

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

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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.

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).

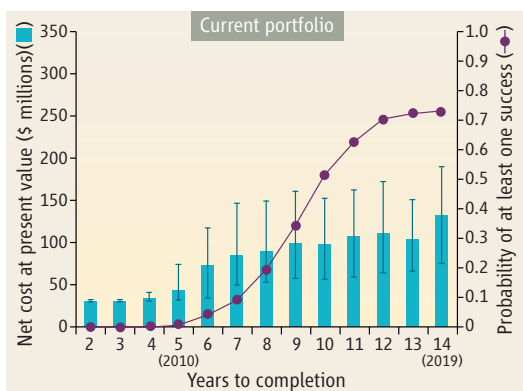
What is the likelihood of bringing a new TB drug to market by 2010? Pharmaceutical firms commonly evaluate drug development efforts using a "portfolio model," a structured process based on principles of decision analysis (9–11). The approach allows companies to value their research-and-development efforts 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)

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Simulation model for the likely global TB drug portfolio in 2005.

(see figure, this page, top). However, the likelihood of the portfolio's generating at least one successful compound by 2010 is less than 5%.

As expected, when we doubled the number of phase I and II compounds in the portfolio, the cumulative success probability for generating at least one compound was higher (93% versus 73%). However, the probability of developing a novel anti-TB compound by 2010 remained less than 5%.

Given that there is a probability of failure at each stage of clinical testing, coupled with the long lag time between discovery and conclusion of phase III testing, the TB Alliance and its partners, to meet their stated goal, must either quickly acquire several compounds (i.e., more than 10) in phases II and III of clinical development or achieve the capacity to oversee parallel phase II trials of different compounds in the hope of organizing a few large phase III trials. The likelihood that such a large number of advanced compounds would become available is infinitesimally small. It is more likely that the number of compounds would increase through discovery and the introduction of new compounds into early clinical testing. Even in this case, a large number of new candidates (i.e., more than 20) would be necessary to ensure a high likelihood of generating a new drug (see figure, this page, bottom). It would likely be nearly 10 years before any of these compounds reached the market.

The model also provides information about the costs likely to be incurred in bringing new anti-TB drugs to market. For example, suppose that the estimated global TB drug portfolio generates a successful compound in year 10. The mean net present value of the development costs for this drug is estimated at \$98 million, with a range of \$56 million to \$152 million. This figure does not include discovery costs, which have been estimated to account for one-quarter of total drug development costs (13). Moving clinical trials to countries with emerging economies, such as Uganda, could reduce this cost to \$45 million.

Our model further suggests that, in

the absence of any compounds currently in phase II trials, the TB Alliance would need 30 compounds in phase I testing to be 95% confident of generating at least one successful drug. Clinical testing in this scenario could take 12 years and cost as much as \$400 million. The TB Alliance's estimates, from which many of our cost inputs were derived, predict that the costs of developing a new drug for TB range from \$120 million to \$240 million. Given that the TB Alliance has an estimated \$36 million in cumulative funding through 2007 (14, 15), our analysis implies an estimated shortfall likely to exceed \$100 million for the first compound (12) and even more if we wanted to be confident of developing a single new therapy.

The findings underscore the need for strengthening collaborative research and development between the public and private sectors. Indeed, the TB Alliance recently announced a partnership with GlaxoSmithKline to develop four novel classes of potential anti-TB agents. The TB Alliance has also established formal relations with several academic medical centers and pharmaceutical firms, the Novartis Institute for Tropical Diseases, and experienced clinical trials groups, including the TB Trials Consortium of the Centers for Disease Control and Prevention. Our findings speak to the potential value of adopting a "product development" approach in the public sector when the goal is to address within a short period of time a specific public health need through the development of new clinical therapies.

Increased funding and cost-sharing strategies are needed as well. At the 2006 meeting of the World Economic Forum, the Bill & Melinda Gates Foundation announced a tripling of its commitment to TB eradication efforts to \$900 million over the next decade. Continued support of this kind can help narrow the funding gap for TB drug development. However, drug development will require substantial investments from the National Institutes of Health (NIH) and agencies in other countries. Current NIH funding for TB is about 1/20th the funding for HIV/AIDS

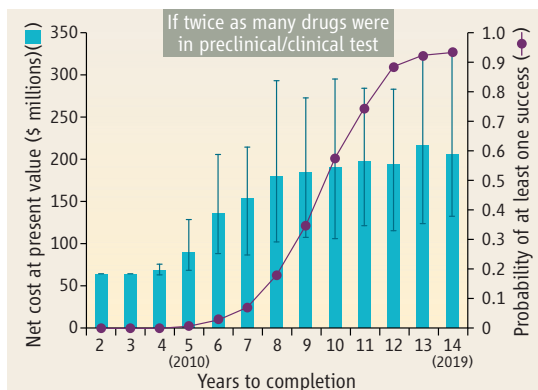
and 1/10th the funding for biodefense. We estimate that a drug portfolio designed to produce a single successful compound would require a commitment of up to \$400 million. This estimate includes only clinical development costs, and not the costs of distributing a new drug and educating health workers about its use.

Conducting trials in developing and transitional countries (where most TB cases are found) may be an attractive option for reducing costs. However, there are obstacles that a public-private partnership must consider. The most significant is the lack of infrastructure needed to conduct trials using best practices. Thus, for phase III trials, laboratories have to be built or revamped, with appropriate safeguards; equipment has to be ordered; taxes (formal and informal) have to be paid for importation; and personnel have to be trained to conduct the tests and quality-assurance activities. Although investments in clinical research capacity in these settings are critical for future drug development, and costs will diminish over time, private industry has not traditionally been willing to develop such sites. Public support for fixed infrastructure will be essential to the development of new therapies. Although the current drug pipeline and levels of funding are unlikely to yield a novel drug by 2010, the TB Alliance's success at bringing public and private parties together and nurturing the drug development process makes the future more promising than the past.

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Simulation model if the number of compounds in preclinical and clinical testing in 2005 is doubled.

Supporting Online Material

www.sciencemag.org/cgi/content/full/311/5765/1246/DC1