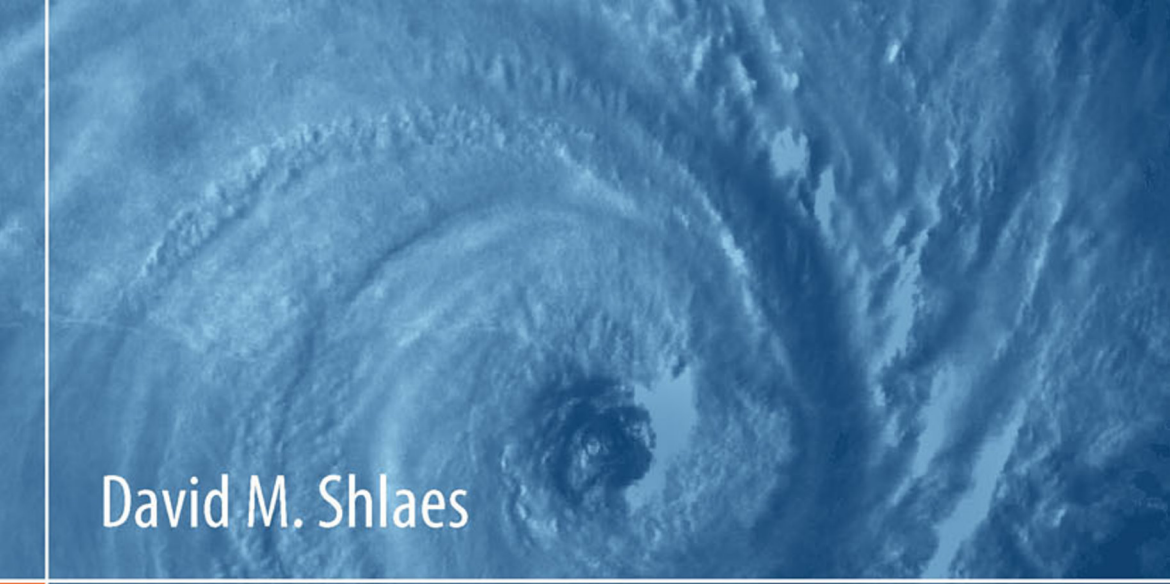

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The Perfect Storm

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To Jan for years of hard work, patience, understanding, love and support.

David M. Shlaes MD, PhD has had a 30-year career in anti-infectives spanning academia and industry with a long-standing scientific interest in antimicrobial resistance. In 1991 he was appointed Professor of Medicine at Case Western Reserve University. In 1996, Dr. Shlaes became vice president for Infectious Diseases at Wyeth Research for 6 years, assuming responsibility for the strategic direction for infectious diseases within Wyeth. In 1998 Dr. Shlaes was the cover feature in the April issue of *Business Week* dedicated to antibiotics research. In 2002, Dr. Shlaes became executive vice president, Research and Development for Idenix, Pharmaceuticals, a company located in Cambridge, MA, focused on the discovery and development of antivirals. In 2005, he left Idenix to form a consulting company for the Pharmaceutical Industry (Anti-Infectives Consulting, LLC). He was recently an independent director for Novexel, S.A, an anti-infectives biotech in Paris that was just sold to Astra-Zeneca. He consults for a number of other anti-infective focused biotechs and frequently works with VC firms in the evaluation of anti-infective companies.

Contents

Chapter 1
The Perfect Storm

On the antibiotics front, the weather has occasionally been bad ever since I can remember. But things have never been as bad as they are today. Bacteria are becoming resistant to the point where none of our available antibiotics work for some of the infections that confront patients and physicians in hospitals around the US and the around world. For these patients we are slipping back in time to a pre-antibiotic era where we have little to offer but comfort for diseases which we have been easily able to cure over the last 50 years.

But in answer to resistance, our antibiotic pipeline is all but dry and the situation is deteriorating. The science of discovering new antibiotics is exceedingly challenging and the economics of antibiotics are becoming less and less favorable. The regulatory agencies like the FDA are contributing to the problem with a constant barrage of clinical trial requirements that make it harder, slower and more costly to develop antibiotics. The pharmaceutical industry, under extraordinary financial pressures, is consolidating at historic rates leaving fewer and fewer large companies standing. The antibiotic market is not as promising as markets for treatment of chronic diseases like high cholesterol or chronic depression or high blood pressure. For those diseases which we cannot cure, the drugs must be taken for long periods of time, frequently for a lifetime. Antibiotics, which actually cure disease, are only taken for days or weeks.

In response to all these pressures, of the large pharmaceutical companies still extant, fewer and fewer are remaining active in antibiotic research. If this isn't The Perfect Storm, I don't know what is.

There are possible solutions to this conundrum. They include incentives to companies for antibiotic research and development, deconsolidation within the pharmaceutical industry and affecting a more balanced approach within the FDA that assures us the ability to develop new antibiotics for resistant bacteria.

Basically, we either invest now with organization, balance and money or we will pay with our lives. Antibiotics are going the way of the dodo but bacterial pathogens are with us for the duration.

I feel like I've been fighting this battle all my life. When I finished training and started my career in academic medicine, I wanted to study antibiotic resistance in bacteria. I felt that if we understood how resistance spread, we could stop it. If we

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could understand the mechanisms by which the bacteria become resistant in detail we could find ways around them with new antibiotics.

My first job put me in an ideal position to do that. I was director of the clinical microbiology laboratory at the Veterans Affairs Medical Center in Cleveland and I worked in the infectious diseases service. So I was seeing patients and their infecting bacterial pathogens every day. The problem was that research doesn't pay for itself. Someone has to provide the money to support the work. The Veterans Administration has a wonderful research support system that allowed me to get started and funded me virtually constantly for the 16 years I worked there. I will always be grateful to the VA for their constant support. Their approach should be contrasted to that at the National Institutes of Health (NIH) where there was, for many years, a bias against funding antibiotic resistance research. They felt that antibiotic resistance was not important or at least that it was somehow not good science. If it was important, the pharmaceutical industry and not the NIH should fund it. The pharmaceutical industry was not so interested in resistance in those days either since it usually did not do any good for marketing their products. I submitted grant requests to the NIH – but they were mostly not successful. It wasn't just me. There were only a very few of us in the United States working on antibiotic resistance and we all knew each other. One reason there were so few of us was that it was so difficult to obtain support for our research. When we got together we realized that we all had the same problem. In 1986 we met and began to investigate the NIH and their funding practices as far as antibiotic resistance was concerned. We confirmed that they did not fund much research in the area and requested a meeting with them. We found that one major reason they did not fund resistance research was that they had very few people working on reviewing grant proposals who were even familiar with antibiotic resistance. Since the NIH relied entirely on the grant reviews provided by their reviewers, resistance researchers were left out. We actually held several small workshops with the NIH over the next 5 or 6 years. One of our main recommendations to the NIH was to establish a special peer group to review grant requests in the area of antibiotic resistance. As a result of our efforts, we were the subjects of an article in the prestigious journal Science that referred to us as disgruntled scientists. Finally, 20 years after our group first met, the NIH established the very peer review group we recommended. Any discrimination against resistance research in the NIH seems to be gone, but grant money is still very hard to come by. The STAAR Act (Strategies to Address Antimicrobial Resistance) is currently under consideration in congress. It seeks to strengthen the surveillance, prevention and control and research efforts in antibiotic resistance in part through additional NIH funding.

In 1996 I took the leap to industry where I became Vice President for Infectious Diseases at Wyeth Pharmaceuticals. I moved to industry for a variety of reasons. One of them was that I learned that if I truly wanted us to have new antibiotics active against resistant bacteria, I needed to be in industry and not academia. And I truly wanted us to have new antibiotics! At Wyeth, as the infectious diseases therapeutic area head, my team (BIG) and I were responsible for discovering and ultimately for developing and even marketing Wyeth's antibiotics. Tigecycline (Tygacil), launched

in 2005, was partly the result of those efforts. Getting tigecycline through the FDA required another battle that I describe in Chapter 4. At least no one was saying I was disgruntled. I stayed at Wyeth until 2002 when I went to a small biotech working on antiviral drugs (where drugs against resistant viruses are important, too). There I was responsible for drug discovery, manufacturing, pharmacology and toxicology. In 2005 I became a consultant. I currently work with a number of companies, mostly small, who are trying to discover and develop new antibiotics for resistant bacterial infections. I still participate in research when I can and I try to stay involved in the ever-changing landscape of FDA-industry relations. I still dream of bringing more new antibiotics that work against resistant bacteria to patients and their physicians. But that dream is becoming harder and harder to realize.

I chose the specialty of infectious diseases because, during my training in the late 1970s, I loved being able to identify the cause of a patient's infection, choose the right antibiotic and watch my patient get better in a matter of hours to days. Of course, it didn't always work that way. Once I was called to the burn unit at the county hospital where I was training in infectious diseases. One of the patients was a severely ill middle aged gentleman with an infection caused by a Gram-negative bacterium. When I arrived, the patient had a high fever and was on a ventilator (breathing machine). Tubes were everywhere. He had severe second and third degree burns on his face, chest and abdomen that were draining a greenish-white material. His doctors had already sent a culture of this material to the microbiology laboratory. The report was in his chart and was the reason his doctors called for help. The bacterium that grew in culture was a Gram-negative organism called *Pseudomonas aeruginosa* and the green pigment it produces was responsible for the color of the purulent drainage from the patient's burn. The microbiology lab had tested the isolate for susceptibility to about 10 different antibiotics. As I went down the list, all I saw was R (for resistant) except for one S (for susceptible). This indicates that the patient's *Pseudomonas* was only killed by one of the antibiotics tested in the lab. The antibiotic with the S was colistin, discovered in 1947, and something I had never used and that was essentially never used even back in the 1970s. The doctors in the burn unit were, of course, already treating him with antibiotics, but the patient had not improved. While I was on the unit, I got a call from the lab informing me that the patient's blood was also growing a Gram-negative bacterium (later shown to be the same *Pseudomonas aeruginosa*). I called my supervisor, explained the situation, and we agreed that we would start the patient on colistin. My supervisor had to help me figure out how much to give and how often because this antibiotic essentially had not been used since the 1960s. The antibiotic was known to be toxic to nerves and to the kidney and because it had been developed so long ago, we didn't really know how well it would work.

I came back to see the patient the next day. He still had fever. His wound was unchanged. The bacterium was sensitive to the antibiotic we had prescribed. I obtained additional cultures of the wound and blood. The surgeons continued to debride the wound as much as possible. There seemed nothing else to do. Within a few days, the new blood and wound cultures were still growing the same organism, still sensitive to the drug we were using to treat him, but he was no better. His

kidney function began to deteriorate and he was dead within a week. This was not the only similar infection that I saw on the burn unit that year. Most, but happily not all, had a similar outcome. Today, physicians are once again forced to use this old antibiotic, colistin, to treat infections caused by bacteria resistant to everything else including all the antibiotics introduced since the late 1970s. There are new studies being conducted to determine whether colistin really works or not and to quantify its level of toxicity. One recent study from a US military hospital where Iraq war veterans have highly antibiotic resistant infections and where they are using colistin fairly often recently reported that 21% of their patients had to stop colistin because of kidney toxicity. In a few years, maybe we'll know the whole story.

I first arrived at the Cleveland Veterans Administration Medical Center in 1980. I had just finished my training in internal medicine and in infectious diseases so this was my first real job. A few years later, I was called to the surgical intensive care unit to see a patient with pneumonia. He was another middle-aged man who had undergone a coronary artery bypass about a week prior to my visit. He was still on a ventilator, but could communicate with me. When I examined him, he had fever and his chest was full of pneumonia on one side. His physicians had obtained cultures of the secretions coming from his pneumonia through his breathing tube. The microbiology report was just like the one from the county hospital a few years earlier – all the antibiotics were R. Colistin was not tested, but I was wary of using it again. I knew that Merck Sharpe and Dohme had a promising new antibiotic in the clinical testing stage and that I might be able to get hold of some for this patient. I called, filled out some (!!) paperwork, obtained informed consent from the patient and discussed the situation with his family who were supportive. We received a shipment of this new antibiotic within 24 hours. I started my patient on the new drug. The bacterium responsible for his pneumonia was susceptible to the new antibiotic. Within a few days, his fever was down and within a week he was able to come off the ventilator. As it turns out, the surgical unit had several cases like this all of which we were able to treat with the experimental antibiotic. We only lost one. The drug, imipenem-cilastatin (Primaxin), was eventually approved by the FDA and is still marketed today.

These true stories illustrate several important points. The first case shows what happens when we don't have antibiotics that work against resistant organisms. We are seeing more and more examples of this as we will see throughout this book. An infection with bacteria resistant to all available antibiotics was a rare occurrence during the "golden years" of antibiotic discovery from 1955 to 1985. During those years, there was almost always something new and active against resistant strains in late stage clinical trials or entering the marketplace. For the really old antibiotics, those approved before, say 1980, we are sometimes not so sure of either how well they work or how toxic they are. Many were never studied as carefully as we study antibiotics today.

The second case illustrates that antibiotics are truly miracle drugs that cure disease and save lives. It also exemplifies a more typical scenario during the golden years where there was always a new antibiotic in the pipeline that we could use to treat patients with antibiotic-resistant infections. Of course we want to try and

prevent or slow the emergence of resistance as much as possible, but we also want to have new antibiotics in the pipeline so that we are not faced with infections we can't treat. Currently, we are not doing as well as we could on the first front and we are failing miserably on the second.

About 2 million people acquire an infection during their hospitalization in the United States each year. 90,000 of them die. Many of these patients will have infections caused by resistant bacteria, and the resistance will contribute to their deaths. Antibiotic resistant infections increase death rates by 50–100% in general. Why? Partly because doctors don't suspect the resistance and will use the wrong antibiotic initially. In fact, if the doctors don't or can't obtain a sample of the infected material for culture, they won't know if the organism is susceptible to the antibiotic they are using or not. And frequently, a culture is not obtained, and the physician plays the odds based on what is known about resistant bacteria in his or her particular community or hospital.

Bacteria in our communities are also becoming more resistant. The latest example is staph (*Staphylococcus aureus*). Staph are bacteria that cause everything from minor skin infections like impetigo in children to minor abscesses to very serious skin infections (so called flesh eating infections) to bloodstream and heart infections which are fatal 30–40% of the time. We have had sequential epidemics of ever more antibiotic-resistant staph infections in our hospitals and communities since the 1950s.

When penicillin was first discovered, even before it was tested in humans, the first resistant bacterial strains were discovered. Like many antibiotics, penicillin is produced by microorganisms found in the soil. They produce antibiotics to help them compete with other organisms in their ecological niche. These organisms have, in turn, evolved ways to resist the chemical weapons of their competitors. So, that we could find bacteria resistant to penicillin even before we started to use it should not be so surprising. When penicillin was finally brought to the public marketplace after World War II, almost all strains of staph were still killed by the drug. By the 1950s, the majority of hospital strains of staph were resistant. By the 1970s both hospital and community strains were equally resistant. Luckily, by then, we had tetracycline, erythromycin and other antibiotics to use since penicillin was no longer effective.

Today, staph that are resistant to many of our most useful antibiotics (called MRSA) cause about 60–70% of staph infections in communities all over the US. The MRSA causing infections in our communities, unlike those in our hospitals, are usually still sensitive to a few of the older antibiotics like bactrim (which contains a sulfa drug) or sometimes tetracycline. But neither bactrim nor tetracycline, since they were approved many years ago, was carefully studied in the treatment of these kinds of staph infections. For these infections, there is only a single oral (a pill) antibiotic, linezolid (Zyvox), which has been well studied and been shown to be safe and effective. Even then, linezolid can be toxic if it is used for longer courses of therapy such as for serious bone infections. Because linezolid is so expensive, physicians still frequently use bactrim and tetracycline to treat resistant staph infections, even though we don't know how well they work. Also, among older folks, bactrim allergies are common and can result in serious reactions. Otherwise, the

only choice is to use intravenous antibiotics. The modern intravenous antibiotics have been much better studied so we are more comfortable with the fact that they will work and we know their toxicities very well. But, to get an IV antibiotic, you would either go to a hospital (bad idea if you can avoid it) or get your IV therapy at home. Our choices are limited. For the past 10 years I have been asking myself, what will happen if staph becomes resistant to the remaining few antibiotics that still work? Will we have something to use then? I'm not so sure . . .And in fact, MRSA have been creeping towards being more resistant to even our remaining IV antibiotics. This day may come sooner rather than later.

With no exceptions, like it or not, the antibiotics we have available to us today came to us fully or at least partly through the efforts of the pharmaceutical industry. The ability of the industry to continue to provide us with new and more active antibiotics is rapidly disappearing. Our ability to discover new antibiotics is decreasing because it is becoming harder and harder to identify non-toxic molecules that will kill bacteria. All the obvious antibiotics have apparently already been discovered. Everything that will come later will come harder.

In this background of growing resistance and more difficult science, the pharmaceutical industry continues to consolidate. By 2003, the industry had undergone a consolidation of more than 90% over the prior 20 years. Since then, Sanofi has merged with Aventis to form Sanofi Aventis, Pfizer has purchased Wyeth and Merck has purchased Schering-Plough. This will result in over a 95% consolidation during the past three decades. This consolidation results in fewer and fewer researchers working on new antibiotics.

Because, since the late 1990s, the pharmaceutical industry has been questioning the market value of new antibiotics, more and more companies have simply abandoned this field of research entirely. After all, if you are selling pharmaceuticals, would you rather sell a Z-pack of azithromycin (Zithromax) to be taken over 5 days or would you rather sell a Lipitor for high cholesterol that has to be taken daily forever? Of course, in my view, this is an oversimplification that has recently been proved wrong by linezolid. We will explore this in greater detail in a later chapter. Nevertheless, among the few large companies that are left, even fewer are actively looking for new antibiotics.

Contributing to the negative view of antibiotics by the pharmaceutical industry are the conscientious efforts by physicians to prevent resistance. Most physicians believe (rightly in my view) that antibiotic resistance is more likely to appear of the antibiotic is heavily used. If a new antibiotic comes out which is active against resistant bacteria, physicians tend to try and reserve it for use only when truly necessary. Don't get me wrong − I'm not saying this is a bad idea. While this may be good for public health, it is not good for the revenues of the pharmaceutical companies that want to sell the antibiotic.

Finally, there is the FDA and other regulatory agencies. The Food and Drug Administration is charged with ensuring the efficacy and safety of drugs allowed on the US market. In their good faith efforts to do their job, the FDA has led us to a situation where their new requirements for studying antibiotics in order to obtain approval will only further alienate the industry from antibiotic research. These tough

requirements may be based on good science, but they render the clinical trials at best impractical and at worst infeasible. Their trial requirements have essentially removed large portions of the antibiotic market from the US for the foreseeable future. As we will see later, introducing a new antibiotic for mild bacterial infections like sinusitis, bronchitis and ear infections to the US market has now become virtually impossible. Even for a more serious infection like pneumonia, the development of new antibiotics has become much more difficult and expensive if not impossible. There may be sound scientific reasons for questioning the benefit of antibiotics for some of these infections, but the industry just sees a black hole in their bottom line for antibiotics.

In the following chapters, I will explore the good and the bad about antibiotics. I will discuss the problem of bacterial resistance, how this happens and the bacterial threats we face today and those on the horizon. I will dissect the history and present state of both the pharmaceutical industry and the FDA in the realm of antibiotics. Finally, I will discuss potential solutions for the industry, the FDA, for researchers and for us as a society, which might allow us to continue to have antibiotics available for use when we need them most.

Chapter 2
The Miracle

The history of antibiotics goes back to mercury and bismuth, heavy metals which are toxic to people, but in correct doses, were more toxic to the organism that causes syphilis, *Treponema pallidum*. Mercury as a therapy for syphilis was first discussed back in the 1400s, but the heavy metals were not widely used until the end of the nineteenth century. Whether they were efficacious or not is not entirely clear since no systematic studies like those we use today were carried out in those times. But there is good reason to believe that this therapy worked at least to some extent. Of course, as all of us who like to eat fish know, mercury is also rather toxic to people.

Salvarsan, an arsenical compound, was discovered by Paul Ehrlich and his co-workers in 1908 and was marketed in 1910. The arsenicals were discovered based on their activity against parasitic microorganisms, but only were developed as antibiotics when they were active in a rabbit model of syphilis. Salvarsan was dubbed Ehrlich's magic bullet. He won the Nobel Prize for his discovery in 1908. Again, the kinds of clinical studies we are accustomed to today were not undertaken, but various testimonials from "miracle" cures were used to demonstrate the efficacy of Salvarsan. In retrospect, there are good reasons to believe that the drug had some efficacy in the treatment of human syphilis. The use of the drug was limited by its toxicity – it was based on arsenic after all.

These early efforts point out one of the great challenges of finding good antibiotics. We are looking for something that will kill the microorganism but that will leave its host (us) unharmed. We want a very specific toxin. This is not so easy. The later discoveries of sulfonamides and then penicillin and its relatives misled many into believing that finding such specific microbe killers that were perfectly safe for humans might be less difficult than it is.

The discovery of the sulfonamide antibiotics by Bayer in Germany in 1932 was the next great leap forward for antibiotics. The first such drug was called Prontosil. It was actually a prodrug because it relied on the human body to metabolize Prontosil into its active form, sulfanilamide. It was first synthesized by Bayer chemists Josef Klarer and Fritz Mietzsch. Prontosil was tested and found effective against some important bacterial infections in mice by Gerhard Domagk, who subsequently received the 1939 Nobel Prize in Medicine. Its utility was dramatized in an article in Time Magazine in 1936.

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> Last month Mrs. Franklin D. Roosevelt, who loves few things better than a big family feast, gave up Thanksgiving dinner at Hyde Park to rush to Boston where Son Franklin Jr. lay abed with what was described to the press as "sinus trouble." The young man did have infected sinuses, and he was in the capable, Republican hands of Dr. George Loring Tobey Jr., a fashionable and crackerjack Boston ear, nose & throat specialist. He also had a graver affliction, septic sore throat, and there was danger that the Streptococcus haemolyticus might get into his blood stream. Once there the germs might destroy the red cells in his blood. In such a situation, a rich and robust Harvard crewman is no safer from death than anybody else.
>
> Not until last week, when his mother and his fiancée, Ethel du Pont, went home, was Franklin Jr. out of danger and fit for Dr. Tobey to operate on his infected right antrum (in the cheek) and ethmoid sinuses (in the brow). Simultaneously, Dr. Tobey let it be known that his notable young patient had been pulled through his crisis by a notable new drug.
>
> When Franklin Roosevelt's throat grew swollen and raw and his temperature rose to a portentous degree. Dr. Tobey gave him hypodermic injections of Prontosil, made him swallow tablets of a modification named Prontylin. Under its influence, young Roosevelt rallied at once, thus providing an auspicious introduction for a product about which U. S. doctors and laymen have known little.
>
> The drug which cured young Roosevelt seems to be a specific cure for all streptococcic infections—septic sore throat, childbed fever, postabortal septicemia. It has helped to cure cases of peritonitis due to ruptured appendix, perforated stomach ulcer or gallbladder. It has been effective in postoperative wounds, endocarditis, suppurative mastoiditis, and tonsillitis. Some cases of erysipelas (also a streptococcic infection) have yielded to Prontosil medication. The drug also has ameliorated severe cases of carbuncles and cellulitis due to staphylococcus, a different kind of germ.

Figure 2.1 below shows the mortality rates at Cook County Hospital in Chicago from erysipelas, a serious skin infection caused by *Streptococcus pyogenes*, the same organism that causes strep throat. Clearly, for this infection, the use of sulfonamides saved lives. The same thing was shown for pneumonia as shown in the table from a 1939 article below.

Dagenan was a sulfonamide antibiotic. As you can see from Table 2.1, the mortality rate for treated patients ranges from 6 to 17.6% while for untreated controls it

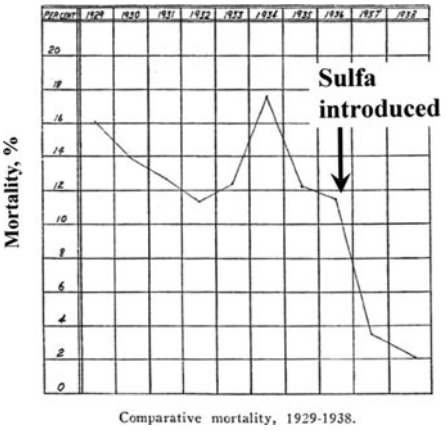

Fig. 2.1 Mortality rates of erysipelas at Cook County Hospital in Chicago, Illinois, from 1929 to 1938. Sulfonamides (sulfa) became generally available in 1936. From Spellberg et al., 2009 with permission

Table 2.1 Pneumonia and mortality 1938

Mortality			
Controls	Controls with positive blood culture	Dagenan treated	Dagenan treated with positive blood cultures
23%	50%	6%	17.60%

ranged from 23 to 50%. There is no doubt that in pneumonia, sulfonamides saved lives and did so in a dramatic way.

Penicillin had even more dramatic effects.

The first patients to be treated with penicillin were in England during 1940. The team of Florey, Chain and Heatley at Oxford University was producing the penicillin. There they had developed a kind of Rube Goldberg apparatus to purify the drug. Florey and Chain went on to win the Nobel Prize for their efforts to characterize, manufacture and test penicillin. There was just a tiny amount of drug such that, because the drug was excreted unchanged in the urine, the urine of the treated patients was collected and the penicillin repurified for use again. One patient, Mr. Alexander, was being slowly "eaten" with a mixed staph and strep infection. He had pus everywhere. One eye had to be removed. His shoulder and lung became infected. Sulfonamides were not helping. He agreed to receive penicillin. Within 24 h, there was dramatic improvement. His temperature returned to normal, his lesions improved and his appetite returned. Five days later, treatment was stopped because they were running out of penicillin and they had not yet had time to repurify the penicillin from the patient's urine. Of course, no one knew how long one should treat in any case. This is still a problem today I might add. Unfortunately, 10 days later, Mr. Alexander had a relapse of his lung infection and there was no more penicillin to be had. He died a month later.

In 18 months of testing in something like five or six patients, 4 million units of penicillin had been used. This would be roughly equivalent to one sixth of the minimum daily dose we would use for a single patient with pneumonia today.

The first American patient was treated at Yale in March of 1942. Mrs. Miller had staph infection of her bloodstream and was dying. One of the penicillin researchers was hospitalized nearby with a viral infection. Mrs. Miller's doctors asked him if he would be able to procur penicillin for Mrs. Miller. He did. From Merck. She lived. Her temperature went from 105.5°F before treatment to normal in less than 24 h.

My father was a physician who practiced internal medicine in Chicago his entire life. He didn't retire until he was 83 years old and was unable to walk independently anymore. He always told a fascinating story about my aunt who had juvenile onset diabetes. Diabetes, for reasons still not very clear, makes people more susceptible to infections. My Dad was doing his internship in New York City in 1944. My aunt developed a breast abscess with staph. The staph then went on to invade her bloodstream. She was septic, on the verge of death. In those days, the military had essentially the entire supply of penicillin (it did not become available to the public

until after the war in 1945), but my Dad knew that this was her only chance. He called the public health office in New York who put him in touch with the military from which he was able to procure a small supply of penicillin. He administered several hundred thousand units – a large dose at the time. Within 24 h my aunt was sitting up in bed eating and talking. Her fever was gone in a few days. Based on this experience and others, he always believed in the miracle of antibiotics.

In Table 2.2 we can see data from the pre-antibiotic years compiled by the Infectious Diseases Society of America. They compare controls where treatment might be expected to be ineffective with sulfonamide and penicillin treated patients with serious skin infections. Possibly because this group included patients with infections that are less serious than erysipelas, the cure rates with ineffective therapy are higher than we saw when we just looked at erysipelas earlier. Nevertheless, both antibiotics work and penicillin seems to work even better than sulfonamides.

Even today, most physicians will be able to relate a story something like my father's. Of course, most do not have to procure their supply of antibiotic from the military, but they will all be able to tell you about a patient on death's door who comes back from the brink after a few doses of an antibiotic.

Table 2.2 Treatment of erysipelas

Penicillin vs. erysipelas/cellulitis	Ineffective therapy	Sulfonamide	Penicillin
Patients cured (%)	1520/2294 (66)	1423/1573 (91)	196/200 (98)

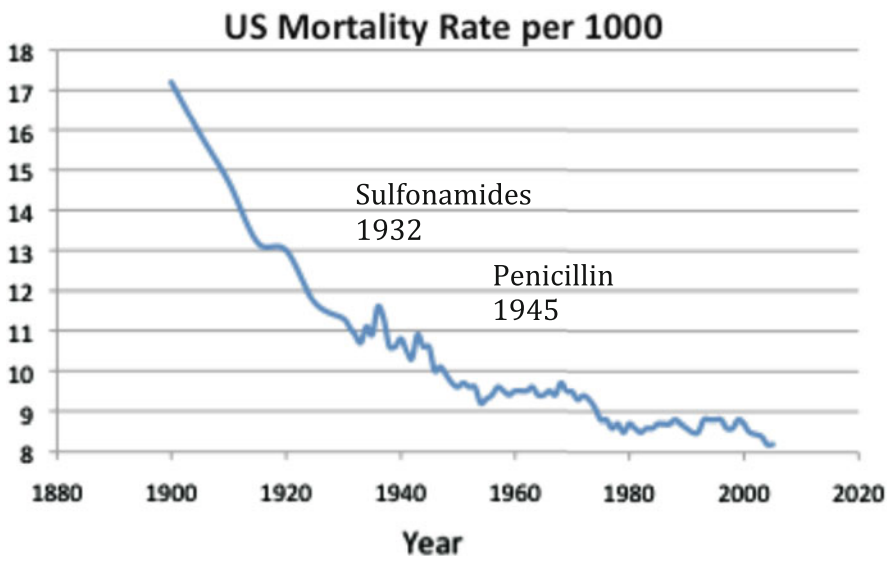

Fig. 2.2 US mortality rate over time