, about 61% (5.5 million) of estimated tuberculosis cases were reported as of 2008, while less than 10% of MDR-TB cases are detected. Overall case detection has been stagnating globally since 2006. This is partly linked to the failure to report cases detected within the non-state sector. For example, between 1999 and 2005, the program in Bangalore, India increased reporting of tuberculosis cases nearly five-fold by involving health providers among NGOs, private, corporate, medical college and other government entities outside of the designated services of the national program. Delayed detection of infectious cases is also a problem, especially where access to services is seriously impaired. Few laboratories in the African Region can test for resistant strains of tuberculosis. In 2008, about 45% of TB patients in Africa were tested for HIV infection, while about 4% of HIV positive persons were screened for tuberculosis infection. Coverage with some key interventions to address HIV-associated tuberculosis has been scaled up in recent years: an estimated 73% of TB/HIV infected Africans were on co-trimoxazole preventive therapy (CPT) for treatment of concomitant bacterial infections in 2008; 31% were placed on anti-retroviral therapy (ART) for treatment of their HIV infection.

In the "syndemic" of dual TB/HIV infection, the two diseases act synergistically to cause excess morbidity and mortality. Tuberculosis is common and deadly in persons with HIV infection, with up to 25-50% dying within months. Persons with such dual infections comprise about 30% of all deaths from tuberculosis. In the African subregion, where this syndemic is most prevalent, HIV prevalence in the general population rose to a peak in about 2000, and in turn triggered an explosion of tuberculosis, which attained peak incidence in about 2004.

Persons with either disease should be screened or tested for the other infection. While the evidence strongly supports the need for TB screening in people with HIV, there is currently no internationally accepted, evidence-based approach to doing so. Persons infected with HIV may lack classic signs and symptoms of tuberculosis, and tests that are routinely used to diagnose TB (sputum smear microscopy and chest radiography) are relatively insensitive in people with HIV. A study by CDC has determined that chronic cough, which is commonly used for TB screening, is very insensitive in people with HIV and should not be used alone for TB screening in this group. The best combination of symptoms/signs to predict likely tuberculosis in HIV infected persons, based on this analysis, is night sweats for at least 3 weeks, or cough or fever of any duration. Patients who lack all of these symptoms are unlikely to have TB. Isoniazid preventive therapy (IPT), if indicated, can be safely started in most cases. Patients who do have one or more of these symptoms require diagnostic evaluation (including sputum smears, chest radiography, and CD4 testing). Most patients with negative sputum smears will require liquid culture of sputum specimens to accurately diagnose TB. Implementing the preferred diagnostic procedures would require scaling up of laboratory capacity to conduct liquid cultures for tuberculosis, especially in the African countries of greatest concern. It is important to start anti-retroviral therapy (ART) as early as possible in co-infected tuberculosis patients, as it can substantially reduce mortality. In people with HIV who do not yet have TB, ART can reduce the incidence of active tuberculosis by about 50%. IPT can also reduce incidence of active tuberculosis in co-infected persons whose tuberculin skin test is positive. Note is also made of examples where behavioral change brought about a significant reduction in the prevalence of HIV infection.[12]

Tuberculosis has had a long association with poverty and low socio-economic status throughout history, and deaths from the disease began declining sharply in wealthier countries long before the advent of anti-tuberculosis drugs. In modern times documented surges in tuberculosis incidence have been associated with adverse economic developments in several countries, reflecting complex and inadequately understood interactions among people, their environment, health services, and tubercle bacilli. Some studies have found an inverse correlation between the risk of tuberculosis and the number and kind of material goods possessed by individuals or their families. The poor suffer by having less access to proper care, by spending a higher proportion of their income on

[1] Lugalla J, Emmelin M, Mutembei A, Sima M, Kwesigabo G, Killewo J, Dahlgren L, 2004. Social, cultural and sexual behavioral determinants of observed decline in HIV infection trends: Lessons from the Kagera Region, Tanzania. *Soc Sci Med* 59(1):185—198.
[2] Kirby D, 2008. Changes in sexual behaviour leading to the decline in the prevalence of HIV in Uganda: Confirmation from multiple sources of evidence. *Sex Transm Infect* 84(Suppl II):ii35–ii41.

health care, and in numerous other poorly understood ways. Other studies suggest significant population attributable fraction of risk of tuberculosis in association with malnutrition, indoor air pollution, cigarette smoking, HIV infection, alcohol abuse, and diabetes. Education is also an important determinant of risk of tuberculosis, apart from level of income. Some such factors (e.g., HIV and diabetes) that are associated with increased risk of tuberculosis must be addressed by other health programs (e.g., HIV/AIDS programs or primary care services) while other determinants (e.g., over crowding, indoor air pollution, malnutrition) by agencies outside of the health sector altogether.

Mathematical modeling of tuberculosis transmission highlights the current overwhelming importance of latent infections in foreign-born residents as the major source of new tuberculosis disease in the United States. Immigrants from a few countries account for a large share of the emerging cases. If current control measures are sustained, preventing progression of latent tuberculosis infection towards active disease will be the most important determinant to stop transmission in the U.S. New tools for preventing, diagnosing, and to provide shorter and safer treatment, particularly among foreign-born persons with latent infections, will be required in order to eliminate tuberculosis from the U.S. in this century.

Task Force members noted the importance of improving the quality and extending the coverage of interventions to all populations at risk for tuberculosis urgently, in order to make better use of existing tools, and to help reduce the spread of TB, MDR-TB, XDR-TB, and reduce the incidence of HIV-associated tuberculosis. Tuberculosis and HIV/AIDS programs need to work together to mutual benefit, in order to ensure that patients with either disease are screened or tested promptly for the other disease and begun on appropriate measures immediately if indicated. Prevention and treatment of HIV infections are powerful weapons for preventing tuberculosis. In this and other areas, tuberculosis programs should aggressively seek synergies with other appropriate programs, including outside of the health sector, by emphasizing to the other programs the benefit of an additional impact on tuberculosis. Given the multiple, disparate risk factors for tuberculosis, control of the disease and, any possibility of elimination will require a multi-dimensional approach. Besides the core interventions against tuberculosis that are part of the Stop TB Strategy, bold policies across the health system, intensified research, and action on the risk factors and the determinants of the disease will be necessary.

Vigorous advocacy on behalf of tuberculosis programs is needed in order to engage other relevant health programs as well as relevant potential allies outside of the health sector. Tuberculosis programs cannot bear the entire burden of such advocacy, but should solicit the help of other members of the government, including the minister of health, and through the minister of health, other ministers, the head of government and the head of state, where necessary. The tuberculosis program should have in hand cogent data on the burden of tuberculosis, the progress and effectiveness of tuberculosis interventions, and the costs of not intervening, as ammunition to help recruit other allies. It was mentioned during the discussion that a study by The World Bank estimated that investment of $1 in

tuberculosis control yields an average of about $10 in benefits. The need to develop and publicize more such data, including the potential numbers of Disability Adjusted Life Years (DALYS) that could be saved by tuberculosis interventions was also emphasized in the discussion. Control of tuberculosis can be presented as a way to combat poverty, and as a driver of improved services to vulnerable, deprived, marginalized groups. More can be accomplished using the tools that we already have to combat tuberculosis.

There was not a separate presentation on the status of tuberculosis research, as planned, due to unforeseen circumstances. It was evident, however, that the existing tools for diagnosis, prevention and treatment of tuberculosis are very old, increasingly outdated, and in the case of available drugs, of diminishing effectiveness. Thanks largely to recent investments by the Bill & Melinda Gates Foundation, some potential new diagnostics, drugs, and a better tuberculosis vaccine are or may be in the pipeline, but the most optimistic time to possible delivery of any successful new tools is still several years away, and their improvement over existing tools may only be marginal. Some knowledgeable members of the Task Force therefore suggested that the current situation calls for a radical re-thinking in the direction of higher risk basic research on tuberculosis and tubercle bacilli in the hope of a possible substantial success in the longer term, while making batter use of currently available tools for the foreseeable future.

Tuberculosis is a chronic disease, and delivering effective health care to prevent and treat it could provide the basis for combating other chronic conditions. In the case of tuberculosis, however, stigma against persons suffering from the disease varies in different cultures, but must be addressed where it occurs. It was pointed out that volunteer or compensated community health workers have proven very effective in some programs, as has the "kinship strategy"[3], and those approaches might be useful to help extend the reach of interventions against tuberculosis and make detection of cases and follow-up of the long 6-month treatment easier.

The need for better surveillance and reporting of tuberculosis cases and for focusing on a limited set of key indicators of coverage (process) and impact (outcome) of tuberculosis programs was discussed extensively. The value of using absolute numbers of cases reported instead of prevalence or incidence rates in order to appreciate priorities for reducing the global burden of the disease was also mentioned. Judicious use of computers to help process reports of cases and the status of interventions as revealed by key indices would help leverage the surveillance data to guide programs. Leaders of the global program were strongly urged to gather whatever reports are available into an annual surveillance summary for publication in the World Health Organization's *Weekly Epidemiological Record*. Experience of other programs has shown the effectiveness of such publications to stimulate improved reporting of cases and of other program data. Members of the Task Force agreed that it is in the self-interest of the US to provide more support for tuberculosis research (operational, laboratory, epidemiologic, health systems)

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[3] Katabarwa MN, Habomugisha P, Agunyo S, McKelvey AC, Ogweng N, Kwebiiha S, Byenume F, Male B, McFarland D (2010). Traditional kinship system enhanced classic community-directed treatment with ivermectin (CDTI) for onchocerciasis control in Uganda. *Trans R Soc Trop Med Hyg.* [in press]

and control, similar to the greatly enhanced support for control of HIV/AIDS and malaria.

Conclusions and Recommendations

1. Implementation of the World Health Organization-led DOTS strategy since 1995 and the enhanced Stop TB Strategy beginning in 2006 has advanced control of tuberculosis significantly. The global Stop TB Partnership, established in 2001 and hosted by WHO, may serve as a model for coordinating collaborative efforts among several stakeholders.

2. Although tuberculosis cannot be eradicated in the foreseeable future with currently available tools, progress towards better control and reduction in transmission rates can and should be accelerated urgently.

3. The neglect of tuberculosis research over several decades has taken a large toll in additional illness and deaths, in increased resistance to available therapeutic drugs, and in lack of new tools for diagnosis, prevention and treatment, but funding by the U.S. National Institutes of Health, the Bill & Melinda Gates Foundation and others has stimulated important new research in recent years. Much more research is needed however, and increase more support by public and private agencies, especially in Europe, is encouraged.

4. The ITFDE emphasized the need for more vigorous political advocacy in support of tuberculosis control, including among potential allies within and outside of the health sector; for significant increase in access and coverage among the poorest and most vulnerable population, using available interventions; and for radical re-thinking of basic, research related to tuberculosis.

5. In order to intervene on the socio-economic determinants of tuberculosis and prevent infection and disease, other sectors must be targeted with proper advocacy strategies. These should be based on the possibility and feasibility to implement pragmatic interventions that would link tuberculosis control efforts with those of the relevant sectors.

6. Tuberculosis control and elimination depend ultimately also on establishing and enforcing policies across the health system which would benefit disease control in general. These include removing financial barriers to diagnosis and care, ensuring availability of quality drugs and regulating the use of all anti-tuberculosis drugs, establishing a network of laboratories where rapid tests are also available, ensuring well-trained and sufficient human resources, etc.

7. The emergence of tuberculosis strains that are resistant to multiple anti-tuberculosis drugs, and the synergy between tuberculosis and HIV/AIDS in co-infected persons are two major challenges to tuberculosis control. Combating the first requires pursuit of the proper strategy of TB control to prevent its emergence and monitoring of use of available drugs and of drug resistance. For the latter, preventing HIV/AIDS infections is one of the most important ways to prevent death from either or both diseases in areas where prevalence of HIV/AIDS is high. For now, TB incidence and

mortality in people with HIV can be reduced through early HIV testing of TB patients, high quality TB screening in people with HIV, increased use of ART and IPT, and scale-up of TB culture capacity.

8. The WHO's Stop TB Tuberculosis Department should publish annual summaries of global surveillance and interventions data, including key indices of programmatic operations, in WHO's *Weekly Epidemiological Record*.

9. Successful expansion of current interventions requires greatly accelerated improvements and extension of laboratory services that can support accurate and rapid diagnosis and treatment, including assessment of drug resistance. With additional support, such improved tuberculosis laboratories could form the base for upgrading laboratory services for other diseases

10. Successful expansion of current interventions also requires effective supervision of long-term treatment, a service that can be a model for addressing other chronic conditions, and which would benefit from existing or newly established effective primary health care services and community care schemes.

11. Most new cases of tuberculosis in the United States are in persons who were born in other countries. Interruption of tuberculosis transmission in the United States therefore would benefit greatly from increased assistance for improved control and research of tuberculosis in selected other countries.