Integrated Screening for Tuberculosis and HIV in Tuberculosis Contact Investigations: Lessons Learned in North Carolina

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ABSTRACT

Combating the syndemics of tuberculosis (TB) and HIV in the United States will require increasing efficiency as the incidence of TB declines. Fortunately, new tools such as the interferon gamma release assays can be combined with existing strategies such as opt-out HIV testing to facilitate simultaneous, integrated testing for both infections. We describe the lessons learned from our experience with integrated testing for TB and HIV in the setting of TB contact investigations in North Carolina. Integrated testing represents a unique opportunity to leverage TB and HIV program resources to enhance case detection and improve linkages to care. However, joint training in field investigations and diagnostics is critical prior to conducting contact investigations. Furthermore, integrated testing must be tightly coupled to treatment and prevention programs to reduce disease transmission and morbidity from untreated disease in communities.

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The incidence of tuberculosis (TB) is at an all-time low in the United States, with 3.4 cases per 100,000 population and a total of 10,521 cases reported in 2011.[1] Unfortunately, funding for TB control in the U.S. is also declining; and if current trends continue, funding is likely to be eliminated before TB disease is eliminated. The ability to conduct thorough and timely contact investigations is crucial to TB control, but it is also time and resource intensive.[2] Furthermore, large contact investigations can rapidly overwhelm the capacity of jurisdictions with low TB incidence and small TB programs. The ability to rapidly mobilize resources on short notice is vital to conducting effective contact investigations when a large number of potentially exposed people are identified.

Fortunately, new tests for TB infection combined with closer collaboration across programs can be used to efficiently rise to the challenge when a large TB contact investigation is needed. Specifically, interferon gamma release assays (IGRAs) provide the ability to test for TB infection with a single blood draw, obviating the need for the second visit required when tuberculin skin testing is performed.[3] Furthermore, using blood-based testing facilitates the integration of TB screening with screening for human immunodeficiency virus (HIV), which is a crucial coinfection to identify in people at risk for TB infection.[4] In this article, we describe the North Carolina experience with integrating HIV testing into large TB contact investigations and the collaborations across programs required to implement this integrated testing.

TB IN NORTH CAROLINA

North Carolina had a reported TB incidence of 2.5 cases per 100,000 population in 2011, ranking 24th among states in incidence and 10th for total number of cases.[5] Among 244 reported TB cases, 148 had culture-positive pulmonary TB, which demonstrates the potential for transmission and would prompt a contact investigation. These 148 cases were associated with a total of 1,455 contacts who were evaluated for TB infection (average <10 contacts per case), of whom 400 (27.5%) were diagnosed with latent TB infection (positive test for infection, no disease).[6] HIV coinfection disproportionately afflicts TB cases, with 4.9% (4,900 per 100,000 population) of TB cases in North Carolina coinfected with HIV, compared with an estimated HIV infection population prevalence of 263 cases per 100,000 population.[7]

RATIONALE FOR INTEGRATED CONTACT INVESTIGATIONS

The Centers for Disease Control and Prevention (CDC) recommends HIV testing as a routine part of medical care for all people aged 13–64 years.[8] The importance of HIV testing is heightened in the setting of a TB contact investigation, as the criteria for interpreting tuberculin skin tests, as well as for initiating treatment of latent TB infection, differ by HIV status.[9] Furthermore, people with HIV who are exposed to a case of infectious TB are at very high risk to progress to TB disease; therefore, they are the highest priority group to target for latent TB treatment after exposure.[10] As such, HIV testing is recommended for all TB contacts, and HIV-infected contacts are considered high priority for evaluation and latent TB treatment.[11] HIV testing in the setting of TB contact investigations provides a unique opportunity to test people who may not otherwise access health care and to engage people who test positive in HIV care. Routine HIV testing of TB contacts is inexpensive and feasible[12] but infrequently performed. In one study of five U.S. health departments, only 19% of TB contacts were tested for HIV; notably, 9% of those tested and 1.6% of the total contacts were HIV infected,[13] which is a rate that falls into the cost-effective range for universal HIV testing.[14]

INTEGRATED CONTACT INVESTIGATIONS IN NORTH CAROLINA

The first contact investigation that integrated TB screening with opt-out HIV testing in North Carolina occurred in 2008.[15] More than 300 people working at a factory had been exposed to an infectious TB case continuously for longer than a year, and a number of secondary cases were diagnosed. At the time, no IGRAs were available for clinical use in North Carolina, but the QuantiFERON®-TB Gold In-Tube test (Cellestis Inc., Valencia, California) had been approved by the U.S. Food and Drug Administration in 2007, and a local commercial laboratory was preparing to offer the test. Because the QuantiFERON test had not been previously used in North Carolina, concurrent tuberculin skin testing was also performed to guard against laboratory failure. Because the testing was conducted at a workplace, patients were not questioned about their HIV status, and opt-out HIV testing was performed. (Opt-out HIV testing, defined as testing in which a patient is informed that he/she will be tested unless he/she specifically declines testing, was permitted in North Carolina under a rule change that occurred in the fall of 2007.) The effort required mobilization

of local health department (LHD) nursing and phlebotomy staff, state TB-control staff, personnel from the commercial laboratory, and physicians from a nearby academic medical center. In all, 326 people were screened within a one-week period, with valid QuantiFERON results obtained for 96% of those screened and HIV testing accepted by 88% of those screened. Of note, even in this workplace setting, 10% of people who were screened failed to return for a tuberculin skin test reading. Two people tested HIV-seropositive. In retrospect, one was aware of prior HIV infection, but the other had fallen out of care one year previously, and the integrated testing provided by the contact investigation proved to be an opportunity to reenter into HIV care. Interestingly, this person initially denied any knowledge of a previous HIV diagnosis; however, after an extensive conversation, it was ascertained that this individual had prior knowledge of HIV infection. Even a confidential survey tool would not have identified such a person. Per North Carolina policy and CDC guidelines,[9] latent TB treatment was offered to all close contacts of infectious TB cases, regardless of tuberculin skin test/IGRA status.

After this positive experience, North Carolina's TB policy manual was changed to encourage opt-out HIV testing as part of large TB contact investigations when IGRAs were also to be used for screening. The first use of T-SPOT®.TB (Oxford Immunotec, Inc., Marlborough, Massachusetts) for an integrated contact investigation occurred in 2010, when residents of a homeless shelter were exposed to an infectious TB case. Health department staff, state TB-control staff, and physicians from a nearby academic medical center were mobilized to assist with the investigation, which took place one evening at the shelter. Sixty-one people were screened, with no phlebotomy failures and only one uninterpretable (i.e., borderline) result; the remainder had negative T-SPOT.TB results. Opt-out HIV testing was accepted by 59 (97%) participants, with none of them found to be HIV-seropositive.

Most recently, a large integrated contact investigation was performed at a public housing complex. From July to December 2011, six cases of active pulmonary TB were identified in a single county in North Carolina. Four of the six cases had matching genotypes, as well as known or probable exposure to a public housing complex for disabled adults, prompting a mass screening at this site. Occupants were screened for symptoms and simultaneously tested for TB infection (using an IGRA, the T-SPOT.TB), HIV, and syphilis with a single blood draw. The screening effort involved 10 state disease intervention specialists (DISs), 13 LHD TB staff, two state TB staff, an Oxford Immunotec representative, a van driver (who transported symptomatic patients for chest radiographs), and four physicians. The LHD nurses coordinated the effort, including scheduling the screening, coordinating site logistics, and creating a master list of people requiring testing. LHD nurses and support staff also performed patient intake and did basic screening for medical history and TB symptoms; one state TB staff member (a nurse consultant) also assisted with intake. The DISs, who have extensive phlebotomy experience, drew blood and prepared the specimens for transport. Symptomatic patients were sent for a physician evaluation, including a chest radiograph. Patients requiring chest radiographs were transported to a local hospital with digital radiography, so radiographs were read in real time by the on-site physicians.

Of 181 total occupants of the housing complex, 167 (92%) were screened. Seven (4%) had positive IGRAs, 138 (83%) had negative IGRAs, 11 (7%) had phlebotomy failures, six (4%) had indeterminate/invalid tests, two (1%) had prior positive tuberculin skin tests, and three (1%) refused venipuncture. Ten HIV-positive people (all previously diagnosed but not reported by participants during screening) and one case of latent syphilis were also identified. Of note, two other people initially had false-positive HIV tests (i.e., a positive enzyme-linked immunosorbent assay, a negative Western Blot, and a positive pooled nucleic acid amplification test) that were negative on repeat testing.

LESSONS LEARNED

Integrated contact investigations are personnel and resource intensive during short periods of time and require significant advance preparation. The assistance of DISs from the HIV/sexually transmitted diseases program was essential, but these specialists were not familiar with issues surrounding TB and contact investigations. Two elements were important for making effective use of the DISs: general TB education and specific on-site education. General TB education was provided in the form of a "TB 101" lecture at a statewide DIS meeting, as well as several similar lectures to smaller groups. Complementing the lectures was on-site training at each contact investigation. Specialists (all of whom had prior phlebotomy training and experience) were trained regarding specimen collection and handling, which differ depending on which IGRA is being used.

To draw upon the workforce across the branch, significant training was required (e.g., a TB lecture for DIS personnel, training on phlebotomy, and the help of on-site staff from the IGRA company). Conversely,

cross-training of TB personnel regarding the basics of HIV is vital. The false-positive HIV tests described previously in the housing project contact investigation provided an important learning experience for both local and state TB-control staff. While the HIV staff were familiar with this type of false-positive result and have a standard protocol for retesting and patient communication, TB staff were not familiar with this protocol. The presumption was that the false-positive tests likely represented people with acute HIV, which resulted in significant consternation and discussion about how best to communicate the results to the patients. After discussion with the HIV program staff, the TB staff learned about the standardized protocol, but this knowledge only came about after a number of consultations with TB medical staff. Ongoing cross-training and education of staff at the state and local levels is essential to maintain the capacity to conduct large, integrated contact investigations.

The benefits of integrating HIV testing into contact investigations were unexpected. We anticipated that we would find previously undiagnosed people with HIV and engage them in health care, but this was not the case. Instead, the value of integrated HIV testing was twofold. First, people who may not have been comfortable disclosing their HIV status in the setting of a mass screening were discretely identified and prioritized for latent TB treatment. Second, several people who were known to be HIV-infected but who had fallen out of HIV care were reengaged in HIV care as a result of integrated contact investigations. One would expect that these people could have been ascertained using questionnaires instead of repeat testing, but this was not the case; several of these individuals denied having HIV infection at the time of screening but later admitted to prior knowledge of HIV status after the positive HIV test result was presented.

FUTURE DIRECTIONS

Integrating HIV screening into TB contact investigations has been a valuable public health tool in North Carolina, and we hope to further develop this tool in the future. Much of the cost of integrated screening derives from personnel and logistics; adding other tests to the integrated screening is relatively inexpensive and may improve the cost-effectiveness of screening. The next logical step will be to examine the feasibility of adding hepatitis C screening into the integrated testing strategy. Universal hepatitis C screening of adults aged 20–69 years has been found to be cost-effective in at least one analysis,[16] but significant issues remain in optimizing the referral and treatment of hepatitis C virus-infected people after diagnosis. To address these issues, structured interventions are needed to link people with hepatitis C into care. Similarly, further training and continuous program evaluation will be necessary to ensure that any people identified with HIV infection during an integrated contact investigation are engaged in appropriate HIV care.

The cost of IGRAs remains a significant barrier to their routine use. Although IGRAs are reportedly cost-effective relative to tuberculin skin testing,[17] their absolute cost still is often cost-prohibitive to public health departments with declining budgets. Cost analyses from the public health perspective, taking local circumstances into account, will be needed to effectively target the use of IGRAs in integrated screening efforts. The additional cost of IGRAs may be counterbalanced by improved programmatic effectiveness (i.e., increased proportion of tested patients with valid results and increased likelihood to start and complete latent TB treatment).[18] As such, overall program costs will need to be carefully weighed against benefits for rational policy-making.

No individual patient data or personal health information were used for manuscript preparation; therefore, institutional review board approval was not required.

REFERENCES

1. Trends in tuberculosis—United States, 2011 [published erratum appears in MMWR Morb Mortal Wkly Rep 2012;61(18):329]. MMWR Morb Mortal Wkly Rep 2012;61(11):181-5.
2. Sprinson JE, Flood J, Fan CS, Shaw TA, Pascopella L, Young JA, et al. Evaluation of tuberculosis contact investigations in California. Int J Tuberc Lung Dis 2003;7(12 Suppl 3):S363-8.
3. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. MMWR Recomm Rep 2010;59(RR-5):1-25.
4. Goswami ND, Hecker EJ, Vickery C, Ahearn MA, Cox GM, Holland DP, et al. Geographic information system-based screening for TB, HIV, and syphilis (GIS-THIS): a cross-sectional study. PLoS One 2012;7:e46029.
5. North Carolina Department of Health and Human Services, Communicable Disease Branch. 2011 tuberculosis statistics for North Carolina. Raleigh (NC): State of North Carolina Department of Health and Human Services, Division of Public Health; 2012. Also available from: URL: http://epi.publichealth.nc.gov/cd/tb/figures/tbannual2011.pdf [cited 2013 Jan 26].
6. North Carolina Division of Public Health. North Carolina Electronic Disease Surveillance System [cited 2012 May 28]. Available from: URL: https://ncedss.ncpublichealth.com/login.do
7. North Carolina Department of Health and Human Services, Communicable Disease Branch. North Carolina epidemiologic profile for HIV/STD prevention and care planning. Raleigh (NC): North Carolina Department of Health and Human Services, Division of Public Health; 2011. Also available from: URL: http://epi.publichealth.nc.gov/cd/stds/figures/Epi_Profile_2011.pdf [cited 2012 May 28].
8. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep 2006;55(RR-14):1-17.

9. Targeted tuberculin testing and treatment of latent tuberculosis infection. ATS/CDC Statement Committee on Latent Tuberculosis Infection membership list, June 2000. MMWR Recomm Rep 2000;49(RR-6):1-54.
10. Linas BP, Wong AY, Freedberg KA, Horsburgh CR Jr. Priorities for screening and treatment of latent tuberculosis infection in the United States. Am J Respir Crit Care Med 2011;184:590-601.
11. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Recomm Rep 2005;54(RR-15):1-47.
12. Li J, Marks SM, Driver CR, Diaz FA, Castro AF 3rd, de Regner AF, et al. Human immunodeficiency virus counseling, testing, and referral of close contacts to patients with pulmonary tuberculosis: feasibility and costs. J Public Health Manag Pract 2007;13:252-62.
13. Reichler MR, Bur S, Reves R, Mangura B, Thompson V, Ford J, et al. Results of testing for human immunodeficiency virus infection among recent contacts of infectious tuberculosis cases in the United States. Int J Tuberc Lung Dis 2003;7(12 Suppl 3):S471-8.
14. Sanders GD, Bayoumi AM, Sundaram V, Bilir SP, Neukermans CP, Rydzak CE, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. N Engl J Med 2005;352:570-85.
15. Person AK, Goswami ND, Bissette DJ, Turner DS, Baker AV, Gadkowski LB, et al. Pairing QuantiFERON Gold In-Tube with opt-out HIV testing in a tuberculosis contact investigation in the Southeastern United States. AIDS Patient Care STDS 2010;24:539-43.
16. Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clin Infect Dis 2012;54:1259-71.
17. Nienhaus A, Schablon A, Costa JT, Diel R. Systematic review of cost and cost-effectiveness of different TB-screening strategies. BMC Health Serv Res 2011;11:247.
18. Grinsdale JA, Ho CS, Banouvong H, Kawamura LM. Programmatic impact of using QuantiFERON®-TB Gold in routine contact investigation activities. Int J Tuberc Lung Dis 2011;15:1614-20.