PUBLIC HEALTH

A National Tuberculosis Archive

Translation of tuberculosis research into benefits for citizens, clinical practice, and policy formation would be facilitated by development of an integrated resource.

Damian Gessler,[1]* Christopher Dye,[2] Paul Farmer,[3] Megan Murray,[4] Thomas Navin,[5] Randall Reves,[6] Thomas Shinnick,[5] Peter M. Small,[7] Terry Yates,[8] Gary Simpson[9]

Currently, no disease has the type of large-scale, systematic biological and informatic integration that permits researchers to cross easily between field-relevant and research-relevant isolates in the context of clinical, epidemiological, and phylogenetic characterizations. This is due, in large part, to the intense demands systematic data collection and organization place on clinicians and the public health apparatus. However, the complete population-based data collection infrastructure necessary for such a resource is already in place for tuberculosis (TB) in the United States.

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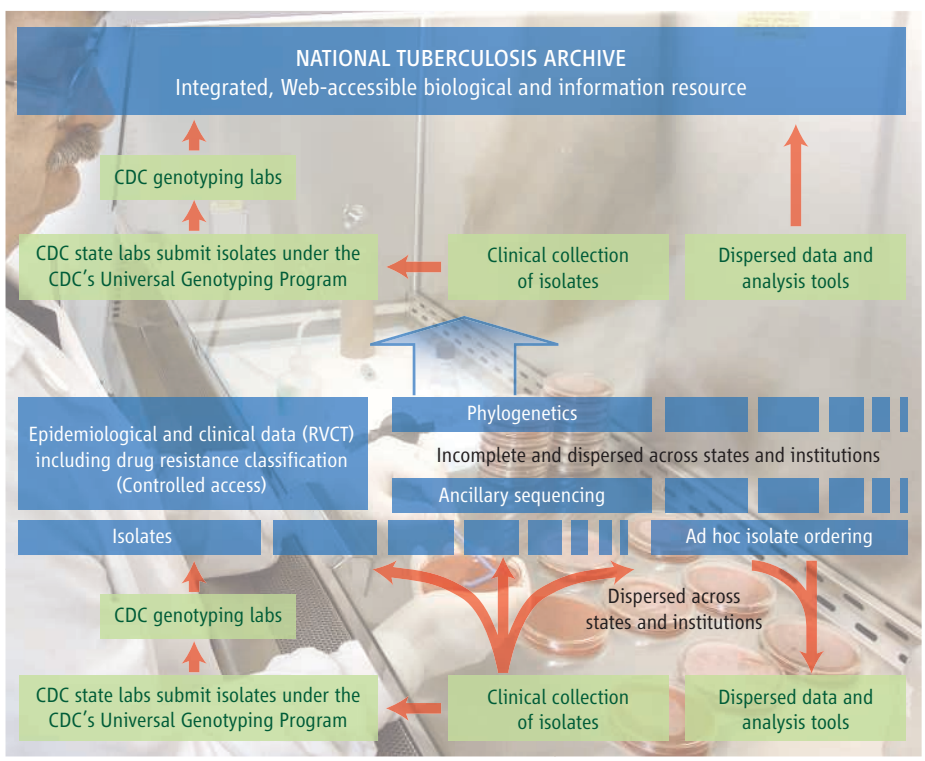
About one-third of the world's population is infected with *Mycobacterium tuberculosis* (MTB) (*1*). TB disproportionately burdens the world's poorest countries (*2*, *3*). The threat of emerging multidrug-resistant (MDR) strains (*4*) is severe. The number of TB cases in the United States is relatively small: just under 15,000 per year (*5*). Yet TB is fundamentally a "transnational" disease, with more than half of all U.S. cases occurring in non–U.S.-born persons (*5*). Schwartzman *et al*. (*6*) estimate that under current practices the United States will spend about $2 billion over the next 20 years just treating immigrants from Mexico. And although "only" 15,000 cases is a public health success story compared with historic epidemics, indolence in efforts to combat the disease would be unwise (*7*). It is estimated that cutbacks in TB-related resources in the late 1970s and 1980s contributed to a resurgence in TB among predominately immunocompromised and socially marginalized patients that cost more than $1 billion to control in New York City alone (*8*).

Every verified TB case in the United States is reported to the Centers for Disease Control and Prevention (CDC), along with clinical and epidemiological information, in a document called the Report of Verified Case of Tuberculosis (RVCT) (*9*). In 2004, CDC began a program to genotype a MTB isolate from every patient reported in the United States under its TB Universal Genotyping Program (*10*, *11*). Other laboratories already have substantial information on strains from countries in which epidemiologic trends are well described (*12*) or drug-resistant MTB is epidemic (*13*, *14*). The genome of MTB has been sequenced (*15*). Collections of genotypic, epidemiological, and/or clinical data are available in electronic databases but are not integrated, and phylogenetic data relating strains are incomplete. What is missing is an integrated, comprehensive, population-based biologic and informatic resource that can drive evidence-based decision-making.

We propose creation of a National Tuberculosis Archive, a comprehensive repository of characterized *M. tuberculosis* isolates along with their genomic, clinical, and epidemiological data (see figure, this page). Such an integrated resource would close the loop between clinical isolates and research data, allowing users to search on metadata criteria and to obtain samples of isolates matching field-relevant criteria. Molecular variation could be readily linked with phenotypic characteristics, and geographic distribution with temporal sampling. Bench scientists could explore fundamental questions about the relation between molecular variation and clinical consequences, health-care providers could alter patient care on the basis of strain-specific pathogen properties, and public health officials could track outbreaks across jurisdictions and back through time. Disparate data would be integrated in a Web-accessible platform for easy access.

Archiving etiologic material along with an integrated information resource has previously proved to be a prescient step in public health preparedness, as was seen in the 1993 hantavirus epidemic when museum archives of rodent sera and tissue samples were crucial in demonstrating that the virus had been widely endemic for years (*16*–*18*). This gave public health policy-makers invaluable baseline information to determine appropriate and targeted responses, while removing biowarfare concerns.



Differences between the current configuration of clinical isolates, research strains, and data and the proposed National Tuberculosis Archive. (**Bottom**) Current unintegrated configuration.

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[1]National Center for Genome Resources, Santa Fe, NM 87505, USA. [2]Stop TB, World Health Organization, Geneva 27, Switzerland. [3]Department of Social Medicine, Harvard Medical School, Boston, MA 02115; [4]Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115; Department of Medicine, Harvard Medical School, Boston, MA 02115; [5]Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, GA 30333; U.S. Department of Health and Human Services, Washington, DC 20201; [6]Denver Public Health, Denver Health and Hospital Authority, Denver, CO 80204; [7]Institute for Systems Biology, Seattle, WA 98103; Global Health Program, Bill & Melinda Gates Foundation, Seattle, WA 98102; [8]Department of Biology and the Museum of Southwestern Biology, University of New Mexico, Albuquerque, NM 87131; [9]Infectious Diseases, New Mexico Department of Health, Santa Fe, NM 87502, USA.

*Author for correspondence. E-mail: ddg@ncgr.org

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Results from prior molecular epidemiologically based efforts are a harbinger of the value of a comprehensive national archive for TB. A population biologic analysis of 10 years of data in San Francisco suggests that strains of *M. tuberculosis* may spread more efficiently in human populations when they are within the sympatric populations in which they evolved (*19*). So knowing an outbreak's characteristic molecular and phylogenetic signature can help in identifying new human ethnic groups at risk. A clinical study in New York City suggests that patients afflicted with specific clades of bacteria manifest a more profound disease (*20*, *21*). Other public health jurisdictions are seeing the full extent of unsuspected transmission and the need for new interventions (*22*). For the MDR-TB outbreaks caused by strain W in New York in the early 1990s, availability of archived samples linked to public health surveillance data enabled investigators to identify the origin of strain W, trace its acquisition of drug resistances, track its spread in New York City and around the country, and develop public health control measures (*8*, *23*, *24*).

The RVCT-based public health infrastructure and CDC Universal Tuberculosis Genotyping Program are already in place. We estimate the cost of integration for TB to be $15 million over 3 years.

Because *M. tuberculosis* is a human pathogen, but a poor candidate for bioterrorism, it is an excellent pilot for a more systematic program of human pathogen socioecological-genomic characterization. Improvements in disaster preparedness will result from a more focused and thoughtful integration of science, medicine, and public health.

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MEDICINE

A Portfolio Model of Drug Development for Tuberculosis

Seth W. Glickman,[1] Emma B. Rasiel,[2] Carol Dukes Hamilton,[3] Arsen Kubataev,[5] Kevin A. Schulman[1,4,6*]

Because of inadequate funding and the lack of promising drugs, no new antituberculosis drugs are likely to become available before 2010.

More than 10 million people develop tuberculosis (TB) annually, and about 2 million die each year (*1*, *2*). Forty years have passed since the last novel anti-TB drug, rifampicin, was introduced. Treatment requires difficult, multidrug regimens for a minimum of 6 months. Rates of multidrug-resistant cases are increasing, particularly in settings where directly observed therapy and standardized drug regimens are not used consistently and where supplies of anti-TB drugs are frequently interrupted (*3*, *4*). New drugs that offer improvements over current therapies are desperately needed.

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Public-private partnerships are promising efforts to combat the global burden of infectious diseases (*5*). Public sector and philanthropic organizations support research and management of drug portfolios while accessing the infrastructure and expertise of the pharmaceutical industry. The Medicines for Malaria Venture was the first such partnership (*6*), and the model has been successful in the campaign against river blindness in West Africa.

In 2000, the Global Alliance for TB Drug Development (TB Alliance) was established to spearhead development of new anti-TB therapies. The TB Alliance establishes partnerships between industry, governments, and academia and manages a portfolio of compounds in various stages of discovery and testing. The TB Alliance has publicly stated a goal of bringing a novel anti-TB drug to market by 2010 (*7*, *8*). According to the strategic plan of the Stop TB Partnership, the current global TB drug pipeline consists of 27 compounds. The TB Alliance manages two of the compounds in clinical testing and numerous others in discovery (*8*).

What is the likelihood of bringing a new TB drug to market by 2010? Pharmaceutical firms commonly evaluate drug development efforts using a "portfolio model," a structured process based on principles of decision analysis (*9*–*11*). The approach allows companies to value their research-and-development efforts and make resource allocation decisions. We developed a Monte Carlo simulation model to evaluate drug development from the perspective of a public-private partnership (*12*). Our model permits calculation of the expected number of successful compounds, expected costs at each stage of development, and all expected development costs for successful and unsuccessful compounds.

Inputs to the model include success probabilities, clinical trial costs, and durations for each stage of drug development (*12*). In calculating expected costs of clinical trials for a given compound, we assumed that the development process follows the standard framework of preclinical through phase III testing. The model also includes the rate of return used to discount future cash flows. We also examined the expected costs for clinical development in Uganda compared with the United States.

First, we used the global TB drug portfolio for clinical trials performed in the United States, which includes four compounds in preclinical development, five compounds in phase I, and two compounds in phase II (*8*). The likelihood that the portfolio will generate at least one successful compound is ~73% by year 14 (2019)

[1]Health Sector Management Program, The Fuqua School of Business, [2]Department of Economics, Duke University, Durham, NC 27708, USA. [3]Division of Infectious Diseases and [4]Division of General Internal Medicine, Department of Medicine, Duke University School of Medicine, Durham, NC 27710, USA. [5]American International Health Alliance, Moscow 125047, Russia. [6]Center for Clinical and Genetic Economics, Duke Clinical Research Institute, Duke University Medical Center, Durham, NC 27715, USA.

*Author for correspondence. E-mail: kevin.schulman@duke.edu