ATTACK OF THE SUPERBUGS
The Law & Medicine of Antibiotic Resistance

Meiring de Villiers*
"[T]here are catastrophes ahead. There is no reason that a great plague could not happen again. We live in evolutionary competition with microbes - bacteria and viruses. There is no guarantee that we will be the survivors."
- Rockefeller University President and Nobel Laureate Joshua Lederberg.¹

ABSTRACT

The microbial world has been described as “complex, dynamic, and constantly evolving”. This complicates the foreseeability issue in medical malpractice involving injury due to an emerging microbial disease. The following generic description of antibiotic resistance provides an illustration. A novel antibiotic resistant form of a known disease may be caused by a novel genetic mutation of a known causative pathogen. The confusing mix of the old and the new and the apparent lack of a direct connection between law and science make the foreseeability analysis appear intractable. The resolution of these and similar issues requires a translation between law and medicine that speaks the language of medicine, yet preserves the meaning and policy rationale of the traditional legal doctrines. The Article develops the methodology and illustrates its application by analyzing the foreseeability of multidrug resistant tuberculosis.

1. INTRODUCTION

Despite extraordinary medical advances in diagnosis, therapy and vaccination we continue to witness the appearance of previously unrecognized diseases and the expansion of known diseases into new geographic areas, often with catastrophic public health and economic consequences. The most prominent recent examples of these phenomena, collectively termed emerging infections and diseases, are disorders such as Acquired Immunodeficiency Syndrome (AIDS) and its etiologic agent, the Human Immunodeficiency Virus (HIV); Ebola Hemorrhagic Fever, caused by the lethal and highly infectious Ebola Virus; Severe Acute Respiratory Syndrome (SARS), caused by the novel

---

SARS Coronavirus, 3 multidrug-resistant tuberculosis,4 and the Zika virus and diseases it causes.5

Emerging infections are diseases that (1) have been recognized in a human host for the first time,6 (2) are caused by known pathogens that have spread into new geographic areas,7 (3) have reappeared after a period of decline,8 or (4) have altered their

---

3 Morens & Fauci, supra note 2, at 1; Mark E. J. Woolhouse et al., Temporal Trends In The Discovery Of Human Viruses, 16 Proc. R. Soc. B 1, 1 (2008); David M. Morens, et al., Emerging Infections: A Perpetual Challenge, 8 Lancet Infect Dis. 710, 710 (Nov. 2008); Mary E. Chamberland, Emerging Infectious Agents: Do They Pose a Risk to the Safety of Transfused Blood and Blood Products?, 34 CID 797, 797–98 (2002); Sophia Zyga & Michail Zografakis-Sfakianakis, Emerging and Re-Emerging Infectious Diseases: A Potential Pandemic Threat, at 5 Health Sci. J. 159, 160 (2011) (“Severe acute respiratory syndrome (SARS) is an often fatal infectious respiratory disease with prominent systemic symptoms. It is caused by a novel coronavirus, SARS coronavirus (SARS-CoV), which was responsible for a global outbreak from November 2002 to July 2003.”).


6 Morens & Fauci, supra note 2, at 1; David L. Heymann & Vernon J. M. Lee, Emerging and Re-Emerging Infections, in Roger Detels et. al., Oxford Textbook of Global Pub. Health (6 ed.), at 2 (Feb., 2015) (“When disease is caused by an organism that is newly identified and not known previously to infect humans or has changed in susceptibility to an anti-infectious drug, it is commonly called an emerging infectious disease, or simply an emerging infection.”).

7 John S. Mackenzie et al., Emerging Flaviviruses: The Spread and Resurgence of Japanese Encephalitis, West Nile and Dengue Viruses, 10 Nature Med. Supplement 98, 107 (2004) (discussing examples of the emerging flaviviruses and showing “the ease and propensity with which these viruses can spread to emerge and establish in new geographic areas.”); Joshua Lederberg, Emerging Infections: Microbial Threats to Health in the United States, Institute of Medicine 1 (Robert E. Shope & Stanley C. Oaks, Jr. eds., 1992) (“Like other living organisms, infectious agents are subject to genetic change and evolution. ... Alterations can also occur in geographic ranges; in some cases, modern transport has led to rapid movement of agents throughout the world.”); Morens et al., supra note 3, at 714.

8 Lederberg, supra note 7, at 34 (“Emergence, or, more specifically, reemergence, may also be used to describe the reappearance of a known disease after a decline in incidence.”); Morens & Fauci, supra note 2, at 1; Sanjeev K. Gupta et al., Emerging and Re-emerging Infectious Diseases, Future Challenges and Strategy, 6(6) J. Clinical & Diagnostic Res. 1095, 1095 (2012) (“[W]ell-
pathogenic mechanisms or genetic features.\textsuperscript{9}

Antibiotic resistance is an increasingly important factor in the emergence of microbial threats to public health.\textsuperscript{10} The discovery of antibiotics has revolutionized modern medicine but bacteria have adapted to new environments by developing mechanisms of resistance to most antibiotics.\textsuperscript{11} Recently, new mechanisms of drug resistance have resulted in the development of highly virulent multidrug-resistant bacterial strains known as superbugs.\textsuperscript{12} The most virulent superbugs are resistant to virtually every antibiotic in mainstream use.\textsuperscript{13} Current notorious superbugs include multidrug resistant strains of \textit{Mycobacterium tuberculosis} (M. TB), the causative agent of tuberculosis,\textsuperscript{14} and the methicillin-resistant bacterium \textit{Staphylococcus aureus} (MRSA).\textsuperscript{15}

\textsuperscript{9} Morens & Fauci, \textit{supra} note 2, at 2 (“Drug resistant mutations have also caused the reemergence’s of certain pathogens such as multidrug-resistant and extensively drug-resistant tuberculosis, drug-resistant malaria, and numerous bacterial diseases such as vancomycin-resistant enterococci.”).


\textsuperscript{12} Id. at 697; Julian Davies & Dorothy Davies, \textit{Origins and Evolution of Antibiotic Resistance}, 74(3) \textit{Microbiology \& Molecular Biology Rev.} 417, 421 (2010) (“Superbugs are not the only microbial threats, but they are recognized as the most menacing with respect to morbidity and mortality worldwide.”).

\textsuperscript{13} Rahul Mishra et al., \textit{Gene Mutations in Mycobacterium Tuberculosis: Multidrug-Resistant TB as an Emerging Global Public Health Crisis}, 95 \textit{Tuberculosis} 1, 2 (2015); M. McGrath et al., \textit{Mutation Rate and the Emergence of Drug Resistance in Mycobacterium Tuberculosis}, 69 J. \textit{Antimicrob. Chemother.} 292, 292 (2014).

\textsuperscript{14} Davies & Davies, \textit{supra} note 12, at 420; Brad Spellberg et al., \textit{The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America}, 46 CID 155, 155–56 (2007).

\textsuperscript{15} Morens & Fauci, \textit{supra} note 2, at 2 (“Drug resistance mutations have also caused the reemergences of certain pathogens such as multidrug-resistant and extensively drug-resistant tuberculosis, drug-resistant malaria, and numerous bacterial diseases such as vancomycin-resistant enterococci.”); R. Jayaraman, \textit{Antibiotic Resistance: An Overview of Mechanisms and a Paradigm Shift}, 96(11) \textit{Current Sci.} 1475, 1476 (2009).
The microbial world has been described as “complex, dynamic, and constantly evolving”. In the words of Professors David Heymann and Vernon Lee, “[i]nfectious organisms reproduce rapidly, mutate frequently, cross the species barrier between animal hosts and humans, and adapt with relative ease to their new environments. Because of these characteristics, infectious organisms are able to alter their epidemiology, their virulence, and their susceptibility to anti-infective drugs.” Unsurprisingly, we frequently observe that old infectious agents cause new diseases, new agents cause old diseases, and occasionally new mutations cause entirely new diseases. The mosquito-borne Cache Valley virus is an example of an old virus that caused new disease manifestations in its usual host, in part due to altered environmental conditions. New versions of the influenza virus that differ significantly from their predecessors have emerged, causing diseases identical to that described for centuries. Occasionally new mutations cause entirely new diseases. Brazilian purpuric fever, caused by a newly emerged clonal variant of *Hemophilus influenzae* biogroup aegyptius, may fall into this category.

---

20 Morens & Fauci, supra note 2, at 1.
21 Id.; Stephen S. Morse, *Factors in the Emergence of Infectious Diseases*, 1(1) EMERGING INFECTIOUS DISEASE J. 7, 9 (Jan. 1995); Joshua Lederberg et al., *Emerging Infections: Microbial Threats to Health in the United States* 90–91 (1992) (describing the emergence in 1984 of Brazilian purpuric fever, a “new disease that is likely to have been the result of a mutation causing enhanced virulence.”); Edwin D. Kilbourne, *New Viral Diseases A Real and Potential Problem Without Boundaries*, 264(1) JAMA 68, 77 (July 4, 1990) (“Either HIV has recently infected humans, in which case we have a new virus and a new disease, or HIV infected humans long ago (being mild and/or restricted in range until recently), in which case we have an old virus and a new
The mêlée of the old and the new creates a mist of uncertainty that complicates the foreseeability issue in medical malpractice involving injury due to an emerging microbial disease. The following generic description of antibiotic resistance provides an illustration. A novel antibiotic resistant form of a known disease may be caused by a novel genetic mutation of a known causative pathogen.\(^{22}\) The confusing mix of the old and the new and the apparent lack of a connection between law and science make the foreseeability analysis seem intractable.

The resolution of these and similar issues requires a translation between law and medicine that speaks the language of medicine, yet preserves the meaning and policy rationale of the traditional legal doctrines. The translation provides a model of the interaction between law and medicine. It identifies the significance of various aspects of scientific phenomena and relates them to the legal issue under consideration. This provides the connection between law and science necessary to facilitate legal analysis.\(^{23}\) The Article develops the methodology and illustrates its application by analyzing the foreseeability of multidrug resistant tuberculosis.

Antibiotic resistant infections such as multidrug resistant tuberculosis are pathologically the same disease as their drug susceptible counterpart, even though the drug resistant version is caused by a genetically mutated version of the susceptible microbe, causes more harm and is more difficult to treat.\(^{24}\) This fact appears to suggest that an emerging antibiotic resistant version of a known susceptible infection must be ruled foreseeable. The general common law rule is that the type of injury needs to be foreseeable, rather than its extent or manner of occurrence. We argue that the common law provides an exception

\(^{22}\) Morse, supra note 21.

\(^{23}\) Lawrence Lessig, CODE AND OTHER LAWS OF CYBERSPACE 109 (1999) ("Just as a language translator constructs a text that is different from the source but has the same meaning as the source, so too does the constitutional translator construct an application that though different from the original application, has the same meaning in the current context as the original did in its context.")

\(^{24}\) Lederberg et al., supra note 21, at 31.
in a limited set of cases. Analysis of a translation of the common law doctrine of foreseeability into medical science shows that an emerging drug resistant disease may be ruled unforeseeable if the mechanism of resistance relies on a genetic mutation that was ex ante unpredictable to scientists.

The Article is organized as follows. Section 2 reviews the principles of antibiotic resistance and the phenomenon of superbugs. Section 3 reviews the biomedical principles of tuberculosis and evolution of its resistance to successive generations of antibiotic drugs. Section 4 analyzes the foreseeability doctrine in the context of medical negligence, and illustrates its application to the foreseeability of multidrug-resistant tuberculosis. A final section concludes.

2. ANTIBIOTIC RESISTANCE

The discovery of antibiotics was a major medical advance of the last century and has been described as a “turning point in human history” and “the foundation of modern medicine.” Its discovery provided a cure for bacterial infections such as meningitis, tuberculosis and endocarditis, diseases that had previously been almost uniformly fatal. In addition to their therapeutic uses, antibiotics are also critical to the success of surgical procedures, cancer chemotherapy, and treatment of inflammatory conditions.

The generic term antibiotic denotes any class of organic molecule that can kill or inhibit the growth of susceptible disease-causing bacteria by interacting with specific bacterial targets. Antibiotics that kill bacteria are termed bactericidal, and those that merely control bacterial growth are termed bacteriostatic. Penicillin and its derivatives are the best-known

25 Davies & Davies, supra note 12, at 417.
27 Peter J. Collignon, Antibiotic Resistance, 177 MJA 325, 325 (Sept. 16, 2002).
28 Davies & Davies, supra note 12, at 429.
29 Id. at 417, 429.
antibiotics.\textsuperscript{31} Other examples include bacitracin, an antibiotic typically used to treat skin and eye infections,\textsuperscript{32} the antituberculosis drugs rifampicin and isoniazid,\textsuperscript{33} and tetracycline, a drug used in the treatment of sexually transmitted diseases.\textsuperscript{34}

Despite the widespread availability of antibiotics infectious diseases remain a leading cause of death worldwide.\textsuperscript{35} The emergence and global spread of antibiotic resistance is the predominant reason for their persistence.\textsuperscript{36} Although the discovery of antibiotics in the 1940s revolutionized the treatment of infectious diseases, the intervening 70 years have seen the emergence of pathogens that are resistant to almost every antibiotic in mainstream use.\textsuperscript{37}

\textsuperscript{31} Davies & Davies, supra note 12, at 417–18.
\textsuperscript{32} Fritz H. Kayser et al., Medical Microbiology 198 (2005).
\textsuperscript{34} Stephen H. Gillespie & Peer M. Hawkey, Principles and Practice of Clinical Bacteriology 326 (2d ed., 2006).
\textsuperscript{35} See Brad Spellberg et al., The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America, 46 Clin. Infect. Dis. 155, 156 (2008).
Antimicrobial resistance occurs when disease-causing bacteria evolve to withstand or reduce the ability of an antimicrobial agent to control or kill the bacteria. Notorious antibiotic resistant pathogens include vancomycin-resistant enterococci, which cause illnesses such as urinary tract and bloodstream infections, and penicillin-resistant Streptococcus pneumonia, a major cause of bacterial pneumonia and meningitis.

Recent times have seen the emergence of highly virulent multidrug-resistant bacterial pathogens, referred to as superbugs. Some superbug strains are resistant to almost every antibiotic in mainstream use. Current notorious superbugs include totally drug-resistant strains of Mycobacterium.
tuberculosis, and the methicillin-resistant bacterium *Staphylococcus aureus* (MRSA). These virulent pathogens, described as “the most menacing [microbial threats] with respect to morbidity and mortality worldwide”, have imposed a significant economic burden on the United States health care system. The Centers for Disease Control and the World Health Organization have both designated the antimicrobial resistance phenomenon as a threat to global health security, and the British Chief Medical Officer advised the British government to include superbugs on the National Risk Register of Civil Emergencies, alongside terrorist attacks and natural disasters.

---


44 See Gabriela Buffet, *Antimicrobial Resistance*, SCOR INFORM 15 (Dec. 2015) (describing that MRSA is strain of S. aureus that has become resistant to antibiotics); R. Monina Klevens et al., *Invasive Methicillin-Resistant Staphylococcus Aureus Infections in the United States*, 298 J. AM. MED. ASS’N 1763, 1763–64 (2007) (“MRSA infection is caused by a strain of S. aureus that has become resistant to the antibiotics commonly used to treat ordinary staphylococcal infections, and can cause severe infections such as infective endocarditis and pneumonia.”); Jayaraman, *supra* note 15, at 147–76.

45 See Julian Davies and Dorothy Davies, *Origins and Evolution of Antibiotic Resistance*, 74(3) MICROBIOL. MOLEC. BIOL. REV. 417, 421 (Sept. 2010).


Mechanisms of antibiotic resistance

The development of drug resistance in previously susceptible bacteria is due to genetic alterations that occur either via genetic mutation or by the introduction of new genetic information by other means.49 These genetic alterations enable biological mechanisms that allow the affected bacteria to develop specific types of resistance.50

We now review the genetic alterations and biological mechanisms of resistance.

Genetic alterations

Drug-susceptible bacteria can acquire resistance through genetic mutations that create a new resistance feature or strengthen an existing one.51 Bacteria may also acquire antibiotic-resistance genes from other bacteria.52 Microbial genes may move from one organism to another, a phenomenon termed horizontal gene transfer.53 Vertical transfer occurs when genes

49 Alanis, supra note 11, at 699.
50 See id. (noting that the genetic alterations may express themselves in different ways).
51 See Koch et al., supra note 37, at 1 (“[H]igh-level [drug] resistance is often associated with mutations in target-encoding or related genes.”); Levy, supra note 37, at 48 (discussing the methods by which bacteria acquire resistance traits); Gerald Pier & David Skurnik, Antibiotic Resistance Doesn’t Make Bacteria Harder to Kill—It Can Actually Make Them Stronger, CONVERSATION (July 24, 2015), http://theconversation.com/antibiotic-resistance-doesnt-just-make-bacteria-harder-to-kill-it-can-actually-make-them-stronger-45074 (“Bacteria can become drug-resistant in two ways—resistance can be natural, meaning that the genes conferring resistance are already present in the bacterial chromosome, or they can be acquired through mutation or by picking up antibiotic-resistance genes from other microbes.”).
52 See Robert V. Miller, Bacterial Gene Swapping in Nature, SCI. AM., Jan. 1998, 67, 68 (“[B]acteria, which are single-cell organisms, often donate antibiotic-resistance genes to other species of bacteria in the human body.”); Levy, supra note 37, at 48 (“Bacteria have evolved several ways to share their resistance traits with one another. Resistance genes commonly are carried on plasmids, tiny loops of DNA that can help bacteria survive various hazards in the environment. But the genes may also occur on the bacterial chromosome, the larger DNA molecule that stores the genes needed for the reproduction and routine maintenance of a bacterial cell.”).
53 Levy, supra note 37, at 49 (“Often one bacterium will pass resistance traits to others by giving them a useful plasmid. Resistance genes can also be
move between a parent and its offspring.  

**Biological mechanisms**

Antibiotic resistance develops when changes in the bacterial genome create *biological mechanisms* that enable the defeat of antibiotic action. The most important resistance mechanisms are: (1) production of enzymes that inactivate the microbial agent; (2) modification of the target site to reduce its affinity to the antibiotic; and (3) mechanisms that prevent antibiotics from entering the bacterial cell and reaching the target.

transferred by viruses that occasionally extract a gene from one bacterial cell and inject it into a different one. In addition, after a bacterium dies and releases its contents into the environment, another will occasionally take up a liberated gene for itself. 

See also Woodford & Ellington, *supra* note 36, at 9 (“Many clinically relevant antibiotic resistance mechanisms are acquired traits. The resistance genes encoding them, which may be incorporated into plasmids, transposons or integrons, or may exist either as gene cassettes or as partial gene fragments released from dead bacterial cells, are acquired by new host strains via horizontal transfer, mediated by conjugation, transformation or transduction. These processes are the primary means of dissemination of acquired resistance genes, but mutation is essential for the evolution and diversification of these acquired genes.”).

Miller, *supra* note 52, at 67.

See Sujeet Kumar & Bhoj Raj Singh, *An Overview of Mechanisms and Emergence of Antimicrobials Drug Resistance*, 1 ADVANCES ANIMAL & VETERINARY SCI. 7, 11 (2013) (“It is the ability of bacteria to resist the activity of a particular antimicrobial agent to which it was earlier susceptible. This is mediated by mutation or horizontal gene transfer (transformation, transduction or conjugation) that brings changes in bacterial genome. This brings alteration in the bacterial structural and functional characteristics leading to resistance against a particular antibiotic.”).

Alanis, *supra* note 11, at 700 (discussing the important resistance mechanisms of the bacterial cell to antibiotics); P. Courvalin, *Predictable and Unpredictable Evolution of Antibiotic Resistance*, 264 J. INTERNAL MED. 4, 4-5 (stating that “[b]acteria have developed four major mechanisms of resistance: (i) modification of the target which leads to loss or decreased affinity of the drug for its target; (ii) production of an enzyme that will detoxify the drug; (iii) impermeability, in particular by diminution of the number or the diameter of a porin (pore in the external membrane”) in Gram-negative bacteria; and (iv) efflux of antibiotics outside the cells by energy-dependent pumps. The common objective of these various mechanisms is to impede interaction of the antibiotic with its target”); Kali Iyer & Nicole Yokubynas, *Investigating the Mechanisms of Antimicrobial Resistance*, 1 CATALYST 1, 4 (2016) (stating that “[t]he major mechanisms of resistance correspond to the main MOA of antibiotics and
The process by which bacteria, such as mycobacterium tuberculosis (M. TB), Escherichia coli (E. coli), and Staphylococcus aureus, develop resistance to the antibiotic rifampicin illustrates the coordination between genetic mutations and resistance mechanisms. Rifampicin kills bacteria by binding to and inactivating an essential bacterial enzyme, RNA polymerase. Genetic mutations in the rpoB gene in the bacterial genome of the above-mentioned bacteria decrease affinity of the enzyme to rifampicin bactericidal action, leading to rifampicin resistance.

**Selection pressure**

The term “selective pressure” refers to environmental conditions that enable the survival and proliferation of drug-resistant bacterial strains. Selective pressure occurs when bacteria that are susceptible to an antibiotic are killed while those capable of resisting the antibiotic survive. The surviving include enzymes that inactivate the microbial agent, mutations in the target site that reduce the binding ability of the antibiotic, and devices that decrease the amount of antibiotic through reduced uptake or increased efflux.

---


60 See Pier & Skurnik, *supra* note 51 (“Antibiotics are wonderful drugs for treating bacterial infections. Unfortunately, disease-causing bacteria can become resistant to antibiotics that are meant to kill them. This is called selective pressure – the bacteria that are susceptible to the drug are killed, but
antibiotic-resistant bacteria are then able to grow with little competition, monopolize resources and outcompete the susceptible bacteria. This results in the emergence and dominance of antibiotic-resistant bacterial strains. As a result, drug-resistant bacteria multiply in the infected host and may spread to other hosts and cause serious disease. Selective pressure is accelerated by the misuse of antibiotics, such as prescription of antibiotics that are not needed, prescription of the wrong type of antibiotic, and improper use of antibiotics by patients.

3. TUBERCULOSIS

Tuberculosis (TB) is a chronic infectious disease caused by the bacterium *Mycobacterium tuberculosis* (M. TB), an airborne pathogen that spreads when an infected person expels bacteria, usually through coughing, sneezing and speaking. The immune response of a healthy person usually kills inhaled disease-causing bacteria, but an infected person with a weakened immune system may develop active tuberculosis. The disease is characterized by the growth of bacteria-infested nodular lesions (tubercles) that multiply and cause damage to infected areas.

---

the ones that withstand the antibiotic survive and proliferate. This process results in the emergence of antibiotic-resistant strains.

61 See Collignon, supra note 27, at 326 (“MRSA (methicillin resistant staph aureus) caused infections in hospital patients in India, Turkey and Poland before methicillin had been used in these countries. However, when methicillin and its derivatives became readily available, MRSA strains were encountered much more often.”).

62 Levy, supra note 37, at 49; Tenover & Hughes, supra note 53, at 301.

63 Alanis, supra note 11, at 701.

64 Tenover & Hughes, supra note 53, at 300-01; Iyer & Yokubynas, supra note 56, at 4.

65 McGrath et al., supra note 13, at 292.


68 See Julia A. Martin, *Proposition 187, Tuberculosis, and the Immigration Epidemic?*, 7 STAN. L. & POLY REV. 89, 90 (“When an infection occurs, the
TB typically attacks the lungs and respiratory system, but can also affect other parts of the body such as the brain, kidneys and lymph nodes. Symptoms include coughing, weight loss, night sweats, fever, and chest pain.

M. TB has been described as the “archetypical human pathogen [that has] evolved with the human race.” By some estimates, nearly one third of the world’s population is infected with M. TB. TB is the world’s second most lethal infectious disease (besides AIDS) and remains a leading cause of death from a single infectious disease. The World Health Organization has declared TB a global emergency.

bacteria cause granulomatous reactions, which are rounded collections of inflammatory cells in the infected tissue. These reactions destroy surrounding healthy cells, causing necrotic cavities filled with the bacteria to form.

69 COMM. ON EMERGING MICROBIAL THREATS TO HEALTH, INST. OF MED., supra note 7, at 31; Martin, supra note 68, at 90; Mishra et al., supra note 13, at 1.

70 Shin-Rou Lin, A Costly Illusion?: An Empirical Study of Taiwan’s Use of Isolation to Control Tuberculosis Transmission and its Implications for Public Health Law and Policymaking, 14 ASIAN-PACIFIC L. & POL’Y J. 107, 114 (“The bacterium that causes TB ... may infect almost any part of the body, such as the brain, kidneys, or spine.”)

71 COMM. ON EMERGING MICROBIAL THREATS TO HEALTH, INST. OF MED., supra note 7, at 212.

72 Davies & Davies, supra note 12, at 420.


74 See Barry R. Bloom & Christopher J. L. Murray, Tuberculosis: Commentary on a Reemergent Killer, 257 SCIENCE 1055, 1055 (1992) (stating that tuberculosis is the “leading cause of death in the world from a single infectious disease”). Brennan, supra note 73, at 263-64 (noting that tuberculosis kills approximately three million people every year, and is especially deadly among persons infected by both HIV and M. tuberculosis); Rhea N. Coler et al., Molecular Cloning and Immunologic Reactivity of a Novel Low Molecular Mass Antigen of Mycobacterium tuberculosis, 161 J. IMMUNOLOGY 2356, 2356 (1998) (reporting that tuberculosis is “the world’s leading killer of adults”); Anna P. Ralph et al., Vitamin D and Solar Ultraviolet Radiation in the Risk and Treatment of Tuberculosis, 13 LANCET INFECTION DISEASES 77, 77 (2013) (“Tuberculosis is the second most common cause of death by infection worldwide.”).

75 WORLD HEALTH ORGANIZATION, TB: A GLOBAL EMERGENCY (1994). See also Parida et al., supra note 43, at 388-89 (mentioning the WHO declaration); Roberto Zenteno-Cuevas et al., Mutations Conferring Resistance to First- and Second-Line Drugs in Multidrug-Resistant Mycobacterium tuberculosis Clinical
Emergence of drug-resistant tuberculosis

TB is a traditional disease that appeared to be almost eradicated, or at least controlled, but has recently re-emerged in the United States.76 Between 1985 and 1992, “there was a twenty percent increase in the total number of tuberculosis cases reported in the United States, compared with a seventy-four percent decline during the previous thirty-two years.” 77

The control of TB has been undermined by the proliferation of antibiotic resistance.78 Antibiotic resistance emerges due to spontaneous gene mutations in M. TB that immunize the bacteria to the most commonly used anti-TB drugs.79 Multidrug

---

76 See Carlos A. Ball & Mark Barnes, Focus on: Urban America: Public Health and Individual Rights: Tuberculosis Control and Detention Procedures in New York City, 12 YALE L. & POLY REV. 38, 38-9 (“Between 1985 and 1992, there was a twenty percent increase in the total number of tuberculosis cases reported in the United States, compared with a seventy-four percent decline during the previous thirty-two years.”); Thomas R. Frieden et al., The Emergence of Drug-Resistant Tuberculosis in New York City, 328 NEW ENG. J. MED. 521, 524 (1993) (reporting an increase in tuberculosis cases over the previous decade, especially in New York City). See also Koch et al., supra note 37, at 1 (“The discovery of antibiotics in the 1940s revolutionized the treatment of infectious diseases and, at the same time, suggested the possibility of eradicating bacterial pathogens as a major cause of morbidity and mortality. The intervening 70 years have, however, seen the emergence of organisms which are resistant to almost every antibiotic that has been introduced into mainstream use. Tuberculosis . . . is no exception.”)

77 Ball & Barnes, supra note 76, at 38-39.


79 See Palomino & Martin, supra note 78, at 329 (Drug resistance . . . emerges as a result of spontaneous gene mutations in M. tuberculosis that render the bacteria resistant to the most commonly used anti-TB drugs.”); Id. at 322 (“The main mechanism of development of fluoroquinolone resistance in M. tuberculosis is by chromosomal mutations.”); Parida et al., supra note 43, at 39 (“Bacterial chromosomal mutations result in drug resistance against anti-TB drugs. These mutations are rare and random events”); Id. at 392 (describing initiatives to identify and catalogue resistance-conferring mutations); Mariam et al., supra note 78, at 1289; Roberto Zenteno-Cuevas et al., Mutations
resistance, defined as resistance to at least the drugs rifampicin and isoniazid, has surged in the United States since the mid-1980s. These two drugs, known as front-line drugs, cure over ninety-five percent of tuberculosis patients. Since 2006, more serious drug-resistant strains of M. TB labeled extensively drug resistant were recognized. These strains are not only multidrug resistant, but also resistant to any of the drugs known as


80 See Rahul Mishra et al., Gene Mutations in Mycobacterium Tuberculosis: Multidrug-Resistant TB as an Emerging Global Public Health Crisis, 95 TUBERCULOSIS 1, 1 (2015); Palomino & Martin, supra note 78, at 329; Parida et al., supra note 43, at 388 (defining drug resistance as “a microbiological diagnosis reflecting the resistance pattern of the clinical isolate of a given pathogen to a defined set of antibiotics”); Rick Weiss, On the Track of “Killer” TB, 255 SCIENCE 148 (1992); Joshua Lederberg et al. (eds.), Emerging Infections: Microbial Threats to Health in the United States, Committee on Emerging Microbial Threats to Health Division of Health Sciences Policy Division of International Health Institute of Medicine (1992), at 95 (“[C]ases of drug-resistant TB have more than doubled since 1984.”); Barry R. Bloom & Christopher J. L. Murray, Tuberculosis: Commentary on a Reemergent Killer, 257 SCIENCE 1055, 1055 (1992) (“After a century of decline in the United States, tuberculosis is increasing, and strains resistant to multiple antibiotics have emerged.”).


82 See S. K. Parida et al., Totally Drug-Resistant Tuberculosis and Adjunct Therapies, 277 J. INT. MED. 388, 389 (2015); Shin-Rou Lin, A Costly Illusion?: An Empirical Study of Taiwan’s Use of Isolation to Control Tuberculosis Transmission and its Implications for Public Health Law and Policymaking, 14 ASIAN-PACIFIC L. & POLY J. 107, 116-7 (“XDR-TB is a subset of MDR-TB caused by strains of bacteria that are resistant to the most effective first-line and second-line drugs.”)
fluoroquinolones and at least one of the injectable second-line drugs, kanamycin, capreomycin or amikacin. In 2007, M. TB strains emerged that are resistant to all first- and second-line drugs tested. These strains were labeled totally drug resistant. The first cases were reported in Italy, and more recently in Iran, India and South Africa.

4. MEDICAL MALPRACTICE

Individuals harmed by infectious diseases such as drug-resistant TB may bring an action in medical malpractice against a healthcare provider responsible for their injuries.

83 “Fluoroquinolones are bactericidal antibiotics currently in use as second-line drugs in the treatment of TB.” See Pedro Eduardo Almeida Da Silva and Juan Carlos Palomino, Molecular Basis and Mechanisms of Drug Resistance in Mycobacterium Tuberculosis: Classical and New Drugs, 66 J. ANTIMICROB. CHEMOTHER. 1417, 1421 (2011).

84 See Juan Carlos Palomino and Anandi Martin, Drug Resistance Mechanisms in Mycobacterium Tuberculosis, 3 ANTIBIOTICS 317, 317 (2014); Roberto Zenteno-Cuevas et al., Mutations Confering Resistance to First- and Second-Line Drugs in Multidrug-Resistant Mycobacterium Tuberculosis Clinical Isolates in Southeast Mexico, Letters to the Editor, 45 INT. J. ANTIMICROB. AGENTS 671, 671 (2015) (“Depending on the particular country, 3–5% of cases are multidrug-resistant TB (MDR-TB) [simultaneous resistance to isoniazid (INH) and rifampicin (RIF)] and 10% of these cases are extensively drug-resistant TB (XDR-TB) (showing further resistance to any quinolone and one of the following second-line drugs: kanamycin, capreomycin or amikacin).”)

85 These drugs are isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide, ethionamide, para-amino salicylic acid, cycloserine, ofloxacin, amikacin, ciprofloxacin, capreomycin and kanamycin. See Juan Carlos Palomino and Anandi Martin, Drug Resistance Mechanisms in Mycobacterium Tuberculosis, 3 ANTIBIOTICS 317, 317 (2014).

86 See Palomino & Martin, supra note 78, at 317; See also Parida et al., supra note 43, at 388 (“Recently, three new drugs, bedaquiline, delamanid and linezolid have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency that may offer therapeutic solutions for TDR-TB.”).


88 Babcock v. Bridgeport Hospital, 742 A.2d 322, 327, 251 Conn. 790, 793 (1999) (malpractice action against hospital for harms arising from spread of MRSA infection due to hospital’s alleged failure to follow recommended infection control practices such as surveillance through regular measurement of bacteria colonization rates); Helman v. Sacred Heart Hospital, 381 P.2d 605, 52 Wash.2d 138 (1963) (defendant held liable for plaintiff’s contraction of staphylococcal
malpractice is a branch of the law of torts that governs professional negligence in the field of medicine. See, e.g., C. KRAMER AND D. KRAMER, MEDICAL MALPRACTICE 5–6 (5th ed. 1983) ("[Medical] malpractice may be defined as bad or unskillful practice on the part of a physician or dentist, resulting in injury to the patient; or the failure of a physician to exercise the required degree of care, skill, and diligence; or treatment by a surgeon or physician in a manner contrary to accepted rules and with injuries resulting to the patient.").


See Vigil v. Herman, 424 P.2d. 159, 159, 102 Ariz. 31, 32 (1967) (stating inaction of physician may have been found by jury to be proximate cause of the development of the patient’s condition into a seriously advanced stage of tuberculosis); Dowling v. Mutual Life Insurance, 168 So. 2d 107, 108–09 (1964).


See Polly J. Price, Ebola and the Law in the United States: A Short Guide to Public Health Authority And Practical Limits, EMORY LAW SCHOOL LEGAL STUDIES RESEARCH PAPER SERIES, Research Paper No. 14-299, 20 ("The hospital in Dallas where an Ebola patient was initially misdiagnosed and who later died agreed to pay a settlement to members of [decedent’s] family. A misdiagnosis that leads to spread of the disease to others might lead to further liability, in addition to delaying care for the patient.").

See, e.g., James G. Hodge et al., Law, Medicine and Public Health Preparedness: The Case of Ebola, 130 PUBLIC HEALTH REPORTS 1, 2 (Mar.-Apr. 2015) ("[C]ontroversial topics at the intersection of law, medicine, and preparedness for Ebola [include] (1) the willingness among health workers and entities to handle patients suspected or known to be infected; (2) novel treatments and administration of experimental drugs; (3) implementation of isolation, quarantine, and other social-distancing measures in medical settings;
compromising patient care as well as for spreading the disease to others. In *Fosgate v Corona*, a physician was held liable to a

and (4) prospective liabilities of health workers or entities for medical errors or omissions in the handling or treatment of Ebola cases.

*See Cal. Health & Safety Code § 3110 (Deering 1996) (“[E]ach health officer knowing or having reason to believe that any case of the diseases made reportable by regulation of the Board of Public Health, or any other contagious, infectious, or communicable disease exists, or has recently existed, within the territory under his jurisdiction, shall take such measures as may be necessary to prevent the spread of the disease or occurrence of additional cases.”); Cal. Health & Safety Code § 3125 (Deering 1995) (“[A]ll physicians, nurses, clergymen, attendants, owners, proprietors, managers, employees, and persons living [in close proximity to], or visiting any sick person, in any hotel, lodging house, house, building, office, structure, or other place where any person is ill of any infectious, contagious, or communicable disease, shall promptly report that fact to the health officer, together with the name of the person, if known, the place where he is confined, and the nature of the disease, if known.”); *Restatement (Second) of Torts* § 319 (Am. Law Inst. 1965) (“[O]ne who takes charge of a third person whom he knows or should know to be likely to cause bodily harm to others if not controlled is under a duty to exercise reasonable care to control the third person to prevent him from doing such harm.”); Davis v. Rodman, 227 S.W. 612, 614, 147 Ark. 385, 391 (1921) (“[I]t is undoubtedly the duty of physicians who are attending patients afflicted with contagious or infectious diseases not to negligently do any act that would tend to spread the infection.”); Gammill v. United States, 727 F.2d 950, 954 (10th Cir. 1984) (“[A] physician may be found liable for failing to warn a patient’s family, treating attendants, or other persons likely to be exposed to the patient, of the nature of the disease and the danger of exposure”); *see Jones v. Stanko*, 160 N.E. 456, 456–58, 118 Ohio St. 147, 148–49, 152-53 (1928) (holding a physician liable for injuries of plaintiff who contracted smallpox while attending infected patient in reliance on physician’s assurance that patient was free from contagious disease.); *Mo., Kan. & Tex. Ry. v. Wood*, 66 S.W. 449, 450–51, 95 Tex. 223, 232–33 (1902) (holding Railway company who had undertaken to quarantine an employee infected with smallpox liable for failing to prevent spread of disease to community); Hofmann v. Blackmon, 241 So. 2d 752, 753 (Fla. Dist. Ct. App. 1970) (holding that a physician has a duty to advise family members of risks associated with disease); *United States v. Comstock*, 560 U.S. 126, 141; 130 S. Ct. 1949 (1960) (“[I]f a federal prisoner is infected with a communicable disease that threatens others, surely it would be ‘necessary and proper’ for the Federal Government to take action, pursuant to its role as federal custodian, to refuse (at least until the threat diminishes) to release that individual among the
patient’s family members who contracted TB after the physician negligently misdiagnosed the disease in the patient. 97

The law of medical malpractice imposes a negligence standard of liability on health care providers. 98 Negligence is generally defined as a breach of the duty not to impose an unreasonable risk on society. 99 It applies to any risk that can be characterized as unreasonable, including risks associated with the diagnosis, treatment and prevention of disease. 100

general public, where he might infect others . . . .”); Williams v. Bennett, 610 S.W.2d 144 (1980) (discussing a physician may be held liable for negligently discharging a patient); Bradshaw v. Daniel, 854 S.W.2d 865, 865 (“[P]hysician [has] a legal duty to warn [a] non-patient of the risk of exposure to the source of [a] patient’s non-contagious disease.”); Derrick v. Ontario Cmty. Hosp., 47 Cal. App. 3d 145, 152, 120 Cal. Rptr. 566, 570 (Cal. Ct. App. 1975) (“[H]ealth and Safety Code, sections 3110 and 3125 were enacted to protect the public against the spread of contagious, communicable diseases and that section 3125 does impose upon Hospital a duty to plaintiffs to report known infectious, contagious, or communicable diseases to local health officer.”); See Price, supra note 96, at 20 (“[T]he hospital in Dallas where an Ebola patient was initially misdiagnosed and who later died agreed to pay a settlement to members of his family. A misdiagnosis that leads to spread of the disease to others might lead to further liability, in addition to delaying care for the patient.”).

97 Id.
98 See Noam Sher, New Differences Between Negligence and Strict Liability and Their Implications On Medical Malpractice Reform, 6 S. CAL. INTERDISC. L.J. 335, 336 (2006–2007) (“The law that currently applies to medical liability sets a negligence standard and is based on the principles of [the law of] torts.”); B. Sonny Bal, An Introduction to Medical Malpractice in the United States, 467 CLIN ORTHOP. RELAT. RES. 339, 340 (2009) (“Medical malpractice is a specific subset of tort law that deals with professional negligence.”).
99 See RESTATEMENT (SECOND) OF TORTS, § 282 (defining negligence as conduct "which falls below the standard established by law for the protection of others against unreasonable risk of harm").
100 See Edward A. Marshall, Medical Malpractice in the New Eugenics: Relying on Innovative Tort Doctrine to Provide Relief When Gene Therapy Fails, 35 GA. L. REV. 1277, 1301 (2000–2001) (“Imposing liability for failure to adhere to a professionally acceptable level of care in dispensing gene therapy could therefore aid in establishing a responsible disincentive to practice the nascent treatment in instances where the procedure poses an unreasonable risk to patients.”); Pitre v. Opelousas General Hospital, 530 So. 2d 1151, 1157 (1988) (“When a physician knows or should know of the existence of an unreasonable risk that a child will be born with a birth defect, he owes a duty to the unconceived child as well as to its parents to exercise reasonable care in warning the potential parents and in assisting them to avoid the conception of the deformed child.”); The HIV/AIDS pandemic unleashed a wave of lawsuits,
To prevail on a medical negligence claim a plaintiff must prove the resulting injury was proximately caused by the defendant's breach.\textsuperscript{101} Simply stated, the doctrine of proximate causation requires the defendant's conduct to be reasonably closely related to the plaintiff's harm.\textsuperscript{102} Proximate cause protects defendants from liability for consequences that as a matter of "fairness, policy, and practicality" fall beyond the scope of their moral accountability.\textsuperscript{103}

The concept of foreseeability is the "touchstone of proximate cause".\textsuperscript{104} A general rule of negligence law is that a defendant is liable only for harm that was foreseeable at the time of alleged


\textsuperscript{101} David G. Owen, \textit{The Five Elements of Negligence}, 35 Hofstra L. Rev. 1671, 1671 (2007) ("Also essential to negligence, evident from an early date, was the necessity of a causal connection between the defendant’s breach of duty and the plaintiffs damage that was natural, probable, proximate, and not too remote."); Ford Motor Co. v. Rushford, 868 N.E.2d 806, 810 (2007).

\textsuperscript{102} See Bhakta v. County of Maui, 124 P.3d 943, 956 (2005) (stating plaintiff must prove a "reasonably close causal connection between the conduct and the resulting injury."); Owen, \textit{supra} note 101, at 1681 ("[P]roximate cause addresses instead the question of whether in logic, fairness, policy, and practicality, the defendant ought to be held legally accountable for the plaintiffs harm that in some manner is 'remote' from the defendant’s breach.").

\textsuperscript{103} See David G. Owen, \textit{Figuring Foreseeability}, 44 Wake Forest L. Rev. 1277, 1294 (2009); Owen, \textit{supra} note 101, at 1681

\textsuperscript{104} Jamison v. Ford Motor Co., 644 S.E.2d 755, 765 (S.C. Ct. App. 2007) ("The touchstone of proximate cause . . . is foreseeability."); see Owen, \textit{supra} note 101, at 1293–94 (2009) (stating that foreseeability is a “touchstone’ or ‘cornerstone’ of proximate cause); see also W. Jonathan Cardi, \textit{Reconstructing Foreseeability}, 46 B.C. L. Rev. 921, 921 ("The concept of foreseeability is fast devouring the negligence cause of action.")
The basic test of foreseeability can be described as "whether one can see a systematic relationship between the type of accident that the plaintiff suffered and ... the defendant's wrongdoing." The foreseeability issue is often resolved without controversy in cases where science has established the requisite systematic relationship. The link between mesothelioma and protracted exposure to asbestos fibers is generally accepted, and medical opinion is near unanimous that lung cancer is a foreseeable consequence of tobacco smoke, based on clinical evidence that carcinogens in tobacco smoke interact with human DNA to cause genetic mutations that result in lung cancer.

Coincidental consequences of malpractice do not satisfy the foreseeability test. Suppose for instance a physician performs a vasectomy negligently, resulting in an unplanned pregnancy. If the child so born subsequently grows up and commits arson, the doctor cannot be held liable for the fire damage for several reasons, including absence of foreseeability. A child born due to a

---

105 See, e.g., Michael S. Moore, Placing Blame: A General Theory of the Criminal 363 (1997) ("The dominant test of proximate cause in torts makes a defendant liable when but only when the harm he in fact caused was, at the time he acted, foreseeable to him."); Lambie v. Schneider, 305 Ill. App. 3d 421, 428, 713 N.E.2d 603, 609 (4th Dist. 1999) ("A malpractice defendant cannot be held liable if the injury could not have been foreseen or reasonably anticipated as the probable result of an act of negligence.").
107 See e.g. Borel v. Fibreboard Paper Prod. Corp., 493 F.2d 1076, 1105 (Scope of asbestos manufacturer’s duty to warn includes foreseeable dangers related to exposure to asbestosis, mesothelioma, and other cancers.); Jenny Steele and Nick Wikeley, Dust on the Streets and Liability for Environmental Cancers, 60 THE MODERN LAW REVIEW 265, 268 (1997).
108 See e.g. Stephen S. Hecht, Tobacco Smoke Carcinogens, 91(4) J. NAT. CANCER INST. 1194, 1194 (21 Jul. 1991); E. Brambilla and A. Gazdar, Pathogenesis of Lung Cancer Signalling Pathways: Roadmap For Therapies, 33 EUR RESPIR J 1485, 1486 (2009) ("Among the 20 carcinogens that are present in tobacco smoke and strongly associated with lung cancer development, the best known are polycyclic aromatic hydrocarbons and nicotine-derived nitrosamines, which lead to genetic mutations through DNA adduct formation.")
109 See Grady, supra note 106, at 295 (2002) ("[A] person should not be liable when the only connection between his lapse and the plaintiff's injury was the purest chance, a total coincidence.")
botched vasectomy operation is not systematically more likely to become an arsonist than one borne any other way. 110

A physician may be held liable for foreseeable consequences of a negligently performed vasectomy, such as medical complications and certain types of child rearing expenses. 111 In Ramey v. Fassoulas,112 a case involving a claim for damages resulting from an unwanted birth due to a negligently performed vasectomy, the court stated “[w]here the child born has substantial mental or physical defects, the tortfeaso physician will be liable in damages for the special medical and educational expenses, as opposed to normal rearing costs, associated with raising such a child to majority ... The parents, on the other hand, are still required ... to bear the normal rearing expenses of clothing, feeding and housing such a child, thereby still imposing upon them a legal duty to support their child by providing necessaries in accord with our settled law.” 113

Foreseeability of multidrug-resistant TB

Negligent diagnosis and treatment of tuberculosis infection frequently give rise to medical malpractice litigation. 114

---

110 See Meiring de Villiers, Free Radicals in Cyberspace: Complex Liability Issues in Information Warfare, 4(1) NORTHWESTERN J. TECH. & INTEL. PTY. 13, 31 (Fall 2005) (“This is clearly a multiple risks case. The primary risk consists of foreseeable medical complications due to the incompetent vasectomy, including an unwanted pregnancy. The ancillary risk is the (unforeseeable) risk that the conceived child may grow up to be a criminal. The proximate cause issue is whether the defendant should be held liable for the harm due to the ancillary risk.”) citing Mark F. Grady, Proximate Cause Decoded, 50 UCLA L. REV. 293, 300-01 (2002).
111 See e.g. Ramey v. Fassoulas, 414 So. 2d 198, 199 (“The law is clear that the parents of a child have a cause of action sounding in negligence against a physician for performing a negligent vasectomy, sterilization, or abortion [or for otherwise performing negligent medical services] which results in the birth of an unwanted child.”)
112 Ramey 414 So. 2d at 198.
113 Ramey 414 So. 2d at 200-01.
114 See e.g. Leonard Berlin, Tuberculosis: Resurgent Disease, Renewed Liability, 190 AJR 1438, 1442 (Discussing potential liability of radiologists for medical malpractice related to tuberculosis-infected patients.); Vigil v Herman (1967) 102 Ariz 31, 424 P.2d 159, later app. Ariz. 282, 464 P.2d 353 (inaction of physician may have been found by jury to be proximate cause of the development of the patient’s condition into a seriously advanced stage of
Foreseeability of the risks created by the alleged malpractice is usually a key element of courts’ liability analysis, as the following case illustrates.

In Wojcik v Aluminum Company of America, a patient whose chest radiographs and pathological tests indicated the presence of active tuberculosis was not informed of those findings for a year. The patient developed tuberculosis and infected his wife and children. His wife and children filed a lawsuit against the physician for negligently failing to inform them of the illness, claiming that living with an infected person foreseeably exposed them to a contagious disease.

Upholding the validity of the lawsuit, the court commented on the foreseeability of the risk, stating “[i]t is common knowledge that tuberculosis is a contagious and communicable disease. The risk of the plaintiff wife contracting tuberculosis from her husband, when unaware that he was so afflicted, was reasonably foreseeable by the defendant. Such a risk is within the range of probability and apprehension of an ordinarily prudent person. The defendant's negligent conduct toward the plaintiff husband under the circumstances was negligence to the plaintiff wife.”

We base our analysis of the foreseeability of multidrug resistant TB on the following paradigmatic hypothetical. A physician misdiagnoses and fails to treat a patient who is infected by susceptible M. TB. The genome of the bacterium subsequently mutates within the patient and transforms the bacterium into a multidrug-resistant version. A multidrug-resistant strain of M. TB is defined as one that is resistant to tuberculosis.); Dowling v Mutual Life Insurance, 168 So. 2d 107 (1964).

---

115 18 Misc 2d 740 (NY 1959).
116 Id.
117 Id. at 745.
118 Id. at 746.
119 The evolution from drug-susceptible TB, through various stages of drug resistance, to eventual extensively drug-resistant TB within a single patient is not unusual. Eldholm and colleagues report observation of an initially susceptible strain that developed resistance to INH, RIF, streptomycin (STR), FLQ, ethionamide (ETH) and AMK as well as low-level resistance to ethambutol (EMB). See V. Eldholm et al., Evolution of Extensively Drug Resistant Mycobacterium Tuberculosis from a Susceptible Ancestor in a Single Patient, 15 GENOME BIOL. 490, 491 (2014).
both frontline antibiotics isoniazid and rifampicin. At this time, resistance to the drug isoniazid is known and foreseeable, but scientists have not yet reported rifampicin resistance.

The patient subsequently transmits the multidrug-resistant pathogen to a third party. The infection develops into a clinically active disease in the third party. Until this point in time, the anti-TB drug rifampicin has been an effective agent against susceptible strains as well as strains resistant to streptomycin and isoniazid, but is not effective against multidrug resistant TB.

See Stephen K. Field et al., New Treatment Options for Multidrug-Resistant Tuberculosis, 6(5) Therapeutic Advances in Respiratory Disease 255, 256 (2012); see also Gillespie and Hawkey, supra note 34 (“MDR-TB is defined as infection with an organism resistant to at least isoniazid and rifampicin.”)


See Thomas R. Frieden et al., The Emergence of Drug-Resistant Tuberculosis in New York City, 328 NEW ENG. J. MED. 521, 525 (1993) (“Patients with drug-resistant tuberculosis may have infectious disease for prolonged periods after treatment has begun and may therefore be more likely to infect others.”); Lawrence O. Gostin, The Resurgent Tuberculosis Epidemic in the Era of AIDS: Reflections on Public Health, Law, and Society, 54(1) MARYLAND L. REV. 1, 90 (1995) (“If a person infected with M. TB reactivates and develops multidrug-resistant tuberculosis because of incomplete treatment, he or she will transmit a strain of infection that is difficult or impossible to treat.”)

See Lincoln P. Miller et al., The rpoB Gene of Mycobacterium Tuberculosis, 38(4) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 805, 805 (Apr., 1994) (“Rifampin, introduced in 1971, has proved to be an effective antituberculosis agent against susceptible strains as well as strains resistant to
The third party brings an action for medical malpractice against the physician.\(^{124}\) The plaintiff must prove that contracting multidrug resistant TB was a foreseeable consequence of the physician’s misdiagnosis.

**Foreseeability analysis**

Multidrug-resistant TB and drug-susceptible TB are pathologically the same disease.\(^{125}\) The only difference is that multidrug-resistant TB is caused by a different mechanism\(^{126}\)

isoniazid or streptomycin.

\(^{124}\) See Davis v. Rodman, 147 Ark. 385, 391, 227 S.W. 612, 614 (1921) (“It is undoubtedly the duty of physicians who are attending patients afflicted with contagious or infectious diseases not to negligently do any act that would tend to spread the infection.”)

\(^{125}\) See Lee B. Reichman, correspondence, Unsexy Tuberculosis, 373 THE LANCET 28, 28 (3 Jan., 2009) (“[T]he key aspect that has been largely forgotten in all of the hype is that XDR-TB, MDR-TB, and drug-sensitive tuberculosis are all the same disease. The only difference is that MDR- TB is drug-sensitive tuberculosis modified by inappropriate treatment or drug taking, and XDR-TB is MDR-TB thus modified. In other words, every person with MDR-TB or XDR-TB was not treated properly, did not take their drugs properly, or were infected by somebody who was not treated properly or did not take their medicines properly.”); Steve Mirsky, Return of a Killer: Tuberculosis in Russia, SCIENTIFIC AMERICAN (Aug. 27, 2008) (“We have this image in our minds that MDR-TB, as it’s known, is a worse disease than TB. That’s not really the case. They are really the same disease. It’s just that they had become much harder to cure, and of course tuberculosis will kill you if you do not successfully treat it.”); Campaign for Access to Essential Medicines Médecins Sans Frontières, Tuberculosis: New Faces of an Old Disease at 12 (“[B]eyond the different categorisations of DR-, PDR-, MDR- or XDR-TB, this is the same disease, albeit one that may require different combinations of drugs in order to treat different people effectively.”)

\(^{126}\) See Medina & Pieper, supra note 58, at 13 (“Resistance to rifampicin is conferred by mutations in the rpoB gene that alter residues of the rifampicin-binding site of the RNA polymerase 3 subunit, leading to low affinity binding.”); Akos Somoskovi et al., The Molecular Basis of Resistance to Isoniazid, Rifampin, and Pyrazinamide in Mycobacterium tuberculosis, 2 RESPIRATORY RES. 164, 164 (2001) (“MDR strains are the result of cumulative mutations.”).
and results in a greater degree of harm to the infected person. This fact appears to suggest that the plaintiff’s contraction of multidrug-resistant TB was foreseeable. The general common law rule is that the type of injury must be foreseeable, rather than its extent or manner of occurrence.

The reasonable ignorance of the relationship doctrine of proximate causality creates an exception to the common law rule. Under the reasonable ignorance doctrine the defendant escapes liability when, even though ex post there is clearly a systematic relationship between the defendant’s wrongdoing and the plaintiff’s harm, scientists could not predict the relationship ex ante.

---

127 See E. André et al., Consensus Numbering System for the Rifampicin Resistance-Associated rpoB Gene Mutations in Pathogenic Mycobacteria, 23 CLINICAL MICROBIOLOGY & INFECTION 167, 167 (2017) (“Multidrug-resistant TB, defined as disease caused by Mycobacterium tuberculosis complex strains resistant to rifampicin and isoniazid, requires prolonged and more complex administration of alternative treatment regimens including second-line anti-TB drugs, and is associated with poorer treatment outcome.”); Amita Jain & Pratima Dixit, Multidrug Resistant to Extensively Drug Resistant Tuberculosis: What Is Next?, 33 J. BIOSCIENCES 605, 608 (2008) (“While tuberculosis is curable, MDR-TB may be fatal and the cure rates are frustratingly low. Management of MDR- TB is most difficult, complicated, challenging, and costlier and needs experienced and highly skilled persons. Tuberculosis is easy to diagnose but diagnosis of MDR-TB depends on reliable and expensive culture and sensitivity test that are not available in most parts of the world. The second line drugs used in cases of MDR-TB are often less effective, more likely to cause side effects and are expensive.”); Anastasia Koch & Robert John Wilkinson, The Road to Drug Resistance in Mycobacterium tuberculosis, 15 GENOME BIOLOGY 520, 520 (2014) (“[M]ulti-drug-resistant (MDR), extensively drug-resistant (XDR) and totally drug-resistant (TDR) forms . . . are successively more difficult to treat. In these circumstances, treatment regime ns involve the use of a larger number of less-effective drugs, which have a narrower therapeutic margin.”).

128 See Michael D. Green, The Federal Employers’ Liability Act: Sense and Nonsense About Causation, 61 DEPAUL L. REV. 503, 541 n.196 (2012) (“Harm may occur due to an unusual concatenation of events, but if the harm is reasonably foreseeable or it results from the risks that made the defendant negligent, liability should follow.”); ERIC E. JOHNSON, 1 TORTS: CASES AND CONTEXT 331 (2015) (“The general rule is unforeseeable extent of harm will not cause a failure of proximate causation. Alternatively stated, under the eyes of the law, the extent of the harm, no matter how great, is considered to be foreseeable.”); Owen, supra note 101, at 1298 (“It commonly is said that responsibility requires only that an actor foresee the type of harm, not the manner of harm nor the extent of harm.”).

129 Grady, supra note 106, at 328.
Doughty v. Turner Manufacturing Co.\textsuperscript{130} illustrates the doctrine.\textsuperscript{131} In Doughty a technician negligently knocked the cover of a vat made of “sindanyo,” a combination of cement and asbestos, into molten sodium cyanide contained in the vat.\textsuperscript{132} A chemical reaction between the molten liquid and the material of the cover caused an eruption that resulted in burn injuries to the plaintiffs.\textsuperscript{133} The fact that sindanyo could undergo this reaction at sufficiently high temperatures was unknown to scientists at the time.\textsuperscript{134}

The type of harm suffered by the plaintiff (burning due to splashing of hot molten liquid) was a foreseeable consequence of the defendant’s reckless handling of the liquid, yet the defendant escaped liability. The systematic relationship between the defendant’s misconduct and the plaintiff’s harm (splashing due to an obscure chemical reaction) was not only unknown to the defendant but also materially different from what was known and foreseeable (splashing due to mechanical action).

The analysis in this Part shows that the foreseeability analysis of multidrug resistant TB turns on facts analogous to those in Doughty.\textsuperscript{135} Although the type of harm suffered by the plaintiff, multidrug resistant TB, is the same disease as susceptible TB, the analysis shows that an essential element in the systematic relationship between the physician’s misdiagnosis and the plaintiff’s injury was (1) unknown to the medical profession at the time of wrongdoing, and (2) not a mere variant of what was known and foreseeable. The defendant may therefore escape liability under the reasonable ignorance doctrine.

The analysis focuses on the following issues:

1. A definition of the systematic relationship between wrongdoing such as medical malpractice and multidrug-resistant TB that faithfully translates the common law

\textsuperscript{130} [1964] 1 QB 518 (Eng.)
\textsuperscript{131} See Grady, supra note 106, at 328-30 (discussing the case).
\textsuperscript{132} Id. at 329.
\textsuperscript{133} Id.
\textsuperscript{134} Id.
\textsuperscript{135} See id. at 330 (analyzing the effect of the reasonable ignorance doctrine in Doughty).
concept into medical science.
2. A determination of whether defendants were reasonably ignorant of the systematic relationship.
3. If defendants were reasonably ignorant, a determination of whether the novel and unexpected element in the systematic relationship was a mere variant of what was known and foreseeable.

Defining “systematic relationship”

The essence of the foreseeability doctrine is the concept of a systematic relationship between a defendant’s wrongdoing and the plaintiff’s harm. The systematic relationship between a medical event and a disease is defined by the etiology and pathogenesis of the disease.\(^{136}\) The etiology of a disease is the cause or set of causes of the disease.\(^{137}\) The pathogenesis is the mechanism by which an etiologic agent produces the disease.\(^{138}\) For instance, the etiology of lung cancer includes carcinogens such as tobacco smoke. The pathogenesis of lung cancer includes mechanisms such as the interaction of carcinogens with human DNA to cause genetic changes that result in lung cancer.\(^{139}\) Lung cancer is a foreseeable consequence of tobacco smoke because of medical evidence that tobacco smoke contains an etiologic agent that initiates the pathogenesis of lung cancer in an exposed person.\(^{140}\)

The etiologic agent of multidrug resistant TB is the bacterium *mycobacterium tuberculosis* (M. TB).\(^{141}\) The pathogenesis of the

---

\(^{136}\) See Michael Witthöft, *Etiology/Pathogenesis*, in *ENCYCLOPEDIA OF BEHAVIORAL MEDICINE* 716, 716 (Marc D. Gellman & J. Rick Turner eds., 2013 ed. 2013) (“The terms ‘etiology’ and ‘pathogenesis’ are closely related to the questions of why and how a certain disease or disorder develops. Models of etiology and pathogenesis therefore try to account for the processes that initiate (etiology) and maintain (pathogenesis) a certain disorder or disease.”).


\(^{138}\) See id. at 535 (defining pathogenesis as “the cellular events and reactions and other pathologic mechanisms occurring in the development of disease”).


\(^{140}\) See id. (describing the interactions of carcinogens in tobacco smoke).

\(^{141}\) Palomino & Martin, supra note 44, at 317.
disease consists of resistance-causing genetic mutations and disease-causing mechanisms that culminate in clinical illness. Two distinct genetic mutations intervened between the defendant’s misdiagnosis of drug-susceptible TB and the plaintiff’s illness. Drug-susceptible M. TB mutated successively to acquire resistance to the frontline anti-TB drugs isoniazid and rifampicin. At the time of wrongdoing drug-susceptible and isoniazid-resistant TB were both predictable, but scientists had not yet reported rifampicin resistance and the genetic mutation that causes it. A key issue in the foreseeability analysis therefore is whether scientists could, at this stage, predict the evolution of rifampicin resistance. If scientists could not predict the genetic mutation of M. TB that makes it resistant to rifampicin, no proximate cause exists, provided the mutation also differs materially from what was known and foreseeable.

The following issues therefore need to be resolved:

1. Whether scientists could predict the rifampicin resistance-causing mutation at the time of wrongdoing.
2. If the defendant could not predict the mutation, whether the mutation is a mere variant of what was known and predictable.

A proper analysis of these issues requires an understanding of the biomedical principles governing the antibacterial action and resistance mechanisms of the antibiotic rifampicin.

**Rifampicin**

In 1943 microbiologist and Nobel laureate Selman Waksman and his team at Rutgers University isolated the first effective

---

142 Id.
143 Grady, supra note 106, at 329-330.
144 Id.
145 Id.
146 See Grady, supra note 106, at 328 (no proximate cause exists if scientists could not predict an essential element of the systematic relationship between injury and wrongdoing).
147 Id.
anti-tuberculosis agent, streptomycin. Many patients were successfully treated with streptomycin but a substantial proportion had a relapse. 

Isolates from non-responding patients showed resistance to streptomycin. Other anti-tuberculosis agents followed but every new antibiotic was promptly met with genetic mutations that conferred resistance to it. Resistance to the antibiotic isoniazid was observed soon after it was introduced in 1952. Subsequently, rifampicin was discovered in Italy in 1965 under supervision of Professor Piero

Sensi, and approved in the United States in 1971. It has proved to be effective against susceptible M. TB strains as well as strains resistant to isoniazid or streptomycin. Inevitably, resistance to rifampicin was observed soon after its first introduction. Isoniazid and rifampicin nevertheless remain frontline anti-TB agents and the basis of the multidrug treatment regimen for TB.

**Mechanisms of rifampicin bactericidal action**

The antibiotic drug rifampicin undermine the viability of a bacterial cell by binding to and inactivating the β-subunit of a bacterial enzyme called RNA polymerase. RNA-polymerase


154 Lincoln P. Miller et al., *The rpoB Gene of Mycobacterium Tuberculosis*, 38(4) ANTIMICROBIAL AGENTS & CHEMOTHERAPY 805, 805 (1994); John S. Blanchard, *Molecular Mechanisms of Drug Resistance in Mycobacterium Tuberculosis*, 65 Ann. Rev. Biochem. 215, 223 (1996) (“Few other anti-tubercular compounds are as rapidly effective as rifampicin.”); JIGAR R. RATHOD, *TEXTBOOK OF BACTERIOLOGY* 101 (“[Rifampicin] has been found to have greater bactericidal effect against M. tuberculosis than other anti-tuberculosis drugs, and it has largely replaced isoniazid as one of the front-line drugs used to treat the disease, especially when isoniazid resistance is indicated.”).


157 Laila Nimri et al., *Detection of Mutations Associated With Multidrug-Resistant Mycobacterium Tuberculosis Clinical Isolates*, 62 FEMS IMMUNOLGY & MED. MICROBIOLOGY 321, 321 (2011) (“Rifampicin acts by binding to the β-subunit of RNA polymerase (rpoB), the enzyme responsible for transcription and expression of mycobacterial genes, resulting in inhibition of the bacterial transcription activity and thereby killing the organism.”); ALBERTS BRAY ET AL., *ESSENTIAL CELL BIOLOGY* 258 (3d ed.); Elizabeth A. Campbell et al., *Structural Mechanism for Rifampicin Inhibition of Bacterial RNA Polymerase*, 104 CELL 901, 901 (2001) (“Rifampicin is one of the most potent and broad spectrum antibiotics against bacterial pathogens and is a key component of anti-
represents an ideal target for antibacterial therapy. Bacteria depend on this enzyme to transcribe genetic information from DNA into RNA, which in turn directs the synthesis of proteins that carry out essential biological functions, such as cell growth. Proteins are also key structural components of cells.
RNA polymerase is therefore essential for the viability of the bacterial cell, and its inactivation will result in the inhibition of essential cellular functions. Rifampicin has been developed to exploit this vulnerability.

Resistance to rifampin is caused primarily by chromosomal mutations in a region of the rpoB gene of M. TB that encodes the β-subunit of DNA-dependent RNA polymerase. The rpoB mutations decrease affinity of the RNA polymerase enzyme to rifampicin bactericidal action, making rifampicin ineffective. This results in rifampicin resistance.

molecular biology.”; Matt Ridley, GENOME THE AUTOBIOGRAPHY OF A SPECIES IN 23 CHAPTERS 17 (1999) (“RNA is a chemical substance that links the two worlds of DNA and protein. It is used mainly in the translation of the message from the alphabet of DNA to the alphabet of proteins.”).

See Alberts Bray et al., ESSENTIAL CELL BIOLOGY (3d. ed.) 677; Id. at G:17 (Proteins are “[t]he major macromolecular [component] of cells”); Michael S. Glickman & William R. Jacobs, Jr. Microbial Pathogenesis of Mycobacterium tuberculosis: Dawn of a Discipline, 104 CELL 477, 479 (Feb, 23, 2001); ROBERT F. WEAVER, MOLECULAR BIOLOGY 35 (5th ed. 2012) (Protein function: “Why are proteins so important? Some proteins provide the structure that helps give cells integrity and shape. Others serve as hormones to carry signals from one cell to another. For example, the pancreas secretes the hormone insulin that signals liver and muscle cells to take up the sugar glucose from the blood. Proteins can also bind and carry substances . . . . Proteins also control the activities of genes, as we will see many times in this book. And proteins serve as enzymes that catalyze the hundreds of chemical reactions necessary for life.”); MATT RIDLEY, GENOME: THE AUTOBIOGRAPHY OF A SPECIES IN 23 CHAPTERS 9 (1999) (“Almost everything in the body, from hair to hormones, is either made of proteins or made by [proteins].”)


See Medina & Pieper, supra note 58 at 13 (2016) (“Resistance to rifampicin is conferred by mutations in the rpoB gene that alter residues of the rifampicin-binding site of the RNA polymerase β-subunit, leading to low affinity
Could scientists predict the rifampicin resistance-causing mutation?

The genetic mutation responsible for rifampicin resistance is an essential element of the systematic relationship between the physician’s misdiagnosis and the plaintiff’s contraction of multidrug resistant TB. Therefore, no liability exists if scientists could not ex ante predict the mutation. The analysis in this section shows that the mutation was unpredictable.\(^{166}\) The analysis is based on three basic observations on the rifampicin resistance mutation:\(^{167}\)

1. Known mutations that precede the rifampicin resistance mutation in time are not leading indicators of rifampicin resistance.
2. The rifampicin resistance mutation is a spontaneous, random event.
3. At the time of defendant’s wrongdoing scientists had not described the rifampicin resistance mutation. Scientists first described the precise rifampicin resistance-causing mutation only decades after the initial emergence of rifampicin resistance.

No leading indicator. Drug-susceptible M. TB acquires resistance to the frontline anti-TB drugs isoniazid and rifampicin through a multistep process of separate and independent mutations.\(^{168}\) Isoniazid resistance is mediated by mutations in

\(^{166}\) See infra note 168.

\(^{167}\) See infra note 169-177 and accompanying text.

the \textit{katG}, \textit{inhA}, \textit{acpM}, and \textit{kasA} genes,\textsuperscript{169} while rifampin resistance is caused primarily by chromosomal mutations in a region of the \textit{rpoB} gene of \textit{M. TB} that encodes the \textbf{\textit{\beta}}-\textit{subunit} of DNA-dependent RNA polymerase.\textsuperscript{170} Scientific evidence that the mutations are independent\textsuperscript{171} and not directly connected\textsuperscript{172} 3114, 3114 (July 2005) ("A dramatic increase in the resistance and spread of MDR-TB strains has been observed in recent years. These MDR strains carry multiple mutations in different resistance-related genes, and each mutation results from an independent mutational event."); Francesca Meacci et al., \textit{Drug Resistance Evolution of a Mycobacterium tuberculosis Strain from a Noncompliant Patient}, 43(7) J. CLIN. MICROBIOL. 3114, 3114 (July 2005) ("An MDR strain is thus the product of a multistep process, in which a progressive accumulation of genetic alterations occurs and results in the selection of a viable and fit bacterium."); Isoniazid resistance usually precedes rifampicin resistance."); D.B.M. Virupakshaiah et al., \textit{Molecular Docking Studies of Mycobacterium tuberculosis RNA Polymerase \textbf{\textit{\beta}}-\textit{subunit} (rpoB) Receptor}, 7(5) INT. J. BIOL. BIOMOLEC. AGRIC. FOOD & BIOTECH. ENG. 314, 314 (2013) (Mono-resistance to isoniazid is common, but resistance to rifampin occurs only after initial resistance to another drug such as isoniazid.; Somoskovi et al., \textit{supra} note 126, at 167 ("Whereas mono-resistance to isoniazid is quite common, mono-resistance to rifampin is rare. Instead, rifampin resistance occurs most often in strains that are also resistant to isoniazid."); L. P. Ormerod, \textit{Multidrug-Resistant Tuberculosis (MDR-TB): Epidemiology, Prevention and Treatment}, 73 & 74 BRIT. MED. BULLETIN 2005 17, 17 (2005) (Separate mutations are required to change \textit{M. TB} from drug-susceptible to multidrug-resistant.)

\textsuperscript{169} S. Somasundaram et al., \textit{Isoniazid and Rifampicin as Therapeutic Regimens in the Current Era: A Review}, 2 J. TUBERCULOSIS RES. 40, 46 (2014).


\textsuperscript{171} See D. Mazel & J. Davies, \textit{Antibiotic Resistance in Microbes}, 56 CMLS, CELL. MOL. LIFE SCI. (1999) 742, 747 (1999) ("[T]he generation of the multi-drug resistant Mycobacterium strains ... requires a series of independent mutations."); Francesca Meacci et al., \textit{Drug Resistance Evolution of a Mycobacterium Tuberculosis Strain from a Noncompliant Patient}, 43(7) J. CLIN. MICROBIOL. 3114, 3114 (July 2005) ("A dramatic increase in the resistance and spread of MDR-TB strains has been observed in recent years. These MDR
suggests that isoniazid resistance is not a leading indicator of rifampicin resistance.

**Randomness.** Resistance to antibiotics, including rifampicin, emerges as a result of random, spontaneous mutations of the M. TB chromosome that immunize bacteria to these antibiotics. A strain carries multiple mutations in different resistance-related genes, and each mutation results from an independent mutational event. An MDR strain is thus the product of a multistep process, in which a progressive accumulation of genetic alterations occurs and results in the selection of a viable and fit bacterium.

---

172 See L. P. Ormerod, *Multidrug-Resistant Tuberculosis (MDR-TB): Epidemiology, Prevention and Treatment*, 73 & 74 BRIT. MED. BULLETIN 17, 17 (2005) (“The isoniazid and rifampicin resistance mutations are not directly connected, and so separate mutations are required for organisms to change from a drug-susceptible isolate to [multidrug resistant]-TB.”).

random process is mathematically unpredictable.\textsuperscript{174} The \textit{spontaneity} of resistance-causing mutations makes the timing of a specific mutation unpredictable. The \textit{randomness} of genetic mutation makes the emergence of resistance to a specific drug such as rifampicin, by a precise mutation and molecular mechanism, unpredictable.\textsuperscript{175}

\textit{Corroborating evidence}. These conclusions are corroborated by the fact that scientists first described the precise rifampicin resistance-causing mutation and molecular mechanisms more than a decade after the initial emergence of rifampicin resistance.\textsuperscript{176} The mutation that causes rifampicin resistance was first described in 1981 for Escherichia coli (E. coli),\textsuperscript{177} and it took


\textsuperscript{174} \textit{See} Antony Eagle, \textit{Randomness Is Unpredictability}, 56 \textit{BRIT. J. FOR PHILOS. SCI} 749, 749 (2005) (“I propose that randomness is to be understood as a special case of the epistemic concept of the unpredictability of a process."); Roman Frigg, \textit{In What Sense is the Kolmogorov–Sinai Entropy a Measure for Chaotic Behaviour?—Bridging the Gap Between Dynamical Systems Theory and Communication Theory}, 55 \textit{BRIT. J. FOR PHILOS. SCI}. 411, 430 (2004) (“[W]e say that an event is random if there is no way to predict its occurrence with certainty.").

\textsuperscript{175} Patrice Courvalin, \textit{Antimicrobial Drug Resistance: “Prediction Is Very Difficult, Especially about the Future”}, 11 \textit{EMERGING INFECTION\,D\,ISEASES} 1503, 1505 (2005) (“It is extremely difficult to think like a bacterium. In other words, predicting the emergence of resistance to a drug class by a precise molecular mechanism is nearly impossible."); R. Craig MacLean \textit{et al.}, \textit{The Population Genetics of Antibiotic Resistance: Integrating Molecular Mechanisms and Treatment Contexts}, 11 \textit{NATURE REV. GENETICS} 405, 405 (“Despite efforts from a range of disciplines, our ability to predict and combat the evolution of antibiotic resistance in pathogenic bacteria is limited. This is because resistance evolution involves a complex interplay between the specific drug, bacterial genetics and both natural and treatment ecology.").

\textsuperscript{176} \textit{See} André \textit{et al.}, \textit{supra} note 127, at 168 (noting that rifampicin resistance was first described in 1981).

\textsuperscript{177} \textit{See id.} at 168 (“Rifampicin resistance is caused by a structural alteration in the RNA polymerase $\beta$-\textbf{subunit}, an enzyme coded by the $rpoB$ gene. This
Scientists most of the subsequent decade to determine that rifampicin resistance in M. TB mirrored the situation in E. coli. In 1993 Professor Amalio Telenti and colleagues first determined the site of mutation and precise molecular mechanisms that resulted in rifampin resistance in M. TB. They used evidence that E. coli became resistant to rifampicin through mutation in the \( \beta \) subunit of the \( rpoB \) gene as the foundation of their experimental work that led to the ultimate discovery for M. TB. Before the work of Telenti and colleagues, research had shown that resistance to rifampicin was related to changes in the RNA polymerase, but scientists had not established the precise molecular mechanism in mycobacteria.

**Materially different?**

We have established that scientists could not predict the rifampicin resistance-conferring mutation. To complete the foreseeability analysis we need to determine whether the mutation differs materially from what was known and foreseeable at the time of wrongdoing. This section argues that the mutation differs biologically from known resistance-conferring mutations and that the distinction is material.

---

178 See O.J. Billington et al., Physiological Cost of Rifampin Resistance Induced In Vitro in Mycobacterium tuberculosis, 43 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1866, 1868 (1999) (describing the similarities between the mutations in Escherichia coli and Mycobacterium tuberculosis).

179 See André et al., supra note 127, at 168 (describing Telenti's team's discovery) (citing Amalio Telenti et al., Detection of Rifampin-Resistance Mutations in Mycobacterium Tuberculosis, 341 LANCET 647 (1993)); Gillespie, supra note 161, at 268 (“Telenti and colleagues were the first to determine the site of mutation that resulted in rifampin resistance in M. tuberculosis. They used the evidence that Escherichia coli became resistant to rifampin through mutation in the beta subunit of the \( rpoB \) gene and sequenced this gene from a series of epidemiologically unrelated strains. They showed that almost all rifampin-resistant isolates had mutations in a small region of \( rpoB \).”).

180 Gillespie, supra note 161, at 268.

181 See Telenti et al., supra note 179, at 647 (“Resistance to rifampicin involves alterations of RNA polymerase.”).
Prior to the introduction of rifampicin, M. TB developed resistance to antibiotics such as: streptomycin (introduced in 1944), isoniazid (1952), pyrazinamide (1952), cycloserine (1952), and ethionamide (1956). The genetic mechanism of resistance in each case differs from rifampicin. For instance, isoniazid and rifampicin have different sites of action and they develop resistance through different genetic mutations. Isoniazid resistance is mediated by mutations in the KatG, InhA, acpM, and KasA genes while rifampin resistance is caused primarily by chromosomal mutations in a region of the rpoB gene of M. TB that encodes the \(\beta\)-subunit of DNA-dependent RNA polymerase. The site of action of isoniazid is mycolic acid synthesis while the site of action of rifampicin is RNA synthesis.

The distinction is material because the addition of rifampicin resistance has a significant negative impact on the prognosis of an infected person. Drug-susceptible TB is one hundred percent curable and isoniazid mono-resistant TB is relatively easy to treat.

---

182 See Keshavjee & Farmer, supra note 4, at 931-32 (discussing the resistance of TB to antibiotics).

183 See Palomino & Martin, supra note 44, at 323 (discussing the resistance to various drugs); Parida et al., supra note 43, at 393 (describing mutations conferring antibiotic resistance to anti-TB drugs, including cycloserine); G. Pozzi et al., rpoB Mutations in Multidrug-Resistant Strains of Mycobacterium tuberculosis Isolated in Italy, 37 J. CLINICAL MICROBIOLOGY 1197 (1999) (describing the specific mutations found in mutated Mycobacterium tuberculosis). See also Somasundaram et al., supra note 167, at 46 (describing anti-TB drugs, their sites of action, and genetic mutations conferring resistance to the drugs); Woodford & Ellington, supra note 36, at 7 (“In certain species, mutation is the main, or sole, cause of clinical resistance problems. One of the best examples is Mycobacterium tuberculosis. Resistance to all therapeutic agents in this species is mediated by mutations: i.e., rifampicin resistance in [the] rpoB [gene]; isoniazid resistance in katC, inhA, oxyR, ahpC and furA; streptomycin resistance in rrs and rpsL; pyrazinamide resistance in pncA; ethambutol resistance in embB; and fluoroquinolone resistance in gyrA and gyrB.”).

184 Somasundaram et al., supra note 169, at 46.

185 See Goldstein, supra note 164, at 625 (“Resistance to rifampicin (RIF) is . . . nearly always due to a genetic change in the \(\beta\)-subunit of bacterial RNA polymerase.”).

186 Ormerod, supra note 168, at 18; Somasundaram et al., supra note 169, at 46.

187 See Jain & Dixit, supra note 127, at 608 (“While tuberculosis is curable, MDR-TB may be fatal and cure rates are frustratingly low.”).
However, when an isoniazid mono-resistant strain of M. TB acquires resistance to rifampicin to become multidrug resistant, the infected person’s prognosis worsens significantly. Multidrug-resistant TB is more difficult to treat, has a higher mortality rate, and leads to longer treatment periods and poorer outcomes. Multidrug resistant TB is also

188 See Zakaria Hmama, Management of Drug-Resistant TB, in TUBERCULOSIS—CURRENT ISSUES IN DIAGNOSIS AND MANAGEMENT 203, 208 (Bassam H. Mahboub & Mayank G. Vats eds., 2013) ("INH monoresistant TB is relatively easy to treat with [standard short-course chemotherapy] treatment."); Patricio Escalante et al., Treatment of Isoniazid-Resistant Tuberculosis in Southeastern Texas, 119 CHEST 1730, 1731 (2001) ("Several regimens have been used successfully to treat patients with [isoniazid-resistant TB] in the past. Treatment failures are rare when regimens containing rifampin (RIF) and two other first-line drugs for 6 months are used."); Zhang & Yew, supra note 131, at 1284 (showing that standard short-course chemotherapy of isoniazid mono-resistant TB can achieve a 88 percent cure rate and less than 5% relapse when all four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) are used throughout a 6-month treatment period).

189 Mono-resistance to isoniazid is common, but resistance to rifampicin occurs only after initial resistance to another drug such as isoniazid. See Somasundaram et al., supra note 169, at 45-46 ("Isoniazid is generally the primary resistance as INH acts first on the multiplying bacteria, in the initial few days of combination therapy. Rifampicin resistance can later occur when the bactericidal cycle shifts to the dormant bacilli."); Somoskovi et al., supra note 126, at 166 ("Whereas monoresistance to isoniazid is quite common, monoresistance to rifampicin is rare. Instead, rifampin resistance occurs most often in strains that are also resistant to isoniazid."); Virupakshaiah et al., supra note 167, at 314 ("Rifampicin resistance occurs most often in strains that are also resistant to isoniazid.").

190 See Hmama, supra note 188, at 209 ("[Rifampicin]-resistant TB often carries a much more ominous prognosis, as the outcome of [standard short-course chemotherapy] treatment is poor in terms of both disease status at the end of the treatment and relapse."); Miller et al., supra note 126, at 805 ("Rifampin resistance heralds a more prolonged treatment for the patient and a poor outcome if the isolate is also resistant to isoniazid."); Ormerod, supra note 168, at 19 ("[T]he loss of [response] to both isoniazid and rifampicin, even without resistance to additional drugs, has . . . major effects on outcome.").

191 See Soumitesh Chakravorty et al., Rifampin Resistance, Beijing-W Clade—Single Nucleotide Polymorphism Cluster Group 2 Phylogeny, and the Ru2629 191-C Allele in Mycobacterium tuberculosis Strains, 46 J. CLINICAL MICROBIOLOGY 2555, 2558 (2008) ("Even rifampin-monoresistant tuberculosis responds poorly to standard therapy."); Gostin, supra note 121, at 17 ("Resistance to isoniazid and rifampicin lengthens the course of tuberculosis treatment from six months to eighteen to twenty-four months, increases greatly the cost of treatment, and decreases the cure rate from nearly 100 percent to 40
relatively difficult and expensive to diagnose,\textsuperscript{192} and managing the condition is resource-intensive.\textsuperscript{193} Unlike drug-susceptible cases that are protocol-driven, treatment of multidrug resistant TB patients must be individualized to take into account idiosyncrasies of the infecting pathogen as well as the patient.\textsuperscript{194}

In summary, an analysis of the reasonable ignorance doctrine of proximate causality shows that the initial outbreak of rifampicin resistance was unforeseeable. The type of harm was foreseeable, but scientists could not predict an essential element of the systematic relationship between the defendant's wrongdoing and the plaintiff's harm. The analysis turns on facts...
analogous to those of *Doughty v. Turner Manufacturing Co.* In *Doughty* the type of harm that had befallen the plaintiff was foreseeable but the defendant escaped liability because scientists could not ex ante predict an essential causal element, namely the chemical reaction that caused the injury.

5. CONCLUSION

The complex and dynamic nature of the microbial world presents challenges not only to public health and medical research, but also to legal analysts faced with issues such as medical malpractice involving injury due to emerging microbial diseases. Prima facie there is no clear logical connection between the chaotic world of microbes and various legal doctrines of medical malpractice; yet the law demands it. This Article develops a methodology that facilitates the legal analysis of these and similar complex medical issues.

The contribution of the Article is twofold. (1) It presents an approach to legal analysis of complex medical issues based on a translation of traditional legal principles into the language of medicine in a way that preserves their meaning and policy rationale. The translation provides a model of the interaction between law and medicine that facilitates legal analysis. (2) It illustrates the theory by analyzing the foreseeability of multidrug resistant tuberculosis.

---

196 *Id.*