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How research can help control tuberculosis

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SUMMARY

Tuberculosis (TB) has played a central role in the history of biomedical science from Koch onwards. Research in the nineteenth and twentieth centuries yielded extremely valuable diagnostic, therapeutic and preventive tools for the control of TB. Following the development of short-course chemotherapy in the 1970s and 1980s, research into TB virtually evaporated. Despite the availability of an array of tools, TB control faltered, and the disease remains a major killer. The failure of the fruits of scientific research to control TB is a result of the shortcomings of the tools themselves as well the inadequate application of the tools in populations burdened by TB. A changing epidemiologic situation, with escalating rates of human immunodeficiency virus-related TB and the emergence of multidrug-resistant TB, further threatens global TB control. A robust TB research enterprise will be required

to meet the global goals for controlling TB in the twenty-first century. Basic research is needed to better understand its pathogenesis and immunology, and to identify targets for diagnostics, drugs and vaccines. Research into better biomedical tools to detect, treat and prevent TB is also a major priority, as all of the existing tools have important shortcomings. In addition, research into understanding how to apply both existing and new tools to control TB at the population level is urgently needed. Global funding for TB research, \$483 million in 2007, is slowly growing but is far behind need. To meet the ambitious goals of the Global Plan to Stop TB and the Millennium Development Goals, a massive investment in research will be necessary.

KEY WORDS: tuberculosis; research; control

TUBERCULOSIS (TB) has played a central role in the history of biomedical research, and efforts to control the disease have benefited enormously from scientific discoveries and achievements. Three Nobel Prizes in Physiology or Medicine, to Robert Koch, Niels Finsen and Salman Waksman, have been awarded for research on TB, and the discoveries of Koch and Waksman remain clinically relevant to this day. The spectrum of scientific inquiry into TB and the fruits it has

borne are truly spectacular. With the cumulative advances of Koch's discovery of the organism and the development of his postulates, Calmette and Guérin's production of the vaccine that bears their name, and the extraordinary progress with drug treatment of the disease, culminating in short-course chemotherapy in the 1970s and 1980s, many felt that science had done all it could do to control the disease. Beginning in the late 1960s, research investment in TB evaporated, victory was declared, and scientists working in the field moved on to other problems.¹ It only remained for clinicians and public health programs to use the tools science had so brilliantly provided for TB to be consigned to history.

The neglect of TB research for several decades has had a considerable impact on efforts to control the disease: the lack of academic interest in TB moved the disease out of biomedical research centers, often meaning that doctors, nurses and health scientists had little or no training in the disease. Complacency in the research community grew, despite the continuing toll of TB on society.² Minimal interest in TB in industry

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meant that very few new tools for TB were developed. Moreover, the consignment of TB to public health programs in some instances led to the perverse attitude that further research into the disease was unnecessary and, perhaps, counterproductive. Most international efforts to address TB control for much of the 1980s and 1990s focused on improving the quality of services delivered by underfunded control programs and downplayed the need for new knowledge, tools and approaches to reducing the burden of TB globally.³

While it was very true that poor performance of programs was (and remains) a major obstacle to the effective control of TB, it was also increasingly evident that the tools available for doing the job were increasingly inadequate. As the global epidemiologic situation has changed dramatically in the past 20 years, the challenges to contemporary control measures have grown. The World Health Organization (WHO) set goals for detecting 70% of all sputum smear-positive TB cases and curing 85% of them as an essential process in global control. While great progress has been made towards achieving these targets, case detection remains unacceptably low in areas such as Africa and Eastern Europe, and even in countries that have achieved the targets, such as Vietnam, incidence rates have not fallen. Reaching the Millennium Development Goals of halving the burden of TB disease and death by 2015 is therefore unlikely. The impact of the human immunodeficiency virus (HIV) on TB has been enormous, with escalating incidence, high mortality rates and changes in the clinical presentation of the disease that make diagnosing, treating and preventing TB more difficult. Smear-based case detection, for ex-

ample, misses at least half of all TB cases, and more so in settings where HIV is prevalent and among children. First-line drugs must be taken for 6 to 8 months, resulting in non-adherence and the risk of recurrent disease and selection of resistance. The emergence of multidrug-resistant (MDR) and, more recently, extensively drug-resistant (XDR) TB renders standard approaches to diagnosing and treating TB ineffective. Notably, most of the 500 000 cases of MDR-TB that occur each year are not even detected or properly treated. Drug-resistant TB requires new agents for successful treatment, given the generally poor responses to existing second-line drugs. The bacille Calmette-Guérin (BCG) vaccine has probably attenuated to impotence in preventing disease in adults.⁴

Over the past decade there has been a growing appreciation of the importance of research for strengthening global TB control. The second Global Plan to Stop TB, published in 2006, makes a strong case for the need for a wide range of research, and lays out a budget to support these activities,⁵ although many feel that even more money is required than is proposed in the plan.⁶ The research agenda for TB control is wide-ranging and multi-disciplinary. Reducing the burden of TB throughout the world and eventually achieving elimination will require a combination of effective biomedical tools and public health strategies.

The basic tools used in disease control—diagnostics, drugs, vaccines—are not magic bullets. To have an impact at the population level, these tools must be applied using effective public health strategies that maximize their benefits. Tables 1 and 2 show the biomedical tools used in controlling TB and the public health

Table 1 Biomedical tools used to control TB

Tools	Currently available	Limitations	In development
Diagnostics	Sputum smear	Poor sensitivity (<50%) especially in HIV-positive patients	Improved yield of sputum smear (e.g., light-emitting diode fluorescence microscopy)
	Solid culture systems (Löwenstein-Jensen)	Slow growth, resulting in long delays in diagnosis and detection of drug resistance; need for biosecurity	Simpler rapid cultures
	Liquid culture systems	Expense, need for biosecurity, high contamination rates, diagnostic delays	Antigen-based detection
	Nucleic acid amplification tests	Sensitivity in smear-negative cases, expense	Line-probe assays
	Tuberculin skin test	Poor specificity, inability to distinguish latent infection from active disease	Genotyping
Preventive therapy	Interferon-gamma release assays	Inability to distinguish latent infection from active disease	Third generation nucleic acid amplification techniques Volatile organic compound detection
	First-line drugs (HRZES)	Drug resistance, toxicity, duration of treatment, drug interactions, especially with antiretroviral agents	Fluoroquinolones Diarylquinolines
Treatment	Second-line drugs for MDR-TB	Low potency, toxicity and duration of treatment, extensively drug-resistant TB	Nitroimidazopyrans Diamines Oxazolidinones
	H, HR	Duration of treatment, toxicity, drug resistance, durability of protection in HIV-infected patients	See above
Vaccines	BCG vaccine	Lack of protection in adults, lack of standardization	Recombinant BCG Subunits Peptides Vectors, e.g., adenovirus Adjuvants

TB = tuberculosis; HIV = human immunodeficiency virus; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin; MDR-TB = multidrug-resistant TB; BCG = bacille Calmette-Guérin.

Table 2 Clinical and public health strategies for use of tools to control TB

Tools	Current strategies	Limitations	Future strategies
Diagnostics	Passive case finding: diagnose symptomatic patients who present to health services	Late detection of infectious cases. Relies on smear in most settings, with sensitivity <50%	Active case finding Contact evaluations Use of new technologies
	Algorithm for smear-negatives	Diagnostic delays, poor sensitivity and specificity	Joint TB-HIV case finding
Treatment	DOTS with first-line drugs	Drug resistance, poor adherence, poor program performance	Shortened treatment Intermittent treatment
	HE continuation phase (decreasing use globally)	Unacceptably high failure/relapse rate	Avoid drug interactions
	Retreatment with HRZES	Amplifies resistance in many patients	Treat based on known susceptibilities
Preventive therapy	Isoniazid for selected high-risk patients	Inadequate uptake, toxicity, adherence and fears of resistance	Shorter regimens with new agents (e.g., rifapentine) Continuous or repeated preventive therapy in high HIV settings Secondary preventive treatment Community-based preventive treatment Mass preventive treatment
Vaccines	Vaccinate newborns with BCG Vaccinate high-risk adults, e.g., nursing and medical students	No efficacy in adults No recent evidence of efficacy in newborns	Vaccinate neonates Booster vaccine for adolescents
Other	Antiretrovirals for advanced HIV disease Infection control	Many patients have tuberculosis before HIV therapy can be started Ignored in most of the world	Earlier detection of HIV and earlier initiation of HIV treatment Enhanced infection control

TB = tuberculosis; HIV = human immunodeficiency virus; DOT = directly observed treatment; H = isoniazid; E = ethambutol; R = rifampicin; Z = pyrazinamide; S = streptomycin; BCG = bacille Calmette Guérin.

strategies used to apply them to patients and communities. The tables list the current situation, important limitations and future directions to improve outcomes. All the tools and strategies currently in use have significant shortcomings. The development of new tools and strategies for delivering them, therefore, is an urgent priority for biomedical and public health research.

Control of TB in the coming decades will surely rest on new discoveries, novel technologies and innovative public health and clinical approaches to curtailing the spread of infection and the development of disease. A broad portfolio of research initiatives is essential to ensure future progress, as no one can say with certainty which ideas and strategies will be most effective. It is sobering to recall that throughout the global campaign to eradicate smallpox in the 1960s and 1970s, a vigorous research program was maintained to ensure that methods that proved ineffective in the field could be replaced with new approaches that might be more efficacious.⁷ Only when the disease was actually eradicated were the research efforts retired. A similar attitude toward TB must be maintained as control methods evolve. The recent declaration by over 60 Ministers of Health in Bamako, Mali, that at least 2% of national health budgets and 5% of donor funding should be earmarked for research, is a reminder of the value of research in promoting human health.⁸

RESEARCH NEEDS FOR NEW TOOLS

Basic science

The sequencing of the *Mycobacterium tuberculosis* genome a decade ago has released a cornucopia of

research on gene expression, drug targets, virulence factors and latency, all of which are necessary for developing new tools to control TB.⁹ Advances in bacteriology, immunology, genetics, biochemistry and a range of other disciplines will continue to foster knowledge that will help develop interventions for disease control. Basic biomedical research is as important as targeted research, as advances in seemingly unrelated fields can contribute to understanding TB biology and control. For example, the development of green fluorescent protein as a tool for studying cell biology, recognized by the 2008 Nobel Prize for Chemistry, has been used by researchers to understand *M. tuberculosis* metabolism and survival under stress conditions.¹⁰ The polymerase chain reaction, recognized by the 1993 Nobel Prize in Chemistry,¹¹ and other nucleic acid amplification techniques not only play a critical role in laboratory research on TB, but are central to several new diagnostic tests. Research in other seemingly remote or unrelated fields will certainly influence developments in TB in coming years, as well.

A key biological characteristic of *M. tuberculosis* is latency, which allows the organism to remain viable for many years without evidence of ongoing replication or damage to the host. Understanding latency will involve a better grasp of regulatory genes, biochemical pathways that sustain viability in the absence of active replication, and triggers of reactivation.¹² A more extensive appreciation for the mechanisms of latency could contribute to better diagnostic tools and new drugs for preventive treatment. Conversely, understanding host factors that are responsible for containing *M. tuberculosis* infection is important for

vaccine development.¹³ The majority of individuals infected with *M. tuberculosis* never develop clinical illness, but the immune responses that protect them are not well understood. Elucidating the correlates of immunity is an essential step for evaluating new vaccines, and could be used prognostically to distinguish those people who are unlikely to progress from latent infection to disease, and who would therefore not require preventive treatment.

Diagnostics

Perhaps the most striking shortcoming of current TB control efforts is the inability of clinicians and programs to accurately diagnose TB in a large proportion of patients, particularly in HIV-infected individuals and children. Globally, more than half of all TB cases are not detected, the result of health care system weaknesses and the inadequacy of available technology. If a diagnosis is absent, patients are not treated, transmission may continue, patients suffer needlessly and many eventually die. Reliance on the sputum smear, introduced by Koch more than 125 years ago, is an unacceptable global standard for case detection. In addition to its poor sensitivity, sputum microscopy cannot identify species and offers no information on drug susceptibility, making detection of drug-resistant TB impossible in settings where smear is the only tool available for diagnosis. Where culture is available, it is most often done with Löwenstein-Jensen medium, a robust but extremely slow method that results in long delays in case detection. Drug susceptibility testing (DST) is generally not available for the vast majority of TB patients, and where it is performed it is often by the laborious and time-consuming proportions method, further contributing to delays in providing proper care.

Research into new tools for TB diagnosis has made considerable progress in recent years, and a number of exciting new tools are under study or clinically available.¹⁴ Liquid-based culture systems, long known to be both more sensitive and faster than solid culture media, have been demonstrated to be feasible and effective in resource-poor settings and are now endorsed by the WHO for routine use in smear-negative, HIV-infected individuals with suspected TB.¹⁵ Recent efforts to bring liquid culture to the field have followed two very distinct paths. On the one hand, use of commercial systems, such as Becton Dickinson's Mycobacterial Growth Indicator Tubes (MGIT), has been demonstrated by a number of groups to be efficient and cost-effective.¹⁶ The advantages of commercial diagnostic products include reproducibility, standardization of training and methods, and management of the supply chain. Limitations to these products include costs, including capital expense for both machines and appropriate buildings for their use, high rates of contamination and training needs. Others have developed liquid culture methods that are not commercial products, but rather processes that can be adopted in

a variety of settings. The most notable of these is the microscopic observation drug susceptibility (MODS) method, a liquid system that is produced locally and has shown high sensitivity, specificity and rapidity for both identification of *M. tuberculosis* and detection of isoniazid and rifampicin (RMP) resistance.¹⁷ Advantages of MODS include low cost, reliance on microscopy skills readily available in many high-burden settings, and simplicity. Challenges with MODS include lack of standardization, variable results with DST, especially for RMP, and biosafety concerns.¹⁸

While the use of liquid culture is a major step forward from reliance on sputum smears, research is needed to bring faster, cheaper and simpler tools into clinical practice. Nucleic acid amplification (NAA) techniques have been used for some time to detect TB in industrialized countries, but these have been limited by expense, technological requirements and moderate-to-poor sensitivity in smear-negative patients. Several newer NAA methods are currently under study and could be used in clinical practice in the near future if their initial promise is sustained. A cartridge-based assay that amplifies specific gene targets to detect the presence of both *M. tuberculosis* and signature mutations associated with drug resistance, with a turnaround time of several hours, is now in late stages of development.¹⁹ Loop-mediated amplification is an isothermal technique that detects DNA using visual inspection of fluorescence in a closed system.²⁰ Research into these and related techniques is essential before they can be introduced in the field, but the prospect of case detection and identification of drug resistance in less than 24 h is extremely appealing.

Other genetic diagnostic techniques are also the subject of research. The use of solid phase amplification of gene targets for detection of *M. tuberculosis* sequences and drug resistance mutations is the strategy that underlies line-probe assays.²¹ Several commercial line-probe assays are already available, and their use has been endorsed by the WHO for detection of drug resistance in areas with high rates of MDR- and XDR-TB. Newer methodologies for detecting *M. tuberculosis* can be borrowed from other fields, such as sensing volatile organic compounds or parsing immunologic responses with novel immunoassay techniques.^{22,23}

While all of the new diagnostic modalities described above would propel TB control forward dramatically, a tool that would revolutionize the fight against this disease would be a point-of-care rapid test, such as a dipstick test, that reliably detected active disease and which could be deployed in primary care settings in high-burden areas. Such a test is currently science fiction, but most technological breakthroughs begin as science fiction and only become reality by dint of investment, innovation and industriousness. The technology for dipstick tests is widely available and extensively used for diagnosing conditions as varied as

pregnancy and HIV infection, but substantial obstacles to a dipstick test for TB must be overcome. For example, detection of antibodies against *M. tuberculosis* antigens is a strategy that has consistently failed in the past, as humoral immune responses are neither sensitive nor specific in assessing the presence of disease. Dipstick detection of *M. tuberculosis* antigens appears feasible for patients with disseminated disease, such as those with advanced HIV infection, but serum or urinary antigenemia appears uncommon in the majority of TB patients. Rapid detection of antigens in sputum or respiratory secretions is a possible method for addressing this problem. It is clear, however, that a vigorous program of applied research is necessary to bring about this essential revolution in diagnosing TB.

Drugs

The current drug armamentarium for TB is remarkable in two respects: first, it is miraculous when one considers that TB was incurable just 60 years ago; but second, it is absolutely inadequate given the current challenges in TB control. The deficiencies of current drug therapy for TB include the lack of high-quality regimens for drug-resistant disease, the long duration of 'short-course' chemotherapy, the potentially life-threatening toxicities of first-line agents and serious drug-drug interactions, particularly with RMP.

Drug-resistant TB has existed since the dawn of the antibiotic era. The majority of patients treated with streptomycin in the first Medical Research Council randomized trial acquired resistance to that drug,²⁴ and resistance to current first-line drugs is a global crisis.²⁵ Use of second-line drugs has predictably led to the selection of further resistance, and the specter of XDR-TB has emerged in the past several years.²⁶ Development of new drugs that are active against MDR- and XDR-TB is imperative. In addition, improving the potency of drug regimens to permit significant shortening of TB treatment would help turn off the spigot of acquired drug resistance by facilitating treatment supervision and treatment completion in resource-limited areas. Moreover, development of new drugs and regimens that are less toxic and that neither induce nor are affected by P450 cytochromes is important for advancing safety and allowing co-administration of TB and HIV drugs in the hundreds of thousands of individuals who require treatment for both diseases.

After a hiatus of almost 30 years, the TB drug development pipeline has of late experienced the beginnings of a renaissance.²⁷ Several existing agents in established drug classes are in advanced clinical trials, and several newer agents are in Phase 1 and 2 trials. Rifapentine, an RMP analogue that has greater potency and a longer half-life, has been shown to be effective in shortening the duration of TB treatment in an animal model, and is now under study for treatment-shortening in humans.²⁸ Moxifloxacin (MXF) is a

potent fluoroquinolone that may permit treatment-shortening and which should also be very active in MDR-TB.²⁹ Several promising clinical trials have been completed, and a large study to determine whether treatment can be reduced to 4 months when MXF is used is now underway. Gatifloxacin is also potent, and studies of this agent are also being conducted.³⁰

New agents with unique mechanisms of action are clearly required for combating MDR- and XDR-TB. Several such agents are currently being evaluated. The adenosine triphosphate synthase inhibitor Tibotec Medicinal Compound 207 has been shown to have excellent activity against MDR-TB in a small Phase 2a trial in South Africa, and a larger trial is ongoing.³¹ The nitroimidazopyran OPC 67683 is being studied in a multinational trial of patients with MDR-TB,³² while a PA 824, a drug in the same class, has recently completed its first Phase 1 trial in TB patients.³³ A new diamine, SQ 107, will enter clinical trials shortly.

The apparent bounty of new agents in clinical trials obscures a critical problem in TB drug development, however. While a handful of new drugs is a huge advance over the situation just a decade ago, the pre-clinical pipeline of anti-tuberculosis drugs is perilously anemic. Substantial investment in basic research to identify new targets and pathways is needed, along with screening of compound libraries to identify existing entities with good activity. A vigorous program to develop new entities and compounds must then be followed by the laborious process of studying the toxicology, pharmacology, formulation and bio-availability issues required to bring a product forward into human clinical trials. This is an expensive and time-consuming process, and many potential drugs are left aside along the way for a variety of reasons. The shortage of pre-clinical compounds is thus a serious problem that portends a paucity of new agents in the coming decade. A strong commitment to funding discovery and preclinical development activities is therefore essential.

Vaccines

BCG is one of the most widely used vaccines in the world, but there is considerable evidence that it has a minimal impact on TB control. While early trials found high efficacy of BCG in preventing TB and death in children, adolescents and adults, more recent studies fail to find a protective effect, and several suggest a harmful effect.^{34,35} Genetic analysis of BCG strains demonstrates a large degree of genomic variation in the various extant strains, suggesting that evolution of the parental vaccine strain of Calmette and Guérin has occurred, rendering current preparations less immunogenic.³⁶ Given that the original BCG strain was not archived, it is not possible to begin again with the effective version of the vaccine. The development of new vaccines is therefore clearly a priority. An effective preventive TB vaccine would have only a modest

Table 3 Progress towards Global Plan to Stop TB targets for new tools

Tool	Global Plan targets	Progress to date/comment
Diagnostics	By 2006: Rapid culture for case detection and DST in demonstration phase	Liquid culture recommended by WHO but not widely used DST still restricted to reference centers
	By 2010: Point of care, rapid culture, improved microscopy, phage detection and simplified nucleic acid amplification tests introduced	Point of care test unlikely in next 3–5 years Phage detection technology of limited value Line probe assays proved effective and reliable, roll out proceeding slowly Comment: Progress in diagnostics is impressive; dissemination and uptake are key challenges
Drugs	By 2006: 27 new compounds in the TB pipeline By 2010: 1–2 new drugs licensed for TB indication; treatment shortened to 3–4 months	7 drugs in clinical trials (2 old and 5 new classes) 7–10 entities in preclinical development Comment: Despite real progress, TB drug pipeline is perilously thin
Vaccines	By 2006: 5 candidates in Phase 1 studies By 2010: 9 vaccines in Phase 2 studies; at least 2 products in Phase 2b studies (proof of concept); beginning of Phase 3 trials	7 products in Phase 1 or 2 trials Comment: Vaccine research is progressing well

TB = tuberculosis; DST = drug susceptibility testing; WHO = World Health Organization.

immediate effect on TB control, but over a period of years to decades could result in major reductions in the burden of disease as new generations gained protection from the vaccine. A vaccine that protected individuals with latent TB infection as well as those not yet exposed to the organism would be of extraordinary value.

Unlike developing vaccines for HIV/AIDS (acquired immune-deficiency syndrome), making a TB vaccine is known to be feasible because it has been done before. A key challenge for vaccine development is understanding the correlates of immunity, as noted above. In addition, the lack of animal models that clearly predict vaccine efficacy in humans is an important limitation. Nonetheless, considerable progress is being made in identifying candidate vaccines, and a number of clinical trials are planned or underway. Approaches being pursued include recombinant BCG with overexpression of antigenic epitopes, other attenuated mycobacteria (e.g., *M. vaccae*), subunit vaccines, peptides, adjuvants and novel vectors.³⁷ Early clinical trials focus on safety and immunogenicity, although determining the most appropriate immune responses is challenging. Clinical trials of vaccine efficacy require extremely large numbers of subjects and many years to complete. So, although it is unlikely that a new vaccine will be available in the coming 5 to 10 years, the impact of an effective product would be enormous for generations.

The Global Plan to Stop TB, as noted earlier, strongly endorsed the need for research to develop new diagnostics, drugs and vaccines for TB control. Table 3 lists the targets for development of these tools and progress toward these goals to date. It is encour-

aging that so much has been accomplished, particularly with respect to diagnostics, but it is also clear that much remains to be done.

RESEARCH NEEDS FOR NEW PUBLIC HEALTH STRATEGIES

A treasure trove of new diagnostics, drugs and vaccines will be of no value if they are improperly or ineffectively deployed to the populations affected by TB. An understanding of the epidemiologic basis of TB control is required to ensure that new tools are utilized to maximize their advantages and to interrupt the chain of transmission and disease that fuels TB epidemics. The current tools for TB control have failed for a variety of reasons, including inadequate performance (e.g., sputum smear), inadequate population coverage (e.g., weak health systems), failings in human behavior (e.g., non-adherence to treatment, resulting in treatment failure and development of resistance) and changing epidemiologic circumstances (e.g., HIV and MDR-TB). Research aimed at understanding and overcoming these obstacles is imperative for new tools to reduce the burden of disease. In the past 4 years, several global expert groups have published ambitious research agendas that address specific priority focus areas within the overall public health and medical strategies for addressing TB disease in specific populations, including among people living with HIV,³⁸ people with drug-resistant TB,^{39–41} and pediatric TB.^{42–45}

Incorporation of new tools into existing TB control programs will be both a major challenge and an important opportunity. Research into where new tools

fit in the diagnostic and treatment algorithms will be important to maximize their impact. For example, should NAA tests replace culture and DST? Should new second-line drugs be added to initial treatment in patients where drug resistance is suspected? Will treatment-shortening regimens require more or less monitoring of treatment response? Determining the best uses of new tools will require additional research beyond proving their efficacy. Operational research, long recognized as important but almost always underfunded, targets the processes and procedures of health care delivery in an attempt to improve performance. There is an extensive agenda of operational research priorities that relate to almost every component of program activity. Examples of this include improving laboratory processes, increasing the yield of screening for TB suspects, improving registries and surveillance systems, reducing barriers to access and addressing infection control in institutional settings, to name a few.

More effective use of biomedical tools also can be achieved through research aimed at enhancing the impact of clinical and public health interventions. Beyond operational research, it is essential to evaluate the strategies used to control TB from an epidemiological perspective.⁴⁶ As shown in Table 2, a number of our strategies are clearly ineffective at present, and new approaches need to be developed and evaluated to reduce the burden of disease.

In the diagnostics arena, it is essential to move beyond passive case finding at health facilities to find TB cases earlier. Intensified case finding at the facility level or enhanced case finding in the community are means by which individuals with disease can be detected sooner than by passive case finding.⁴⁷ Studies of the best ways to efficiently target those individuals with active TB and provide diagnosis and treatment sooner are needed to determine the most effective means of reducing transmission in the community and limiting unnecessary suffering and death from undiagnosed disease. As new tools become available it will be imperative to evaluate their impact in community settings, not just in clinics and hospitals.

New drugs for TB are the only hope that patients with MDR- and XDR-TB can be reliably cured. Yet, if they are given without assurance of adequate support for adherence, resistance to new agents is inevitable. Research into methods to promote adherence through a variety of modalities is necessary to guarantee that all patients are cured and to avoid the emergence of further resistance. Preventive therapy for TB is woefully underutilized at present, despite extensive evidence of its effectiveness at both individual and population levels. Mathematical models of TB control demonstrate that treatment of latent infection, with either drugs or vaccines, will be essential for the elimination of the disease.⁴⁸ Strategies for selecting appropriate populations for preventive treatment, including

but not limited to household contacts and those with HIV infection, need to be assessed and the means of ensuring that treatment is adhered to requires additional research. The impact of mass preventive treatment, as was done in Alaskan Eskimos in the 1950s and 1960s,⁴⁹ should be evaluated in other high-risk populations—a study of this approach in South African gold miners is currently underway.⁵⁰ As new agents that target latent organisms are developed it might be worth considering restricting their use to prophylactic treatment, thereby ensuring that resistance will not become a barrier to prevention and that options for those exposed to MDR- or XDR-TB are available.

Additional strategies for controlling TB are also important. Infection control has been completely neglected throughout the developing world until very recently, for example. The importance of institutional transmission of both drug-susceptible and drug-resistant TB to health care workers and other patients, particularly in settings with a high HIV burden,⁵¹ has become apparent, however, and research into the methods to control this source of infection is now a global priority. The research agenda in infection control is extremely broad, and includes management, hygiene, diagnostics, engineering, behavioral sciences and physics, to name just a few of the disciplines that can contribute to this effort.

Other interventions that may play an important role in controlling TB operate at the population level. This includes earlier use of antiretroviral treatment in people with HIV infection, improved general and micronutrient nutrition, and the availability of housing with better ventilation and less crowding. While all of these may seem investments that are worthwhile in their own right, research into the relative benefits and costs of each will enable policy makers to choose between options for the use of limited resources.

FUNDING

The research agenda for TB, as outlined above, is large, ambitious and urgent. But funding for TB research is anemic, paltry and insufficient. Despite the extraordinary global burden of TB in terms of lives lost, disability and health care and societal costs, investment in studying the control of the disease is miniscule. The Global Plan to Stop TB 2006–2015⁵ estimates that a minimum of \$9 billion—or \$900 million per year—should be spent on applied TB research between 2006 and 2015 to develop new drugs, diagnostics and vaccines, and yet current TB research and development (R&D) investments total less than half that amount. Moreover, recognizing that the Global Plan does not even include budget recommendations for basic science—the foundation of all progress in science—or for operational field studies to validate the use of new tools and to define the most successful control strategies in standard program settings, some

Table 4 Worldwide investment in tuberculosis research in 2007 by funding source (US\$; from Treatment Action Group Report)⁶

2007 rank	Institution	Amount (\$USD)	2007 rank	Institution	Amount (\$USD)
1	US National Institute of Allergy and Infectious Diseases, NIH	131 378 370	20	Canadian Institute of Health Research	3917 387
2	Bill & Melinda Gates Foundation	124 213 521	21	UK Health Protection Agency	3907 664
3	European Commission Framework 6/7	23 366 617	22	Statens Serum Institute, Copenhagen, Denmark	3 611 407
4	Otsuka Pharmaceutical Company	20 766 495	23	Germany, Max Planck Institute for Infectious Biology	2 336 000
5	US Centers for Disease Control & Prevention	17 874 795	24	Company Y	1 770 000
6	US other institutes & centers, NIH	17 257 593	25	New Zealand, Health Research Council	1 160 335
7	Wellcome Trust	15 448 553	26	South Africa Medical Research Council	1 096 987
8	UK Medical Research Council	15 021 383	27	Ellison Medical Foundation	1 020 900
9	Netherlands Ministry of Foreign Affairs	13 735 741	28	Mexico National Institute of Public Health	814 746
10	Novartis Institute for Tropical Diseases	11 700 000	29	Dafra Pharma International Ltd.	673 770
11	US National Heart, Lung, and Blood Institute, NIH	11 579 120	30	Swedish International Development Cooperation	572 337
12	Eli Lilly Foundation	10 450 000	31	Denmark Ministry of Foreign Affairs	353 246
13	US Agency for International Development	10 000 000	32	Brazil (amalgamated)	321 481
14	Company X	7 900 000	33	Anda Biologicals	130 711
15	AstraZeneca	7 650 000	34	Russian TB Institutes	120 316
16	Institut Pasteur	7 468 821	35	KNCV Tuberculosis Foundation	36 720
17	UK Department for International Development	6 006 379	36	US Food and Drug Administration	35 000
18	Sequella, Inc	4 735 000	37	Korean Institute of Tuberculosis	30 000
19	Irish Aid	4 050 000		Total	482 511 395

NIH = US National Institutes of Health.

have recommended that TB R&D needs investment of at least \$2 billion per year to achieve the goals of developing new tools that can set the stage for TB elimination by 2050.⁶ According to the most complete reported data set on global investments into TB research and development in the years 2005 and 2006—covering the launch of the Global Plan, in 2007, only \$483 million was spent on all TB R&D, including basic science and operational research, two categories not addressed by the Global Plan (Table 4).⁶ This represented a 12% increase over the \$429 million reported on TB R&D for 2006, but it still falls

far short of the need and targets of the Global Plan. As noted in the Treatment Action Group's (TAG's) 2008 report on TB research funding, 'expenditures are still woefully inadequate by almost fivefold when measured against the Global Plan and TAG's estimates of annual need in TB research and development. The overall impression is one of inadequacy and failure of political will'.⁶

The largest single funder of tuberculosis research, the United States National Institutes of Health (NIH), spends just five cents on TB for each dollar spent on HIV/AIDS research (Figure 1), despite the two diseases'

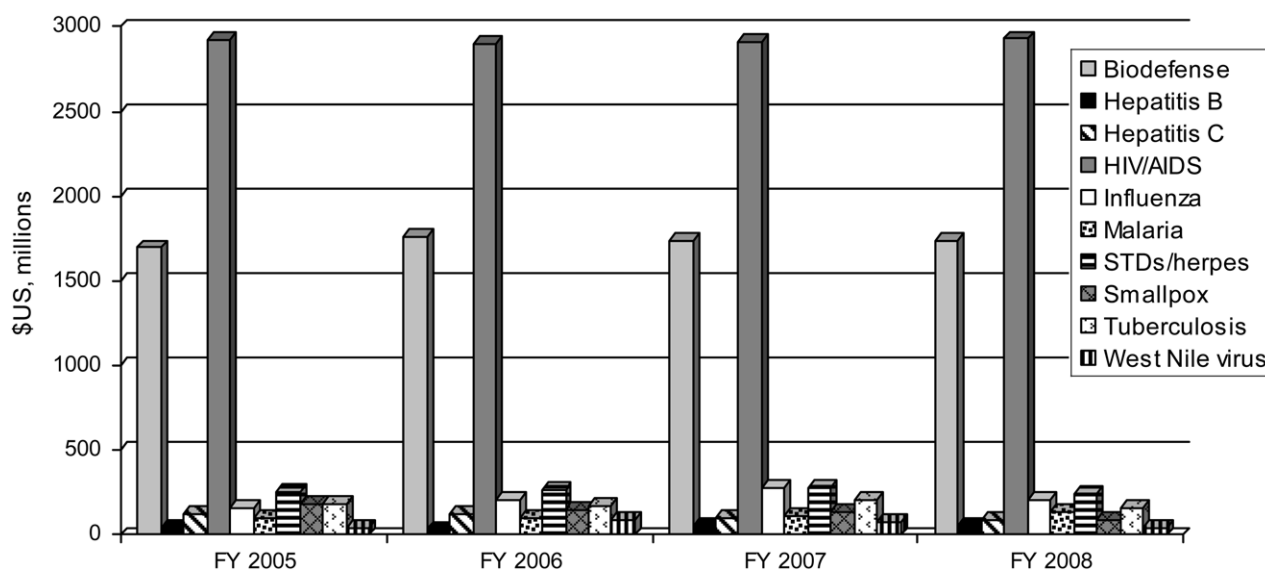


Figure 1 US National Institutes of Health spending on selected infectious diseases, 2005–2008. (From: Estimates of funding for various research, condition, and disease categories [RCDC], <http://report.nih.gov/rcdc/categories/>). FY = financial year; HIV/AIDS = human immunodeficiency virus/acquired immune-deficiency syndrome; STDs = sexually transmitted diseases.

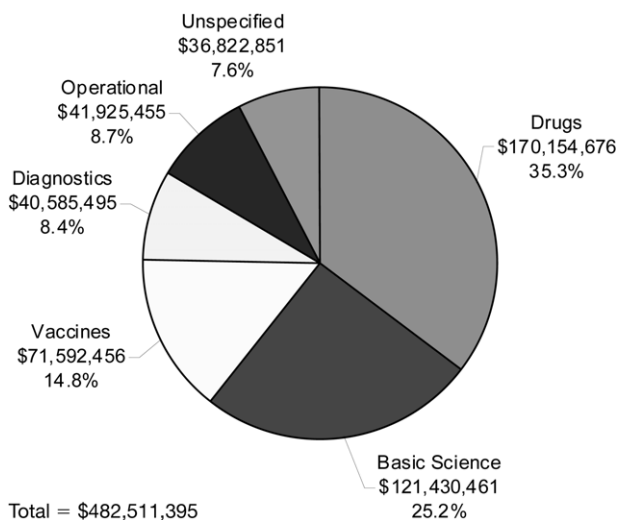


Figure 2 Worldwide investment in tuberculosis research in 2007 by category (from Treatment Action Group Report⁶).

similar global scale, scope and deadline. Figure 2 shows the TAG's tally of global TB research investment for 2007, highlighting the low levels of funding for basic science, new tools (drugs, diagnostics, and vaccines) and operational research. Even TB treatment research—the most well-funded research category—is, at \$170 million per year, less than half of the \$403 million in estimated direct costs to bring a new drug to market.^{52*}

CONCLUSION

Success at the mid-twentieth century in making TB a curable disease resulted in catastrophic declines in research funding, leaving the world unprepared for the resurgence of TB disease in the late century, fueled by the HIV pandemic and by collapsing health systems in the former Soviet Union, which created the opportunity for the devastating spread of drug-resistant TB. Now these two forms of TB are converging to form a 'perfect storm' which could render TB essentially untreatable without new measures.⁵¹ Despite new commitments made by the World Health Assembly,⁵³ the United Nations General Assembly Special Session's political declaration,⁵⁴ and world leaders at the launch of the Global Plan to Stop TB 2006–2015,⁵⁵ new public and private investment in TB research continues to lag far behind the needs; new philanthropic

initiatives such as those supported by the Bill & Melinda Gates Foundation, while laudable, will not be able to fill the estimated funding gap of about \$1.5 billion per year. To invest in the basic science, applied research and operational studies that are all necessary to develop, validate and refine the new tools essential to eliminate TB as a public health threat by 2050, governments in industrialized and in high-burden countries, as well as industry and the non-profit and philanthropic sectors, need to increase their funding for TB R&D to at least \$2 billion per year.

Control of communicable diseases such as TB is complex and costly, requiring years of sustained efforts. While much has been accomplished in our quest to develop the appropriate tools and strategies to contain this disease over the past 60 years, much more innovation and creativity is needed. Research into better methods to combat TB must continue until the disease is eliminated, as was the case for smallpox. To abandon research before achieving that goal would be foolhardy and risky. We will know we have performed enough research into controlling TB only when we have controlled it. As the American baseball legend and quipster Yogi Berra so famously said, 'It ain't over till it's over.'

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* The authors focus on new molecular entities and estimate an additional \$399 million per drug in indirect and opportunity costs. For a more recent and balanced overview of the costs of new drug development, see Congressional Budget Office, 'Research and development in the pharmaceutical industry', CBO publication no. 2589, October 2006, at <http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf> (accessed 17 December 2008). Conceivably, developing a new TB drug could be cheaper than an average new molecular entity if expedited development and approval procedures were used.

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R É S U M É

La tuberculose (TB) a joué un rôle central dans l'histoire de la science biomédicale depuis Robert Koch. Au dix-neuvième et vingtième siècles, la recherche a produit des outils extrêmement valables pour le diagnostic, le traitement et la prévention dans la lutte contre la TB. A la suite du développement de la chimiothérapie de courte durée dans les années 1970 et 1980, la recherche en matière de TB s'est virtuellement évaporée. En dépit de la disponibilité de toute une série d'outils, elle s'est mise à hésiter, et la maladie reste un tueur redoutable. L'échec des fruits de la recherche scientifique dans la lutte antituberculeuse résume des défaillances des outils eux-mêmes tant que de l'application inadéquate de ceux-ci dans les populations affectées par la TB. Une situation épidémiologique en voie de modification, avec des taux croissants de TB liées au VIH et avec l'émergence de la TB à germes multirésistants, menace davantage la lutte antituberculeuse mondiale. Pour arriver aux objectifs mondiaux de lutte antituberculeuse au cours du vingt-et-unième siècle,

il faudra une hardiesse robuste de recherche en matière de TB. Une recherche fondamentale est nécessaire pour mieux comprendre la pathogénie et l'immunologie ainsi que pour identifier les cibles pour le diagnostic, les médicaments et les vaccins. La recherche d'outils biomédicaux de meilleure qualité pour la détection, le traitement et la prévention de la TB constitue également une priorité majeure, car tous les outils actuels ont d'importantes limitations. En outre, la recherche s'impose d'urgence pour comprendre la façon d'appliquer les outils existants et à venir pour lutter contre la TB au niveau de la population. Le financement mondial destiné à la recherche en matière de TB, soit 483 millions de dollars US en 2007, augmente progressivement mais reste largement inférieur aux besoins. Un investissement massif dans la recherche sera nécessaire si l'on veut rencontrer les objectifs ambitieux du Plan Mondial Stop TB et les Objectifs du millénaire pour le développement.

R E S U M E N

La tuberculosis (TB) ha representado un papel central en la historia de la ciencia biomédica a partir de los trabajos de Koch. La investigación durante los siglos diecinueve y veinte aportó instrumentos diagnósticos, terapéuticos y preventivos extremadamente valiosos en la lucha contra la enfermedad. Tras la formulación de la quimioterapia breve en las décadas de 1970 y 1980, la investigación en TB prácticamente desapareció. Pese a la existencia de un conjunto apreciable de instrumentos, el control de la TB se ha debilitado y la enfermedad continúa siendo una causa importante de mortalidad. El fracaso de los frutos de la investigación científica en la lucha contra la TB es consecuencia de deficiencias propias de los instrumentos, pero también de una aplicación inadecuada de los mismos a las poblaciones agobiadas por la enfermedad. Las condiciones epidemiológicas cambiantes, con una tasa progresiva de TB vinculada con la infección por el virus de la inmunodeficiencia humana y la aparición de TB multidrogorresistente, amenazan aún más el control mundial de la TB. Con el objeto de cumplir la meta mundial de

erradicar la TB en el siglo veintiuno, se precisará una iniciativa sólida de investigación en este campo. Se requiere investigación fundamental a fin de profundizar los conocimientos sobre la patogénesis y la respuesta inmunológica y con la intención de detectar blancos para el diagnóstico, los medicamentos y las vacunas. Asimismo, constituye una prioridad importante la investigación sobre instrumentos biomédicos más eficaces para la detección, el tratamiento y la prevención de la TB, pues todos los existentes presentan deficiencias mayores. Además, se precisa en forma urgente la investigación sobre estrategias de aplicación de los instrumentos actuales y los nuevos, al objeto de luchar contra la TB a escala de la población. Los fondos mundiales destinados a la investigación en TB, 483 millones de dólares en 2007, están aumentando lentamente pero son todavía ampliamente insuficientes frente a las necesidades. Con la finalidad de cumplir las ambiciosas metas del Plan Mundial para Detener la Tuberculosis y los Objetivos de Desarrollo del Milenio será necesaria una inversión masiva en investigación.