

Translating Tuberculosis Research into Practice: Collaboration Between Academic Researchers and Public Health Departments in North Carolina

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Successful collaborations between academic researchers and local health departments are vital for public health research, but developing and maintaining such partnerships is often difficult. However, in the North Carolina Tuberculosis Control Program, such partnerships have flourished and have led to notable improvements in patient care.

Between 1995 and 2010, medical consultants for the North Carolina Tuberculosis Control Program initiated and conducted 7 different studies, which were published in 6 papers [1-6]. During that same period, other researchers published the results of 2 multicenter clinical trials of tuberculosis treatment, both of which included sites in North Carolina [7, 8]. All 9 studies had a direct impact on clinical practice, with rapid movement from study results to policy changes and improved patient care. We describe these studies and discuss how close ties between academic researchers and public health professionals in North Carolina have promoted rapid implementation of evidence-based tuberculosis treatment.

Background

Collaborations between academic institutions and local health departments have long been critically important to the success of public health research; indeed, without the combined resources of both entities, some questions would be impossible to answer. In tackling such problems, the university brings expertise, funding, and occasionally additional staff members, while the health department brings practical knowledge of the target community and, most importantly, access to patients.

Although academic researchers often design studies and then seek to collaborate with public health departments, the cooperation between academic centers and local health departments does not (and should not) always begin with a study protocol. Researchers often get their ideas for studies through contact with local public health providers and patients. Such contact can (and should) lead to collaborative research projects that fully and equitably call on the strengths of both the academic researchers and the public health providers. Such cooperation is a component of what

is now called *community-based participatory research*, which has been identified as an area of focus for future public health education by the Institute of Medicine of the National Academies [9].

Despite these advantages, collaborations between academic researchers and public health departments are often difficult to establish and maintain. Barriers to research at local health departments include limited capacity, the perception that research has little relevance to the functions of the health department, uncertainty regarding how research fits into the professional roles of health department staff members, and the perception that university researchers are out of touch with the needs of the community [10]. That said, health department staff members believe that research contributes to their knowledge, their professional growth, and improvements in clinical practice [10].

Of course, there are many examples of successful partnerships. In this paper, we describe one such partnership and show how collaboration between an academic medical center and a local tuberculosis control program led directly to changes in public health policy that benefited both staff members and patients.

Translating Study Results into Improved Patient Care

In 2011 North Carolina had 244 cases of active tuberculosis [11]. By law, all patients in the state who are receiving treatment for active tuberculosis must have each dose directly observed by a health care worker [12]. Thus, virtually all individuals with tuberculosis are treated through local health departments, in most cases using standardized protocols. For complicated cases, medical consultative services are provided by 2 faculty members in the Division of Infectious Diseases at Duke University Medical Center (D.P.H. and J.E.S.). Within North Carolina, Wake County is

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the second most populous county, but it has the highest case rate for tuberculosis. J.E.S. serves at the staff physician for Wake County's tuberculosis clinic.

In this section, we describe and discuss several tuberculosis research projects that were conducted at sites in North Carolina. These 9 studies are summarized in Table 1.

Human immunodeficiency virus (HIV) testing in tuberculosis patients. One of the first studies we performed was a retrospective review of all patients treated for tuberculosis in North Carolina during the period 1993-1999 [1]. Of the 3,119 tuberculosis patients for whom information about HIV testing was reported, more than 34% had not received HIV testing; 604 (19%) of these 3,119 patients had never been offered the test, and 465 (15%) had refused HIV testing. HIV testing appeared to be targeted to those individuals thought to be at high risk of infection, but many patients with epidemiologic risk factors for HIV infection were not offered testing.

In 2007 North Carolina discontinued its policy of requiring HIV pretest counseling. Immediately afterward, the North Carolina Tuberculosis Control Program instituted a policy of offering opt-out HIV testing to all tuberculosis patients, regardless of their perceived risk for HIV infection. As a result of this change, HIV testing of tuberculosis patients dramatically increased. In 2008 only 3 (0.9%) of 335 tuberculosis patients were not offered HIV testing [13], and in 2010 only 1 patient was not offered HIV testing [14]. In the latter case, the patient died just 2 days after beginning tuberculosis treatment, before HIV testing could be offered.

Isoniazid (INH) and rifapentine in the continuation phase of tuberculosis treatment. The Tuberculosis Trials Consortium (TBTC) is a multisite clinical trials group funded by the Centers for Disease Control and Prevention (CDC) and tasked with conducting "programmatically relevant" research regarding tuberculosis diagnostics and therapeutics. One such project was TBTC Study 22 [7], which demonstrated the efficacy of once-weekly administration of INH and rifapentine in the continuation phase of tuberculosis treatment for HIV-negative patients with no cavitary lesions on initial chest radiograph. Several North Carolina sites participated in this study. Study 22 also showed that individuals with cavitary disease and positive mycobacterial sputum cultures at 8 weeks had a probability of relapse greater than 20%, even when they were treated with standard therapy of INH, rifampin, ethambutol, and pyrazinamide for 2 months followed by INH and rifampin for 4 months. This latter finding was later supported by the results of a retrospective systematic review that assessed clinical trials of rifamycin-containing treatment regimens [15].

As a result of these findings, the North Carolina Tuberculosis Control Program added once-weekly combination therapy with INH and rifapentine to its list of approved treatment regimens. Additionally, anticipating CDC recommendations in advance of published guidelines, we extended treatment duration to 9 months for all patients with cavitary

disease and for those whose sputum cultures were positive after 2 months of treatment.

Rifampin plus pyrazinamide for treatment of latent tuberculosis infection. Rifampin plus pyrazinamide has been used in selected patients for the treatment of latent tuberculosis infection since 1999. After reports of fatal hepatotoxicity related to this regimen began to emerge [16], we conducted a retrospective review of 114 patients who had received this regimen at Wake County Human Services between December 1999 and May 2002 [2]. In this cohort, 67.5% of individuals completed the full course of therapy, which is a good rate of completion, considering that 60.5% of the study population was homeless. Of the 114 patients who did not complete therapy, 8 patients (7%) stopped therapy due to toxicity, and 106 patients (93%) were lost to follow-up. Unfortunately, 5.3% of patients taking the regimen acquired confirmed or suspected hepatitis during treatment.

In response to these data, we decided to place stringent controls on use of combination therapy with rifampin and pyrazinamide, although we did not go so far as to completely discontinue use of this treatment regimen. The regimen can now be prescribed only with the approval of the medical director of the North Carolina Tuberculosis Control Program and must be given according to a strict clinical protocol under the direct supervision of a physician (ie, there are no nursing protocols). We have had no deaths or hospitalizations from this regimen.

Epidemiology of pediatric tuberculosis. To learn more about the epidemiology of pediatric tuberculosis in North Carolina, we reviewed all 180 tuberculosis cases that occurred among children in the state from January 1, 1994, to December 31, 2002 [3]. We found that pediatric tuberculosis in North Carolina is limited almost entirely to African American and Hispanic children; specifically, 88.3% of the pediatric patients with tuberculosis in our study were non-white. Furthermore, one-third of these pediatric tuberculosis cases were "foreign-associated" (either the child was foreign-born, or the parents of the child were foreign-born); half of these foreign-associated cases were in US-born children of foreign-born parents [3].

Pilot screening program for pediatric tuberculosis. As a result of our epidemiologic study of pediatric tuberculosis in North Carolina, we designed a pilot screening program for US-born children of foreign-born parents who had emigrated from tuberculosis-endemic regions; this program was carried out in the Wake County Human Services pediatric clinic [3]. Beginning in July 2004, all children who met the aforementioned screening criteria were administered a tuberculin skin test; if the test result was positive, they were treated for latent tuberculosis infection. Unfortunately, the yield of this screening program was quite low, with only 0.32% of US-born children of foreign-born parents having a positive tuberculin skin test result. Thus the project was discontinued after about 5 months. (Sometimes, our projects show us what does *not* work.)

TABLE 1.**Research Projects Conducted from 2002 to 2010 that Impacted Policy and Patient Care in the North Carolina Tuberculosis Control Program**

Project	Description	Findings	Policy impact
HIV testing in tuberculosis patients [1]	This study assessed HIV testing practices for tuberculosis patients in North Carolina from 1993 to 1999.	- At least 34% of tuberculosis cases had not been tested for HIV. - HIV testing seemed to be targeted at groups believed to be at high risk. - Although HIV testing rates had improved over time, many persons had not been offered HIV testing.	- North Carolina now provides opt-out HIV testing to all tuberculosis patients regardless of age or perceived risk. - In 2008 only 3 (0.9%) of 335 patients were not offered HIV testing, and only 11 (3.3%) refused testing.
Rifapentine and INH in the continuation phase of tuberculosis treatment (TBTC Study 22) [7]	This study compared the safety and efficacy of once-weekly rifapentine and INH to twice-weekly rifampin and INH in the continuation phase of treatment for pulmonary tuberculosis. Several North Carolina sites participated.	- Once-weekly INH and rifapentine is safe and effective in the continuation phase of treatment for HIV-negative patients without cavitory disease. - Relapse was associated with acquired rifamycin resistance in HIV-positive patients with lower CD4+ cell counts. - Failure/relapse in HIV-negative patients was associated with cavitation on chest radiograph and a positive sputum culture at 2 months.	- INH and rifapentine can be used in the continuation phase of treatment if the patient is HIV-negative, has no cavitory disease, and has negative sputum cultures at 8 weeks. - All patients with cavitory disease and positive sputum cultures at 8 weeks must have 9 months of treatment.
Rifampin plus pyrazinamide for treatment of latent tuberculosis infection [2]	This study evaluated the safety and tolerability of 2 months of rifampin plus pyrazinamide for treatment of latent tuberculosis infection in 114 patients in Wake County, North Carolina, 60.5% of whom were homeless.	67.5% completed therapy. 5.3% developed confirmed or suspected hepatitis. - There were no hospitalizations or deaths.	- Rifampin plus pyrazinamide may only be used when a strict clinical protocol is being followed under the direction of a physician. - Use of rifampin plus pyrazinamide must be approved by the medical director of the North Carolina Tuberculosis Control Program.
Epidemiology of pediatric tuberculosis [3]	This study examined the epidemiology of tuberculosis in children in North Carolina from 1994 to 2002 (180 cases).	- Most cases of pediatric tuberculosis in North Carolina occurred in children who were African American or Hispanic. 1/3 of pediatric tuberculosis cases were "foreign-associated." - Half of foreign-associated cases were US-born children of foreign-born parents.	- A pilot screening program of US-born children of foreign-born parents was initiated at the pediatric clinic at Wake County Human Services, but yield for latent tuberculosis infection was low. - The project was discontinued, and such screening is not recommended.
Twice-weekly treatment of HIV-related tuberculosis (TBTC Study 23) [8]	This study evaluated the rate of confirmed treatment failure and relapse with an intermittent rifabutin-based regimen for the treatment of HIV-related tuberculosis. Several North Carolina sites participated.	5.3% of subjects had treatment failure or relapse. - Failure or relapse was associated with low CD4+ cell count (<100 cells/μL) at baseline. 89% of subjects with treatment failure or relapse had acquired rifamycin resistance.	- Recent CD4+ cell count (within 3 months) is required for patients coinfecting with HIV and tuberculosis. - Those with a low CD4+ cell count (<100 cells/μL) at the initiation of tuberculosis therapy receive a daily regimen for the entire course of therapy.
Therapeutic drug monitoring in patients coinfecting with HIV and tuberculosis [4]	Conducted between March 2002 and September 2007, this study analyzed INH and rifampin concentrations for 21 patients coinfecting with HIV and tuberculosis who had a low CD4+ cell count (<100 cells/ μ L). Levels were compared with reference ranges, and drug doses were adjusted to achieve desired serum concentrations.	86% had low serum concentrations of at least 1 drug. - All patients successfully achieved desired serum concentrations with higher doses. - No patient demonstrated any adverse effects attributed to higher doses of tuberculosis drugs.	- Measurement of serum drug levels should be considered for all patients coinfecting with HIV and tuberculosis who have a low CD4+ cell count (<100 cells/μL) and are taking INH or rifampin as part of therapy. - Therapeutic drug monitoring is also recommended for patients experiencing treatment failure or early relapse.
HIV care and mortality in patients coinfecting with HIV and tuberculosis [5]	This study analyzed HIV-associated health care utilization and mortality in North Carolina patients coinfecting with HIV and tuberculosis from 1993 to 2003.	- Patients with known HIV infection had a high risk of dying before tuberculosis diagnosis or during tuberculosis treatment. - Only one-third of patients with known HIV infection had seen a physician for their HIV in the previous 6 months. - Having a higher baseline CD4+ cell count and starting HAART during tuberculosis treatment were associated with reduced mortality.	- The North Carolina Tuberculosis Control Program routinely records HIV care data for all patients coinfecting with HIV and tuberculosis. - One of the state's tuberculosis medical consultants (all of whom are experienced HIV providers) reviews each of these coinfection cases in real time to look for problematic drug interactions and to advocate for the best HIV care.
Pairing tuberculosis testing with opt-out HIV testing [6]	This was a large-scale contact investigation at a meat packing facility that combined IGRA testing for tuberculosis with opt-out HIV testing (326 contacts tested).	88% of patients accepted HIV testing. 2 patients tested positive for HIV; both already knew their HIV status but had not disclosed it to health department staff. 95.7% of patients had adequate IGRA specimens. 10% of patients had IGRA results but no tuberculin skin test results.	Opt-out HIV testing is routinely performed in all contact investigations in which IGRA testing is used to screen for tuberculosis.

Note. HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IGRA, interferon gamma release assay; INH, isoniazid; TBTC, Tuberculosis Trials Consortium.

Twice-weekly treatment of HIV-related tuberculosis with rifabutin. TBTC Study 23, which was performed at sites in North Carolina, evaluated the safety and efficacy of twice-weekly regimens containing rifabutin for treatment of HIV-positive patients who are also being treated for active tuberculosis [8]. The overall rate of culture-positive treatment failure or relapse in this study was 5.3%; more importantly, 8 (89%) of the 9 individuals who relapsed showed newly acquired resistance to rifamycin. Relapse was associated with low baseline CD4+ lymphocyte counts (less than 100 cells/ μ L), low levels of INH, and low levels of rifabutin (although the latter was found in only 1 study) [17-20].

Because rifamycin resistance greatly increases the length and cost of tuberculosis treatment [21], the North Carolina Tuberculosis Control Program instituted a policy of requiring CD4+ cell counts for all HIV-positive patients being started on treatment for active tuberculosis; any HIV-positive patient with a CD4+ cell count less than 100 cells/ μ L is now required to receive medications daily throughout the course of tuberculosis treatment. Again, participating in this project allowed us to anticipate CDC recommendations and to institute them in advance of official guidelines. Since our policy was put into place, we have had no occurrences of acquired rifamycin resistance in patients who are coinfectd with tuberculosis and HIV.

Therapeutic drug monitoring for patients coinfectd with tuberculosis and HIV. Because of the association between relapse and low drug serum levels, Wake County Human Services instituted a therapeutic drug monitoring program for all patients coinfectd with HIV and tuberculosis. After being started on tuberculosis therapy, patients came to the clinic and were administered a dose of their medications, after which blood was drawn at 2 hours to determine levels of INH and rifampin, at 3 hours to determine levels of rifabutin, and at 6 hours to determine levels of all 3 drugs.

In 2009 we published the results of a retrospective analysis of the 21 patients treated under this protocol from its inception in March 2002 through September 2007 [4]. We found that 86% of these coinfectd patients had low serum levels of at least 1 drug when blood was drawn after 2 or 3 hours, but that therapeutic drug levels could be achieved with higher doses. No adverse events were associated with higher drug doses. Although our study was not designed to detect a clinical benefit from therapeutic drug monitoring, our findings suggest that low serum drug levels are common and that a therapeutic drug monitoring program can be successfully implemented in a local health department. Therefore, we suggest that therapeutic drug monitoring be performed for all HIV-positive tuberculosis patients with a CD4+ lymphocyte count less than 100 cells/ μ L (as well as for any patient experiencing treatment failure or early relapse).

HIV care and mortality in patients coinfectd with tuberculosis and HIV. To better understand those patients who are coinfectd with tuberculosis and HIV, we performed a retrospective review of all HIV-positive tuberculosis cases

reported in North Carolina from 1993 to 2003 [5]. We found that patients with known HIV infection had a high rate of death; 27 (5%) of the 542 patients in this cohort died prior to tuberculosis diagnosis, and 70 (13.6%) of the remaining 515 patients died during tuberculosis treatment. We also found that a higher baseline CD4+ lymphocyte count and use of highly active antiretroviral therapy (HAART) during tuberculosis treatment were associated with reduced mortality. In addition, only one-third of patients whose HIV status was known before they were diagnosed with tuberculosis had seen a physician for HIV treatment during the 6 months preceding their tuberculosis diagnosis.

These data were worrisome and clearly merited a response on the part of the tuberculosis control program. Ideally, each of these patients would be managed by an expert in the treatment of HIV and tuberculosis coinfection, but unfortunately many of these coinfectd patients live in rural or semirural areas far from major medical centers. To compensate for this lack of local expertise, local health departments have been asked to collect data on HIV care for all patients who are coinfectd with HIV and tuberculosis. One of the tuberculosis medical consultants then reviews this information in real time to look for potential drug interactions and to ensure optimal tuberculosis care. The consultants also assist with obtaining the best possible HIV care for tuberculosis patients and recommend therapy when appropriate.

Since this policy was implemented, the state nurse consultants have become more attuned to the specialized needs of patients coinfectd with HIV and tuberculosis, and they have developed strategies for getting these patients into HIV care. HIV care data have also been incorporated into the state's tuberculosis cohort review so that we can continue to monitor the effect our intervention is having on HIV-related mortality.

Pairing tuberculosis testing with opt-out HIV testing. Per CDC guidelines, HIV-positive individuals who are exposed to tuberculosis should receive treatment for latent tuberculosis infection regardless of their tuberculin skin test results [22]. However, many HIV-infected patients are unaware of their HIV status. Incorporating HIV testing into tuberculosis contact investigations would be an ideal way of identifying these high-risk patients and would perhaps prevent incident tuberculosis, but implementing such a strategy as a regular policy has proven challenging.

One barrier to routine HIV testing of tuberculosis contacts was removed when North Carolina lifted its requirement for pretest HIV counseling. Shortly thereafter, we conducted a large-scale single-site investigation of the contacts of a person with highly infectious tuberculosis who worked at a meat packing factory. We used that opportunity to test the feasibility of interferon-gamma release assay testing for tuberculosis combined with opt-out HIV testing [6]. Each contact received a tuberculin skin test and had blood drawn for interferon-gamma release assay testing; HIV testing was

offered on an opt-out basis. Of the 326 contacts screened, 88% accepted HIV testing; 2 of these individuals were HIV seropositive. Although both of these individuals knew their HIV status prior to testing, neither had revealed this fact to health department staff members. Also, neither of them tested positive for tuberculosis with either the tuberculin skin test or the interferon-gamma release assay; thus, without knowledge of their HIV status, the health department would not have offered them treatment for latent tuberculosis infection. We now routinely perform opt-out HIV testing during any investigation in which an interferon-gamma release assay is used for tuberculosis screening.

Summary

Incorporating the results of research into clinical practice is often a slow and inconsistent process, with uptake of proven interventions often occurring years after publication of the study that showed the intervention to be effective. Effective alliances between researchers and policymakers have been cited as potent tools to accelerate implementation of research results [23].

All of our projects were made possible by a close collaboration between researchers at Duke University School of Medicine, staff members of the North Carolina Tuberculosis Control Program, and local health departments. When health department staff members help generate research questions, they can easily see how the project will have a direct impact on their ability to care for patients. In fact, many of the aforementioned studies began as quality improvement activities. Other studies of tuberculosis-related interventions have demonstrated that early involvement of clinical and administrative staff members in research facilitates uptake of the research results [24]. Of course, such collaborations do not materialize overnight; we have been involved with the North Carolina Tuberculosis Control Program for more than 10 years.

One important point is that large-scale, multisite studies such as those performed by the TBTC have also directly benefited our patients. The primary benefit has been our ability to institute new recommendations quickly, as data become available, but there are additional benefits as well. Because the treatment regimens evaluated in such studies may eventually make it into CDC guidelines, study cohorts should be representative of the patients seen in clinical practice; by participating in research, we can ensure that our patients are represented in these groups. Furthermore, by having participated in the research projects, health department nurses are already familiar with the new drugs and regimens when they are released. We have also seen that a health department's participation in clinical research improves patient care throughout the department's clinics.

In summary, the North Carolina Tuberculosis Control Program maintains an active research agenda focused on patients. The results of the research studies we have conducted at local health departments have had a direct, rel-

evant impact on tuberculosis treatment policies and have improved patient care. In other words, our research benefits our patients. **NCMJ**

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