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BALANCING THE BARRIERS: EXPLOITING AND CREATING INCENTIVES TO PROMOTE DEVELOPMENT OF NEW TUBERCULOSIS TREATMENTS

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Tuberculosis is one of the great medical paradoxes of our age. There are powerful drugs to cure the disease, yet it is far from being eradicated. Instead, it has re-emerged with the deadly form—the multidrug-resistant tuberculosis . . . and it is gaining the upper hand unless other new effective drugs are discovered soon . . . .[1]

I. INTRODUCTION: TUBERCULOSIS AS A GLOBAL PROBLEM

As we face the tuberculosis epidemic of the twenty-first century, we have before us a very different war than that which confronted our forefathers of the nineteenth and early twentieth centuries.[2] Not only is the tuberculosis bacilli endemic, infecting a third of the world's population,[3] but it has developed the capacity to resist our badly antiquated antibiotic weapons.[4] Tuberculosis (TB) is now the leading cause of death from a single disease, accounting for over a quarter of the

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1. K K Tan, *Tuberculosis—Fighting a Losing Battle?*, 36 Sing. Med. J. 209, 211 (1995).

2. Tuberculosis was the leading cause of death in 19th century America, killing one in five persons. Sheila M. Rothman, *Living in the Shadow of Death—Tuberculosis and the Social Experience of Illness in American History* 2 (1994). Although other plagues such as the bubonic "Black" plague and the 1918 flu epidemic have produced similar devastation, they lasted only a short period of time and then were eradicated or burned themselves out. Laurie Garrett, *The Coming Plague—Newly Emerging Diseases in a World out of Balance* 157–58, 238–39 (1994) Unlike these plagues, tuberculosis has remained an ongoing public health threat for several centuries. *Id.* at 240–41.

3. *See* Charles Marwick, *Do Worldwide Outbreaks Mean Tuberculosis Again Becomes 'Captain of All These Men of Death'?*, 267 JAMA 1174 (1992); Phyllida Brown, *A Disease that is alive and kicking; tuberculosis returns to industrialized nations*, World Health, July 1993, at 4.

4. *See* Alan B. Bloch et al., *Nationwide Survey of Drug-Resistant Tuberculosis in the United States*, 271 JAMA 665 (1994); Thomas R. Frieden et al., *The Emergence of Drug-Resistant Tuberculosis in New York City*, 328 New Eng. J. Med. 521, 524 (1993); Kent A. Sepkowitz et al., *Trends in the Susceptibility of Tuberculosis in New York City, 1987–1991*, 18 Clinical Infectious Diseases 755 (1994).

world's avoidable deaths.[5] Recent estimates predict ninety million new TB cases by the end of this decade.[6] In dealing with the modern "white plague,"[7] we no longer have the luxury of dealing with the epidemic on a community-by-community or nation-by-nation basis. We live in a global village, linked to other nations and cultures by an ever increasing mobility that renders us all increasingly susceptible to tuberculosis.[8]

Further complicating the epidemic is the increasing number of tuberculosis cases resistant to one, two, or all of the existing anti-tuberculosis drugs.[9] This difficult-to-treat "multidrug resistant" disease (MDR-TB) ensures the global spread of tuberculosis in ever more

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5. Every year there are eight million new cases of tuberculosis and three million deaths caused by tuberculosis. The disease accounts for 6.7% of all deaths in the developing world, 18.5% of all deaths in adults aged 15 to 59 years, and 26% of avoidable adult deaths. John Porter et al., *The challenge is international*, World Health, July 1993, at 10. Currently TB kills more people worldwide than any other infection, including AIDS and malaria. *See* Brown, *supra* note 3. It is estimated that TB will claim 30 million lives during the coming decade; over 95% of these will occur in the developing world, but industrialized nations will also experience dramatic increases in TB disease and death. Dale I. Morse, *Directly Observed Therapy for Tuberculosis: Spend Now or Pay Later*, 312 Brit. Med. J. 719, 719–20 (1996); Hiroshi Nakajima, *Tuberculosis: A Global Emergency*, World Health, July 1993, at 3.

6. Mario C. Raviglione et al., *Global Epidemiology of Tuberculosis: Morbidity and Mortality of a Worldwide Epidemic*, 273 JAMA 220, 220 (1994).

7. The term "white plague" refers to the pallor of the patient afflicted with tuberculosis. The term was popularized by Rene and Jean Dubos, in their history of tuberculosis in the 19th and early 20th centuries. *See* Rene & Jean Dubos, *The White Plague—Tuberculosis, Man and Society* (1952). For other renditions of TB's historical impact, see Barbara Bates, *Bargaining for Life—A Social History of Tuberculosis, 1876–1938* (1992); Rothman, *supra* note 2; and F.B. Smith, *The Retreat of Tuberculosis 1950–1950* (1988).

8. Joan Stephenson, *Health at Home Means Watching the Global Village*, 273 JAMA 1648 (1995). In 1993, the World Health Organization (WHO) declared TB to be a global health emergency, a designation that had never before been applied to any single disease. Tuberculosis is now considered the greatest single threat to the world's public health. *See id.* Lee B. Reichman, *How To Ensure the Continued Resurgence of Tuberculosis*, 347 Lancet 175 (1996).

9. The development of drug resistance is due to inadequate or incomplete treatment of the traditional strain of tuberculosis. Although public health clinicians in the mid-20th century had at their disposal sanitaria and enforceable public health laws, both of these diminished in the latter part of the century. As a result, adherence to treatment plans eroded. Patients became less likely to complete their treatment regimens. In addition, physicians became less familiar with tuberculosis and its pathogenesis as the disease decreased in incidence; thus the medical profession became less effective at administering adequate therapy. Michael D. Iseman, *Evolution of Drug-Resistant Tuberculosis: A Tale of Two Species*, 91 Proc. Nat'l Acad. Sci. U.S. 2428 (1994). "We have turned a disease that was completely preventable and curable into one that is neither." Dr. Lee B. Reichman, President, Am. Lung Ass'n, *quoted in* Michael Specter, *Neglected for Years, TB Is Back with Strains That Are Deadlier*, N.Y. Times, Oct. 11, 1992, at A1. This phenomenon is not unique to TB, but applies to virtually all infectious diseases. Microbes are vested with high intrinsic mutability and rapid replication. As such, they present a constantly-evolving adversary. *See* Joshua Lederberg, *Infectious Diseases—a Threat to Global Health and Security*, 476 JAMA 417 (1996).

dangerous forms.[10] Unlike the TB of old, this virulent MDR-TB can result in quick death, especially if the patient's immune response is compromised by age, concurrent human immunodeficiency virus (HIV), or other chronic illness.[11] TB is already out of control in most of the world, and has become a substantial threat even in nations previously regarded as "safe."[12] In order to reverse this epidemic, the dense social, economic, and cultural barriers preventing effective prevention and treatment must be alleviated or circumvented.[13] This will be virtually impossible unless new, more effective treatments are discovered.

This Article considers the many barriers that health-care providers and public health authorities face in stemming the modern TB epidemic. Part II reviews historical public health measures, their results, and their adaptability to resurgent and MDR-TB. Part III considers the fundamental barriers to a successful global effort using these public health strategies, concluding that these barriers are insurmountable given the current arsenal of anti-tuberculosis therapies. Part IV examines the reasons why research and development of new anti-tuberculosis drugs and vaccines have stagnated over the last quarter century. Finally, part V explores incentives that might revive research and development of such therapies and thus tip the scales toward control of this dangerous new white plague.

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10. In the 1960s and 1970s, only one to two percent of tuberculosis strains evidenced resistance to existing drugs, and the resistance was limited to only one of the available drugs. The propensity for drug resistance has risen steadily. In 1992, 33% of tuberculosis strains found in New York City patients were resistant to at least one drug; 19% were resistant to two or more drugs. In developing nations, drug resistant strains are present in over 30% of cases. Iseman, *supra* note 9, at 2428. Others report even higher incidences of drug resistance. *See* Marwick, *supra* note 3. By 1991–92, one strain of tuberculosis (the "W-strain"), appearing initially in New York City, had developed resistance to every available drug and had a 50% mortality rate. Laurie Garrett, *The Return of Infectious Disease*, Foreign Aff., Jan.-Feb. 1996, at 66.

11. For example, HIV patients are extremely susceptible and vulnerable to MDR forms of tuberculosis: "[I]n fact, the HIV-positive are 40 times more likely to contract and develop tuberculosis that those who are HIV negative." Rosemary G. Reilly, *Combating the Tuberculosis Epidemic: The Legality of Coercive Measures*, 27 Colum. J.L. & Soc. Probs. 101, 104 (1993).

12. *See* Nakajima, *supra* note 5. Asia illustrates the tuberculosis epidemic at its worst; notably, HIV is also prevalent in developing Asian nations. It is estimated that nearly half the Asian population is infected with TB. The death rate for patients dually infected with TB and HIV is doubling every three to five years. *See* U.S. Dep't of Health & Human Servs., *Tuberculosis, HIV Co-epidemic to Multiply Sevenfold in Asia*, Pub. Health Rep., Jan.-Feb. 1995, at 108.

13. The tuberculosis epidemic, like most other infectious disease epidemics, is rooted in "conditions of social despair inflicted by one class of human beings upon another." Garrett, *supra* note 2, at 214 (citing Dubos & Dubos, *supra* note 7).

II. TUBERCULOSIS AND TRADITIONAL PUBLIC HEALTH STRATEGIES: TRIED, BUT NO LONGER TRUE

Tuberculosis is an ancient disease, dating back to the dawn of humanity. Evidence suggests that TB was present in ancient Babylonia, Egypt, and Greece.[14] For most of TB's long history, its cause was mysterious and elusive. Ancient Egyptians believed tuberculosis was rooted in the supernatural. Later, in the fifth century B.C., the Greek physician Hippocrates meticulously chronicled the signs and symptoms of tuberculosis, naming it *phthisis*, meaning to melt and waste away.[15] Well into the nineteenth century, some healers believed tuberculosis to be a hereditary weakness; others believed, more accurately, that *phthisis* was contagious and transmitted through the air. The ancient Greeks were prescient; an isolation treatment philosophy prevailed well into the twentieth century. Early physicians also employed various methods of "bleeding" and administered a variety of caustic medications, both orally and directly into the chest cavity, to treat *phthisis*.[16]

By the mid-nineteenth century, *phthisis* had acquired the Anglicized name *consumption*. Modern scientific inquiry had revealed that *phthisis* resulted from pathologic tubercle lesions found in the bones and tissues of patients with consumption.[17] Nevertheless, most cultures continued to view consumption as an immutable fact of life, a back-handed act of God, visited upon rich and poor alike, and largely resilient to any human intervention.[18] "Tuberculosis was inscrutable as Providence."[19] This attitude began to lose credibility in 1882, when Robert Koch, a German

14. For example, the bones of 3000-year-old Egyptian mummies show signs of tuberculosis; similarly, bony deformities associated with TB are represented in statuary dating back to 4000 B.C. Dubos & Dubos, *supra* note 7, at 5.

15. J. Arthur Myers, *Captain of All These Men of Death—Tuberculosis Historical Highlights* 11 (1977).

16. *See id.* at 12–17. Hippocrates and the physicians that followed him believed that good nutrition and exposure to healthful air were critical to prevention and treatment of the disease; as a result climatic changes and relocation to the mountains or seaside were recommended.

17. *Id.* at 34. These tubercle lesions are the result of the baccilli's destruction of normal lung tissue and replacement with small collections of necrotic matter. *See* 1 Kurt J. Isselbacher et al., *Harrison's Principles of Internal Medicine* 711–12 (13th ed. 1994).

18. Dubos & Dubos, *supra* note 7, at 210.

19. Smith, *supra* note 7, at 1. Nevertheless, as Smith documents, "Tuberculosis respected rank." Although the rich were as vulnerable to tuberculosis exposure as the poor, those with financial and social resources fared better in escaping active infection and in availing themselves of earlier access to treatment. *Id.* at 10.

bacteriologist, discovered the microscopic bacillus responsible for the tubercles and the disease.[20]

Once *Mycobacterium tuberculosis*[21] had been defined as the cause of tuberculosis, the contagious nature of the disease received more dedicated attention. Indeed, the discovery of the microbiologic etiology of tuberculosis and other contagious diseases produced a pronounced shift in public health policy. Prior to these scientific discoveries, public health efforts had targeted public hygiene, attempting to improve general living conditions and provide safe food and water supplies.[22] These efforts were not in vain; in the decades prior to the discovery of *Mycobacterium tuberculosis*, the mortality rate from tuberculosis markedly declined.[23] With the discovery of a microbiologic etiology for tuberculosis and other common infectious diseases, public health efforts began to focus on protecting individuals from the hazards of their environment, rather than changing the environment.[24] In the case of tuberculosis, now known to be caused by an airborne bacilli passed from the infected to the non-infected, this translated to increased momentum for public health detection, isolation, and mandatory treatment of infected patients.

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20. Dubos & Dubos, *supra* note 7, at 101, 210.

21. Tuberculosis results from chronic infections with *Mycobacterium tuberculosis*; the bacteria infects tissues of the lung, bone, and other organs, resulting in the formation of granulomas—areas of inflammation and decay. *See* Isselbacher et al., *supra* note 17, at 711–12. *Mycobacterium tuberculosis* is one of more than 30 members of the genus *Mycobacterium*. Other member of the genus also infect humans, notably, *Mycobacterium leprae*, the microbe responsible for leprosy. *See id.* at 710.

22. The public health efforts to improve living conditions were tremendously successful. Numerous infectious diseases, including cholera and typhoid, lost their status as mass killers as a result of improved sanitation and public health education. *See generally* John Duffy, *The Sanitarians: A History of American Public Health* (1990); John Duffy, *A History of Public Health in New York City* (1968); Garrett, *supra* note 2.

23. By 1900, the mortality rate from tuberculosis had dropped to half of what it had been in the middle of the 19th century, both in Europe and in the United States. Dubos & Dubos, *supra* note 7, at 186; Smith, *supra* note 7, at 236–37. How much of this decline was due to improved living conditions and how much was due to the periodic waning that is characteristic of infectious diseases is unknown.

24. Sylvia N. Tesh, *Miasma and "Social Factors" in Disease Causality: Lessons From the Nineteenth Century*, 20 J. Health Pol. Pol'y & L. 1001, 1004 (1995). Tesh notes that a second factor fueling the change in public health strategy was the political ideology of the time. The public health concentration upon sanitary reform and improved living conditions went hand-in-hand with the economic liberalism of the time. As this political theory lost vitality, the public support for the sanitation effort waned, and support for more aggressive public health actions in the form of quarantines and other coerced treatments gained strength. *Id.* at 1005.

A. *The Old Tuberculosis: A Historical Overview of Public Health Measures*

After the discovery of the tuberculosis microbe and the growing consensus that consumption was an infectious disease, New York City took the lead in devising a public health approach to the disease.[25] In 1889, the New York City Commissioner of Health commissioned a summary report on the contagiousness of tuberculosis. One of the physicians preparing this report, Dr. Herman Biggs, went on to submit a plan to control tuberculosis in the city. The plan called for the following: a systematic public education campaign to inform citizens of tuberculosis risks and preventive measures; compulsory reporting of all tuberculosis cases; new laboratories to aid in rapid and efficient diagnosis of patients; public health inspectors dedicated to monitoring the homes and treatment of patients known to have tuberculosis; establishment of special isolation wards in hospitals; and a new specialty hospital dedicated solely to care of tuberculosis patients.[26] Dr. Biggs's public health strategy, originally conceived in 1893, did not enjoy easy acceptance;[27] it was not until 1907 that the plan was fully implemented by New York City.[28] Nevertheless, it would become the model for public health authorities throughout the United States as they attempted to control tuberculosis.[29]

Most states passed laws to codify the public health strategy to be applied to tuberculosis.[30] The typical state law provided for mandatory screening of certain populations, frequently schoolchildren or persons

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25. Myers, *supra* note 15, at 59; Barron H. Lerner, *New York City's Tuberculosis Control Efforts: The Historical Limitations on the "War on Consumption,"* 83 Am. J. Pub. Health 758, 758–59 (1993).

26. Lerner, *supra* note 25, at 758–59.

27. In fact, the medical profession bitterly opposed the Biggs plan and sought to enjoin its implementation by proposing a series of bills to the State Legislature that would strip the Board of Health of any authority in dealing with tuberculosis as an infectious disease. Myers, *supra* note 15, at 59. The basis for their opposition was manifold: some adhered to the "anticontagionist" philosophy which held that genetically predisposed individuals contracted tuberculosis by exposure to harmful "miasmas"; others alleged that the mandatory reporting required them to breach a patient confidence. Lerner, *supra* note 25, at 758–59.

28. Myers, *supra* note 15, at 59.

29. Dubos & Dubos, *supra* note 7, at 211. Nearly 40 states have laws addressing control of tuberculosis, most of which were drafted around the turn of the century and are similar to the New York City model. *See* Lawrence O. Gostin, *Controlling the Resurgent Tuberculosis Epidemic: A 50-State Survey of TB Statutes and Proposals for Reform*, 269 JAMA 255 (1993); Karen H. Rothenberg & Elizabeth C. Lovoy, *Something Old, Something New: The Challenge of Tuberculosis Control in the Age of AIDS*, 42 Buff. L. Rev. 715, 743 (1994).

30. Gostin, *supra* note 29, at 255.

working in the food or health-care industries. Other provisions required testing of persons suspected to be harboring infectious tuberculosis; positive results were reported to the state or local authorities; this then triggered enhanced public health education efforts and monitoring.[31] When an individual was found to have active TB, and was recalcitrant or otherwise deemed an infectious danger to others, he or she could be confined to a TB treatment facility under the color of state law.[32]

1. Isolation and Supportive Care as Treatment

The increased isolation and institutionalization of tuberculosis patients dovetailed neatly with the sanitarium movement popular in Europe at the turn of the century.[33] Perhaps as a result of societal acceptance, institutionalization frequently was accomplished without resorting to state police power, through voluntary enrollment by the patients. The campaign to prevent and cure tuberculosis enjoyed wide public support.[34] Many patients eagerly sought care in a tuberculosis sanitarium, even if the institution was a public one; in fact, demand soon outpaced supply. Unfortunately, sanitarium treatment produced few miracles. Many patients, arriving too sick to derive significant benefit from the care, became permanent residents. Others stayed long enough to regain their strength, but, pressed to return to their family responsibilities, left while still contagious with TB.[35] As an unfortunate aside, while the tuberculosis campaign focused on the sanitarium model of treatment,

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31. *See* Kathryn Render, *Tuberculosis Chapters: A Model for Future AIDS Legislation?*, 32 St. Louis U. L.J. 1145, 1149–56 (1988). For a state-by-state breakdown of specific provisions applicable to public health powers, see Gostin, *supra* note 29, at 256–57.

32. *See* Render, *supra* note 31, at 1157. A recent survey of state laws revealed that 19 states provide for emergency detention for reasons of health. Nine of these vest the authority for such detention solely in the discretion of a health officer; eight require a court order, and four provide for detention in the context of commitment. The criteria for detention range from failure to comply with counseling suggestions to being deemed a public health threat. *See* Gostin, *supra* note 29, at 258.

33. The European model of treatment was based on the theory that stress and complicated urban life impeded recovery from tuberculosis. In this model, patients were institutionalized in healthcare facilities and given the opportunity to rest, receive a nutritious diet, and breathe healthy, preferably cold, mountain or sea air. Sanitaria flourished throughout Europe; in the United States, the premier sanitarium was at Saranac Lake in the Adirondacks. *See* Dubos & Dubos, *supra* note 7, at 176–78.

34. This support coincided with a shift in the perception of who would be the caretaker of the sick. Whereas in the previous century, the caretakers were the family and friends of the patient, the twentieth century saw this role increasingly assumed by physicians, nurses, clergy, and other care-taking professions. Bates, *supra* note 7, at 329.

35. *Id.* at 331.

public health energies were deflected from social reform, public sanitation, and improvement of living conditions.[36]

Tuberculosis was fostered by substandard, crowded living conditions in which the tuberculosis patient lived until he or she gained entry to a sanitarium or succumbed.[37] Once institutionalized, the patient either became a chronic care resident of the sanitarium or recovered enough to return home, potentially infect others, and/or become reinfected with tuberculosis. The system and infrastructure that had been created to prevent and cure tuberculosis evolved into a long-term care system that did neither.[38] The battle against tuberculosis had evolved into a standoff.

2. *Science Searches for an Effective Cure*

Science continued to delve into a variety of treatments for tuberculosis. Much research focused on the search for a vaccine, such as those that had been developed for smallpox and anthrax.[39] Almost immediately, it became evident that tuberculosis was a far more complex pathogen. Numerous vaccines were attempted with little success. In 1926, the most promising of them, the Bacillus Calmette Guerin (BCG), was mistakenly implicated in a research tragedy that claimed the lives of seventy-six hospitalized infants in Lubeck, Germany.[40] The incident provoked great fear and chilled tuberculosis vaccine research.[41]

In 1943, Dr. Selman Waksman isolated a drug from a stain of bacteria; it proved to be effective in reversing and curing even severe cases of tuberculosis. By 1947, this drug, streptomycin, became the primary "first-line" treatment for tuberculosis patients.[42] In 1948, para-amino-salicylic acid, another anti-tuberculosis drug, became available. This was

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36. Lerner, *supra* note 25, at 760.

37. Poor sanitation and crowded living conditions provided an ideal environment for the spread of tuberculosis. *See* Dubos & Dubos, *supra* note 7, at 202.

38. *See* Bates, *supra* note 7, at 329–31.

39. *See* Myers, *supra* note 15, at 36–37.

40. Instead of the non-virulent BCG vaccine, the infants were vaccinated with live human tuberculosis bacilli. *See* Dubos & Dubos, *supra* note 7, at 122–23, 160–62.

41. *See id.* at 162. BCG later was found to be somewhat effective in immunizing against tuberculosis. However, the immunizing effects of BCG are extremely variable and inconsistent; its efficacy as a vaccine remains inconclusive to this day. *See infra* part IV and accompanying notes.

42. Dr. Waksman faced innumerable difficulties in getting the new drug tested and used as treatment. He was not a medical doctor, but a soil bacteriologist; this hindered the acceptance of his research, even though the results were dramatic. As a result the drug was not distributed until 1947. Smith, *supra* note 7, at 246.

followed by a third drug, isoniazid, in 1952.[43] Several other drugs followed, with the last major anti-tuberculosis drug, rifampin, being introduced in 1972.[44]

The advent of effective antibiotics revolutionized care of patients with tuberculosis. Finally, patients who required hospitalization were likely to return home with cured or quiescent, noninfectious tuberculosis.[45] More important, the vast majority of patients could be treated effectively on an outpatient basis, never requiring hospitalization.[46] The death rates from tuberculosis plummeted; for example, in England and Wales, mortality among young women fell by ninety-nine percent from 1951 to 1961.[47] By the mid-1950s, the massive institutional infrastructure that had provided care to tuberculosis patients began to dissolve; tuberculosis wards and sanitaria closed or were rededicated to other uses.[48] By the 1970s, dedicated TB facilities and units were virtually nonexistent.[49]

The dramatic success of the new anti-tuberculosis drugs sparked tremendous optimism, giving rise to the widespread delusion that tuberculosis would soon be eradicated.[50] As mortality rates continued to decline, efforts to control tuberculosis became less rigorous. Funding for large scale tuberculosis education projects and public health monitoring shifted to other acute medical and societal problems.[51] Private philanthropic organizations founded to aid in the prevention and cure of tuberculosis broadened their mission to include all respiratory diseases.[52]

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43. *Id.*

44. Rifampin is the second most important anti-tuberculosis drug, after isoniazid. As in the case of isoniazid, liver dysfunction is a adverse side effect. *See* Isselbacher et al., *supra* note 17, at 706. It is substantially more expensive than isoniazid.

45. Lerner, *supra* note 25, at 760.

46. Smith, *supra* note 7, at 247.

47. *Id.*

48. Bates, *supra* note 7, at 339–40.

49. *See, e.g.*, Lerner, *supra* note 25, at 761 (discussing situation in New York City).

50. This optimism was not confined to tuberculosis. The post-World War II world believed that the antibiotics, antimalarials, and vaccines that had been developed had indeed effected a "health transition" and that infectious diseases were no longer a major threat to mankind. This view was supported by the successful eradication of smallpox. Unfortunately, the much lauded "health transition" was founded on two false assumptions: that bacteria and other microbes were immutable and unchanging and that outbreaks of disease could be sequestered. *See* Garrett, *supra* note 10.

51. For example, targeted federal funding for tuberculosis projects gave way to nonspecific "block grants" that gave the states and local government discretion as to how the funds were used. *See* Reichman, *supra* note 8, at 176.

52. Lerner, *supra* note 25, at 762. For example, the National Tuberculosis Association renamed itself the National Tuberculosis and Respiratory Disease Association in 1968. *Id.*

Many believed that the "white plague" had been effectively conquered.[53] "Doctors and the directors of public health programs thought of it as a defeated disease. They looked away."[54]

Despite the glorious success of antibiotic therapy, there were indications as early as 1951 that TB had not retreated, but was merely retrenching. By 1951, *Mycobacterium tuberculosis* was exhibiting resistance to streptomycin, then the "first-line" antibiotic drug of choice.[55] More important, even in the early 1950s, public health officials experienced growing difficulty in exacting compliance as they attempted to deliver full courses of antibiotic treatment to infected persons.[56] TB was poised for a comeback.

B. Revitalizing Traditional Public Health Measures in the Face of MDR-TB: A Futile Task

Tuberculosis was well on its way to reemerging as a major public health risk by the 1970s. The incidence of TB in New York and other urban areas in industrialized nations was slowly but steadily increasing, as was the incidence in the developing world. In addition, a small but significant percentage of never-treated new patients harbored drug-resistant strains.[57] Nevertheless, these danger signals failed to trigger a

53. Smith, *supra,* note 7, at 247. This misconception died hard. Throughout the 1970s and 1980s, many public health authorities, including the U.S. Office of the Surgeon General, continued to predict that, like smallpox, tuberculosis would be eradicated from the globe. In fact, during the Bush Administration, the Centers for Disease Control assured state governments that fiscal commitments dedicated to TB could be decreased because the threat was so diminished. Garrett, *supra* note 10.

54. Jonathan Weiner, *The Beak of the Finch: A Story of Evolution in Our Time* 261 (1994).

55. Smith, *supra* note 7, at 247.

56. Compliance presented problems for New York City's public health efforts even at the turn of the century; the noncompliant "rounders" were detained and incarcerated in healthcare facilities, but generally were released while still infected. The availability of antibiotics did not erase the noncompliance problem. New York City municipal hospitals were able to discharge 9000 tuberculosis patients between 1950 and 1954; approximately one-third of these left against medical advice and presumably before they had been rendered non-infectious. In addition, audits of outpatient therapy revealed that noncompliance was common; in 1979, only 53% of cases followed by the New York City Health Department had completed the full courses of outpatient treatment for tuberculosis. Lerner, *supra* note 25, at 761.

57. This was particularly marked in New York, where 9.6% of new, never-treated patients had drug resistant strains, compared to a national average of 6.9%. The fact that these patients with newly diagnosed TB had a resistant strain indicated that such resistant tuberculosis bacilli could be transmitted directly and was not necessarily the product of prior inadequate treatment. As a result, any individual, regardless of prior history of TB, may contract virulent MDR-TB Lerner, *supra* note 25, at 762.

public health response.[58] It was not until TB collided head-on with the AIDS virus (HIV) that the depth and breadth of the "new" TB epidemic gained public attention.[59] By the mid-1980s, MDR-TB was ravaging not only HIV patients,[60] but also residents of correctional institutions, patients in hospitals and other healthcare facilities,[61] chronic abusers of alcohol and drugs,[62] and other immunosuppressed persons.[63] Between 1981 and 1991, tuberculosis increased 125 percent in New York City.[64] Many patients in the "new" TB epidemic had a disease that was resistant to the first-line drug therapies.[65]

Moreover, the dangerous MDR-TB could be transmitted directly from the MDR-TB patient to a patient uninfected with any tuberculosis

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58. Lerner, *supra* note 25, at 762.

59. *See id.*; *see also* Karen Glanz & Haiou Yang, *Communicating about Risk of Infectious Diseases*, 275 JAMA 253 (1996) (discussing role of media in informing and awakening public as to perils of infectious diseases including tuberculosis).

60. *See* Consuelo Beck-Sague et al., *Hospital Outbreak of Multidrug-Resistant* Mycobacterium Tuberculosis *Infections: Factors in Transmission to Staff and HIV-Infected Patients*, 268 JAMA 1280 (1992); Charles L. Daley et al., *An Outbreak of Tuberculosis with Accelerated Progression Among Persons Infected with the Human Immunodeficiency Virus*, 326 New Eng. J. Med. 231 (1992); Maria de Lourdes Garcia Garcia et al., *Epidemiology of AIDS and Tuberculosis*, 29 Bull. Pan Am. Health Org. 37 (1995).

61. *See* Stephen Luby et al., *A Nosocomial Outbreak of Mycobacterium Tuberculosis*, J. Fam. Prac., July, 1994, at 21; Michele L. Pearson et al., *Nosocomial Transmission of Multidrug-Resistant Mycobacterium Tuberculosis: A Risk to Patients and Health Care Workers*, 117 Annals Internal Med. 191 (1992); Sarah E. Valway et al., *Multidrug-Resistant Tuberculosis in the New York State Prison System, 1990–1991*, 170 J. Infectious Diseases 151 (1994); *see also* Ruth E. Brown et al., *Health-Care Expenditures for Tuberculosis in the United States*, 155 Archives Internal Med. 1595 (1995).

62. *See* Keith Brudney & J. Dobkin, *Resurgent Tuberculosis in New York City: Human Immunodeficiency Virus, Homelessness, and the Decline of Tuberculosis Control Programs*, 144 Am. Rev. Respiratory Diseases 745 (1991); Centers for Disease Control, *Crack Cocaine Use Among Persons with Tuberculosis—Contra Costa County, California, 1987–1990*, 40 Morbidity & Mortality Wkly. Rep. 485, 485–87 (1991). The risk of tuberculosis in substance abusers is undoubtedly linked to their higher risk of HIV, or incipient HIV, and homelessness. Rothenberg & Lovoy, *supra* note 29, at 723. The risk is further magnified by the fact that these patients frequently are unaware of their increased susceptibility to tuberculosis. Salynn Boyles, *At-Risk Populations IVDUs Need More Information about TB*, TB Wkly., July 31, 1995, *available in* WESTLAW, 1995 WL 10089953.

63. One such immunosuppressed group is the homeless, who frequently fall through the cracks of TB treatment and develop MDR-TB. *See* Rebecca Voelker, *New Push to Control Drug-Resistant TB*, Am. Med. News, Jan. 20, 1992, at 3. Another group frequently prone to increased risk on the basis of immunosuppression is the chronically ill elderly. *See* Centers for Disease Control, *Prevention and Control of Tuberculosis in Facilities Providing Long Term Care in the Elderly*, 39 (RR-10) Morbidity & Mortality Wkly. Rep. 7 (1990).

64. *See The World as a Hot Zone: New and Re-Emerging Diseases*, Vaccine Wkly., Mar. 20, 1995, *available in* WESTLAW, 1995 WL 10090736, at *4.

65. Iseman, *supra* note 9, at 2429.

infection.[66] MDR-TB does not necessarily require the new victim to be immunocompromised nor is it limited to those who acquire it by failing to comply with treatment regimens.[67] Already, several U.S. cities,[68] as well as far flung corners of the world, have witnessed mini-epidemics of MDR-TB.[69] Such outbreaks are not limited to the slums; there have been documented cases of MDR-TB transmission on commercial airline flights,[70] in suburban high schools,[71] and among church choirs.[72]

Confronted with an impending epidemic, most public health authorities sought to counter resurgent tuberculosis by reinstating modernized versions of the classic public health measures to detect infected and at-risk persons and to provide treatment, using coercive measures if necessary.[73]

1. The Challenge of Detection

Detection and diagnosis of tuberculosis is a multistage process. The initial method of screening for potentially infected patients is the tuberculin test.[74] A positive tuberculin, however, does not conclusively establish that the patient suffers from active TB. Once the test is positive,

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66. *Id.*

67. For example, one study of 25 patients with MDR-TB who were not HIV positive found that only eight of them had a history of inadequate treatment for tuberculosis and nine of them had known exposures to MDR-TB patients as healthcare workers (eight) or fellow patients (one). Three of the remaining patients were residents of a homeless shelter. However, four patients had no previously established risk factors for tuberculosis. *See* Edward E. Telzak et al., *Multidrug Resistant Tuberculosis in Patients without HIV Infection,* 333 New Eng. J. Med. 907, 909–10 (1995).

68. *See* Centers for Disease Control, *Outbreak of Multidrug Resistant Tuberculosis—Texas, California and Pennsylvania,* 264 JAMA 173 (1990) (reporting outbreaks of MDR-TB, each traced back to index patients and perpetuated by their contacts); *U.S. Reports TB Outbreak Killed 29 of 32 Patients,* Chi. Trib., July 14, 1993, at C7 (reporting outbreak of drug resistant TB in New York hospital).

69. *See* Iseman, *supra* note 9, at 2429; *Rise of Drug-Resistant Tuberculosis Alarms Thai Doctors,* Agence France-Presse, June 30, 1995, *available in* WESTLAW, 1995 WL 7823493.

70. Centers for Disease Control, *Exposure of Passengers and Flight Crew to Mycobacterium Tuberculosis on Commercial Aircraft, 1992–1995,* 273 JAMA 911 (1995); Cynthia R. Driver et al., *Transmission of Mycobacterium Tuberculosis Associated with Air Travel,* 272 JAMA 1031 (1994).

71. *California School Becomes Notorious for Epidemic of TB,* N.Y. Times, July 18, 1994, at A1.

72. Reichman, *supra* note 8.

73. *See* Josephine Gittler, *Controlling Resurgent Tuberculosis: Public Health Agencies, Public Policy and the Law,* 19 J. Health Pol. Pol'y & L. 107, 124 (1994).

74. The tuberculin test consists of an intradermal injection of a purified protein derived from tuberculosis cultures that is usually injected into the skin of the forearm. If the injection produces a significant inflammatory reaction after two days, the test is positive for tuberculosis infection. Isselbacher et al., *supra* note 17, at 714–15.

diagnosis hinges on positive x-ray findings and evidence of active tuberculosis bacilli in the lungs. This requires a positive culture of respiratory secretions, a process that routinely requires three to six weeks; conclusive diagnosis of MDR-TB requires even more time, often two months or more.[75]

This initial tuberculin test typically is administered as a screening device to individuals in certain at-risk groups, such as health-care workers, nursing home residents, and prisoners. Forty-four states provide for required screening of such groups.[76] Such compulsory testing measures generally have been upheld in the courts on the grounds that the tuberculin test is relatively noninvasive and has a low risk of adverse side effects.[77]

Most TB screening programs are passive in nature—that is, they rely upon at-risk individuals seeking screening or being placed in a situation where screening is advantageous.[78] Unfortunately, reliance on passive screening means that many, if not most, at-risk patients escape screening. Many of those at risk for tuberculosis have little or no access to acute health-care services, let alone services aimed at prevention and screening.[79] Homeless persons, alcoholics, or intravenous drug abusers are unlikely to receive the tuberculin test and even less likely to have the results read in a timely fashion or to pursue additional testing.[80] Other

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75. *See id.* at 714. Until very recently, the research underlying the diagnosis of tuberculosis was several decades old and unaffected by newer biotechnologic techniques. The vast majority of diagnoses are still derived using these time-consuming methods. Brown, *supra* note 3. Recently available techniques have improved the length of time for MDR-TB diagnosis to about three weeks. Lawrence O. Gostin, *Tuberculosis and the Power of the State: Toward the Development of Rational Standards for the Review of Compulsory Public Health Powers,* 2 U. Chi. L. Sch. Roundtable 219, 229 (1995). Even at three weeks, however, there is an appreciable risk of the patient failing to follow through or otherwise being lost to follow-up.

76. *See* Gostin, *supra* note 75, at 249.

77. *Id.*

78. *See* Gittler, *supra* note 73, at 116. For example, one group typically screened are persons working in the healthcare industry. Such healthcare workers will be predisposed to agree to screening programs by virtue of their medical knowledge and the fact that it is a requirement for employment in their profession.

79. For example, in the United States, approximately 20% of the population is uninsured. *See* Laurie Abraham, *Tough Times Ahead,* 14 Bus. & Health 59 (1996). In addition, an even greater percentage of the population is "underinsured"—that is, they may have baseline coverage that does not include preventive health and screening measures. Twenty-seven percent of Americans cannot depend on consistent healthcare coverage. *See* Frederick Schmitt, *67M in U.S. Had Lapse in Health Cover,* Nat'l Underwriter Life & Health-Fin. Servs. Edition, July 8, 1996, at 2. Elsewhere in the world, particularly in developing nations, healthcare services may be inaccessible or non-existent.

80. These patients frequently are unreliable as a result of their substance abuse disorders, underlying mental illness, and lack of options for transportation to and communication with health-

vulnerable patients frequently lack insurance coverage for health-care services or lack access, despite having such coverage.[81] Unfortunately, these are the very patients who are most prone to tuberculosis.[82]

Another difficulty in detecting tuberculosis is that the tuberculin test may fail to reveal the presence of infection when the patient is immunosuppressed.[83] Such "anergy" is common in the elderly and in patients afflicted with chronic or debilitating diseases.[84] The hallmark of AIDS is massive immunosuppression; as a result, HIV-positive patients are prone to test falsely negative upon tuberculin testing.[85] This propensity to false negative tuberculin testing is doubly dangerous, given that immunosuppressed patients, especially those with AIDS, are at high risk for exposure to tuberculosis and development of drug resistant forms of the disease.[86] Such patients frequently are not detected until their tuberculosis infection is fully established, or even fulminant in nature. Not only is tuberculosis more difficult to treat in its more advanced stages, but the patient has had greater opportunity to serve as a vector, disseminating active tuberculosis to family members, caretakers, and others in his or her personal orbit.

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care facilities and providers. Such a patient might have a tuberculin test placed, but not return for the follow-up reading of the results; likewise if the test is positive, the patient might not appear for the radiographic and laboratory studies. With several stages necessary for the diagnostic process, many at-risk patients never attain diagnosis, let alone treatment of their tuberculosis. *See* Stephen E. Weis et al., *The Effect of Directly Observed Therapy in the Rates of Drug Resistance in Tuberculosis*, 330 New Eng. J. Med. 1179 (1994).

81. Among the vulnerable populations are racial and ethnic minorities; they comprise 70% of TB patients. In fact, there is some research data that indicates that certain minorities may be genetically more susceptible to tuberculosis. However, it is more likely that the increased susceptibility is due to a variety of social, economic, behavioral, and biologic factors. *See* The NHLBI Working Group, *Respiratory Diseases Disproportionately Affecting Minorities*, 108 Chest 1380 (1995). These vulnerable patients frequently reside in a crowded, substandard living situation that is ideal for easy transmission of tuberculosis. Rothenberg & Lovoy, *supra* note 29, at 722. Moreover, these are the very populations that lack adequate insurance coverage for healthcare service. Similarly, the homebound elderly person, who may live in a lower socioeconomic neighborhood, be immunologically compromised as a result of age and chronic illness, and be well enough to shop and ambulate in the immediate neighborhood (where TB is prevalent), may face transportation and financial barriers in obtaining routine non-emergency health care.

82. Rothenberg & Lovoy, *supra* note 29, at 722.

83. *See* Isselbacher et al., *supra* note 17, at 715.

84. Anergy is the incapacity of the patient to mount a reaction to the tuberculin test despite the fact the tuberculosis is indeed present. Approximately one-third of patients with new tuberculosis exhibit anergy upon tuberculin testing. Anergy is associated with immunocompromised states. Elderly patients, children, and infants frequently exhibit anergy as do patients suffering from chronic illness. *See id.* at 715.

85. *See id.*

86. *See* Iseman, *supra* note 9, at 2429; Telzak, *supra* note 67, at 907.

The problems with detection are exponentially increased in the undeveloped and still developing corners of the world. These countries frequently have little or no public health resources with which to mount a tuberculosis-screening program.[87] Indeed, the health-care system for caring for acute medical problems may be rudimentary, and then available only to certain urban cores of the population. The transportation difficulties, scarce medical facilities and personnel, and poverty in these nations make diagnosis of tuberculosis at an early stage unlikely, if not impossible.

2. *Assuring Treatment: The Role of Directly Observed Therapy*

Once the tuberculosis patient is identified, he or she must submit to treatment. Ideally, if the tuberculosis infection is latent rather than active, and is due to a strain of tuberculosis that is not drug-resistant, the patient will be able to forestall development of active tuberculosis by completing a twelve-month course of isoniazid.[88] Treatment of active tuberculosis infection requires a more rigorous course of antibiotic therapy. Patients with active TB that is not MDR-TB are treated with several drugs, including isoniazid and rifampin, for a minimum of six months.[89]

It is an onerous regimen, replete with significant inconvenience and a number of unpleasant side effects.[90] The beleaguered patient frequently decides that the cure is worse than the now asymptomatic disease and

87. For example, in Asia, where the tuberculosis epidemic is most severe, most Asian governments have not undertaken significant public health efforts. *See* U.S. Dep't of Health & Human Servs., *supra* note 12, at 108.

88. Such chemoprophylaxis is prescribed when the patient tests positive with a tuberculin test, but otherwise tests negative for tuberculosis. Chemoprophylaxis is indicated for all patients under the age of 35 and for patients belonging to risk groups who demonstrate a positive tuberculin test. Isselbacher et al., *supra* note 17, at 717.

89. There are a number of drug regimens that effectively treat tuberculosis; all contain a minimum of two drugs, usually rifampin and isoniazid. The usual course of treatment requires the patient to take these two medications for six to twelve months. Additional or different drugs are required when there is a need to shorten the course of treatment, when the patient is at risk for MDR-TB, when the patient is afflicted with HIV, renal failure, or other maladies that affect response to the drugs, or is pregnant. *Id.* at 716.

90. Side effects of first-line drugs include hepatitis, peripheral neuropathies, fever, and flu-like symptoms. Unfortunately the liver toxicity and hepatitis associated with isoniazid and similar drugs is a particularly common side effect in Asians; approximately 30% of Asian patients develop this adverse effect, making treatment in the TB-endemic areas of Asia even more difficult. *See id.* Deafness and renal impairment are associated with streptomycin and most of the second-line drugs. Other deleterious side effects may also occur, but are less common. *Id.* at 715.

stops taking the medications.[91] During a hiatus from treatment, the partially treated, still-infectious patient contributes bacilli to the airborne epidemic. Worse still, the result of incompleted treatment may be the patient's conversion to more active disease status or infection with a more virulent, drug-resistant strain of tuberculosis.[92] When the patient has contracted MDR-TB, the treatment includes the major first-line drugs, plus additional "second-line" drugs; in MDR-TB, the duration of treatment may be as long as twenty-four months.[93]

Regardless of whether the TB strain is drug resistant or not, the multiple drug regimen must be carefully adhered to by the patient in order to work. Although adherence to the medication regimen in "regular" TB will produce a cure in virtually all cases, patients with MDR-TB have a much worse prognosis. The mortality rates for HIV negative patients are as high as forty-six percent; up to seventy percent of HIV-positive patients with MDR-TB will die from it.[94]

As a result of patient noncompliance and the public health risk it presents, public health authorities have sought to improve compliance by monitoring treatment through directly observed therapy (DOT).[95] In DOT

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91. Patients frequently fail to finish their treatment program. Default rates as high as 40% to 60% are not uncommon; rarely is the default rate less than 15%. Most of the defaults occur within the first six months of therapy. As a result, more intensive short-course regimens have been developed in the hopes that patients will be more likely to complete the course. *See id.* at 716. Psychiatric disease, alcoholism, drug addiction and other substance abuse, and homelessness are all positively correlated with noncompliance. Age, sex, religion, education, race, and socioeconomic status are not positively correlated with compliance. *See* Weis, *supra* note 80.

92. When a patient has a recurrence of tuberculosis, after having failed to adhere to their past treatment regimen, the likelihood of the recurrence being due to drug resistant tuberculosis is about two chances in three. Isselbacher et al., *supra* note 17, at 717.

93. Five major drugs are available to treat TB: they are streptomycin (the first anti-TB drug, discovered in 1944 by Waksman), isoniazid (INH, a 1912 drug rediscovered in the 1950s and found to be effective against TB), ethambutol (1950s), pyrazinimide (PZA, developed in the 1960s), and rifampin (1972). Tuberculosis strains frequently have developed resistance to two or more of these drugs. There are also several second-line drugs, including para-amino-salicylic acid, ethionamide, cycloserine, capreomycin, kanamycin and amikacin, thioacetazone, rifabutin, and quinolones; tuberculosis has developed resistance to these drugs as well. *See* Isselbacher et al., *supra* note 17, at 715.

94. Marian Goble et al., *Treatment of 171 Patients with Pulmonary Tuberculosis Resistant to Isoniazid and Rifampin*, 328 New Eng. J. Med. 527, 530 (1993). The more drugs the patient is resistant to, the higher the mortality rate. Sriram Prasad Tripathy, *Multidrug-resistant Tuberculosis*, World Health, July-Aug. 1993, at 19.

95. Although DOT has become part of the vernacular associated with the current TB epidemic, its origins date back to the late 1940s and early 1950s, where it was used successfully by British researchers to treat patients in Africa, Asia, and London. It also demonstrated successful results when it was implemented on a small scale in the United States during the same era. *See* Ronald Bayer & David Wilkinson, *Directly Observed Therapy for Tuberculosis: History of an Idea*, 345

programs, public health workers visually supervise the patient, verifying that the patient is indeed taking the prescribed medications. This observation may be accomplished by either having the patient report to the clinic or treatment facility, or alternatively, by having the public health worker visit the patient and observe administration of the medication.[96]

Diligent DOT programs produce excellent results. For example, one DOT program attained treatment completion rates as high as 96.5 percent, coupled with a thirty percent decrease in new cases of TB—a dramatic testimony to the effectiveness of the program in preventing and curing tuberculosis.[97] In addition, DOT is a cost-effective alternative to hospitalization.[98] Treating a "regular" TB patient in a DOT program will cost approximately $600, while hospitalization for the treatment will cost $25,000. When the patient has MDR-TB, the cost of both DOT and hospitalization is multiplied by a factor of ten.[99]

Only a minority of the world's patients, however, have access to DOT programs.[100] And although DOT is a community-based service that can be coordinated with other social services, many areas in which TB is endemic have no such community and social services. In industrialized countries, local governments may choose to fund programs serving other constituencies deemed more worthy of limited resources; alternatively, in countries like Great Britain, which have long-standing national health programs, the political impetus for an adjunctive DOT program may be lacking.[101]

Lancet 1545 (1995). However, DOT was believed to be too costly and labor intensive for widespread use, until desperation caused New York and other urban U.S. cities to try DOT programs. *See* Morse, *supra* note 5, at 719.

96. This visitation may take place at the residence, workplace, or other agreed-upon site (shelter, school, food bank, etc.). Successful DOT program are flexible, seeking out the TB patients in tent cities, approaching those working the streets, and offering incentives of food to encourage compliance. *See* Scott Winokur, *Traveling With the TB Trolley,* S.F. Examiner, Sept. 14, 1993, at A19.

97. Rothenberg & Lovoy, *supra* note 29, at 727.

98. A DOT public health worker who prevents even two hospitalizations justifies the cost of the worker's salary. Seven hundred patients can be treated in a DOT program for what it would cost to hospitalize just one patient with MDR-TB. *See* Morse, *supra* note 5, at 719.

99. Rothenberg & Lovoy, *supra* note 29, at 728.

100. In the United States, approximately 15% of patients are involved in DOT programs. *Id.* at 727. However, as noted *infra* note 126 and accompanying text, 97% of patients with tuberculosis are located in the developing world, where intensive DOT programs are not feasible.

101. *See* Morse, *supra* note 5, at 719.

In developing nations, the community bureaucracy necessary to mount a DOT program does not exist. In many of these nations, legions of tuberculosis patients are scattered over a wide, often perilous span of geographic territory. The sheer size of such a program, combined with the absence of funding, facilities, personnel, and medications, is a daunting barrier to widespread implementation of DOT.[102]

Moreover, DOT does not assure patient compliance with a treatment regimen. TB patients are frequently members of a shadow society. They may be homeless or lack a permanent address; in such cases, it is easy for the patient to drop out of sight and out of the DOT program.[103] They may be intravenous drug abusers who resume their drug habits. Similarly, the recent immigrant[104] may choose to return to his or her homeland or join other friends or relatives in another town or state, without informing the program.[105] In some of these cases, the public health authorities may consider the patient such a risk that coercion and detention is sought to ensure that the patient is adequately treated.

3. *Enforcing Treatment: Detention and Coercion*

Although the quarantining of infectious-disease patients was an effective strategy earlier in this century, it is a tarnished alternative today. Many states and local governments have long-standing, albeit somewhat dated, statutes providing for the detention and treatment of infectious tuberculosis patients.[106] In the past several years, several states, including Washington,[107] have retooled their statutes, updating the provisions to withstand modern legal scrutiny.[108] However, even disregarding the individual rights and due process concerns,[109] quarantining of patients is no panacea.

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102. *Id.*

103. *See* Winokur, *supra* note 96.

104. In 1993, 29.6% of reported tuberculosis cases in the United States occurred in persons born outside the United States; overall foreign-born persons account for 60% of the increase in tuberculosis cases from 1986 to 1993. *See* Raviglione, *supra* note 6, at 223.

105. For example, one study documented that 89% of patients being treated in a Harlem treatment program were ultimately lost in follow-up. *See* Brudney & Dobkin, *supra* note 62, at 747.

106. *See* Gostin, *supra* note 29, at 255, 257–58.

107. *Id.* at 255.

108. *See generally* Lisa A. Vincler & Deborah L. Gordon, *Legislative Reform of Washington's Tuberculosis Law: The Tension Between Due Process and Protecting the Public Health*, 71 Wash. L. Rev. 989 (1996). For a discussion of due process issues arising in the context of existing TB control laws and proposals for reform, see Gostin, *supra* note 29 and Gostin, *supra* note 75.

109. *See infra* part III.C.2.

History has shown us that isolation of patients did not quell the tuberculosis epidemic of the past. Although it created a long-term care system for some victims, sanitarium treatment did not prevent patients from returning to their communities still infected and contagious. The abeyance of tuberculosis in the first half of this century was not the result of treatment in a quarantined setting, but rather a combination of improved living conditions, a general waning of the disease entity, and the discovery of antibiotics.[110]

Further countering the wisdom of quarantining large numbers of patients is the cost and availability of modern inpatient care. Costs of such care have escalated dramatically over the past several decades; the cost of treating tuberculosis on an inpatient basis may be as high as a $250,000.[111] Moreover, the increasingly cost-conscious health-care industry has spent the last decade decreasing the supply and staffing of inpatient units, often replacing inpatient facilities with outpatient clinics.[112] Any move to return to an inpatient model, even in a case as specialized as TB, diametrically opposes market-borne trends of the past several years.[113]

Unfortunately, such fundamental, systemic barriers limit the promise of all of the public health strategies described here. This becomes glaringly obvious when one considers the tuberculosis epidemic not from the local public health perspective, but as a worldwide global epidemic inherently linking industrialized countries to the developing and undeveloped nations of the world.

III. FUNDAMENTAL BARRIERS TO APPLICATION OF PUBLIC HEALTH STRATEGIES ON A GLOBAL BASIS

Our world has changed materially from the world that dealt with tuberculosis in the last century. Fundamental obstacles make efficient comprehensive treatment of TB patients on a worldwide basis virtually impossible. These obstacles include: an inadequate international public health infrastructure in developed and developing nations alike;

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110. *See supra* notes 37–49 and accompanying text.

111. Rothenberg & Lovoy, *supra* note 29, at 728.

112. *See* Russell C. Coile, Jr, *Assessing Healthcare Market Trends and Capital Needs: 1996–2000*, Healthcare Fin. Mgmt., Aug. 1, 1995; Price Colman, *State Hospitals Continue to Shrink: Outpatient Increases Show Growing Trend Toward Managed Care*, Rocky Mtn. News (Denver), June 8, 1995, at 51A.

113. *See generally* Coile, *supra* note 112; Michael S. Jacobs, *When Antitrust Fails: Public Health, Public Hospitals, and Public Values*, 71 Wash. L. Rev. 899 (1996).

increasing and virtually uncontrollable mobility facilitating the spread of tuberculosis; enhanced individual rights mitigating against coercive treatment tactics; the prohibitively high cost of treatment, especially for developing nations; and finally, that the available drugs and vaccines are outmoded and wholly inadequate to meet a global threat of this magnitude.

A. Public Health Infrastructure: Reconstructing a Relic?

Throughout the world, the public health infrastructure[114] has been allowed to deteriorate, while resources have been diverted to other needs perceived to be more compelling.[115] In large measure, public health is a victim of its own success; having vanquished devastating infectious diseases early in the twentieth century, it has turned to other serious, but more ubiquitous, healthcare issues.[116] As a result, most nations, both industrialized and developing, are ill equipped to meet the global epidemic of resurgent and drug resistant tuberculosis.[117]

Consider first the United States as a prototypical industrialized country. Its public health infrastructure, long dismantled, must be reconstructed[118] to deal with increasing numbers[119] of tuberculosis

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114. Public health infrastructure has been defined as: "individuals and institutions that, when working effectively together, promote and protect the health of people. The public health system in America consists of the strategies, facilities, the material resources and, above all, the human resources committed to transforming our national health." William L. Roper et al., *Strengthening the Public Health System*,107 Pub. Health Rep. 609 (1992).

115. *See* Lederberg, *supra* note 9; Philip R. Lee, *The Evolution of Public Health*, 272 JAMA 1315 (1994). The complacency that fostered this deterioration has also contributed to lack of compliance with medication programs and abuse and overuse of antibiotics. Lederberg, *supra* note 9; *See also* Brudney & Dobkin, *supra* note 62, at 748.

116. Alfred Sommer, *Whither Public Health*, 110 Pub. Health Rep. 57 (1995). Many of the problems that have been embraced by the public health movement are deeply rooted in societal determinants, for which successful intervention is undefined. This results in precious resources being devoted to problems which cannot be resolved at the expense of problems which might be alleviated. *Id.*

117. Worldwide disease surveillance is inadequate and deteriorating; this is largely due to a lack of a public health infrastructure to underpin such an endeavor. In most cases, although the public health infrastructure can respond to a short-term emergency crisis, it cannot sustain the vigilant effort that is required for a long-term global threat such as tuberculosis. *See generally* Charles Marwick, *Effective Response to Emerging Diseases Called An Essential Priority Worldwide*, 273 JAMA 189 (1995).

118. For a discussion of how such a reconstruction could be effected in the age of healthcare reform, see Philip R. Lee & Kathleen E. Toomey, *Epidemiology in Public Health in the Era of Health Care Reform*, 109 Pub. Health Rep. 1 (1994). *See also* Kristine Gebbie, *Rebuilding a Public Health Infrastructure*, 21 J.L. Med. & Ethics 368 (1993); Margaret A. Hamburg, *Rebuilding the Public Health Infrastructure: The Challenge of Tuberculosis Control in New York City*, 21 J.L. Med.

patients, including a substantial percentage of patients who have MDR-TB. This would be a formidable struggle even if public health authorities could use the techniques of isolation and comprehensive, medically controlled treatment. However, the public health strategies that forced tuberculosis into retreat in the past no longer have the same vitality.

Many public health functions have been subsumed by the private health-care systems over the last several decades. In the United States, the private health-care system is only just beginning to adopt principles of preventive health care and total case management. Whether the new managed-care arrangements and health plans will be able to deal effectively with public health threats like tuberculosis remains to be seen.[120]

Other industrialized nations have also allowed their public health infrastructures to languish,[121] although it is possible that the universal health-care systems found in nearly all industrialized nations will substantially aid mounting public health efforts. In these nations, all persons have access to basic healthcare services regardless of social or financial status.[122]

It is unlikely that funds will be allocated to resuscitate the public health infrastructure to a level that could counter the threat of tuberculosis and other emerging and reemerging infectious diseases. In 1994, the Centers for Disease Control (CDC) announced a plan to upgrade public health measures and the accompanying infrastructure for this purpose. The proposed plan had a price tag of $125 million per year; Congress appropriated only $7.7 million and the plan was dramatically scaled back.[123] On a global level, the World Health Organization has

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& Ethics 352 (1993); Stephen C. Joseph, *New York City, Tuberculosis, and the Public Health Infrastructure*, 21 J.L. Med. & Ethics 372 (1993); Roper et al., *supra* note 114.

119. TB is predicted to be responsible for 30 million deaths worldwide in the coming decade. *See* Nakajima, *supra* note 5.

120. *See Siege Relief*, Am. Med. News, Jan 8, 1996, at 35. However, some postulate that unless the public health system survives and strengthens to the point that it is able to effectively work with private healthcare efforts, the private healthcare financing and delivery system will be overwhelmed with illnesses and injuries caused by public health problems they are powerless to control. *See generally* Edward L. Baker et al., *Health Reform and the Health of the Public: Forging Community Health Partnerships*, 272 JAMA 1276 (1994).

121. *See* Earl S. Hershfield, *Prevention in the Developed World*, 346 Lancet 813 (1995).

122. All industrialized nations with the exception of the United States and South Africa have universal healthcare systems providing care for their populations. Note, however, that several of the systems, notably that in the United Kingdom, have recently sought to privatize certain segments of health-care services.

123. Christina Kent, *A Long-Neglected System Strains to Respond to a Rising Threat*, Am. Med. News, Jan. 8, 1996, at 9.

declined to dedicate a significant portion of its budget to the TB emergency. It provided six million dollars in aid targeted for TB in 1994, but only fourteen percent of this came from WHO's budget; the remainder was derived from donor nations.[124]

In the case of the less developed countries, especially those in Africa, Asia, and South America, there is no vestige of a public health infrastructure to revitalize. There are no medical personnel to treat the patients, no facilities from which necessary medication might be dispensed, and no centralized, computerized medical records system to keep track of who was treated, their medical and social history, and response to treatment.[125] In addition, inadequate living conditions provide an even more significant barrier. In many of these countries, the malnourished population lives in crowded, poorly ventilated, unhygienic housing—an ideal breeding ground for tuberculosis bacilli. It is no wonder that ninety-seven percent of tuberculosis cases occur in developing countries.[126] Even when such a nation appreciates the tuberculosis threat, the cost of identification and treatment of patients is both overwhelming and secondary, when that nation may be struggling simply to feed its citizens.

B. Global Ghettos and the Age of Geographical Mobility

Unlike the AIDS virus, TB is airborne, rather than blood-borne: "The principal risk behavior for acquiring TB is breathing."[127] In developing countries, where TB is most prevalent, the rich breathe the same air as the poor; visitors from the developed world visit the slums as well as the Hilton, even if they only pass through the same narrow street or use public transit. Exposure to and the spread of tuberculosis is inevitable.[128]

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124. *See* Reichman, *supra* note 8, at 175.

125. *See* Ronald J. Waldman, *Public Health Surveillance on the World Health Agenda*, Speech delivered at International Symposium on Public Health Surveillance, *in* 41 Morbidity & Mortality Wkly. Rep. 201 (1992) (describing information and system needs for world health surveillance). *But see* Lawrence O. Gostin et al., *The Public Health Information Infrastructure: A National Review of the Law on Health Information Privacy*, 275 JAMA 1921 (1996) (discussing confidentiality and privacy concerns of enhanced informational systems).

126. More than one-fifth of the 5.6 billion people in the world live in extreme poverty, almost a third of the world's children are undernourished, and half the global population lacks access to medications. *See WHO Widening Gaps Between Rich and Poor Pose Global Health Threat*, Vaccine Wkly., May 1, 1995, *available in* WESTLAW, 1995 WL 10090893, at *1; *see also* Brown, *supra* note 3.

127. Weiner, *supra* note 54, at 261.

128. The role of travel and migration in the spread of tuberculosis has been appreciated since the turn of the century. With the invention of the locomotive, rail travel brought tuberculosis to many

The last several decades have seen world population growth coupled with unprecedented travel and movement of people.[129] In 1994, thirty million people moved from rural areas to urban areas within their own countries; this intra-nation migration into urban ghettos fosters the spread of tuberculosis.[130]

Even more problematic for the dissemination of tuberculosis and other infectious diseases is the ease and frequency of international travel.[131] Every day, one million people cross an international border; one million people a week traverse between the industrial and developing world.[132] In developing nations, even if tuberculosis medications are available, there is no public health infrastructure to guarantee patient adherence or to verify that travelers into these countries are not infectious. Recent U.S. public health policies have espoused a need for improved global surveillance, including closer scrutiny of persons and products crossing national borders and enhanced dispersal of information with respect to the risk of infectious disease transmission inherent in travel.[133] However, as one prominent scientist has noted, such measures provide little safety when a disease's incubation time exceeds that of air travel.[134]

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areas in which tuberculosis had been rare. Moreover, these new frontier areas frequently were unable and unwilling to accept the chronically ill tuberculosis patient who stepped off the train. *See* Rothman, *supra* note 7, at 190–91.

129. *See* Lederberg, *supra* note 9.

130. One of the greatest potential causes of infectious disease epidemics, including tuberculosis, is the development of the third world and the urbanization of industrialized nations. As persons from rural areas devoid of an infectious disease are exposed to urban areas rife with risk, the disease is able to spread geographically. *See International (North and South America) Spread of Infectious Disease Continues*, AIDS Wkly. Plus, June 3, 1996, *available in* WESTLAW, 1996 WL 2093337. From 1950 to 1990, the world's urban population increased from 29% to 45% of the planet's population. Concerned about the public health implications of this movement into cities, the World Health Organization has urged nations to offer incentives to their citizenry to deter such migration. Phil Gunby, *1992 Could Be Pivotal Year in Efforts to Improve Health of People Everywhere*, 267 JAMA 15 (1992).

131. *See* Garrett, *supra* note 10; *see also* Mitchell L. Cohen, *Epidemiology of Drug Resistance: Implications for a Post-Antimicrobial Era*, 257 Science 1050 (1992).

132. *See* Garrett, *supra* note 10.

133. *See* Lederberg, *supra* note 9; Working Group on Emerging & Re-emerging Infectious Diseases, National Science & Technology Council, *Infectious Disease—A Global Health Threat* (last modified Nov. 7, 1996) <http://www.whitehouse.gov/WH/EOP/OSTP/CISET/html/ciset.html>.

134. *See* Lederberg, *supra* note 9. Surveillance for infectious disease at airport entry ranges from grossly inadequate to biologically irrational to non-existent. Infectious diseases may not be symptomatic or evident for days, weeks, or months after entry. *See* Garrett, *supra* note 10. In the case of TB, a patient would have to exhibit significant signs of active disease to be detected given that rapid testing for the tuberculosis is unavailable.

In addition to casual travel, at least 110 million people immigrated to a new country in 1994.[135] In most cases, the immigrant will be seeking a better life by moving to an urban center in a more developed nation. Even in the poorest of nations, a subset of the population will immigrate to the United States and other industrialized nations, bringing TB infection along as an unwanted companion.[136]

In the case of immigration to the United States, some individuals will be diagnosed with tuberculosis and refused entry.[137] Nevertheless, many entering the country will do so on short-term visas and will escape screening and detection.[138] In addition, some immigrants enter illegally. In their quest to find a better life for themselves and their families, they may not realize that part of their misery is due to tuberculosis infection;[139] once they have successfully crossed the border illegally, they are unlikely to draw attention to their presence by seeking care for illness.

Even if a nation could sequester and adequately treat its own citizens with TB, neither the United States nor any other nation can insulate itself from exposure to tuberculosis arriving with travelers and immigrants. The obvious conclusion is that we cannot begin to control tuberculosis in industrialized countries until we find a way to sharply decrease its incidence in developing and undeveloped nations.[140] Absent some means

135. *See* Garrett, *supra* note 10.

136. Immigration from developing nations increases the risk of MDR-TB. The immigrant may have received inadequate treatment prior to leaving the native country and may be incubating drug resistant TB. The immigrant is likely to settle in an urban area, often in a enclave of other recent immigrants who might harbor tuberculosis. In addition, the new immigrant may lack access to health care in his or her new home and allow the disease to progress before seeking treatment. *See* Alan B. Bloch et al., *Preventing Multidrug Tuberculosis*, 275 JAMA 487 (1996); Garrett, *supra* note 10. In the United States, for instance, foreign-born patients are markedly more prone to be diagnosed with tuberculosis. U.S. Dep't of Health & Human Servs., *Tuberculosis Morbidity—United States, 1994*, 44 Morbidity & Mortality Wkly. Rep. 387, 395 (1995). In New York, where the TB epidemic is strongly identified with the incidence of HIV and substance abuse, one-third of the patients are foreign born. In other areas of the United States, TB primarily affects immigrant populations. Similarly, in other industrialized nations, more than half of new TB cases are found among foreign-born persons. *WHO Urges Making Directly-Observed Therapy the Priority in Global Tuberculosis Control; Praises New York as Model to Stop TB Epidemic*, U.S. Newswire, Mar. 20, 1995.

137. *See* Sana Loue, *Immigrants, Immigration Law, and Tuberculosis*, 71 Wash. L. Rev. 969, 979-85 (1996).

138. *See id.*; Stephenson, *supra* note 8, at 1648.

139. *See* Stephenson, *supra* note 8.

140. Nakajima, *supra* note 5.

to address TB more effectively and globally, the disease is predicted to cause thirty million deaths over the next decade.[141]

C. *Individual Rights and Due Process vs. Coerced Treatment and Detention*

Compounding administration of effective tuberculosis treatment is the important question of individual rights and autonomy. A long legal and cultural tradition in the United States recognizes the power of the state to protect the public health even at the expense of individual liberty. Dating back to the seminal case of *Jacobsen v. Massachusetts*,[142] public health authorities have enjoyed support from the courts as they battled infectious disease and other public health threats.[143] In the case of tuberculosis, many states enacted targeted public health laws providing for coerced treatment and detention, if necessary.[144] Such laws were upheld throughout the nineteenth and twentieth century, so long as the state's power was not exercised in an arbitrary and capricious manner and detention was based upon a reasonable threat.[145]

However, the last few decades have witnessed greater weight accorded to substantive and procedural due process. In the United States, our doctrine of constitutionally guaranteed due process has evolved to imbue the individual with rights of liberty and privacy that make mandatory, enforced, long-term treatment and even enforced prophylaxis legally problematic.[146]

Thus, when coercive measures such as detention, quarantine, enforced treatment or even directly observed therapy (DOT) are implemented, public health officials and medical providers must walk a fine line between administering necessary treatment and abridging the patient's fundamental rights. Generally, treatment programs must be carefully

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141. *Id.*

142. 197 U.S. 11 (1905). In *Jacobsen,* the Supreme Court held that a Massachusetts man had to comply with a mandatory smallpox vaccination law, despite the fact that it infringed upon his individual liberty rights. The Court reasoned that individual liberty rights may be curtailed under the police powers of a state when the health and safety of the general citizenry are at risk. *Id.* at 26–27.

143. *See* Gittler, *supra* note 73, at 124.

144. *See* Gostin, *supra* note 29, at 257–59; Rothenberg & Lovoy, *supra* note 29, at 733–37.

145. Rothenberg & Lovoy, *supra* note 29, at 733.

146. For a detailed analysis of the interplay between individual rights to substantive and procedural due process in the context of prevention and treatment of tuberculosis, see Gostin, *supra* note 75.

tailored to be no more coercive than can be reasonably justified by the level of the threat.[147]

Industrialized nations frequently share the due process norms found in the United States, even if their constitutions and laws do not specifically articulate them. These nations too, while attempting to resuscitate long-neglected public health strategies, are likely to find that expanded tenets of individual rights foreclose use of even necessary coercive measures.

Developing nations and those still enmeshed in poverty may have cultures and legal frameworks that are more accepting of coercive techniques of tuberculosis screening, prevention, and treatment. Tuberculosis is often rampant in these countries. However, these countries frequently lack the economic resources to carry out programs of the scope necessary to curb the incidence of tuberculosis within their borders. In addition, because inadequate or incomplete treatment may result in conversion to the more dangerous MDR-TB, it is possible that harsh coercive programs in such developing nations might actually worsen the epidemic.

D. Paying the Bill: The High Cost of Fighting a Global Epidemic Using Current Strategies

Dealing with the tuberculosis epidemic on a global basis using current detection and treatment techniques would require substantial medical personnel, establishment of laboratory and other healthcare facilities, drugs, vaccines and other treatments, and the logistical support to disseminate them all. The cost of such a global program, even if it were feasible, would be astronomical in today's high-cost health-care market.

In the United States, a subcommittee of the National MultiDrug Resistant Tuberculosis Task Force determined that estimated expenditures for treating TB in 1991 were $703.1 million with sixty percent of the amount devoted to inpatient treatment, twenty-six percent to outpatient treatment and the remaining fourteen percent used for screening and preventive therapy activities.[148] The fact that the lion's share of expenditures for TB are for inpatient care indicates that our efforts to control the infections at an early, more easily treated stage, are inadequate. Moreover, these costs are projected to grow to as much as $2.2 billion by 2000.[149] This astronomical sum will be needed just to

147. *See* Reilly, *supra* note 11, at 140–41.

148. Brown, *supra* note 61, at 1595.

149. *Id.*

treat the tiny minority of the world's TB cases found in the United States.[150]

Because of a major appropriation of cash and attention to the problem of tuberculosis in New York and other U.S. cities, tuberculosis has begun to decline, albeit only slightly.[151] However, even in the best of times, the United States would be unable to fund unilaterally and supply such a comprehensive program worldwide.[152] Even countries with national health-care systems may have insufficient financial resources to provide the extended, expensive medication regimen to TB patients, often their poorest, most powerless citizens.

The cost of TB drugs is an unaffordable burden for many developing countries—even aside from the costs of structuring a delivery system to administer them reliably.[153] Drug-resistant strains of TB present a virtually insoluble problem for such nations, given that the cost of institutionally treating a single MDR-TB patient may rise to an estimated $250,000.[154] Added to this is the cost of surveying compliance. DOT is known to be cost effective and would prevent the costly complications of hospitalization and progression to drug-resistant disease.[155] However, even with the lower labor costs in many developing nations, the cost of implementing such a massive program would be prohibitive for many nations.[156]

Nor is it likely that world relief organizations will be able to provide the sufficient aid to curtail the tuberculosis epidemic in any meaningful

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150. *Id.*

151. In the United States, there were 24,361 cases of active tuberculosis in 1994; a year later, as a result of conscientious renewed public health efforts in cities like New York, the number decreased to just under 23,000. *See* Thomas R. Frieden et al., *Tuberculosis in New York City—Turning the Tide*, 333 New Eng. J. Med. 229 (1995); *TB's Resurgence Calls for New Drugs*, Seattle Post-Intelligencer, Mar. 26, 1996, at A6.

152. *See* Lederberg, *supra* note 9. And these are not the best of times; like many other nations, the United States faces an ever more constrained budget. *Id.*

153. Many developing countries tend to refrain from using rifampin, a more expensive drug, if possible. Often, they instead use thiacetazone, a cheap but less effective anti-TB drug that also has a propensity for fatal adverse reactions when administered to AIDS patients. In addition, because developing countries are heavily dependent upon donor drug supplies from pharmaceutical companies or other nations, they may have little control over the content and quantity of their supply of anti-tuberculosis drugs. *See* Alwyn Mwinga, *Treatment in Developing Countries*, 346 Lancet 812 (1995); Brown *supra* note 3. Obviously this presents significant problems in Asia, where risk of hepatic toxicity from isoniazid is high and access to rifampin limited; the net result is that developing nations may find themselves deprived of both first-line drugs. *See supra* note 90.

154. Rothenberg & Lovoy, *supra* note 29, at 728.

155. *See supra* notes 97–102 and accompanying text.

156. *See* Morse, *supra* note 5, at 719.

way. The World Health Organization, other medical aid organizations, and industrialized donor nations cannot begin to cope with the massive TB problem in the developing world. In 1990, when almost two million people died of TB, only sixteen million dollars were funneled to the developing countries where it is endemic.[157] In theory, this amount could be consumed by fully treating only forty-eight MDR-TB patients in one city of one developing nation.[158]

Public health measures, even if funded at an adequate level in the developed world, would still be hampered by the profound poverty and abject living conditions that give rise to tuberculosis infection in developing nations. The mobility of our modern world ensures transmission. Thus, even if strenuous public health efforts temporarily win the battle in New York and other U.S. cities, tuberculosis will prevail in the global war.[159]

Given the many roadblocks that stand in the way of implementing public health strategies worldwide, we desperately need new weapons with which to combat this versatile infectious enemy. In addition to new, more rapid means of diagnosing TB, new drugs are needed to prevent and treat both the traditional and drug resistant strains. The new drugs need to be capable of eradicating TB with a much more abbreviated course of treatment than is required by the current agents, with fewer side effects.[160] Most importantly, they must be capable of mass production at a reasonable cost. Moreover, efforts to find a vaccine that can preempt infection altogether should be accelerated. The goal should be to diagnose and treat or prevent tuberculosis over a very short treatment time span, ideally one visit. Unfortunately, research and development of modern tuberculosis treatment options remained locked in the past, even as tuberculosis reemerged as a global public health threat.

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157. *See Fighting TB—U.S. Must Join Global Health Effort*, Dallas Morning News, Dec. 29, 1993, at 18A.

158. Moreover, in relative terms, the amount of currently allocated aid is woefully inadequate when compared to other medical problems of the developing world. For example, in contrast to the $16 million allotted to TB in 1990, $77 million was devoted to treatment of leprosy, a disease which claimed only 2000 lives that year. *Id.*

159. Tan, *supra* note 1, at 211.

160. *See* Richard J. O'Brien, *WHO's Role in Tuberculosis Research*, World Health, July 1993, at 13.

IV. TUBERCULOSIS DRUGS AND VACCINES: LOCKED IN THE PAST

Research and development of new anti-tuberculosis drugs and vaccines have been largely ignored for the last several decades. The sad fact is that the last major first-line drug specifically approved for the treatment of TB was rifampin.[161] It was approved by the FDA in 1972, although it had been marketed in Europe several years earlier.[162] Recently new combination medications, combining already approved anti-tuberculosis drugs, have been marketed,[163] but for the most part, research for new antibiotic agents has been stalled for many years.[164] On the vaccine front, the primary vaccine now available is Bacillus Calmette-Guerin (BCG). BCG was originally developed from an attenuated live vaccine derived from cows in the early twentieth century. When initially developed, it was hoped that BCG would offer a safe and effective TB immunization. Unfortunately, although BCG did evidence limited ability to prevent infection, its performance was erratic and inconsistent.[165] Initially it was plagued by a tragic research accident that colored the view of BCG for many years.[166] Periodic reexamination of its utility has not found any way to predict or standardize its effectiveness. Questions regarding its variability and efficacy have remained unresolved.[167]

Recently, however, in response to the gradually dawning realization of the new TB threat, there have been fledgling efforts to renew research

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161. Five major first-line drugs are available to treat TB; several second-line, less effective drugs may also be used. *See supra* notes 89–90, 93 and accompanying text.

162. Reichman, *supra* note 8, at 175.

163. These drugs, Rifater, and Rifamate, contain two or more anti-tuberculosis drugs in one capsule. They offer dosing advantages over multiple single agents. *See id*; Thomas Moulding et al., *Fixed-dose Combinations of Antituberculous Medications to Prevent Drug Resistance*, 122 Archives Internal Med. 951, 951 (1995).

164. *See WHO Accuses Industry of Indifference to TB Dilemma*, Pharmaceutical Bus. News, Mar. 27, 1996, at 14.

165. At the time, this was thought to be due to a myriad of factors, not the least of which were the technical limitations of the time. *See* Dubos & Dubos, *supra* note 7, at 163.

166. *See generally supra* notes 40–41 and accompanying text.

167. *See supra* notes 40–41 and accompanying text. A recent review of the literature indicated that BCG significantly reduces the risk of TB, but that there is insufficient information to determine its efficacy, especially as related to age of vaccination. Graham A. Colditz et al., *Efficacy of BCG Vaccine in the Prevention of Tuberculosis: Meta-analysis of the Published Literature*, 271 JAMA 698 (1994). Perhaps the greatest problem with BCG is the incredibly variable protection it provides—ranging from zero to 80%. In seeking to clarify its efficacy, one study found that the effectiveness of the vaccine appears to be affected by geography, sunlight, temperature, manufacturing and storage conditions, and genetic factors. P.E.M. Fine, *Variation in Protection by BCG: Implications of and for Heterologous Immunity*, 346 Lancet 1339 (1995).

into anti-tuberculosis agents. Most of these have been initiated by companies experienced in new biotechnologic techniques.[168] Several types of vaccines are being researched. They include an improved version of BCG that has been genetically manipulated, a new live vaccine consisting of a genetically altered non-virulent strain of TB, and new DNA vaccines with specially coded genes.[169] This new vaccine research is heartening, especially because research for additional new drugs has not been forthcoming during the decade of resurgent TB.[170]

A. Social Barriers Hindering New Drug and Vaccine Development

A variety of social and financial barriers have allowed research for new TB therapies to languish despite the growing incidence of the disease worldwide. First and foremost, the tuberculosis epidemic has failed to capture the attention of politicians; similarly, it has been unable to stimulate a groundswell of public outrage. Its victims in industrialized nations are no longer the interesting, intellectual writers and poets who exemplified the nineteenth century victim.[171] TB's new victims are far less socially acceptable. In the United States, tuberculosis patients are typified by the chronic substance abuser who may also be infected with AIDS; prison inmates; the homeless; or the recent, frequently non-English speaking immigrant, who even as a legal resident is viewed as an interloper.[172] None of these patients are perceived as sympathetic victims.

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168. *See* Daniel J. DeNoon, *New Strategies Revolutionize Vaccinology,* Vaccine Wkly., Nov. 13, 1995.

169. M. Harboes, *Novel Developments: Vaccines against Tuberculosis,* Vaccine Wkly., Apr. 1, 1996.

170. *See* Joseph H. Bates, *Tuberculosis Chemotherapy: The Need for New Antituberculosis Drugs is Urgent,* 151 Am. J. Respiratory Critical Care Med. 942, 943 (1995). Note however, that several trials are ongoing with respect to new versions of existing drugs and combinations of existing drugs to decrease the length and absolute number of doses to effect cure. *See* Reichman, *supra* note 8, at 175.

171. Many historians have commented upon the strange association between tuberculosis and intellectual and creative activities, citing its more famous victims as examples: Voltaire, Keats, Shelley, Robert Louis Stevenson, and Saint Francis of Asissi. *See generally* Lewis J. Moorman, *Tuberculosis and Genius* (1940).

172. In the United States, 29.6% of tuberculosis cases occur in persons born outside the United States. Raviglione, *supra* note 6, at 223. Foreign-born persons are increasingly viewed as outsiders regardless of their immigration status, as is illustrated by the recent legislative proposals to limit government benefits and other entitlements available to legal immigrants. Bruce B. Auster et al., *A Blizzard of Bills from Congress: Will Welfare Reform Worsen Life for the Poor?,* U.S. News & World Rep., Aug. 12, 1996, at 25; Faye Fiore, *Welfare Reform Increases Health Risks, Experts Warn,* L.A. Times, Aug. 24, 1996, at A12; Janice Somerville, *AMA: Maintain Health Care for Legal Immigrants,* Am. Med. News, July 17, 1995, at 5.

Second, the vast majority of TB victims reside in the less developed world.[173] No newsworthy flood, famine, or war brings them to the attention of the powers and public consciences of industrialized nations and the decision-makers within the pharmaceutical industry. TB is an insidious, nondescript killer, claiming most of its three million victims silently without drama or poster children. In short, TB is neither classy nor mediaworthy.

Another social and cultural barrier results from tuberculosis's status as an "old" disease. Perhaps because Americans and citizens of other industrialized nations enjoy so many inventions never even dreamed of by previous generations, they are extraordinarily enamored of that which is "new." New technologies, new discoveries, and new diseases benefit from this long-standing romance with the novel; old problems like domestic violence and TB do not. Rather, old unsolved problems are relegated to the depths of our cultural consciousness. The author submits that a pivotal reason why TB vaccine research has been more active than drug research is that the former offers the opportunity to use new, scientifically "sexy" gene coding and biotechnology techniques.

B. Financial Barriers: Regulatory, Economic, and Marketing Issues

The social and cultural barriers are rivaled by a formidable regulatory approval regime that is costly and time consuming. The regulatory morass enhances the economic and marketing difficulties fueling pharmaceutical industry reluctance to develop any product that is not certain to be profitable and win regulatory approval.

Although recent public policy reports have recognized that pharmaceutical companies have an indispensable role to play in defeating reemerging infectious diseases like tuberculosis, reports offer no guidance as to how to finance the investment in research and development of such products.[174] Generally research and development for new pharmaceutical products will be undertaken only when the investment will result in a significant profit margin.[175] In the case of

173. There is some evidence that tuberculosis undermines developing nations' efforts to build more functional economies in that it strikes potential workers before or in their most productive years. U.S. Newswire, *supra* note 136.

174. Lederberg, *supra* note 9; *see also WHO Accuses Industry of Indifference to TB Dilemma*, *supra* note 164.

175. *See* Kent, *supra* note 123.

tuberculosis, much of the market will be poor, profit is uncertain, and costs of compliance with regulatory hurdles and legal liability are high.[176]

With both drug and vaccine development, pharmaceutical manufacturers face difficult regulatory environments. This is particularly true in the United States, but other industrialized countries also require compliance with onerous approval processes.[177] Moreover, until very recently, there has been little or no reciprocity among nations with respect to approval processes for drugs and vaccines.[178]

Recent efforts to standardize approval processes throughout European Community nations have not yet been mimicked by the FDA, an agency nicknamed the "foot-dragging and alibi" agency by its many detractors.[179] The FDA process is the most conservative, arduous, and time consuming of the world's drug approval processes; it has been accused of "deadly over-caution" in the lay press,[180] not a wholly undeserved label.

First of all, the FDA has more than one set of rules. It approves and regulates drugs using one process mandated by the Food, Drug and Cosmetics (FD&C) Act,[181] biologics such as vaccines by another, the Public Health Services (PHS) Act;[182] and medical devices by a third, the

176. *See* Lederberg, *supra* note 9.

177. *See generally* Rosemarie Kanusky, *Pharmaceutical Harmonization: Standardizing Regulations among the United States, the European Economic Community, and Japan*, 16 Hous. J. Int'l L. 665 (1994).

178. *See generally id.*

179. Federal News Service, Hearing of the Oversight and Investigations Subcomm. of the House Commerce Comm., Feb. 29, 1996, *available in* WESTLAW, 1996 WL 5509259, at *146 (comments by Chair of Subcomm., Rep. Joe Barton).

180. Carolyn Lochhead, *"Deadly Over-Caution"/ FDA Assailed for Slow Testing of New Drugs*, S.F. Chron., Oct. 26, 1992, at A1.

181. 21 U.S.C. §§ 301–393 (1996). The 1938 Food, Drug and Cosmetics (FD&C) Act superseded the Food and Drug Act of 1906, expanding the scope of product regulation dramatically. The 1938 Act imposed requirements upon drug manufacturers to file a new drug application before they marketed their products to the public. A series of amendments have modified and further expanded the scope of the 1938 Act, usually enacted in response to the expanding frontiers of science. These range from amendments added in 1941 to address a new biologic, insulin, to the Prescription Drug User and Generic Drug Enforcement Acts of 1992. Throughout its long history, the FDA has focused on regulating food and drug manufacturing to ensure safety and effectiveness. *See* Alan H. Kaplan, *Fifty Years of Drug Amendments Revisited: In Easy-to-Swallow Capsule Form*, 50 Food & Drug L.J. 179 (1995).

182. 42 U.S.C. § 262 (1994). Curiously, the statutory provisions governing biologics like vaccines actually predate the 1906 Food and Drug Act. Congress took action to regulate such biologics in 1902 after a number of highly publicized deaths resulted from contaminated smallpox vaccine. Despite the early legislative action and statutory authority, regulation of biologics was

Medical Devices Amendments (MDA).[183] In the case of many biological products, the FDA exerts authority over the product, requiring compliance with both the PHS and FD&C Acts.[184]

The complications presented are readily evident by reviewing the approval process for a new drug—the least complicated of the regulatory regimens. The FDA has rigorous safety and effectiveness standards guaranteed by a lengthy four-stage approval process applied to new drugs. This FDA regimen proceeds from an initial pre-clinical testing phase performed on animal subjects, followed by an investigational new drug (IND) phase with three stages of clinical trials on human patients. The accumulated data is then submitted to the FDA in a new drug application (NDA) for evaluation, review and additional safety and effectiveness testing prior to FDA approval.[185] This extended process routinely takes a decade or more to complete and is extremely costly for the pharmaceutical manufacturer.[186] After approval, the fourth phase commences: it consists of post-marketing surveillance and monitoring of the drug's safety and efficacy.[187]

Partially because of the high costs of research, development, and approval for new drugs, the pharmaceutical industry focuses on the markets in industrialized nations.[188] These are the nations that provide

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largely unenforced until the 1950s. Gary E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 Food & Drug L.J. 213 (1994).

183. 21 U.S.C. § 360 (1994).

184. For discussion of the relationship and interplay between the FD&C Act and the PHS Act provisions, see Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 Food & Drug L.J. 123 (1995). Korwek notes that biologics products are simultaneously either biologics and drugs or biologics and devices under existing law. Thus, the major distinction is whether or not the contemplated product is a biologic; if so, it will be susceptible to two sets of regulatory requirements. *Id.* at 128. Another layer of complication is that within the regulatory bureaucracy, separate regulatory centers deal with different FDA products. Drugs are evaluated by the Center for Drug Evaluation and Research (CDER) and biologics by the Center for Biologics Evaluation and Research (CBER). *See* Gamerman, *supra* note 182, at 213–16.

185. The delays and time required in the current process are inextricably linked with cost. Industry experts report that taking the average drug from laboratory to market costs $400 million and requires 15 years. Moreover, they estimate that 90% of the average cost is secondary to the regulatory delays. *See* Julie C. Relihan, *Expediting FDA Approval of AIDS Drugs: An International Approach*, 13 B.U. Int'l L.J. 229, 237 (1995).

186. Elizabeth M. Rutherford, *The FDA and "Privatization"—The Drug Approval Process*, 50 Food & Drug L.J. 203, 212 (1995); Tanya E. Karwaki, Comment, *The FDA and the Biotechnology Industry: A Symbiotic Relationship?*, 71 Wash. L. Rev. 821, 828 (1996).

187. John Patrick Dillman, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 Vand. L. Rev. 925, 929 (1991); Relihan, *supra* note 185, at 237.

188. The United States, European Community nations, and Japan generate 90% of all pharmaceutical research and constitute 75% of the market. Kanusky, *supra* note 177, at 667.

profit. Therefore, drug development targets these populations and the ailments that affect them. For example, in 1992, Parke-Davis, a large U.S.-based pharmaceutical firm, planned to begin clinical trials for a new anti-tuberculosis drug, sparfloxacin (a fluroquinolone), for which it held limited U.S. development rights. However, these trials never got underway because the world license holder, a Japanese company, rescinded Parke-Davis' license, choosing to forego developing this drug as a TB drug.[189] The owner was concerned that once sparfloxacin obtained an TB indication, marketing the drug for other more prevalent and profitable conditions like bronchitis and pneumonia[190] might be harmed.[191] It feared that the drug would be stigmatized and less marketable if its utility in treating TB was a primary treatment indication.[192]

By the late 1970s, it had become evident that the complex FDA regimen was chilling new drug and vaccine development.[193] Unless a drug was projected to be a clear "winner" in the market, the manufacturer could not sustain the research and development costs plus the expense of the lengthy approval process. In addition to much-delayed return on a manufacturer's investment, the testing and approval process also regularly consumed half or more of the period of patent protection.[194] Although amendments in 1987 and 1994 alleviated this difficulty in part by providing patent term extensions to offset delays,[195] the manufacturers argued that they still had inadequate time to recoup the costs of research and development. As a result, manufacturers chose to develop only drugs that would yield a higher profit margin. This meant that drugs targeted at

189. Reichman, *supra* note 8, at 175.

190. Such "profitable" conditions are suffered by a higher quotient of the adequately insured populations of the world; the majority of tuberculosis patients, on the other hand, are poor, powerless, and uninsured.

191. Reichman, *supra* note 8, at 175.

192. Since then, WHO reportedly has received permission to study this drug for treatment of TB in Europe. WHO continues to complain bitterly about the pharmaceutical industry's apparent disinterest in developing new therapies to combat TB. Moreover, it argues that given the enormous market for the current TB drugs, the prices could and should be lowered. *WHO Accuses Industry of Indifference to TB Dilemma*, *supra* note 164.

193. *See generally* Kanusky, *supra* note 177; Christina Kent, *Controversial FDA Overhaul Advances in Congress*, Am. Med. News, Apr. 22, 1996, at 3.

194. Until recently, the length of the patent term was 17 years. However, as of June 8, 1995, the patent term length was increased to 20 years. *See* 35 U.S.C. § 154 (1996).

195. *See* 35 U.S.C. §§ 155–156 (1996) (detailing conditions pertaining to such extensions). Despite the extensions, critics argue that they fail to adequately address the problems faced by manufacturers. Jonathan L. Mezrich, *The Patentability and Patent Term Extension of Lifesaving Drugs: A Deadly Mistake*, 6 J.L. & Health 111, 116–17 (1991–92).

small or poor patient populations had little chance of getting off the drawing board.[196]

Moreover, even if a manufacturer decided to forego the FDA process in the United States in favor of the slightly less arduous processes of the United Kingdom,[197] other European countries,[198] and Japan,[199] there was no reciprocity that would allow marketing in the lucrative U.S. market.[200]

Once the new drug or vaccine finally came to market, there was a significant risk of product liability, particularly for vaccine manufacturers. As a result of adverse events allegedly associated with childhood immunizations, between 1980 and 1984 vaccine manufacturers faced suits claiming up to $3.5 billion in damages.[201] Several major manufacturers stopped making vaccines altogether.[202]

By the mid-1980s, childhood vaccines were in short supply and new vaccine development was at a standstill.[203] Drugs for rare but devastating illnesses were not being developed.[204] As the effects of AIDS became obvious, the inability of the pharmaceutical industry to deliver new drugs in a timely fashion became a source of public consternation and outrage.[205] As a result, Congress acted to provide incentive programs to

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196. Janice M. Hogan, *Revamping the Orphan Drug Act: Potential Impact on the World Pharmaceutical Market*, 26 L. & Pol'y Int'l Bus. 523, 525–27 (1995). The length of the approval process proved to be a barrier in responding to new disease challenges, as became glaringly evident with the AIDS epidemic. In fact, a 1981 congressional survey revealed that 80% of drugs considered "public service" drugs were the result of serendipitous discoveries, rather than from research targeted to a specific disease. Peter S. Arno et al., *Rare Diseases, Drug Development, and AIDS: The Impact of the Orphan Drug Act*, 73 Milbank Q. 231, 233 (1995).

197. Veronica Henry, *Problems with Pharmaceutical Regulation in the United States: Drug Lag and Orphan Drugs*, 14 J. Legal Med. 617, 637–39 (1993); Relihan, *supra* note 185, at 245–49.

198. *See* Kanusky, *supra* note 177, at 676–84.

199. *See id.* at 684–87. Although the perception is that foreign regulations are much less arduous and time-consuming than the U.S. process, in reality the differences are slight. For example, a new product in the United States typically takes 12 years to develop and costs $231 million to market while a new product in a European Community nation takes 12–14 years to develop and costs $220 million to market. *See id.* at 682–83.

200. Indeed, even within the European Community, member states subject pharmaceutical products to separate regulation. *Id.* at 680.

201. Randall B. Keiser, *Deja Vu All Over Again? The National Childhood Vaccine Injury Compensation Act of 1986*, 47 Food & Drug L.J. 15, 16 (1992); *see also* Philip M. Boffey, *Experts Warn of 'Precarious' Vaccine Supplies*, N.Y. Times, July 30, 1985, at C10.

202. *See* Subcomm. on Health & the Env't of the House Comm. on Energy & Commerce, 99th Cong., 2d Sess., *Childhood Immunizations* 86 (Comm. Print 1986).

203. *Id.* at 70–71.

204. *See* Carolyn H. Asbury, *The Orphan Drug Act: The First 7 Years*, 265 JAMA 893 (1991).

205. Ronald Podraza, *The FDA's Response to AIDS: Paradigm Shift in New Drug Policy?*, 48 Food & Drug L.J. 351, 352–54 (1993). There was widespread perception that the FDA attitude

stimulate research and development of new treatment for certain diseases and patient groups[206]—incentives that might now be exploited or modified to similarly stimulate research directed at the tuberculosis epidemic.

V. EXPLOITING AND CREATING DRUG AND VACCINE DEVELOPMENT INCENTIVES

Although changing cultural consciousness and stimulating sympathy and interest in TB victims here and abroad is beyond the immediate power of law and regulation, the law can and should be used to provide regulatory, economic, and marketing incentives to the global pharmaceutical industry to spur research and development of new drugs and vaccines.[207] Indeed, we have already seen such incentives applied to new treatments for AIDS in the form of a "fast track" regulatory process, for drugs designed to treat so-called "orphan diseases," and to certain vaccines. It also is possible that in the course of more fundamental, far-reaching FDA reform, the regulatory climate might be altered to favor research and development of treatments for global epidemics.

A. Incentives Facilitating Development of New Drug Therapies

In response to demands by special-interest groups, Congress and the FDA have provided pharmaceutical manufacturers with a series of incentives to foster development of drugs and therapies for rare and devastating diseases. Some of these incentives, such as the "fast track" procedures applicable to new AIDS treatments, are designed to bring new drugs to the market more quickly. Others like the "Orphan Drug Act" stimulate the development of drugs and treatments that would not be developed in the absence of such incentives. Both types of incentives might be invoked and, if need be, reworked to facilitate research and development of new tuberculosis drugs and vaccines.

1. Tuberculosis: An Orphan Under the Orphan Drug Act?

During the 1970s and 1980s, it became evident that new drugs for rare diseases or diseases primarily affecting poor, uninsured populations were

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towards AIDS and AIDS patients was "obstructionist, insensitive, inflexible and otherwise cruelly oblivious of their plight." *Id.*

206. *See id.* at 363.

207. *See* Reichman, *supra* note 8, at 175–77.

not being developed.[208] Such diseases were tagged orphan diseases—orphaned because no one sought to offer pharmaceutical treatments and remedies for them. Such orphan diseases, while frequently tragic, affected relatively few unfortunate victims.[209] Developing a drug for an orphan disease would not produce a profit for the increasingly profit-driven pharmaceutical manufacturer.[210]

Congress acted to remedy this situation by passing the Orphan Drug Act of 1983,[211] through which pharmaceutical firms were provided with three separate incentives to develop drugs for such orphan diseases. First, Congress provided for tax credit—a credit, not just a deduction—of fifty percent of the cost of the clinical trial during the time the designated orphan drug is seeking approval.[212] Second, the Act provided for additional government planning assistance to the company throughout the course of the clinical trials and approval process.[213] Finally and most importantly, the Orphan Drug Act granted the pharmaceutical company seven years of market exclusivity, regardless of whether or not the new orphan drug was patentable.[214]

The benefits of the Orphan Drug Act were subject to certain limits, however. First, only in very select situations will more than a single drug be deemed an orphan drug for a given disease.[215] In addition, the incentives, especially the market exclusivity incentive, are only available to a narrow class of prospective drugs. The orphan drug designation is limited to drugs developed for diseases affecting less that 200,000 persons in the United States.[216] The narrow classification was somewhat broadened by a 1985 amendment to the Act, under which drugs for diseases affecting more than 200,000 people in the United States qualify for orphan drug status if there is no reasonable expectation that the costs

208. *See supra* notes 196–204 and accompanying text.

209. *See* Asbury, *supra* note 204, at 893; Donna Brown Grossman, *The Orphan Drug Act: Adoption or Foster Care?*, 39 Food Drug Cosmetic L.J. 128 (1984); Hogan, supra note 196, at 525.

210. *See* Henry, *supra* note 197, at 629.

211. 21 U.S.C. §§ 360aa–360ee (1994).

212. *See* 26 U.S.C. § 28(a) (1996). This tax credit was available only for expenses incurred through the end of 1994. 26 U.S.C. § 28(e) (1996).

213. 21 U.S.C. § 360aa.

214. 21 U.S.C. § 360cc.

215. A second drug can be approved for the same indication when the first manufacturer is unable to produce the drug in adequate quantities, when the second company obtains the consent of the first to enter the market, when the first chooses to exit the market, or when the second newer orphan drug is proven to be superior to the initial drug for the treatment indications. Hogan, *supra* note 196, at 529.

216. 21 U.S.C. § 360bb(a)(2).

of development and manufacturing can be recouped from U.S. sales.[217] Moreover, the market exclusivity provision remains applicable even if the target population grows during the period of exclusivity to greater than 200,000.[218]

Passage of the Orphan Drug Act had an almost immediate effect upon drug development for orphan diseases, such as cystic fibrosis[219] and Gaucher's disease.[220] Although only ten drugs treating such orphan diseases had traversed the FDA regulatory maze to approval in the decade preceding the Orphan Drug Act, eighty-seven new drugs were brought to market in the first decade after implementation of the Orphan Drug Act.[221] Clearly the Orphan Drug Act has achieved its purpose of facilitating new drug development for rare, frequently devastating diseases.

However, the Act has had some unintended consequences that tarnish its image. Many pharmaceutical companies have managed to extract windfall profits by high pricing despite the small numbers of orphan disease patients targeted. For example, Genentech's human growth hormone, an orphan drug that treats a pituitary deficiency,[222] earned $580 million during its first five years of exclusive marketing, thus recovering over ten times the forty-five million dollars of research and development costs.[223] A single year's supply of the orphan drug Ceredase, used to treat Gaucher's disease, costs $350,000.[224] These astronomical costs generally are paid by the health plan—assuming of course that the patient is lucky

217. 21 U.S.C. § 360bb(a)(2).

218. 21 U.S.C. § 360ee.

219. Cystic fibrosis is a hereditary disorder characterized by pancreatic dysfunction and chronic progressive respiratory disease; patients frequently succumb as young adults.

220. This hereditary enzyme deficiency presents in several different forms, ranging from a devastating infantile form to a milder adult form. The adult form of the disease is characterized by disorders of blood and clotting, pulmonary disease, and liver dysfunction; more severe forms of the disease impair the neurologic system. Care and treatment of patients with Gaucher's disease has changed materially with the development of a replacement enzyme, marketed as Ceredase, which was developed as an orphan drug.

221. Hogan, *supra* note 196, at 530; *see also* Arno et al., *supra* note 196, at 232.

222. Patients with this type of deficiency have a dysfunction of the pituitary gland, a small gland in the brain. The pituitary is responsible for triggering the release of a variety of hormone necessary for normal life, including reproductive hormones, thyroid hormones, and growth hormone. The latter is responsible for normal growth; if it is lacking, it must be supplemented to assure normal height and maintain certain other metabolic parameters within normal range.

223. Hogan, *supra* note 196, at 530.

224. *Id.* at 531.

enough to qualify for insurance or a liberal Medicaid plan.[225] In addition, pharmaceutical companies have learned to divide a more common disease into discrete, narrow subdivided disease entities or indications to qualify for the orphan drug designation; this practice is referred to as "slicing the salami" by industry pundits.[226] Alternatively, a pharmaceutical company may ostensibly seek orphan drug status for a new drug to treat a rare hormone disorder, even while realizing the drug will have great utility in treating a common malady like infertility.[227] Upon reaching the market, physicians and patients are made aware of the orphan drug's versatility, and physicians simply prescribe the drug "off-label" for the more common condition.[228] Several legislative attempts to ameliorate these problems have been unsuccessful.[229]

The Orphan Drug Act and its unintended loopholes may well provide the most fertile ground for facilitating the development of new TB drugs. Only a tiny percentage of the world's tuberculosis is found in the United States. In fact, despite 100 million patients infected with MDR-TB worldwide, and predictions for thirty million deaths in the next decade, there were only 22,812 cases of active tuberculosis reported in the United States in 1995,[230] well under the 200,000 threshold for orphan disease designation. In addition, it might well be possible to gain a second orphan drug designation for a drug dedicated to MDR-TB, and potentially a third designation for a drug targeting the combination disorder TB and HIV. Such "slicing of the salami" remains possible

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225. Use of insurance health plans and Medicaid plans for coverage of such expensive drugs has far-reaching implications. If the patient is a member of a small health plan the cost of the premium for the coverage may increase dramatically as the small group's subscribers offset the cost of this extreme expense. *See id.* at 531–32. Similarly if the patient is covered under a state Medicaid plan, this single patient may use so many financial resources that many other worthy Medicaid patients are foreclosed from eligibility.

226. *Id.* at 533; *see also* Arno et al., *supra* note 196, at 237.

227. For example, a new drug, D-Nase, developed by Genentech for cystic fibrosis (CF) may have orphan status on the basis of its use for CF, but it also may be effective against more common afflictions, like bronchitis and pneumonia—afflictions likely to be widespread in developed nations. *See* Hogan, *supra* note 196, at 533.

228. *See id.*; Arno et al., *supra* note 196, at 240. "Off-label" use means that the drug is used for an indication not authorized by the descriptive label approved by the FDA. For a more in depth discussion of off-label use of drugs and the scientific, ethical, and economic implications of this practice, see Richard M. Cooper, *Unapproved Uses of Drugs: An Analysis and Some Proposals,* 49 Food & Drug L.J. 533 (1994).

229. *See* Hogan, *supra* note 196, at 535–36.

230. *TB's Resurgence Calls for New Drugs*, *supra* note 151. Note, however, that these promising statistics are not found elsewhere in the world, particularly in the developing world where 97% of tuberculosis occurs. This will make continued success of public health efforts in industrialized nations ever more susceptible to erosion.

under the Act as currently implemented. Moreover, assuming the best-case scenario in which three manufacturers could develop orphan drugs for each of the these three indications, each might benefit from market exclusivity and also exploit more general utility—and profit—from the new drugs through wide "off-label" use. Although Congress and the FDA do not condone this practice, neither have they prohibited it.

With respect to global use of the drugs, the pharmaceutical industry will not find complementary Orphan Drug Acts in other countries. In fact, no other countries have implemented such incentives.[231] As a result, the global community gets a free ride to orphan drugs.[232] In the case of drugs applicable to diseases that are global orphans—that is, diseases that are rare throughout the world—manufacturers frequently shift the cost to U.S. consumers because pricing of drugs is stringently controlled in other industrialized nations, the majority of which have nationally regulated universal healthcare systems.[233] This, of course, markedly increases the price of the orphan drug for U.S. consumers, who purchase at a market price that covers the manufacturer's costs plus whatever profit the market will bear.[234] However, in the postulated case scenario for new TB drugs, this cost shifting will be minimized by virtue of the large global volume of patients. Thus, although pharmaceutical companies might not, in the United States, make a "windfall" profit like that enjoyed by Genentech,[235] a healthy profit could easily be achieved without massive cost-shifting, given the enormous incidence of tuberculosis worldwide.[236]

2. *Expediting FDA Approvals: Jumping onto the "Fast Track"*

Pharmaceutical manufacturers who developed new TB drugs targeting MDR-TB and TB/HIV patients might also avail themselves of one or

231. Hogan, *supra* note 196, at 537.

232. *Id.* at 537–38.

233. *See International Prescription Drug Prices: Hearing Before the Subcomm. on Health and the Env't of House Comm. on Energy and Commerce*, 103d Cong., 1st Sess. (1993).

234. Hogan, *supra* note 196, at 548.

235. *See supra* notes 220–232 and accompanying text.

236. The cost of a typical orphan drug can be shared among only a finite number of patients around the world. Cost sharing is further permuted by the fact that many countries limit the price that can be charged for pharmaceutical products in their countries. As a result, the cost-shifting burden on the U.S. patient is multiplied. Unlike most orphan drugs that are dedicated to rare orphan diseases afflicting a small number of patients new TB drugs would treat disease, that, although relatively rare in the United States, is rampant elsewhere in the world. Thus, given the great volume of patients, the cost shifting burden is unlikely to be as severely disproportionate, and may even be negligible.

more of the expedited FDA processes originally provided to stimulate development and dissemination of new AIDS therapies. These "fast track" and early-access provisions inaugurated a new era in drug regulation in the United States. For the first time, disease severity and urgency of market need became factors in the FDA review and approval process.[237] As such, they somewhat alter the long-standing primacy of incontrovertible proof of "safety and efficacy" as the sole standard for FDA approval and marketing.[238]

One category of provisions provides patients with early access to drugs and therapies that are still in the research pipeline. These provisions include the "treatment use of an investigational new drug" ("Treatment IND") program[239] and the parallel track program.[240] Use of the latter program is limited to drugs dedicated to HIV,[241] but with the strong association between HIV and TB, new drugs targeting TB should be able to use the parallel track program. However, neither of the two early access programs are likely to be useful in developing and disseminating new drugs to masses of patients, as would be necessary in the case of tuberculosis. Both are designed to deliver drugs to a small, carefully followed population of patients.

Of greater promise with respect to fostering new drugs for TB are the so-called "fast track" provisions. Two major fast track options are currently available to pharmaceutical manufacturers and could be utilized in conjunction with widespread distribution of new TB drugs.

The first of these, the "Subpart E" provisions,[242] allow for compression of the clinical investigation phase of drug review; the

237. Sheila R. Shulman & Jeffrey S. Brown, *The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 Food & Drug L. J. 503, 503 (1995).

238. *See infra* notes 179–187 and accompanying text.

239. *See* 21 C.F.R. § 312.34 (1996). The treatment IND program builds on several previous access programs that allowed patients suffering from life-threatening or serious illness to have "compassionate" access to new drugs that were not yet fully approved for marketing. *See* Frank E. Young et al., *The FDA's New Procedures for the Use of Investigational Drugs for Treatment*, 259 JAMA 2267 (1988).

240. The parallel track process, announced at 57 Fed. Reg. 13,250 (1992), provides an administrative process to expand availability of new drugs directed at HIV patients. Under the parallel track, patients who would otherwise be unable to participate in clinical trials of promising new drugs are allowed access to the drugs. However, the attending physicians are required to file reports and data with the FDA and there are several layers of oversight. *See* Shulman & Brown, *supra* note 237, at 509–10.

241. 57 Fed. Reg. 13,250 (1992) ("This parallel track policy describes processes specifically for AIDS and other HIV-related diseases.").

242. 21 C.F.R. § 312.80 (1996).

amount of compression is tailored to the severity of the disease threat and the availability of alternative treatments.[243] Initiated in 1988,[244] this "fast track" allows the FDA to provide a shortcut through the lengthy phase III[245] testing process for drugs aimed at patients suffering from life threatening and seriously debilitating diseases.[246] Tuberculosis easily qualifies under this criteria. This expedited process was used to bring AZT and several other drugs to market quickly to meet the critical needs of HIV patients.[247] Subpart E has succeeded in materially decreasing the time required for FDA review.[248] In fact, a recent study determined that use of subpart E could shave 3.3 years off the total regulatory phase required to bring a new drug to the market.[249]

Yet another "fast track" that pharmaceutical manufacturers could use for anti-tuberculosis drugs is the new "surrogate marker" program.[250] The "surrogate marker" program requires the manufacturer to show that the drug is effective with respect to a surrogate endpoint[251] that can be reasonably correlated to a clinical benefit for patients suffering from a similar, but not identical, seriously debilitating disease or disorder.[252] Under this 1993 program, approval is even more accelerated, but there may be conditions attached that limit rapid dissemination of the new therapy.[253] This new program is still "finding its feet" in the FDA

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243. Subpart E states:

> The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.

21 C.F.R. § 312.80 (1996)

244. 21 C.F.R. § 312.84 (1996).

245. *See* text accompanying notes 185–186.

246. This "fast track" also allows clinical study of new drugs without requiring there to be a "placebo" control group. *See* Relihan, *supra* note 185, at 240.

247. *See* Shulman & Brown, *supra* note 237, at 511.

248. *Id.* at 517. For example, Flutamide, a drug used to treat prostate cancer completed FDA review in a record 3.7 months. *Id.* at 525.

249. *Id.* at 513.

250. *See* 21 C.F.R. §§ 314.500, 601.40 (1996).

251. A surrogate endpoint is a desirable outcome demonstrated in the context of a similar, but not identical set of clinical circumstances or patient population. *See* 21 C.F.R. § 314.510 (1996).

252. *See* 21 C.F.R. §§ 314, 601 (1996).

253. *See* Shulman & Brown, *supra* note 237, at 515–16.

panoply of regulations and programs and has been utilized only marginally.[254]

The fast track programs could and should be used to expedite FDA review and approval processes, thereby decreasing the cost and time required to develop and disseminate new anti-tuberculosis products. It is also possible that development of new tuberculosis therapies might be enhanced by extending protection against liability to the pharmaceutical companies. As discussed below, this method was successfully utilized to stimulate the production of childhood vaccines.

B. Liability Protection: Building on the Past to Stimulate Vaccine and Drug Development

More than drug manufacturers, vaccine manufacturers have experienced the harsh reality of legal action for harms resulting from allegedly defective or contaminated treatments.[255] Injured parties can bring claims against manufacturer primarily on two theories: negligence—that is, that the manufacturer breaches its duty, causing harm to the patient; and strict liability—in which the patient will recover damages because the product is defective, regardless of the conduct or "fault" of the manufacturer.[256] In strict liability, the theory is that a manufacturer should have greater monetary exposure because it is in the best position to provide for and insure against defective products.[257] This strict liability approach is limited however, when the product is "unavoidably unsafe" as is the case with many vaccines.[258]

Despite the fact that many injuries resulting from vaccines are the result of their "unavoidably unsafe" nature,[259] vaccine manufacturers have experienced heavy losses, both in the monetary and public relations sense.[260] A number of high profile suits in the 1960s and 1970s alleged

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254. *See id.* at 516.

255. *See* H.R. Rep. No. 99-908, at 4 (1986), *reprinted in* 1986 U.S.C.C.A.N. 6344, 6347–48; *supra* notes 201–203 and accompanying text.

256. W. Page Keeton et al., *Prosser and Keeton on the Law of Torts* § 96, at 688 (5th ed. 1984).

257. *Id.* § 98, at 692–94.

258. *Id.* § 99, at 701–02.

259. *See supra* notes 201–203 and accompanying text; *see also* Subcomm. on Health & the Env't of the House Comm. on Energy & Commerce, 99th Cong. 2d Sess., *Childhood Immunizations* 21–33 (Comm. Print 1986).

260. *See Vaccine Injury Compensation, 1984: Hearings on H.R. 556 before the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce*, 98th Cong., 2d Sess. 295 (1984) (statement of Dr. Daniel Shaw, Jr. Vice President, Wyeth Laboratories).

injury resulting from both oral polio vaccine and children's DPT vaccine.[261]

In 1976, with the nation expecting an epidemic of swine flu and vaccine manufacturers reluctant to produce a vaccine because of liability fears, Congress acted swiftly and boldly to assuage their fears and facilitate delivery of a vaccine.[262]

1. *Government Assumption of Liability: Lessons Learned from the Swine Flu Vaccine Program*

In response to the swine flu scare, Congress quickly enacted an amendment to the Federal Tort Claims Act[263] that allowed victims injured by the new vaccine to seek recovery from the federal government.[264] Under this scheme, the federal government, rather than the manufacturer, would be the party compensating victims. The federal government could go back to the manufacturer secondarily if the claim was based on negligence—that is, where the manufacturer had committed a breach of its duty of care in the manufacturing process—but the plaintiff-friendly strict liability claims for a defective product would be effectively covered by the federal government pursuant to the Federal Tort Claims Act.[265]

Vaccine manufacturers rapidly developed and manufactured the new swine flu vaccine. Forty million people in the United States were immunized.[266] Unfortunately, the vaccine had an untoward side effect; a minority of patients developed Guillain-Barre Syndrome, a dangerous

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261. *See, e.g.*, Givens v. Lederle Lab., 556 F.2d 1341 (5th Cir. 1977); Reyes v. Wyeth Lab., 498 F.2d 1264 (5th Cir.), *cert. denied*, 419 U.S. 1096 (1974); Davis v. Wyeth Lab. Inc., 399 F.2d 121 (9th Cir. 1968).

262. *See* Thomas E. Baynes, Jr., *Liability for Vaccine Related Injuries: Public Health Considerations and Some Reflections on the Swine Flu Experience*, 21 St. Louis U. L.J. 44, 64–66 (1977). This congressional action was further spurred by the Legionnaire's Disease mini-epidemic in Philadelphia during that congressional session. Although swine flu is remembered as only a minor footnote today, in 1976 there was concern that it might rival a similar earlier flu that had taken 20 million lives worldwide. *See* H. William Smith, III, *Vaccinating AIDS Vaccine Manufacturers against Product Liability*, 42 Case W. Res. L. Rev. 207, 219 (1992). *See generally* Richard E. Neustadt & Harvey V. Fineberg, *The Epidemic That Never Was: Policy Making and the Swine Flu Affair* (1983).

263. 28 U.S.C. §§ 2671–2678 (1994).

264. Arnold W. Reitze, Jr., *Federal Compensation for Vaccination Induced Injuries*, 13 B.C. Envtl. Aff. L. Rev. 169, 178–79 (1986).

265. *See* Baynes, *supra* note 262, at 68.

266. Smith, *supra* note 262, at 221. The swine flu epidemic did not fully materialize.

paralysis sometimes causing death and permanent disability.[267] By 1985, the cost of settlements and suit judgments was approaching $100 million, far exceeding the budget allotted for the program.[268]

Congress learned some valuable lessons from the swine flu episode—lessons that it applied a few years later when it enacted the National Childhood Vaccine Injury Act. The federal government would not again assume liability with such naiveté.

2. *Creation of a No-Fault Compensation System: The National Childhood Vaccine Act Model*

As noted above,[269] manufacturers of children's vaccines began to feel the bite of liability in the 1960s. In fact, some manufacturers began to curtail their exposure as early as 1967 by getting out of the vaccine production business.[270] It was not until the early 1980s, however, that supplies of childhood vaccines became dangerously low, not only globally but also in the United States.[271]

Once again, Congress acted to relieve manufacturers of some of their liability concerns. In 1986, it enacted the National Childhood Vaccine Injury Act,[272] which put in place what is, in effect, a no-fault insurance system for vaccine injuries sustained from compulsory childhood vaccines. The program is funded by a excise tax on the vaccines.[273] Patients sustaining a vaccine-related injury are eligible for compensation under a defined injury-based compensation schedule that provides for costs of medical and rehabilitative care, lost earnings, pain and suffering and death benefits.[274] Once the patient takes advantage of the no-fault compensation, they are foreclosed from taking their claim to court.[275]

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267. *See* Reitze, *supra* note 264, at 181–82.

268. Smith, *supra* note 262, at 219. By the mid-1980s, the cost of claims was at $83 million and rising. Reitze, *supra* note 264, at 185.

269. *See supra* notes 260–263 and accompanying text.

270. *See supra* notes 259–260 and accompanying text.

271. Daniel A. Cantor, *Striking a Balance between Product Availability and Product Safety: Lessons From the Vaccine Act*, 44 Am. U. L. Rev. 1853, 1959 (1995); Keiser, *supra* note 201, at 16.

272. Pub. L. No. 99-660, 100 Stat. 3755 (codified at 42 U.S.C. §§ 300aa-2 to 6, 10 to 17, 19, 21, 23, 25 to 28, 31 to 33 (1994)).

273. 26 U.S.C. §§ 4131–4132 (1994).

274. *See* 42 U.S.C. §§ 300aa-11 to 16 (describing the filing process and requirements, vaccine injury tables, and compensation provisions and requirements).

275. 42 U.S.C. § 300aa-21.

This no-fault program has been well received; by 1990, $56.8 million had been disbursed to claimants. Moreover, legal and attorney costs were minuscule—only three percent. There is also some evidence that the program stabilized the vaccine market and prices.[276]

A provision similar to the National Childhood Vaccine Injury Act could provide incentives to potential manufacturers of new TB vaccines. Like childhood vaccines, a TB vaccine would have wide use throughout the world, and therefore would generate sales sufficient to compensate for research and development costs. The fact that the vast majority of vaccine would be used in poor, developing nations unable to pay high prices and in nations with tightly regulated drug pricing systems would be offset by the much diminished risk of liability costs in the United States.

It is also possible that limitation of liability, its attendant costs, and its effects on pharmaceutical development of drugs and vaccine for global public health threats might be addressed in the context of more fundamental reform of the cumbersome FDA regulatory scheme.

C. *Revamping the Regulatory Regimen: FDA Reform*

Many of those in the pharmaceutical industry as well as concerned consumer groups believe that fundamental FDA reform is necessary to decrease the costs and delays of the FDA process.[277] As a result, we now stand on the threshold of more formidable FDA reform, perhaps even reform that radically changes the underlying FDA regulatory regimen.[278] The more likely possibility, however, is that some level of incremental reform will be made in the foreseeable future.

One de minimus reform might include some contracting out of FDA regulatory review to private firms in order to decrease the cost and time required for review and approval. In the case of more far-reaching reform of the same ilk, the move toward privatization of FDA functions might

276. Smith, *supra* note 262, at 227–28. California subsequently enacted a similar statute targeting development of AIDS vaccines. The California statute included no-fault provisions, but the patient was not foreclosed from seeking recovery from the manufacturer as well, although no "double dipping" was allowed. *Id.* at 229–30. This provision was short-lived and appears not to have been implemented in any substantive way prior to its repeal in 1995.

277. *See generally* Dillman, *supra* note 187.

278. *See* Charles Marwick, *Congress Moving to Improve FDA Performance*, 275 JAMA 670 (1996). There is, of course, no guarantee that FDA reform will improve upon the system; radical reform might so shake up the FDA regulatory bureaucracy that drug approval could be subject to even more delay and confusion.

be more profound.[279] For example, the government might choose to divest itself of the FDA, selling it or leasing it to private enterprise.[280] Although it is unclear how such "privatization" would affect development of drugs for the TB epidemic, it is likely that this reform would not provide greater impetus to develop anti-tuberculosis drugs and vaccines.

FDA reform might invoke greater, more general application of fast tracks and expedited access provisions. Similarly, accentuated enforcement mechanisms to force the FDA to comply with firm time frames for each phase of the FDA process, and other streamlining measures, have also been proposed.[281] This type of reform would facilitate the rapid dissemination of new drugs, including those aimed at TB.

Yet another possibility is that Congress might take a page from the Orphan Drug Act and provide tax incentives[282] and additional patent protections to pharmaceutical manufacturers who develop drugs that improve the global public health. Such incentive would promote the development of not only anti-tuberculosis drugs, but also other needed but less profitable drug therapies.

Additionally, it is possible that Congress might rewrite the Orphan Drug Act. This might broaden the Act to target not only orphan drugs but also public health focused drugs. Alternatively, Congress might act to limit windfall profits, and thereby limit the unintended, but possibly beneficial, loopholes available to companies developing new drugs. Such a reform could therefore present a double-edged sword for new tuberculosis drug development.

It is also possible, although somewhat unlikely, that Congress may end to drugs or vaccines federal preemption of certain state law causes of action that could be brought against the manufacturers. Although medical device manufacturers enjoyed protection from liability under such a preemption doctrine in the past, a recent U.S. Supreme Court case

279. *See* Rutherford, *supra* note 185, at 205–24.

280. *See id.* at 209–10.

281. *See id.* at 216. For an example of a recent bills proposing such measures, see Food and Drug Administration Performance and Accountability Act of 1995, S. 1477, 104th Cong., 1st Sess. (1995) and the Drug and Biological Products Reform Act of 1996, H.R. 3199, 104th Cong., 2nd Sess. (1996).

282. For a detailed analysis of and proposal for such a reform, see Nina J. Crimm, *A Tax Proposal to Promote Pharmacologic Research, to Encourage Conventional Prescription Drug Innovation and Improvement, and to Reduce Product Liability Claims* 29 Wake Forest L. Rev. 1007 (1994).

severely limited the scope of this preemptive protection.[283] As a result, enactment of such a preemption is a remote possibility.

Perhaps the most fervent and popular proposed FDA reform is that the United States at long last address the fact that the pharmaceutical market is a global one. Although many decry the industry's apparent apathy with respect to our reemerging tuberculosis epidemic, it cannot be denied that drug and vaccine manufacturers answer to many masters in complying with each nation's unique drug approval process.[284] Much could be achieved by harmonizing our drug approval system with that of other industrialized nations.[285] This would decrease research and development costs by eliminating duplicative research trials, and would provide better access to diverse populations for such trials.[286] At the very least harmonization would foster cooperation among nations and pharmaceutical firms at a global level, providing a better base upon which to develop new medications to treat and cure the global tuberculosis epidemic.

V. CONCLUSION

Tuberculosis has returned to bedevil the world's population, and it has returned in much more virulent forms. The public health strategies and drugs that forced it into submission in the past are no match for the new "white plague." Modernized public health techniques face insurmountable barriers as a result of an obsolete and underfunded infrastructure, due process constraints prohibiting enforced mandatory treatment, and massive, virtually uncontrollable geographic mobility. All of these factors guarantee ever greater spread of tuberculosis. If the nations of the world and their public health efforts are to make any appreciable headway in curbing this epidemic, they must have new, more effective drugs and vaccine therapies that allow them to circumvent these formidable barriers.

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283. *See* Medtronic, Inc. v. Lohr, 116 S. Ct. 2240 (1996) (holding that clause in Medical Devices Act preempting states from regulating safety and effectiveness of medical devices did not preempt all state law causes of action brought by injured patient against manufacturer of defective pacemaker).

284. *See* Kanusky, *supra* note 177, at 688–95; Eric M. Katz, *Europe's Centralized New Drug Procedures: Is the United States Prepared to Keep Pace?*, 48 Food & Drug L.J. 577 (1993).

285. There has already been some promising movement in this direction. For example, the recent extension of the patent term from 17 to 20 years was largely for the purpose of harmonizing the length of the term with that of other nations.

286. *See* Kanusky, *supra* note 177, at 703–06.

After a long period of stagnation, the pharmaceutical industry is finally beginning to respond to public health pleas for new drugs to combat TB. Finally there are early reports of promising new drug and vaccine research.[287] Nevertheless, such research and development faces a harrowing maze of regulatory, financial, and market obstacles. Regulation of the pharmaceutical industry should be restructured to encourage these fledgling efforts by providing incentive programs to overcome industry reluctance of developing new therapies for tuberculosis before this epidemic extracts an even higher price in human suffering and healthcare costs.

287. *See, e.g.*, Daniel J. DeNoon, *Mycobacterial Antigen 85: Key to Effective TB Vaccine?*, Vaccine Wkly., Apr. 8, 1996, *available in* WESTLAW, 1996 WL 2001405; *Licensing/Collaboration Agreement on TB Vaccine Completed*, Vaccine Wkly., Oct. 16, 1995, *available in* WESTLAW, 1995 WL 10121617; Warren Wilson, *PathoGenesis' New TB Fighter Shows Promise*, Seattle Post-Intelligencer, Sept. 17, 1996, at B4.