Meeting of the Federal Tuberculosis Task Force April 8, 2013, Bethesda Maryland

Public Health Track:

This breakout group was intended to inform participants about resources and programs to implement 1) rapid drug resistance testing domestically and globally including the CDC MDDR service and Xpert TB/RIF, and 2) how can collaborations/handoffs between USG agencies be improved to expedite setting up structural entities to address issues of drug and biologic shortages.

Rapid drug resistance testing

The session was started with a presentation by Dr. Michael Iademarco (CDC) who summarized the current issues surrounding rapid drug resistance testing domestically and globally including the CDC MDDR service and Xpert TB/RIF.

CDC's Molecular Detection of Drug Resistance service provides state-of-the-art diagnostic services, assuring national coverage, for patients and providers to interrupt the transmission of drug-resistant tuberculosis through the earlier identification of resistant forms of the disease (ahead of results based on slower, culture-based methods). The service detects mutations associated with resistance to eight classes of first-line and second-line drugs and has reduced average turnaround time for preliminary results to two days as compared to the turnaround of 28-35 days for the final culture-based methods. It provides rapid detection of drug resistance or confirmation of known drug resistance and provides information which may be used by clinicians to guide therapy decisions in cases with resistant forms of disease.

The National Genotyping Program provides a genetic bacterial fingerprint for every culture confirmed case of tuberculosis in the United States. DTBE Laboratory Branch funds and provides oversight and technical review of two public health contract laboratories that provide genotyping for M. tuberculosis. The genotype data generated from this service are merged with information from the National Tuberculosis Surveillance system in the Tuberculosis Genotyping Information Management System (TBGIMS).This system enables the joint analysis of genotyping and epidemiologic data to help identify persons with disease involved in the same chain of recent transmission. Genotyping gives state and local tuberculosis control programs important information to help direct the application of public health interventions. In some situations it has been a critical link in control efforts that cross state lines, providing a practical, credible framework for states to work together. The effectiveness of the program is rooted in the partnership between CDC and state and local public health practitioners.

Since December 2011, substantial activity has resulted from previous efforts of the Diagnostics Workgroup of the Federal Tuberculosis taskforce, including the establishment of an FDA and NIH co-sponsored frozen trial bank, the NIH-sponsored TB Diagnostics Research Forum, bilateral CDC-NIH joint activity on improvements to diagnostic testing for pyrazinamide resistance, CDC and NIH coordination with WHO on moving R&D to field demonstrations for the molecular detection of drug resistance, and FDA policy efforts related to devices to detect M. tuberculosis and related drug resistance.

Guided by the workgroup's recognition of the importance of biomarkers for TB treatment efficacy and resulting workshops (Yasinkaya Y, et al, IJLD, 2011; Nahid et al, AJRCCM 2011) the FDA and NIH are sponsoring a clinical-trial specimen bank (Frozen Trial Initiative) to aid in biomarker discovery. The Consortium for TB Biomarkers is currently comprised of the TB Alliance, the AIDS Clinical Trial Group, and the TBTC, and efforts are underway to store prospectively collected specimens from TB Clinical trials.

Similarly, the workgroup's prioritization of molecular diagnostics has led to a number of coordinated and collaborative activities between U.S. agencies and other partners. Much of this activity has focused around improving the diagnosis of pyrazinamide (PZA) resistance because of its unique and essential role in both current and future TB drug regimens. Ongoing efforts include improving PZA phenotypic testing, development of pncA sequencing as eligibility criteria for clinical trials, improving understanding of pncA mutations and their role in PZA resistance, enlarging a database of PZA resistant isolates, and heightening understanding and cooperation between developers of new molecular diagnostics and the TB drug development field.

FDA has continued reexamination of the regulation of nucleic acid TB diagnostic assays following a 2011 FDA Microbiology Devices Panel meeting devoted to this issue. Draft guidance regarding reclassification of Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of Mycobacterium tuberculosis Complex in Respiratory Specimens was published March, 2012. Reclassification has been affected by passage of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), and there are efforts at many levels to move forward with reclassification in the context of the new law.

Concerns have been expressed regarding regulatory challenges for the clearance of devices that detect the presence of resistance mutations for drugs that are not FDA approved for the treatment of TB, e.g., quinolone drugs. This issue is also the subject of vigorous internal discussion.

Future priorities of the workgroup include the use of important drugs besides PZA (e.g., fluoroquinolones and new drugs) for drug-susceptible and drug-resistant TB, the use of molecular detection of drug resistance for drug resistance surveillance, and pediatric diagnostics.

Drug and biologic shortages

This presentation was followed by a presentation by Dr. Terence Chorba who discussed issues concerning current TB drug and biologic shortages, specifically difficulties that programs were experiencing in accessing isoniazid (INH) and tubersol (PPD). CDC commented on drug shortages, costs climbing out of reach of uncovered patients, multi-step processes for procurement, stress on programs, and the need to for U.S. Government intervention for:

1. the establishment of a monitoring and early warning system
2. potential solutions to ensure the proper supply chain management of TB
3. consideration of the pros and cons of formal designation of TB in the United States as a disease conforming to the principles underpinning the Orphan Drug Act (see references)

Fundamental to the discussion of shortages are the cornerstones of TB disease treatment:

- **WHO, STOP TB Strategy:** Pursue high-quality DOTS expansion and enhancement…Ensure effective drug supply and management. In that strategy, Component 1, Element 4 is to insure an effective drug supply and management system:
  - Uninterrupted and sustained supply of anti-TB drugs
  - Reliable system of procurement and distribution of anti-TB drugsAnti-TB drugs available free of charge, both because patients are poor and may not afford them, and because treatment has benefits that extend to society
  - Legislation related to drug regulation
- **WHO, IUATLD, ATS:** 5 Components of DOTS: a regular, uninterrupted supply of all essential anti-TB drugs
- **CDC:** Ensure that patients with TB disease receive appropriate treatment until they are cured

Unfortunately, the results of drug shortages on the carte of patients are grim, including medication errors or adverse events, adverse consequences related to using alternative medication, delays in treatment or procedures, a need to use less effective drugs, rationing or restricting drugs, Increases in drug costs, and staff time being dedicated to drug procurement and labor costs for these activities.

In November 2012, TB programs began alerting program consultants in CDC's Division of TB Elimination (DTBE) of their inability to procure INH. The FDA drug shortage website posted information from Teva Pharmaceutical Industries (Teva) and Sandoz Generic Pharmaceuticals, Division of Novartis (Sandoz) confirming that there were shipping delays of INH 300 mg tablets, but that 100 mg tablets were in inventory. The shortages were anticipated to end in mid- to late December 2012. However, delays continued and in January 2013, VersaPharm, one of the three U.S. companies that had been manufacturing INH, sent a letter to its customers informing them that it would not be filling any further orders or back orders of INH until 2014. This left INH production in the United States to Teva and Sandoz, who then anticipated that their shortages would last until March or April. DTBE and FDA collaborated to summarize disseminate information as it became available:

- MMWR Notice to Readers, 12/23/2012
- Health Advisory in the Health Alert Network, 1/28/2013
- Dear Colleague Letters, 1/28/2013 and 2/1/2013
- An MMWR article that subsequently published in May discussing findings from another survey by the National TB Controllers Association. This found that 79% of the responding U.S. health departments reported difficulties with procuring INH within the last month, with 15% citing they no longer had INH and 41% citing they would no longer have supply within one month of the survey. Due to the local interruption in INH supply, TB programs were changing INH suppliers (69%), prioritizing high-risk patients for the treatment of latent TB infection (LTBI, 72%), delaying LTBI treatment (68%) and changing to alternative treatment regimens (88%).

In January 2013, Teva began releasing 10% of its INH for emergency allocation to TB programs in need of the drug. Teva agreed to sell INH to programs that are not usually its customers, and did not raise its prices. The emergency supply was being allocated using TB Treatment Guidelines. CDC published a health advisory via the Health Alert Notification (HAN) January 28, 2013 (see references) to help in priority setting:

1) Patients being treated for active TB disease

2) Patients being treated for latent TB infection if they belong to any of the following categories:
    - Diagnosed during a contact tracing of a patient with contagious TB
    - Immunocompromised (e.g., persons with HIV infection, or receiving immunomodulating medications)
    - Less than 5 years of age

TB programs also shared pricing information from the pharmacies where they purchase INH manufactured by Sandoz; these (which can be set by the manufacturer, the distributor, the pharmacy, or all three) were reported as being up to 35 times higher after the shortage was reported than prior to it. DTBE and FDA spoke with representatives of Sandoz to explain how INH shortages and price increases affect TB programs, which are publicly funded and have little budget flexibility for drug purchases. Sandoz has concessionary pricing for 340(b) programs, such as Federally Qualified Health Centers (FQHCs), but was unaware that these are different from TB programs in health departments. While some TB programs receive drugs through the 340 pricing program, they encouraged TB programs to consider bulk purchasing with the FQHC's and said that they would take the request to offer concessionary pricing to health departments under consideration. At the time of the April 8 meeting, FDA's website indicated that product is available from both Teva and Sandoz.

Potential long term solutions have been identified and should be of interest and focus of any workgroup that takes on the shortage program:

- Facilitate importation of INH from the Global Drug Facility (GDF). FDA does not automatically allow importation of GDF-approved drugs, so CDC has shared the list of FDA requirements with GDF. If GDF drugs were approved for importation, purchasers and distribution chain would need to be identified.
- Develop a CDC-administered strategic stockpile. DTBE is exploring different models within CDC now, including partnering with HHS Supply Center – Perry Point as a source of strategic stockpiles either through storage of pharmaceuticals or agreement with manufacturers on establishing a "safety net."
- DTBE is exploring the use of CDC's Countermeasure Tracking Systems, which could allow CDC and state/local TB programs to track availability of pharmaceuticals and to respond to shortages in a timely manner.

DTBE has provided comments to FDA's Drug Shortages Task Force and Strategic Plan, stating that CDC would be in favor of developing systems to 1) establish a qualified manufacturing partner program for drugs used in the treatment of diseases that pose a threat to the public's health, such as "essential pharmaceutical list" as described by the United Health Foundation, 2) accelerate review of requests for importation of quality assured drugs from the TB Global Drug Facility (GDF), 3) allow early warnings of impending shortages, and 4) form a strong regulatory and inspection network with other countries.

The issues of shortages are not limited to pharmaceutics. Biologics as well are effected. At the time of the April 8 meeting, Tubersol in the 50 dose vial (5mL) and 10-dose vial (1mL) was becoming unavailable. Sanofi-Pasteur reported that a supply interruption would be experienced until late-spring 2013 due to a temporary delay in production, as a consequence of which, CDC was advising use of Aplisol until supplies of Tubersol would be back to normal.

Generalized agreement was expressed that a workgroup is needed to facilitate participation of CDC, FDA, and other federal agencies in addressing this issue in a concerted, proactive fashion. DTBE/CDC, in

overseeing the National TB Program's prevention and control activities, needs to consider undertaking new roles including oversight of a dashboard, warehousing, and facilitation of access to alternative sources. Specifically, there was much discussion for establishing a workgroup to develop recommendations from the Federal TB Task Force regarding mechanisms to avoid or temper future drug/pharmaceuticals shortages. Participants at the meeting specifically recommended that the Membership or Overseers on this Work Group should include:

- CDR Diane Elson, DrPH, Immigration and Customs Enforcement (ICE), Enforcement and Removal Operations, IHSC, Chief, Epidemiology Branch
- CAPT Orville (Don) Brown III, Director Pharmacy Program, DHS/ICE
- Brent Gibson, MD, VP of Operations, National Commission on Correctional Health Care (NCCHC)
- Thomas Chiang, Senior Tuberculosis Technical Advisor in the Office of Health, Infectious Diseases, and Nutrition, USAID
- CAPT A. Martin Johnston, RPh, Chief, Pharmacy Logistic Support, Fed Bureau of Prisons
- HRSA representation from the 340B Program and Perry Point
- Jouhayna Saliba, FDA
- Neha Shah, MD; Terence Chorba, MD; Ann Cronin; Sundari Mase MD; Glen Christie, CDC/DTBE
- Steven Gitterman, MD, PhD, FDA/CDRH/Office of In Vitro Diagnostic Device Evaluation and Safety
- Barbara Laughon, PhD, Office of the Director NIH/NIAID/Division of Microbiology and Infectious Diseases (DMID)
- Consultancy from NTCA (Jenny Flood, MD) and Ed Zuroeste, MD, Chief Medical Officer for Migrant Clinicians Network

In summary, shortages in MDR-TB medications have been experienced by many TB programs nationally. Shortages in MDR-TB medications have adverse consequences. Many agencies, staff and resources are needed to resolve drug shortages issues. Issues of budget cuts and preparation for the National TB Conference in June have occupied CDC/DTBE since the April 8 meeting, but after the June conference is over, DTBE intends to take leadership in addressing organization of the proposed Workgroup and exploring a proactive and multi-pronged approach to positioning measures that will predict and ameliorate future shortages of anti-TB pharmaceutics and biologics.

References for Rapid drug resistance testing section

FDA

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/UCM260828.pdf

PZA

Early data from studies presented at three national meetings show the importance of PZA for any regimen that might use a new anti-tuberculosis drug. All three meetings are well documented on the website of the Stop TB Partnership's Working Group on New TB Drugs, including the study presentations.

In May 2011, the National Institutes of Health (NIH) hosted a workshop, "Essentiality of PZA." The gathering laid the groundwork for exploring the subject further in-depth. Richard Hafner (Division of Acquired Immunodeficiency Syndromes (DAIDS)) concluded that "PZA has potent sterilizing activity and

is a highly important drug in current anti-tuberculosis combination therapy. Unfortunately, while PZA-resistant TB has been increasing worldwide, rapid and reliable diagnostic tools for the detection of PZA-resistant TB are still unavailable. This presents a major barrier for treatment, especially for multidrug-resistant and extensively drug-resistant disease. PZA is the least understood anti-TB drug due to its complex mechanisms of action and obstacles in establishing animal models for PZA testing."

http://www.newtbdrugs.org/meetings/pza-workshop.php

In December 2011 in Atlanta, CDC hosted a meeting to review in detail our research activities related to PZA in order to enhance alignment with NIH and Food and Drug Administration (FDA) goals and priorities. The Global Alliance for TB Drug Development was also in attendance. CDC presented information on the surveillance of PZA resistance, experience in providing clinical microbiologic service, and preliminary results on approaches to improve drug susceptibility testing for PZA. A series of concrete actions steps were laid out for the various federal agencies to strengthen internal U.S. government interaction. The goal was to facilitate ongoing partner planning and efforts to advance PZA drug susceptibility testing in both the short-term and long-term. Assistant Surgeon General Kenneth G. Castro, USPHS and co-chair of the Federal TB Task Force remarked on the importance of ongoing inter-agency discussion tied to concrete tracking of action.

http://www.newtbdrugs.org/downloads/resource-docs/2011-12-25-Summary-PZA-Day-at-CDC.pdf

In September 2012 in Baltimore, in follow-up, NIH and Johns Hopkins University hosted a broader, partner workshop: "Demystifying PZA—Challenges and Opportunities." Topics included mechanisms of action; drug resistance and associated testing; combination therapy; and toxicity. In-depth presentations in these four areas led to lively and stimulating discussion, capitalizing on previous meetings and contributing significantly to the growing momentum needed to tackle the issues. The next step was announcement of a NIH-sponsored "TB Diagnostics Research Forum," designed to facilitate future dialog and collaboration; this will be the subject of a future report to TB Notes.

http://www.newtbdrugs.org/meetings/pza-workshop-2012.php

Frozen Trial Initiative www.fda.gov/downloads/.../CriticalPathInitiative/.../UCM289182.doc

The **last two formal meetings**, sponsored by the TB Federal Task Force Diagnostics Workgroup have been documented and productive. Please see a May 2012 supplement in JID, http://jid.oxfordjournals.org/content/205/suppl_2.toc

1) Clinical Research and Development of Tuberculosis Diagnostics: Moving From Silos to Synergy
2) Opportunities and Challenges for Cost-Efficient Implementation of New Point-of-Care Diagnostics for HIV and Tuberculosis
3) Perspectives on Introduction and Implementation of New Point-of-Care Diagnostic Tests
4) Evaluation of Tuberculosis Diagnostics in Children: 1. Proposed Clinical Case Definitions for Classification of Intrathoracic Tuberculosis Disease. Consensus From an Expert Panel

5) Evaluation of Tuberculosis Diagnostics in Children: 2. Methodological Issues for Conducting and Reporting Research Evaluations of Tuberculosis Diagnostics for Intrathoracic Tuberculosis in Children. Consensus From an Expert Panel
6) New Drugs for the Treatment of Tuberculosis: Needs, Challenges, Promise, and Prospects for the Future
7) Innovative Trial Designs Are Practical Solutions for Improving the Treatment of Tuberculosis
8) Viewpoint: Challenges and Opportunities in Tuberculosis Research

And most recently, "Alignment of new tuberculosis drug regimens and drug susceptibility testing: a framework for action," in Lancet Infect Dis. 2013 Mar 22.

References for Drug and biologic shortages section

Orphan Drug Act

(http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/OrphanDrugAct/default.htm)

Health Alert Notification (HAN)
(http://emergency.cdc.gov/HAN/han00340.asp)