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Tuberculosis in Low Incidence Areas: Where are the Resources for Control or Elimination?

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The World Health Organization (WHO) estimates that globally, 1.7 million deaths resulted from TB in 2004. Both the highest number of TB deaths and the highest TB mortality per capita are in the African continent, where HIV has led to rapid growth of the TB epidemic, and increases the likelihood of dying from TB. In 2004, estimated per capita TB incidence was stable or falling in five out of six WHO regions, but growing at 0.6% per year globally. In the United Estates and Western Europe the incidence per capita increased during the late 1980s and early 1990s, but peaked and has since fallen. From 1992 through 2006, the number of reported TB cases in the United States declined every year. This trend has been associated with a measured increase in the essential activities for TB control. These activities include increasing the percentage of those persons diagnosed with TB who are started on standard four-drug regimen (41-82%, 1993-2004), are given only directly observed therapy (22-55%, 1993-2002), and complete treatment in less than one year's time (64-80%,1993-2002)[1]. These achievements were accomplished along with high rates of reporting, and recognition of the obligation of the United States to contribute to global TB control. In addition, there have been substantial improvements in the rates of HIV testing (46-67% in persons aged 25-44 years; and from 30-54%, in persons of all ages, 1993-2003); and a decrease in the rates of TB and HIV co-infection if HIV tested (29-16% in persons aged 25-44 years old; and 15-9% in persons of all ages, 1993-2003); and in the numbers of cases with drug resistance (from 1564 to 832 isolates resistant to at least isoniazid, and from 485 to 124 isolates resistant to at least isoniazid and rifampin, 1993-2004)[1].

However, after 12 years of decline in the TB case rate from 1993 to 2004, the United States finds itself at crossroads. In 2004, the rate of decline in both the rate and number of cases was slower than previous declines. From 1993 to 2000, the annual rate of decrease of the number of cases averaged 6.0 (range 3.6-7.4%) and the decrease in the rate per 100,000 population averaged 7.1 (range 4.8-8.5%). From 2000 through 2004, the percentage decrease in the number and the rate has been less: 2.9% and 3.8%. The declines in three of these last fours have been the smallest over the 12 years of decline. This trend may reflect slow erosion in the ability to sustain long-term progress as resources to prevent and control TB in the United States have remained relatively fixed and have not kept up with inflation.

The decrease in TB incidence to historic low levels creates challenges for public health officials who are working to sustain programs and systems. Moreover, TB elimination is threatened by several converging factors, including the:

- Retreat of TB into high-risk populations at the margins of society where it can resist detection.
- The persistent disparities in TB rates between U.S.-born and foreign-born persons and between whites and racial/ethnic minorities.
- Persistence and growth of the global TB epidemic.
- Limitations of current control measures and recognition of the need for new tests and treatments, plus an improved vaccine.
- Changes in the health care system that makes the current context for TB elimination very different from that of a decade ago.

Distinctive challenges to TB control have arisen in regions where cases occur infrequently. Tuberculosis outbreaks have occurred in such areas and have produced severe and long-term effects. Low-incidence states or local jurisdictions with minimal TB control programs sometimes are unprepared to detect and contain these outbreaks. Likewise, shifting migration patterns are rapidly altering

the TB epidemiology in communities and states that previously had not had large immigrant populations who are at risk for TB. In this scenario, existing TB control programs that are equipped only for infrequent cases are confronted with an abrupt increase of cases and unfamiliar cultural issues. In addition, because of the rarity of TB, some healthcare providers in these settings lack either proficiency in TB diagnosis or familiarity with the latest treatment guidelines. Effective TB control and prevention in the United States require sufficient resources, continued collaborative measures with other countries to reduce TB globally, and interventions targeted to U.S. populations with the highest TB rates.

Tuberculosis is an infectious but chronic, relapsing-and-remitting disease that has profound effects on the persons it affects. As an illness, it also places a huge burden on health care services. Tuberculosis affects socioeconomically disadvantaged populations across the world. In resource rich countries it affects the poor, and in resource poor countries it affects the poorest of the poor. The treatment for this disease is long and arduous, and includes prolonged and sometimes coercive interactions with public health. Persons who are ill with TB - or will become ill with TB in the future - are those with the most at stake with regard to future progress and developments in TB treatment and prevention. However, these populations have not self-identified nor been sought after and engaged in the TB research endeavor. Thus, the resources needed for the care, control and development of new interventions for TB must come from the countries of the world that are resource-rich and were less than 10% of the patients affected with TB reside.

A particular challenge is how to procure and allocate resources for the control of TB crisis, considering that, like malaria and HIV, TB does not elicit a complete and committed reaction from the potential donor countries with the resources needed for sustaining TB control programs. Human resource allocation is also a problem, considering that the magnitude of the reaction needed to combat adequately the devastating crisis caused by TB, is both enormous and time-consuming. Other efforts require that public health officials keep up with fast-paced technologic developments. Also very important is the added necessity of the public health sector to build new relationships with nontraditional partners. People and groups in the United States dedicated to eliminating TB must increasingly reach out to other communities and persons affected by TB and primary care health professionals to enforce the message, "Think TB," especially as the incidence in the United States continues to decrease.

Control of TB: Why do it?

In attempting to prevent another cycle of neglect, to accelerate the decline in TB, and to proceed at a reasonable pace toward elimination, we must avoid the substantial risk of renewed complacency in the face of declining TB cases in the United States. To end the cycle of neglect that has characterized TB control in the United States, the Institute of Medicine report, *Ending Neglect,* recommended an aggressive strategy to:

– Maintain control of TB.

– Accelerate the decline in TB incidence.

– Develop new tools for TB diagnostics, treatment, and prevention.

– Increase efforts in the United States to help fight the global epidemic.

– Mobilize and sustain public support for TB elimination, and track progress[2].

As a first step toward addressing these issues, CDC has prepared a response to the Institute of Medicine's report[3] which outlines goals and objectives that will move us toward elimination. In addition, the U.S. Federal TB Task Force has drafted a more comprehensive response that incorporates the role and responsibilities of other federal agencies involved in TB-related activities, such as the Food and Drug Administration, the National Institutes of Health (NIH), the Agency for Health Care Policy and Research, the Federal Bureau of Prisons, the Health Care Financing Administration, the U.S. Agency for International Development (USAID), the Occupational Safety and Health Administration, the Department of Veterans Affairs, the Department of Housing and Urban Development, and the U.S. Marshall Service.

Control of TB: How to do it?

In 2002, the National Coalition for the Elimination of Tuberculosis (NCET) commissioned an analysis of the resources required to implement the recommendations provided in the Institute of Medicine report Ending Neglect The NCET report, *Tuberculosis Elimination:* The Federal Funding Gap estimated a total of US $528 million was necessary[4]. In 2004 update, NCET identified priority areas for intensified support[5]. These respond to current epidemiologic trend, and include efforts to:

– Reduce racial and ethnic disparities in the incidence of TB.

– Prevent, detect, and treat TB in persons who cross the U.S. Mexico border.

– Intensify use of universal genotyping for all culture-positive TB cases to improve our understanding and ability to interrupt transmission dynamics.

– Research to improve the diagnosis and treatment of TB. The report *Ending Neglect* concludes with the following thought: "as has been demonstrated in the past century of control efforts, social mobilization is critical to sustaining TB-control programs. Moreover, the TB-control community must pay as much attention to social mobilization efforts as it pays to the technical, medical, and scientific issues[2]".

As a result of increased attention, unparalleled since the early part of the 20th century, there has been a significant and measurable growth in interest in TB prevention and control. These advocacy efforts are challenged by the fact that a majority of those who contract TB are disenfranchised and at the margins of societies. This reality complicates their access to health care and the preventive benefits of public health, and is accompanied by a limited ability to influence and guide our nation's decisions on health priorities.

Therefore, bringing people with TB and their views to the forefront is a necessary step to raise awareness of the problem and to address unmet needs. This can only happen through mobilization and active partnership with communities of persons at high risk for TB, health-care professionals (private and public), industry, media, and policy makers[1]. Also, the elimination of TB is necessarily tied to increased and sufficient financial resources to accomplish the requisite tasks. A recent report published by the NCET posited, "Resurgence is again a threat. Given the huge resources required to reestablish control in the 1990s, the prudent action now is to provide the funding needed to accelerate progress toward eliminating TB in the United States. The alternative is to allow people in this country and around the world to suffer unnecessarily from this terrible, yet preventable and treatable, disease"[5]. Furthermore, U.S. engagement and significant participation in broad global efforts to improve health is necessary to reap global TB control. Specific objectives and actions steps are outlined in *The Global Plan to Stop TB*, published by the WHO-hosted Stop TB Partnership[6]. This document is now being updated to be consistent with Millennium Development Goals, 2006-2015[7] and describes the ubiquitous nature of TB, its global toll in illness and death-along with its socio-economic impact, and acknowledges that "threats to effective TB control are threats to global health". The crucial role of advocacy at the global, national, and local level is described. The agreed-upon mission of this global partnership consists of four parts:

– To ensure that every TB patient has access to effective diagno-sis, treatment, and cure.

– To stop the worldwide transmission of TB.

– To reduce the inequitable social and economic toll of TB.

– To develop and implement new preventive, diagnostic, and therapeutic tools and strategies to eliminate TB.

It has become increasingly clear that the successful elimination of TB necessitates going beyond technical remedies and must include socioeconomic interventions aimed at improving the overall welfare of individuals and communities.

Conclusions

Eliminating TB from the United States will require:

– sustained and increased efforts such as those that have been initiated over the past several years,

– Continued support to rebuild and update the country's health-care infrastructure, and prevent it from deteriorating again.

– Continued direct involvement and support for global TB control.

– The maintenance of an effective surveillance system to enable rapid identification of changes in disease trends and to adjust and target our prevention and control strategies accordingly.

– Continued epidemiological studies to improve our understanding of the dynamics of TB transmission and to use the data to model effective interventions.

– Research for the development of new diagnostic tests, therapeutics, and a safe and effective vaccine[1].

To succeed in eliminating TB, we must build an expanding coalition of governmental and nongovernmental partners to increase the impact of our prevention and control activities. Because people with TB are commonly afflicted with other health or social problems, TB-control programs' efforts should ideally facilitate referrals and access to other needed services, such as HIV treatment and care, drug rehabilitation services, and correctional and immigrant/refugee health services. We must also establish priorities for activities and increase their efficiency. With adequate attention to the problem and resources, the control and elimination of TB in the United States will eventually be achieved[1].

Support for TB research needs to at least triple to achieve the goals of *The Global Plan* to Stop TB. Public sector sources, research-funding agencies, and development agencies based in the United States, the United Kingdom and the European Union, are currently the world's major funders of TB research. Much greater investment is needed in basic research in order to assure that the current pipeline of promising new TB diagnostics, drugs, and vaccines, is replenished. Much greater investment in clinical trials infrastructure and operational research is also needed to support product development and introduction of new TB tools into TB and HIV/AIDS control programs in resource limited settings. Donors, funders, and developing countries need to create better mechanisms to track and report spending on research, including basic, applied, and operational TB research and development.

The philosopher Plato once said, "The punishment wise men suffer from indifference to public affairs is to be ruled by unwise men". In other words, if you don't get involved in the solution to a public health problem, you have no one to blame but yourself if you don't like what the world is not doing to combat TB. Saving 1.7 million lives a year, you might think, is a cause with which politicians and humanitarians would be inclined to be associated. But tackling tu-berculosis has never had the high profile of other public-health crises. There's much to do; though experts know what interventions can reduce needless deaths, getting them in place is not always easy. There is an infrastructure problem and a development problem that we, the resource-rich countries of the world, have not cared to deal with. If the world wants to avoid the needless deaths from the leading cause of fatalities due to a curable infectious disease, it's time that we did.

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Modificaciones de los programas de TB en prisiones ante el fenómeno migratorio

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Clásicamente el estar encarcelado, o haberlo estado, se ha considerado como un factor de riesgo para la tuberculosis (tb) que tal vez sea el principal problema de salud en las prisiones, de hecho se ha informado que la tuberculosis es hasta 100 veces más frecuente en el medio penitenciario, convirtiéndose las prisiones, a menudo, en reservorio de la enfermedad[1] lo que sin duda puede tener un importante impacto de la TB en la sociedad a la que vuelven los internos y en la que viven los trabajadores penitenciarios; esta circunstancia, junto a la obligación de los gobiernos de velar por la salud de los internos, obliga a los estados a asegurar que los presos sean custodiados en condiciones compatibles con la salud tal y como se recoge en la numerosa normativa internacional existente al respecto[2].

En los últimos años se está produciendo un gran incremento del fenómeno migratorio desde los países socioeconómicamente más desfavorecidos, generalmente con elevadas tasas de tb, hacia áreas más desarrolladas lo que nos hace pensar que se va a complicar el control de esta enfermedad, de hecho se estima que en Europa occidental, Canadá y EE.UU. más de la mitad de los nuevos casos de TB se producen entre inmigrantes extranjeros[3]. Hay controversias sobre la repercusión de la inmigración en las tasas de TB pero es claro el enlentecimiento en la caída de las tasas en los países desarrollados receptores de inmigrantes procedentes de países de alta endemia. En estos países se observa que, en la población autóctona, los casos de TB siguen una curva descendente mientras que entre los inmigrantes el número de casos se mantiene constante o aumenta[4].

En España, paralelamente al aumento de la llegada de inmigrantes, la población extranjera encarcelada se ha ido incrementando hasta llegar a constituir, en junio de 2006, casi un tercio de la población recluida; la Tabla 1 resume las áreas de procedencia de los internos que, de acuerdo con la estimación de distribución global de la tu-

berculosis que hizo la O.M.S. en el año 2005[5], provienen de zonas de elevada incidencia: es evidente el número ascendente de población extranjera con predominio de procedencia de países de elevada prevalencia, lo que, extrapolando lo referido para la población general, podría repercutir de forma negativa en el control de la TB en el medio penitenciario.

La tuberculosis en el medio penitenciario español

Desde 1993, y coincidiendo con el asentamiento del programa de prevención y control de la tuberculosis en el medio penitenciario iniciado en 1990, se produce un incremento progresivo del número de casos declarados hasta 1997 en que comienza a decaer (Tabla 2), este descenso acompaña al que se produce con los casos SIDA y coincide con la introducción de los tratamientos antirretrovirales de gran actividad (TARGA) por tanto es un descenso que, sin duda, también está muy influenciado por la buena respuesta de los infectados por el VIH a la terapia específica.

En cuanto a la infección: en el año 2005 al 67,9% de la población reclusa se le había efectuado el PPD con una prevalencia de positividad del 51,6% (7), aunque estos datos tienen el sesgo de que no todos los Centros Penitenciarios envían los datos recogidos en la aplicación informática estandarizada en la que se basan estas cifras.

Características del programa actual

El programa[8] que actualmente seguimos en las prisiones españolas da prioridad a las actividades encaminadas a conseguir un diagnóstico precoz de la enfermedad tuberculosa, por medio de la sospecha clínica y búsqueda activa de semiología sugerente de TB en consultas programadas fundamentalmente, y al tratamiento correcto de la misma mediante el tratamiento directamente observado (TDO), lo que se adapta a las recomendaciones recogidas por la mayoría de los organismos y sociedades nacionales e internacionales. El programa prioriza las actividades en función de los riesgos, de forma que se priman las actividades enfocadas a situaciones o internos con factores de riesgo de padecer la enfermedad[8].

Las medidas centradas en el screening de la infección tuberculosa, apoyadas en la intradermorreacción de Mantoux, base del programa original surgido en el año 1990, han quedado en un segundo lugar debido a que el elevado número de internos tuberculín-positivos generaba gran carga de trabajo en cuanto a realización de pruebas diagnósticas con baja rentabilidad (la mayoría de los casos de enfermedad no se diagnosticaban mediante el screening)[8] a lo que se unía una baja cobertura de los tratamientos de la infección tuberculosa latente (TITL) debido a la idiosincrasia del medio.

Modificaciones en los programas por el fenómeno migratorio

En las cárceles la situación puede ser distinta a la mencionada, de descenso de tasas en la población autóctona e incremento en la

Total extranjeros	Dic/1996 6153	Dic/2000 7642	Dic/2003 15205 (27%)	Dic/2004 17302 (29,1%)	Jun/2005 18004 (29,5%)	Jun/2006 19541 (30,7%)
Asia	54	48	68	156	189	202
Europa del Este	113 (Rumanía 12)	225 (Rumanía 60)	1006 (Rumanía 629)	1366 (Rumanía 889)	1536 (Rumanía 1012)	1771 (Rumanía 1199)
África subsahariana	877	645	1003	1058	1032	1221
Noráfrica	2219 (Marruecos 1498)	3214 (Marruecos 2167)	4998 (Marruecos 3911)	5640 (Marruecos 4398)	5777 (Marruecos 4404)	5898 (Marruecos 4451)
Iberoamérica	1483 (Colombia 831)	2049 (Colombia 1343)	3461 (Colombia 1809)	3735 (Colombia 1706)	4056 (Colombia 1764)	4866 (Colombia 1919)
% de área de alto riesgo	66,53%	80,88%	69,29%	69,1%	69,92%	71,42%

Tabla 1. (Países entre paréntesis: los que aportan internos de forma más significativa. Fuente: Dirección General de Instituciones Penitenciarias, Subdirección General de Tratamiento y Gestión).

inmigrante, dadas las características propias del medio (masificación, malos hábitos higiénicos, presencia de otros factores de riesgo…), que pueden favorecer la transmisión de la TB y que esa "doble ola" epidémica apreciada en la sociedad se convierta en una ola ascendente en las prisiones. No hay evidencia de que esto esté ocurriendo por ahora, también es cierto que prácticamente no hay estudios al respecto, pero es una situación que se debe tener en cuenta.

Cualquier modificación que se realice en estos programas debe ir encaminada a agilizar el diagnóstico precoz y tratamiento de la enfermedad y detectar los infectados, sobre todo los de más riesgo, es en este grupo donde, de acuerdo con lo recogido en los primeros párrafos de este escrito, habría que incluir a los inmigrantes en las cárceles, especialmente los provenientes de países con elevadas tasas de TB a pesar de que en la población inmigrante tuberculin positiva, y sin factores de riesgo asociados, se desconoce el riesgo real de progresión a enfermedad tuberculosa, lo que si se ha observado en éstos es que hay una mayor frecuencia de enfermedad en torno a los 2-3 años de su llegada lo que hace suponer en que llegaron recién infectados o se infectaron hace años y las situaciones de debilitamiento a las que se ven sometidos les hacen desarrollar tuberculosis por reactivación endógena[4].

Actualmente muchas prisiones, no todas, están dotadas de equipos radiográficos con suficiente calidad para efectuar los estudios oportunos y hay trabajos que demuestran que la radiografía de tórax puede ser más rentable como screening para los inmigrantes que la intradermorreacción de Mantoux[9,10] en tanto no se generalicen pruebas diagnosticas que aporten más fiabilidad a la detección de la infección, pero prácticamente no hay dotación de personal técnico para manejarlos; en general hay buenas relaciones y convenios de colaboración con los estamentos sanitarios extrapenitenciarios lo que soluciona, en parte, la cuestión de estudios microbiológicos . La cuestión del tratamiento está claramente resuelta, en la práctica totalidad de los centros penitenciarios se efectúa de forma TDO y las notificaciones de los casos a las autoridades, tanto penitencia-

	Nº de casos	Tasa (*1000)
1993	278	
1994	444	
1995	520	
1996	523	
1997	502	13,4
1998	316	8,2
1999	269	6,8
2000	224	5,7
2001	177	4,4
2002	177	4,1
2003	172	3,7
2004	102	2,9

Tabla 2. Evolución de los casos de TB en las prisiones españolas (Administración Central)[6]

rias como extrapenitenciarias se efectúa con regularidad, a pesar de los diferentes modelos de declaración que las distintas autoridades implementan, se suelen notificar las excarcelaciones de los enfermos en tratamiento para la continuidad del mismo fuera de la prisión. En las pautas de quimioprofilaxis se van extendiendo las de corta duración directamente observadas, aunque sigue habiendo unas cifras de adherencia al TITL más bien baja.

En las prisiones tenemos la gran ventaja del acceso inmediato al individuo, lo que en teoría facilita la aplicación rápida de las medidas que se adopten. En contraposición a esta ventaja nos encontramos con el inconveniente de que el medio "per se" choca con el tema sanitario: entre los trabajadores no sanitarios priman otras actividades no sanitarias como son las relacionadas con la guardia y custodia.

Es evidente que los programas para el control de la TB en las prisiones deben de formar parte de un esfuerzo amplio e integrado para mejorar y controlar la TB tanto dentro como fuera de las prisiones[1], el programa que actualmente seguimos en la prisiones españolas está demostrando su eficacia como se desprende de la Tabla 2; a mi parecer es un programa muy útil y que no precisa apenas modificaciones, "ni en el espíritu ni en la letra", por el incremento de la población reclusa inmigrante, tal vez lo comentado anteriormente en cuanto al mayor peso del screening radiológico, para lo cual habría que mejorar notablemente las dotaciones materiales y de personal adecuadas, sobre el PPD e incrementar las acciones de educación para la salud no sólo entre los internos sino también entre los trabajadores para concienciar sobre la importancia del problema.

El cambio debe realizarse a nivel institucional, y no por el aumento del número de extranjeros, sino porque los sistemas sanitarios penitenciarios no deben de estar separados del resto del sistema público de salud, debe ser parte de él porque las personas encarceladas tienen derecho a una asistencia sanitaria en las mismas condiciones que el resto, sin olvidar la repercusión que este tipo de enfermedades pueden tener sobre la salud en la sociedad general a la que van a volver; que no haya que depender del voluntarismo y de la buena disposición personal y de las mejores o peores relaciones con los estamentos sanitarios de la comunidad, ya que esto hace que no haya uniformidad en los resultados; debe ser la modificación a realizar no sólo en este programa, sino en todos los programas de salud que llevamos a cabo en las prisiones y éste es un cambio que únicamente depende de los responsables políticos.

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New Drugs for Treatment of TB

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In the past five years, there has been a resurgence in TB drug research, resulting in a global portfolio of compounds and projects in various stages of development, including at least six compounds currently in human testing. The TB Alliance and its partners are conducting two of these clinical programs; one (PA-824) is in Phase I and the other (moxifloxacin) is in Phase II/III development.

Current treatment of patients with tuberculosis is lengthy - 6-8 months of 4 drugs taken in combination, it is outdated - drugs discovered in 1940s, 1950s, armamentarium dwindling. Furthermore it is cumbersome - direct monitoring by healthcare workers, <50% of smear +ve cases receive standard of care yielding poor results. Incomplete treatment results in drug-resistant strains and relapse. TB and HIV treatment not easily co-administered. The bottom line is that we need a new treatment! The strategic approach is advancing novel regimens rather than single drugs through the later drug development pipeline.

Shortening and Simplifying Treatment: Two to three month regimens should be achievable with new, more effective drugs.

– Moxifloxacin (2RMZ/RM) could shorten therapy to 3-4 months in Grosset model
– J&J (TMC 207) and Lupin (LL-3858) compounds: may sterilize lungs in 2 months
– PA-824, OPC-67683 have sterilizing activity

Clinical Development Pipeline (Table 1)

PA-824 (Nitroimidazole) and OPC-67683 (nitro-dihydroimidazo-oxazole)

These two compounds have a potent bactericidal activity against replicating and static *M. TB* which has a high potential for shortening therapy. These have a novel mechanism of action.(Stover *et al*, Nature (2000);405:962). Furthermore they are active against drug sensitive and multi-drug resistant (MDR) strains of *M. TB* with a arrow spectrum of activity.

Moxifloxacin

Belongs to the class of fluoroquinolone antibiotic with significant potency against M. tuberculosis. Moxifloxacin has a novel mechanism of action for TB with an excellent safety record in humans (>40 million uses). Preclinical data indicates that a MRZ-based regimen could potentially shorten therapy to 4 months or less. The Chennai

data showed that fluoroquinolone could potentially shorten therapy to 3 months or less.

Overview of Clinical Development Plan-Moxifloxacin in TB (Table 2)

Identification of candidate biomarkers to streamline TB drug clinical testing

A serious shortcoming of the current drug development process for TB is the length of time it takes to validate cure. The identification of biomarkers predictive of TB treatment efficacy would represent a significant advance in TB drug development by shortening currently lengthy and expensive TB clinical trials. The TB Alliance initiated a project to identify both biomarkers for initial demonstration of potential efficacy in Phase I and II trials and validated surrogate endpoints for Phase III studies. two types of biomarkers:

– First, biomarkers of drug efficacy that provide an early indication of a drug's ability to shorten treatment duration.
– Surrogate markers of treatment efficacy that predict relapse and eliminate the need to conduct 1-2 year post-treatment follow-up.

The first phase of the project consisted of two sets of experiments; *in vitro* and *in vivo*. The purpose of the in vitro experiments was to identify analytes of bacterial (as opposed to those arising from the host animal) origin during disease or treatment.

The *in vivo* studies were aimed at identifying biomarkers (both bacterial and mammalian) in plasma samples from infected mice that were treated or left untreated.

Secondly the plasma samples were profiled against its range of proprietary metabolomic (Lipid LC/MS, Polar LC/MS & GC/MS) and proteomic (LC-MALDI-MS) bioanalytical platforms.

– Biomarkers of Drug Efficacy
– Biomarkers to Predict Relapse

Key Results and Next Steps

This initial study successfully identified a set of candidate biomarkers of Drug Efficacy. A total of 115 biomarkers, including pipecolate, whose profile was altered both by disease and by drug treatment were identified and designated as Drug Efficacy biomarkers. These biomarkers need to be studied further to confirm their validity as biomarkers of Drug Efficacy, and also for the possibility that they might reveal significant information about the physiology of TB disease.

The biomarker project also yielded 212 biomarkers potentially capable of determining future relapse. The utility of these biomarkers in predicting cure versus relapse now needs to be confirmed through a new study in which mice will be followed through a 3-month period without treatment to allow relapse to occur, and then samples from both cured and relapsed groups will be analyzed.

The Global Alliance for TB drug development (TB Alliance)

The TB Alliance is a product development partnership (PDP) with the central goal of markedly improving TB therapy by developing new drugs and novel combinations that will significantly shorten and simplify TB treatment, bringing it closer to the standard treatment of two weeks or less for most other types of bacterial infections.

The vision of the TB Alliance is to develop cost effective, affordable new and better anti-tuberculosis drugs in a way that is consistent with equitable access for all those who need them most. To ensure equitable access of new TB treatments especially for patients in high-burden countries whilst working closely with communities, governments and National TB Programme coordinators to ensure the future drugs will be adopted into TB Programmes. It coordinates and catalyzes TB drug development activities worldwide.

Compound	Development Stage	Sponsor / Coordinator
Gatifloxacin	Phase III	EC / OFLOTUB Consortium; IRD*; WHO TDR**; Lupin Ltd.
Moxifloxacin	Phase II / III	Bayer; TB Alliance; CDC***; University College of London; Johns Hopkins University
TMC 207	Early Bactericidal Activity	Johnson & Johnson (Tibotec)
OPC-67683	Early Bactericidal Activity	Otsuka Pharmaceutical Co.,Ltd.
PA-824	Phase I	TB Alliance
LL-3858	Phase I	Lupin Ltd.

Table 1. *Institut de Recherche pour le Developement
**World Health Organization, Tropical Disease Research
***Centers for Disease Control and Prevention

Trial (sponsor)	Study Design	Countries	Total # subjects	Status
TBTC #27 (CDC)	Moxi replaces Ethambutol (PII)	USA, Canada, Uganda, South Africa	336	Completed 6/05
TBTC #28 (CDC)	Moxi replaces Isoniazid (PII)	USA, Canada, Uganda, South Africa, Brazil, Spain	410	Trial initiated 2/06
JHU	Moxi replaces Ethambutol (PII)	Brazil	170	Trial initiated 10/04
REMox TB (UCL)	Moxi replaces Isoniazid (PII) Moxi replaces Ethambutol (PIII)	Tanzania, South Africa, Zambia	1500	Trial initiation planned for 2H2006

Table 2.