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TBeat

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Special Report

CDC Division of TB Elimination Announces Launch of TB GIMS in Spring 2010

The National Tuberculosis Genotyping Service (NTGS) started in 2004 when state laboratories from all TB programs in the United States voluntarily started submitting *Mycobacterium tuberculosis* isolates from culture-confirmed patients to two CDC-contracted laboratories in Michigan and California. TB genotyping is a laboratory-based approach used to analyze the genetic material (e.g., DNA) of *Mycobacterium tuberculosis*. The total genetic content is referred to as the genome. Specific sections of the *M. tuberculosis* genome form distinct genetic patterns that help distinguish different strains of *M. tuberculosis*. Since 2004, use of TB genotyping results has significantly improved our understanding of TB transmission nationally and within the Heartland region. Below are typical applications for genotyping use:

- Discover unsuspected transmission relationships between TB patients
- Identify unknown or unusual transmission settings, such as bars or clubs, instead of traditional settings like home and workplace
- Uncover interjurisdictional transmission
- Establish criteria for outbreak-related case definitions
- Identify additional persons with TB disease involved in an outbreak
- Determine completeness of contact investigations
- Detect laboratory cross-contamination events
- Distinguish recent infection (with development of disease) from activation of an old infection

However, since its inception in 2004, managing genotyping data has been a challenge to individual state programs, particularly in monitoring data for significant clusters and attaching individual patient clinical and demographic surveillance information to genotyped isolates. Although some informal agreements have been arranged between states, no comprehensive national TB

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genotype database has been available. Given the mobility of TB patients, and the tendency for outbreaks to involve multiple states, the National TB Controllers Association (NTCA), including states within the Heartland Region, have advocated for the ability to readily view the national picture of genotype clusters, automate cluster identification, and characterize clusters further based on the clinical and demographic makeup of clustered TB patients.

On December 9, 2009 the CDC Division of TB Elimination announced the launch of the "TB Genotyping Information Management System" (TB GIMS) in spring of 2010. This will be a free web-based software program available to State TB controllers. TB GIMS will link genotyping results to the epidemiologic data from surveillance reports. Queries and reports can then be generated for comparing genotyping results locally and nationally. Ultimately, TB GIMS will generate alerts or notifications of suspected recent transmission and help identify TB clusters and direct public health action. Specifically, TB patient surveillance information will be linked to genotype results in TB GIMS by the following process:

- State TB labs submit isolates to contract labs in Michigan and California and enter initial isolate information in TB GIMS
- Genotype results are entered into TB GIMS (now both state TB programs and genotyping labs have access to information)
- CDC lab updates and manages information on *Mycobacterium tuberculosis* strains/lineages
- A state-assigned "super user" adds the state case number that will link the genotype results with the TB patient surveillance data (i.e. the Report of Verified Case of TB)
- CDC will complete the linkage between surveillance and genotyping information
- Reports and maps will be generated at the patient level for isolates that have been linked with a state case number

Combining patient-level data with genotyping results in one accessible, national web-based system will be a tremendous advantage for State TB Controllers. This also means confidentiality and security will be crucial to TB GIMS success. Therefore, access to TB GIMS will be restricted to authenticated and approved users in the TB Control community, and data will not be available to the public. Authorized users will be designated only by State TB Controllers or their designees. "Super users" will be authorized to edit or export patient-level data from their jurisdiction. For more information on TB GIMS and patient confidentiality, visit http://www.cdc.gov/tb/publications/factsheets/statistics/TBGIMS.pdf.

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The Heartland National TB Center is looking forward to supporting the implementation of TB GIMS in our region. TB GIMS training will enhance each state's TB Program's ability to:

- Integrate genotyping analysis into routine TB prevention and control activities
- Identify transmission patterns and examine clusters
- Analyze ongoing transmission temporally, geographically and by risk factors

The timeline for spring is as follows:

- January 2010 – registration to access TB GIMS begins
- March 2010 – state laboratories will transition to submitting isolates using TB GIMS
- March 2010 – State super users will begin linking surveillance and genotyping data
- March-April 2010 – CDC will launch TB GIMS live-webinar training and pre-recorded webinars for state TB control programs.

For questions please contact Heartland National TB Center or email tbgims@cdc.gov.

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The VISION of Heartland is to provide *excellence*, *expertise*, *innovation* in training, medical consultation, and product development to reduce the impact of tuberculosis in our region.

The MISSION of the Heartland National TB Center is to build capacity with our partners. We will share expertise in the treatment and prevention of tuberculosis by: developing and implementing cutting-edge trainings, delivering expert medical consultation, providing technical assistance, and designing innovative educational and consultative products.

Recent Publications

Is the QuantiFERON-TB Blood Assay a Good Replacement for the Tuberculin Skin Test in Tuberculosis Screening? A Pilot Study at Berkshire Medical Center. Zhao, X., D. Mazlagic, E. A. Flynn, H. Hernandez, et al. **American Journal of Clinical Pathology** November 2009; Volume 132, Number 5: pp. 678-686.

Estimating Diagnostic Accuracy of Tests for Latent Tuberculosis Infection Without a Gold Standard Among Healthcare Workers. Girardi, E., C. Angeletti, V. Puro, R. Sorrentino, et al. **Euro Surveillance** October 29, 2009; Volume 14, Number 43. pii: 19373.

Annual Incidence of Latent Tuberculosis Infection Among Newly Employed Nurses at a Tertiary Care University Hospital. Lee, K., M. K. Han, H. R. Choi, C. M. Choi, et al. **Infection Control and Hospital Epidemiology** December 2009; Volume 30, Number 12: pp. 1218-1222.

QuantiFERON-TB Gold in the Identification of Latent Tuberculosis Infection in Rheumatoid Arthritis: A Pilot Study. Shovman, O., M. Anouk, N. Vinnitsky, U. Arad, et al. **The International Journal of Tuberculosis and Lung Disease** November 2009; Volume 13, Number 11: pp. 1427-1432.

Interferon-Gamma Release Assay Test Characteristics Depend Upon the Prevalence of Active Tuberculosis. Davidow, A. L. **The International Journal of Tuberculosis and Lung Disease** November 2009; Volume 13, Number 11: pp. 1411-1415.

Free Article/Research Sites:

BMC Microbiology published by BioMed Central is an open access journal publishing original peer-reviewed research articles in analytical and functional studies of prokaryotic and eukaryotic microorganisms, viruses and small parasites, as well as host and therapeutic responses to them, and their interaction with the environment. BMC Microbiology (ISSN 1471-2180) is indexed/tracked/covered by PubMed, MEDLINE, BIOSIS, CAS, EMBASE, Scopus, FSTA, Thomson Reuters (ISI) and Google Scholar http://www.biomedcentral.com/bmcmicrobiol/

The CDC National Prevention Information Network (NPIN) is the U.S. reference and referral service for information on HIV/AIDS, viral hepatitis, sexually transmitted diseases (STDs), and tuberculosis (TB). NPIN collects, catalogs, processes, and electronically disseminates materials and information on HIV/AIDS, viral hepatitis, STDs, and TB to organizations and people working in those disease fields in international, national, state, and local settings. All NPIN services are designed to facilitate sharing of information and resources on education and prevention services, published materials, research findings, and trends among users. Specifically for tuberculosis, you can find the most recent activities, news, or publications about TB elimination. http://www.cdcnpin.org/scripts/tb/index.asp

Listservs:

Stop-TB is an e-mail discussion forum for various stakeholder groups to network, share experiences, and ask for advice on issues related to community, programmatic and policy aspects of TB control, and TB/HIV integration. Stop-TB is a moderated eForum, with support from a virtual network of experts called the eForum Resource Team. Subscribe through the Website. http://www.healthdev.org/eforums/cms/individual.asp?sid=105&sname=Stop-TB

TB Behavioral and Social Science Listserv provides the opportunity to exchange information and engage in ongoing discussions about behavioral and social science issues as they relate to tuberculosis prevention and control. The TB Behavioral and Social Science Listserv is not meant to be a forum to answer medical/clinical questions and is an unmoderated listserv. Subscribers have the option of receiving immediate delivery of each message, or once-daily delivery of a digest containing all messages posted in a 24-hour period. The TB Behavioral and Social Science Listserv is sponsored by the Division of Tuberculosis Elimination (DTBE) of the Centers for Disease Control and Prevention (CDC) and the CDC National Prevention Information Network (CDC NPIN). http://www.cdcnpin.org/scripts/listserv/tb_behavioral_science.asp

Case Presentation
Using Genotyping to Confirm a Suspected Case of Tuberculosis Cross Contamination

Case History:

Patient A was a 45-year old US-born white female with a six month history of illness characterized by a twenty pound weight loss, dry cough, shortness of breath (SOB), and chest pain. She was seen by a physician on December 12, 2003 to evaluate a spontaneous pneumothorax and rule out lung cancer. A Computed Tomography (CT) of her chest revealed large bilateral cavitary lesions. She underwent a bronchoscopy exam on December 19, 2003. An acid-fast bacillus (AFB) smear-positive specimen was obtained using bronchial-alveolar lavage (BAL). The sputum was culture-positive for *Mycobacterium tuberculosis*, and on February 20, 2004 *Mycobacterium tuberculosis* was isolated from her BAL and sputum. The isolated organism was pansensitive. She was started on isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) at the time of her TB diagnosis and received nine months of treatment due to her large cavitary lesions and advanced TB disease.

Patient B was a 56-year old US-born male. In July 2001 he was diagnosed with lung cancer and an upper and middle lobectomy was performed. On December 12, 2003 he underwent a bronchoscopy to evaluate new symptoms of SOB and new bilateral pulmonary infiltrates (on chest radiograph). A BAL obtained was AFB smear negative.

On January 7, 2004 a preliminary report from the hospital indicated that *Mycobacterium tuberculosis* complex had been isolated from the BAL specimen for Patient B. The State Lab confirmed pansensitive *Mycobacterium tuberculosis* on January 27, 2004. Patient B underwent treatment with INH, RIF, PZA, and EMB starting January 9, 2004 and continued though completion on July 2, 2004. This was a single-positive-specimen (SPS); no other sputum specimens were ever collected from Patient B.

The genotypes for Patient A and Patient B became available several months later and were reviewed by the State TB Control Program. These two patients had a unique genotype. No other matches were found in the state or neighboring states. Both their spacer oligonucleotide type (spoligotype) and Mycobacterial Interspersed Repetitive Unit (MIRU) matched; however they lived in different parts of the state and had no known epidemiological links. Further review indicated that both patients were diagnosed in the same hospital at the same time. Due to the unique matching genotype, no known social link, Patient B's SPS, and their link to the same hospital, an investigation into possible cross contamination was launched.

The hospital was notified when the possible cross contamination was determined by the State TB Control Program. On August 18, 2004 state program staff visited the hospital to investigate. They met with the following staff: the Infection Control Nurse, the Microbiology Lab Director, the Director of Respiratory Therapy (Bronchoscopy Laboratory), and the Director of Employee Health. The hospital staff was receptive and cooperative with the investigation, and had conducted their own internal review of procedures prior to the State TB program staff's visit.

The investigation revealed that the same bronchoscope was used on both patients. A third patient underwent bronchoscopy with this scope on December 26, 2003, but all TB smears and cultures collected on this patient were negative. Due to a change in vendors at the end of the year, this scope had not been used again.

Patient A was considered the "hot" patient; bronchoscopy was performed on December 19th (Friday). Due to the patient's critical condition the physician requested that specimens be processed as soon as possible. The specimens were processed on December 20th (Saturday) and were not batched with other specimens. Patient B was the next patient to undergo a bronchoscopy exam on December 22nd (Monday) and that specimen was processed the same day. The state reference lab also received specimens from the two patients on different days and only for culture identification after specimen growth. Laboratory cross contamination was therefore considered unlikely as the specimens were not processed in any lab at the same time.

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The hospital conducted a review of its bronchoscopy laboratory procedures; there was no new staff in the Bronchoscopy Laboratory. Procedures called for single-patient use of a lidocaine spray and nozzle when anesthetizing the patient's airway. All accessory instruments used during procedures were also single-patient use. Bronchoscopes were all cleaned by hand prior to disinfection and scopes were disinfected with Cidex (with appropriate soak times and solutions).

Those involved with the investigation believed that bronchoscope contamination was the likely the source of Patient B's positive tuberculosis culture; however since the scope in question had long since been discarded there was no conclusive evidence. Lab contamination was improbable since specimens were processed two days apart in the hospital and arrived at the state reference lab after isolate growth. The hospital took these concerns seriously and used this issue to develop a quality improvement process aimed at assuring that cross-contamination is minimized during bronchoscope processing, handling, and cleaning/disinfection. They were open to suggestions by the State TB Control Program staff to decrease this risk in the future. Both Patient A and Patient B completed anti-tuberculosis treatment.

Key Concepts:

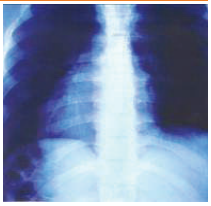
- Universal genotyping allows programs to identify links between TB patients that would otherwise be unrecognized. Key to this investigation was access to genotyping results of both specimens and recognition by the State TB Control Program of the significance of a single positive specimen that matched a highly infectious TB patient. All TB Control Programs should have procedures in place to readily detect genotyping matches and SPSs, and launch timely investigations of possible cross-contaminations (CDC 2004). It should be noted that this investigation was not completed until eight months after the contamination due to delays in laboratory procedures at the time and lack of an automated surveillance system. The national web-based program, TB GIMS, will substantially improve a TB Program's ability to recognize possible cross contamination cases faster and intervene earlier.
- An estimated 0.1 – 3% of active TB diagnoses are based on false positive specimens or cross contamination of specimens. False-positive TB diagnoses result in needless treatment for the patient, delays in an accurate diagnosis, and misrepresentation of the actual incidence of TB. (Djelouadji, Z., et al 2009) In this instance, bronchoscope contamination resulted in the likely nosocomial infection with *M. tuberculosis* for Patient B.
- Cross contamination of specimens via contaminated bronchoscopes are less frequent than laboratory cross contamination, but certainly possible. Several examples have been published in the literature. Any possibility of bronchoscope contamination should result in a thorough review of infection control procedures (Djelouadji, Z., et al 2009; Shoch, O. D. et al 2003; and Larson, J. L. et al 2003) as happened in this event.
- TB GIMS will enhance the utility of genotyping data for state TB programs. In addition to gaining ability to identify cross contamination events, genotyping can (CDC 2004):
    - Establish criteria for outbreak-related case definitions
    - Identify additional persons involved in a TB outbreak
    - Distinguish recent infection (with development of disease) from activation of an old infection
    - Determine completeness of contact investigation
    - Uncover interjurisdictional and atypical transmissions of tuberculosis

For questions please contact the Heartland National TB Center or email tbgims@cdc.gov.

References *on Page 7*

Heartland National TB Center provides a ***Medical Consultation Line*** that is staffed Monday to Friday, 8:00 AM to 5:00 PM (CST). After business hours, voice mail is available and will be returned in one business day:

Toll Free Telephone Number: 1-800-TEX-LUNG (1-800-839-5864)



Case Presentation *continued from Page 6*

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TBit

The ***Minnesota Department of Health*** has recently posted a new web page called "TB Class Arrivals" that may be of interest to the states in the Heartland Region. The page includes:

- A link to the *2007 Technical Instructions for TB Screening and Treatment* used by doctors overseas when evaluating refugees and immigrants before arrival in the US
- An explanation of the TB Class Conditions
- Recommended follow-up for people with TB Class Conditions
- Links to related websites or agencies

You can access the webpage at:
http://www.health.state.mn.us/divs/idepc/diseases/tb/classarrival.html

Marge Higgins is the TB Program Refugee and Immigration Coordinator for the Minnesota Department of Health. This position was created to develop systems, track outcomes, and provide assistance and guidance for TB screening and treatment specific to Refugees and TB Class arrivals in Minnesota with the goals of identifying and treating persons with latent TB infection and TB disease. Marge recently served as faculty for Heartland's December 1, 2009 webinar "Refugee Updates" and is available for questions concerning Minnesota's program and refugee and immigration issues surrounding tuberculosis: Marge.Higgins@state.mn.us or 651-201-5523.