Working Paper 20-133

Case Histories of Transformational Advances

Cephalosporins – Fighting Hospital Infections

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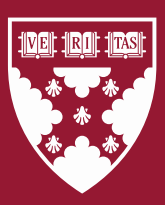

Harvard Business School

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Cephalosporins —Fighting Hospital Infections

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Abstract: This case history describes the development of three generations of cephalosporins – antibiotics that have significantly reduced hospital infections. Specifically, we chronicle how: 1) Early (pre-cephalosporin) antibiotics were developed in the first half of the 20th century. 2) Drug companies developed first-generation cephalosporins in the 1960s using foundational discoveries made by researchers in Italy and the UK in the 1940s and 1950s. 3) Continued modifications of cephalosporin molecules resulted in the second and third generations of the drugs in the 1970s and 1980s.

Note: Like the other histories in this series, this advance is included in a list compiled by Victor Fuchs and Harold Sox (2001) of technologies produced (or significantly advanced) between 1975 and 2000 that internists in the United States said had had a significant impact on patient care. The case histories focus on advances in the 20th century (i.e., before this millennium) in the United States, Europe, and Japan -- to the degree information was available to the researchers. Limitations of space and information severely limit coverage of developments in emerging economies.

Cephalosporins —Fighting Hospital Infections

Cephalosporins play an important 'behind the scenes' role in preventing and treating hospital infections. Three generations of these antibiotics helped cut the rate of infections in patients recovering from operations in hospitals by more than half between the 1960s and 1990s. In 1986, just six years after "third generation" cephalosporins were introduced, they accounted for 80% of the antibiotics administered in US hospitals and have remained the top antibiotic given to hospitalized patients, according to a 2010 survey. Some physicians call cephalosporins "wonder drugs" that, like penicillin, helped produce a "golden age" in antibiotic treatments; however, their story is not as well known.

This case history starts with an introductory overview of antibiotic development and its challenges. It then describes how:

- Early (pre-cephalosporin) antibiotics were developed in the first half of the 20th century.
- Drug companies developed first-generation cephalosporins in the 1960s using foundational discoveries made by researchers in Italy and the UK in the 1940s and 1950s.
- Continued modifications of cephalosporin molecules resulted in second and third generations of the drugs in the 1970s and 1980s.

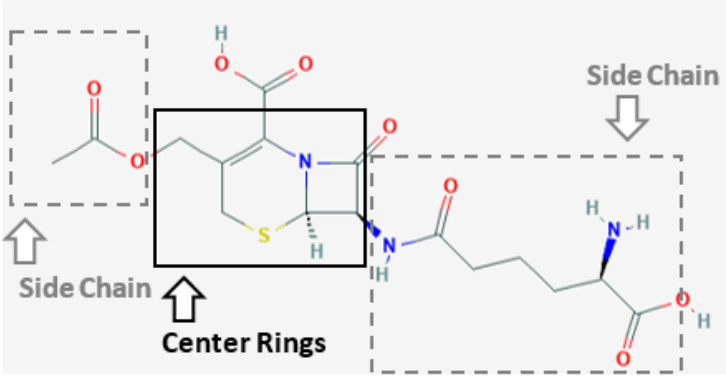
1. Overview of Antibiotic Development

Trillions of bacteria live in soil and water and on plants, animals, and humans, and many can benefit humans.[1] However, a few bacteria can cause deadly diseases, including typhoid, cholera, plague, pneumonia, and tuberculosis: in 1900, before the development of effective antibiotic treatments, such diseases were the top causes of death worldwide -- and of periodic pandemics. In hospitals, where many different disease-causing germs can flourish, weakened patients recovering from operations are vulnerable to multiple bacterial infections. In addition, bacterial infections spread through sexual contact can cause chronic, debilitating diseases, such as syphilis and gonorrhea.[2]

Antibiotic molecules used to treat bacterial infections usually have ring and side-chain structures.[3] (See **Figure 1**) Variations in the structures determine how the molecules attack bacteria and, thus, the diseases they can treat. For instance, penicillin predominantly attacks the cell walls of bacteria that do not have a protective outer membrane. Other antibiotics, notably ciprofloxacin,[4] predominantly attack bacteria with cell walls protected by an outer membrane.[5] However, those that attack bacteria with protective membranes are not necessarily effective against bacteria without protective membranes. "Broad spectrum" antibiotics—such as third generation cephalosporins--can attack bacteria with or without protective membranes.[6]

This case history does not present original research or new thesis. Instead, it summarizes historical developments and includes questions to stimulate reflection and discussion.

Figure 1 Molecular structure of cephalosporin



Source: US National Library of Medicine, National Center for Biotechnology Information, PubChem Database Cephalosporin C, CID=65536, https://pubchem.ncbi.nlm.nih.gov/compound/Cephalosporin-C, accessed December 11, 2019).

Development of antibiotic drugs, which typically takes about a decade and can cost more than half a billion dollars, begins with molecules extracted from a living organism or synthesized from chemicals. Nearly all antibiotics used today are derived from molecules discovered in the "golden age" of antibiotics, roughly from the 1940s through the 1970s. Since the 1980s, new antibiotics have been developed mainly by modifying the side chains of previously discovered molecules.[7]

Modifications seek to improve potency, overcome drug resistance, reduce side effects, and make doses easier to administer to patients. Promising modifications are tested in labs, then on animals, and eventually in human trials. The US Food & Drug Administration (FDA) regulates the design of the trials and evaluates the results to decide whether and for what diseases (or "indications") new molecules can be marketed to treat. Concern about bacteria developing antibiotic resistance is believed to make the FDA particularly cautious in approving the marketing of new antibiotics.[8]

The development process is both economically and technologically risky. Bacteria can acquire resistance to new antibiotics before companies have recouped their investments.[9] Patents cover specific molecular structures or production processes. However, they provide limited protection: competitors can easily invent around molecules, and some countries do not recognize process patents.[10]

2. Early antibiotics (before cephalosporins)

Synthesis and Screening. German physician Paul Ehrlich collaborated with chemists and bacteriologists to synthesize the first widely used antibiotic in 1909. Ehrlich had studied dyes synthesized in the nineteenth century by German chemical companies and found that they selectively stained only some microbes. The finding led him to believe that a synthesized drug might work like a "magic bullet" that killed disease-causing germs without harming healthy cells. In 1904, he began to systematically search for a drug effective against syphilis, which until then had to be treated with mercury salts that caused severe side effects. However, he did not start with dyes. Instead, he synthesized and tested variants of an arsenic-based compound that veterinarians gave to animals but was toxic to humans."[11]

Ehrlich's team synthesized and screened hundreds of variants. The 606th compound they tested cured syphilis-infected rabbits, and subsequent trials suggested it could treat syphilis in humans. In 1910, Ehrlich collaborated with the German chemical company Hoechst to introduce the compound, which they first called "606,"[12] as "Salvarsan." By the 1930s, it was widely used to treat syphilis in Europe and the United States. However, Salvarsan could not effectively treat other bacterial infections. Additionally, it needed to be packaged in sealed vials with nitrogen gas.[13]

Pharmaceutical companies followed Ehrlich's method of screening numerous synthesized compounds as they searched for new antibiotics. Notably, the German pharmaceutical company Bayer used the process to develop the first of the so-called "sulfa drugs," known as "Prontosil." Introduced in 1935, Prontosil, which did not need special packaging, was used for "strep" infections, pneumonia, meningitis, and uterine infections. However, sulfa drugs had limited effectiveness, and patients sometimes suffered serious side effects and allergic reactions. Sulfa drugs' reputation also suffered in 1937, when over one hundred people in the US died after taking 'Elixir Sulfanilamide,' a sulfa drug dissolved in a then-common but highly toxic solvent.[14] (Sulfa drugs are still used to treat urinary tract infections today, however.)[15]

Medicine from a Mold. Penicillin—extracted from a mold (a multicellular fungus) rather than synthesized—followed the chemically synthesized antibiotics. Healers from antiquity had noted the antibacterial effects of molds, but their medicinal properties had not been systematically researched. In 1928, Scottish physician and microbiologist Alexander Fleming, who researched, taught, and practiced at St. Mary's Hospital Medical School (London), noticed a mold killed bacteria he had cultured in a lab dish. Fleming distilled a crude extract from his mold and found it killed the bacteria that caused influenza, diphtheria, and pneumonia. He then tried to enlist chemists to purify the antibacterial substance further, which researchers would later identify and name 'penicillin.' But at the time, Fleming failed to generate interest and discontinued his research.[16]

About ten years later, Oxford University biochemist Ernst Chain and pharmacologist Howard Florey revived penicillin research. In 1940, they described a process to purify penicillin and reported that the purified substance attacked many disease-causing bacteria. In 1941, the Oxford researchers tested the penicillin they had purified on a local policeman who had developed a serious wound infection from a scratch by a rose thorn. The treatment improved the policeman's condition, but after Chain and Florey's supply of penicillin ran out, the wound infection spread, and he eventually died. The results, however, encouraged Florey and Chain to continue their research. In 1942, Florey and his Oxford colleague, biochemist Edward Abraham, determined the chemical composition of penicillin. Shortly after, Oxford chemist Dorothy Crowfoot Hodgkin used X-ray crystallography to photograph the ring and side chain structure of the molecules.[17]

Meanwhile, the outbreak of the Second World War had created an urgent need to treat soldiers with wound and pneumonia infections. Initially, military first aid kits contained powdered sulfa drugs, which soldiers were told to sprinkle on wounds to prevent bacterial infections. However, as mentioned, sulfa drugs had limited effectiveness. Penicillin offered the promise of greater effectiveness; however, not much penicillin could be extracted from the then-available molds, and the existing extraction process introduced contaminants.[18]

Florey first tried to persuade British pharmaceutical companies to improve the production process and make penicillin on a large scale. But, the companies already had commitments to supply other drugs to the military, and the bombing of their facilities had severely strained their research and production capabilities. Then, in July 1941, Florey traveled to the United States, which was half a year away from entering the war, to solicit support. A former Oxford classmate introduced Florey to researchers at the US Department of Agriculture's Northern Regional Research Laboratory, who agreed to help. Within a year, the American researchers had identified a fast-growing mold from which more penicillin molecules could be quickly extracted.[19]

Scaling Up. The high-yielding mold and military demand after the US entered the war spurred rapid improvements in quantity and purity. In 1943, American drug companies produced only 29 pounds of penicillin; in 1944, they made about 3,000 pounds; and in 1945, they produced about 14,000 pounds, exceeding military needs. Concurrently, the improved filtration of contaminants changed the color of penicillin powder from brown to yellow to white.[20]

(The War also left a regulatory mark. A War Production Board had required drug companies to test each batch of penicillin they produced. In 1945, the US Congress authorized the FDA to also require such testing for penicillin produced for civilian use. The FDA did not require testing of individual batches for other drugs. The FDA eventually stopped requiring testing for antibiotics in the 1980s.)[21]

Soil Searching. Penicillin's success prompted a hunt for other antibiotics. In 1943, Rutgers researchers led by Selman Waksman (awarded a Nobel Prize in 1952) extracted streptomycin from ("good") bacteria found in New Jersey farm soil. Other researchers also searched for antibiotics in soil, and in 1945, Lederle Laboratories researchers extracted chlortetracycline from bacteria found in an experimental agricultural plot at the University of Missouri. Streptomycin and chlortetracycline had different structures (with different center rings) than penicillin, and they attacked a wider range of bacteria. However, bacteria quickly developed resistance to chlortetracycline, and streptomycin had serious side effects, though it continues to be used today.[22]

Questions (for reflection and discussion):

Before reading any further, please write down (in less than ten words) what you found most striking about the early development of antibiotics.

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And think about the differences in the approaches and contributions of different players in this period.

3. First-Generation Cephalosporins (mid-1940s through the 1960s)

Foundational Research. ***A fungus found in sewage water in 1945, rather than soil, provided an unexpected break***through. Giuseppe Brotzu, a pharmacologist who taught at the University of Cagliari on the Italian island of Sardinia, had mapped outbreaks of typhoid fever in Cagliari. From the pattern of outbreaks, he inferred that a mold in sewage might be attacking bacteria that caused typhoid. He then tested the sewage where outbreaks were rare and discovered a fungus, which he identified as Cephalosporium acremonium.[23] Brotzu conducted lab tests on the fungus and tested it on human volunteers; the tests suggested that it might cure several diseases that penicillin could not, including cholera and bubonic plague.[24]

Brotzu, who lacked the means to continue research, contacted a British medical officer he had met during the recently ended war. The officer introduced him to Oxford scientists who had worked on penicillin, and, in 1948, Brotzu sent them samples of the sewer-dwelling Cephalosporium fungus. A team led by biochemist Edward Abraham extracted two molecules ("cephalosporin P" and "cephalosporin N") that attacked many of the same bacteria penicillin did.[25]

Abraham's team then extracted a third molecule—" cephalosporin C"—that attacked an even wider range of disease-causing bacteria. It also showed evidence of the ability to attack penicillin-resistant bacteria, which had become a large problem in hospitals.[26]

In 1957, a team at Britain's Antibiotics Research Station found a mutant strain of the Cephalosporium fungus that yielded more cephalosporin C molecules. More plentiful molecules helped Abraham and his Oxford colleagues determine cephalosporin C's structure: two adjacent rings with a chain on each side. (As shown in Section 1, **Figure 1**)

Licensing. Before the Oxford researchers had discovered the ring-and-chain structure, Abraham had, in 1953, contacted the British National Research Development Corporation (NRDC). The NRDC was a government agency established in 1948 to promote the commercialization of British research. Famously, Chain and Florey had chosen not to patent their penicillin discoveries and had made their work freely available.[27]

The NRDC patented and then licensed the Oxford researchers' cephalosporin molecules, first to Glaxo Laboratories in London, England, and, shortly after that, to Eli Lilly and Company in Indianapolis, Indiana, in the United States. Both companies had been producing pharmaceuticals since the nineteenth century and were leading producers of penicillin: Glaxo produced approximately eighty percent of the United Kingdom's penicillin at the time, and Lilly was one of the top seven penicillin producers in the United States (and had helped develop the mass production process for the drug). [28]

Drug Development. Lilly researchers modified one of the cephalosporin molecule's side chains using techniques developed in the 1950s to modify streptomycin, chlortetracycline, and penicillin. Lilly researchers also developed a way to extract eighty times the number of molecules from the mutant Cephalosporium fungus, enabling large-scale production. In 1962, the FDA gained authority to require clinical trials to demonstrate the safety and effectiveness of new drugs before approving the drugs for marketing; Lilly passed the trials by showing that their drug cured infections in patients that other antibiotics had failed to cure. The company then marketed the drug under as "Keflin" in 1964.[29]

The terms of the NRDC license required Lilly to share its ongoing findings with other licensees, which enabled Glaxo to introduce a more potent molecule just months after Lilly's Kelfin debuted. Meanwhile, the NRDC continued to issue licenses to and share research with companies in Europe, the US, and Japan. In the next ten years, four other longtime pharmaceutical makers--one in the United Kingdom, two in the United States, and one in Japan--introduced cephalosporin drugs with slightly different molecular structures. These drugs were formulated to have fewer side effects or to be taken orally; most previous antibiotics, including penicillin, streptomycin, chlortetracycline, and the first two cephalosporins had to be injected or administered intravenously.[30] (See **Exhibit 1)**

Sales and Marketing. Worldwide sales of these "first-generation" cephalosporin drugs reached $640 million in 1974 (about $3.3 billion in 2019 dollars). Drug companies promoted adoption through heavy marketing, especially to hospitals. Marketing efforts highlighted clinical trials showing that cephalosporins caused fewer side effects than penicillin and recommendations from medical researchers urging the use of the drugs on patients with penicillin allergies.[31]

Sales in Japan were also helped by the government's reimbursement rules. A 1961 law required companies to sell all drugs directly to physicians rather than to pharmacies (or other merchants). The physicians then dispensed the drugs to patients at government-regulated prices. Regulated prices were usually lowered on old drugs as new drugs became available, encouraging physicians to favor the new drugs. Therefore, when a longtime Japanese pharmaceutical maker, Fujisawa, introduced "cefazolin" in 1971, it quickly became a bestseller.[32]

Questions (for reflection and discussion):

Write down (in less than ten words) which decision, event, or condition you found the most surprising or significant in developing "first-generation" cephalosporin drugs.

- _____

4. Second- and Third Generation cephalosporins (1970s through 1990s)

Improved Efficacy. The first-generation drugs had predominantly attacked bacteria without a protective outer membrane; they were also excreted before the body fully absorbed them. Therefore, researchers continued to search for ways to modify the side chains of cephalosporin molecules to improve effectiveness and increase absorption. They improved effectiveness by modifying both side chains; earlier, researchers had changed one or the other. However, the "second-generation" drugs were unable to improve absorbability.[33] (See Exhibit 2)

Markets and Competitors. Improved efficacy helped cephalosporin sales grow worldwide from $640 million in the early 1970s to over $1 billion in the early 1980s (or over $5.2 billion in 2019 dollars).[34]

Demand from hospitals was particularly strong. One reason was that second-generation drugs could be used to treat bacteria that had grown resistant to previous antibiotics. Additionally, physicians put patients undergoing surgery on intravenously administered cephalosporins to prevent infection. (However, this preventative use of cephalosporins was controversial because cephalosporin producers had sponsored some of the studies that encouraged it.)[35]

Lilly increased its dominance in the 1970s and, by 1982, had secured a seventy-five percent share of the US market. The company offered five cephalosporin drugs (targeting different infections and conditions), whereas almost all its competitors sold just one. Lilly also marketed other top-selling antibiotics it had developed, such as vancomycin and erythromycin. One competitor, Smith Kline, had successfully challenged the legality of Lilly's "bundled" discounting of its five drugs to hospitals in the mid-1970s. However, Smith Kline's victory in the case, which went all the way to the US Supreme Court, could not dislodge Lilly from its top position.[36]

Third-generation Drugs. Refined side-chain-altering techniques, like those used for second-generation cephalosporins, improved treatments: patients could take smaller, less frequent doses and better tolerate treatment. [37] Importantly, this "third generation," introduced in the late 1970s and 1980s, was "broad spectrum," meaning that the drugs attacked bacteria with or without protective membranes (whereas second-generation cephalosporins mainly targeted bacteria with protective membranes).[38]

Broad-spectrum cephalosporins were valuable in treating infections contracted by patients after having appendicitis, cesarean sections, cancer treatments, and spine and brain infections. The new cephalosporins could also treat bacteria resistant to penicillin and first-generation cephalosporins.[39]

Japanese companies led the development of the third generation. Following 1967 legislation that had lowered the threshold of originality required for new patents, Japanese pharmaceutical companies invested heavily in research; they designed "super germs" to help identify the most potent antibiotic molecules in tests, developed a new antibiotic group (fluoroquinolones), and developed seven of the ten third-generation cephalosporin drugs introduced between 1978 and 1987.[40] (See **Exhibit 3)**

After the introduction of third-generation drugs, worldwide sales of cephalosporin drugs increased more than 8-fold from 1982 to 1992, reaching $8.55 billion (or about $44.6 billion in 2019 dollars). Sales in the US and Japan, the two largest markets, amounted to about $3 billion each. After a brief fall in 1995, sales rose even higher in 1996 to about $10 billion (or about $52.2 billion in 2019 dollars).[41]

Observers had hoped that the less frequent dosing, broad spectrum of activity, and greater effectiveness of third generation cephalosporins would lead to cost savings for hospitals. However, the prices of some third generation cephalosporins were three times higher than those of second-generation cephalosporins and fifteen times higher than those of other antibiotics. Hospitals were apparently willing to pay more to treat virulent bacteria that had developed resistance to previous antibiotics. Some physicians, however, questioned "whether such excessive antimicrobial 'firepower' [was] really necessary,"[42] and some studies suggested that third generation cephalosporins were cost-effective treatments only for some diseases.[43]

The Situation in 2000.

Some drug companies were developing cephalosporins to treat specific antibiotic-resistant bacteria. Notably, Takeda, based in Japan, and Hoffmann-La Roche, based in Switzerland, had targeted a virulent

strain of "staph" bacteria. (The strain had developed resistance to other antibiotics and proliferated in hospitals).[44] Overall, however, antibiotic research had declined in the 1990s along with approvals of new drugs: only seventeen new antibiotics (including cephalosporins) were approved for sale in the US in the 1990s, down from about thirty in the 1980s. And in the late 1990s, the FDA adopted even stricter rules for antibiotics as part of a broader revision of clinical trial guidelines in the late 1990s.[45]

By the end of the decade, Aventis, Bristol-Myers Squibb, Eli Lilly, Glaxo SmithKline, Proctor and Gamble, Roche, and Wyeth were severely reducing, eliminating, or spinning off their antibacterial research, whereas generic producers selling older cephalosporins whose patents had expired were expanding. Similarly, generic cephalosporins sold in high-population, low-income countries had become significant by volume (though not by revenue).[46]

Questions (for reflection and discussion):

As Eli Lilly, would you continue withdrawing from the antibiotic market or attempt to take a different approach (e.g., to development or commercialization)?

• Continue withdrawing from antibiotics /Take a different Approach.

Exhibit 1 First-Generation Cephalosporin Molecules

Generation	Year	Antibiotic Molecule Name	Company (Origin)	Clinical Advantages
First	1964	Cephalothin	Eli Lilly (USA)	Attacks bacteria without a protective membrane, such as "staph" and "strep" bacteria that cannot be treated with penicillin, as well as gastrointestinal, urinary tract, respiratory, blood, and skin infections (like all first-generation cephalosporins); can be taken by injection
First	1964	Cephaloridine	Glaxo-Wellcome (UK)	More potent than Cephalothin
First	1965	Cephaloglycin	Eli Lilly (USA)	More potent than Cephalothin; can be taken orally
First	1967	Cephalexin	Eli Lilly (USA)	More potent than Cephalothin; can be taken orally; fewer side effects than previous cephalosporins
First	1970	Cephapirin	Bristol Labs (UK)	Attacks bacteria without a protective membrane (as did previous cephalosporins) and a few types of bacteria with protective membranes
First	1971	Cephadrine	Squibb (USA)	Can be taken as a tablet or syrup
First	1971	Cefazolin	Fujisawa Pharmaceutical (Japan)/ Smith Kline Beecham (USA)	Can be taken by injection or intravenously; has fewer side effects than previous cephalosporins
First	1974	Cefadroxil	Bristol Myers (USA)	Can be taken as a capsule, tablet, or liquid; has fewer side effects than previous cephalosporins

Source: Compiled from Bran JL, Levison ME, Kaye D. "Clinical and in vitro evaluation of cephapirin, a new cephalosporin antibiotic. Antimicrob Agents Chemother." 1972 Jan;1(1):35-40. doi: 10.1128/aac.1.1.35. PMID: 4596741; PMCID: PMC444162; S. Shadomy, C. G. Mayhall, Elaine Apollo, In Vitro Activity of Five Oral Cephalosporins against Anaerobic Pathogenic Bacteria, The Journal of Infectious Diseases, Volume 136, Issue 5, November 1977, Pages 697–700, https://doi.org/10.1093/infdis/136.5.697; Annetine C. Gelijns and Ethan A. Halm. "The Changing Economics of Medical Technology," 1991. National Academy Press, Washington, DC. 224 pages. ISBN: 0-309-04491-X. Bulletin of Science, Technology & Society. 1993;13(3):178-178. doi:10.1177/027046769301300382; Kumazawa J, Yagisawa M. "The history of antibiotics: the Japanese story." J Infect Chemother. 2002 Jun;8(2):125-33. doi: 10.1007/s101560200022. PMID: 12111564; Thomas J. Dougherty, Michael J. Pucci "Antibiotic Discovery and Development," Springer US, 2012; and Drugs.com, accessed November 2020.

Exhibit 2 Second-Generation Cephalosporin Molecules

Generation	Year	Antibiotic Molecule Name	Company (Origin)	Clinical Advantages
Second	1973	Cefamandole	Eli Lilly (USA)	Attack hard-to-treat bacteria with protective outer membranes, such as gonorrhea, some influenzas, and *E. coli* (like all second-generation cephalosporins); attacks some bacteria that had developed resistance to first-generation cephalosporins; taken by injection or intravenously
Second	1976	Cefaclore	Eli Lilly (USA)	Taken orally
Second	1978	Ceforanide	Bristol Myers (USA)	More potent; taken by injection or intravenously
Second	1983	Cefprozil	Bristol-Banyu (Japan)/Bristol Labs (UK)	Taken in tablet form; also attacks hard-to-treat bacteria in bronchial tubes, sinuses, ears, throat, tonsils, and skin
Second	1984	Cefuroxime	Glaxo Wellcome (UK)	More potent; taken in tablet or liquid form; also attacks hard-to-treat bacteria in bronchial tubes, sinuses, ears, throat, tonsils, and skin
Second	1987	Cefuzonam	Lederle Japan (Japan)	Attacks hard-to-treat bacteria with protective outer membranes likely to cause urinary tract infections in hospitals

Source: Compiled from Bran JL, Levison ME, Kaye D. "Clinical and in vitro evaluation of cephapirin, a new cephalosporin antibiotic. Antimicrob Agents Chemother." 1972 Jan;1(1):35-40. doi: 10.1128/aac.1.1.35. PMID: 4596741; PMCID: PMC444162; S. Shadomy, C. G. Mayhall, Elaine Apollo, In Vitro Activity of Five Oral Cephalosporins against Anaerobic Pathogenic Bacteria, The Journal of Infectious Diseases, Volume 136, Issue 5, November 1977, Pages 697–700, https://doi.org/10.1093/infdis/136.5.697; Annetine C. Gelijns and Ethan A. Halm. "The Changing Economics of Medical Technology," 1991. National Academy Press, Washington, DC. 224 pages. ISBN: 0-309-04491-X. Bulletin of Science, Technology & Society. 1993;13(3):178-178. doi:10.1177/027046769301300382; Kumazawa J, Yagisawa M. "The history of antibiotics: the Japanese story." J Infect Chemother. 2002 Jun;8(2):125-33. doi: 10.1007/s101560200022. PMID: 12111564; Thomas J. Dougherty, Michael J. Pucci "Antibiotic Discovery and Development," Springer US, 2012; and Drugs.com, accessed November 2020.

Exhibit 3 Third- and Fourth-Generation Cephalosporin Molecules

Generation	Year	Antibiotic Molecule Name	Company (Origin)	Clinical Advantages
Third	1978	Cefoparazone	Toyama Chemical (Japan)/Lederle (UK)	Attack many different bacteria (those with protective outer membranes and those without); effective against hard-to-treat bacteria that automatically expel foreign molecules; builds up less in kidneys; fewer side effects; taken by injection or intravenously
Third	1979	Cefotiam	Takeda Chemical (Japan)/Abbott (USA)	More potent
Third	1979	Ceftizozime	Fujisawa Pharmaceutical (Japan)	More potent as a prophylactic
Third	1979	Cefotaxime	Hoechst-Roussel (Germany)	More potent as a prophylactic
Third	1979	Cefixime	Fujisawa Pharmaceutical (Japan)/Lederle (UK)	Can be taken orally, in tablet or sachet form
Third	1980	Ceftazidime	Glaxo-Wellcome (UK)	Can be used to treat central nervous system infections
Third	1981	Ceftriaxone	Hoffmann-La Roche (Switzerland)	More potent
Fourth	1983	Cefepime	Bristol-Banyu (Japan)/Squibb (USA)	More rapidly attacks bacteria (those with protective outer membranes and those without), as well as hard-to-treat bacteria that automatically expel foreign molecules; effective against bacteria that have developed resistance to other cephalosporins
Third	1984	Cefpodoxime	Sankyo (Japan)/Pharmacia & Upjohn (Sweden/USA)	Can be taken orally; effective against bacteria that have developed resistance to other cephalosporins
Third	1985	Ceftibuten	Shionogi (Japan)/Schering (Germany)	More potent; builds up less in kidneys
Third	1987	Cefdinir	Fujisawa Pharmaceutical (Japan)/Abbott (USA)	More potent, especially against resistant staph bacteria
Fourth	1989	Cefpirome	Hoechst-Roussel (Germany)	More potent; attacks bacteria faster

Source: Compiled from Bran JL, Levison ME, Kaye D. "Clinical and in vitro evaluation of cephapirin, a new cephalosporin antibiotic. Antimicrob Agents Chemother." 1972 Jan;1(1):35-40. doi: 10.1128/aac.1.1.35. PMID: 4596741; PMCID: PMC444162; S. Shadomy, C. G. Mayhall, Elaine Apollo, In Vitro Activity of Five Oral Cephalosporins against Anaerobic Pathogenic Bacteria, The Journal of Infectious Diseases, Volume 136, Issue 5, November 1977, Pages 697–700, https://doi.org/10.1093/infdis/136.5.697; Annetine C. Gelijns and Ethan A. Halm. "The Changing Economics of Medical Technology," 1991. National Academy Press, Washington, DC. 224 pages. ISBN: 0-309-04491-X. Bulletin of Science, Technology & Society. 1993;13(3):178-178. doi:10.1177/027046769301300382; Kumazawa J, Yagisawa M. "The history of antibiotics: the Japanese story." J Infect Chemother. 2002 Jun;8(2):125-33. doi: 10.1007/s101560200022. PMID: 12111564; Thomas J. Dougherty, Michael J. Pucci "Antibiotic Discovery and Development," Springer US, 2012; and Drugs.com, accessed November 2020.

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Endnotes

[1] As described in the Note on Fecal Transplants bacteria in the gut maintain good health; others as we will see in this Note can yield molecules that can be used to fight disease.

[2] Infectious diseases are less of a threat than in the past; nevertheless, they killed six million people worldwide in 2016—about two thirds the number of cancer deaths and one third the number of deaths from heart attacks and stroke. David Greenwood, *Antimicrobial Drugs: Chronicle of a Twentieth Century Medical Triumph* (Oxford ; New York: Oxford University Press, 2008); Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*, 1st Edition. (Springer Verlag, 2012); Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; Martin J. Blaser, "The Past and Future Biology of the Human Microbiome in an Age of Extinctions," *Cell* 172, no. 6 (March 8, 2018): 1173–77, https://doi.org/10.1016/j.cell.2018.02.040; "The Top 10 Causes of Death," accessed August 19, 2019, https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death; "WHO | Fact Sheets: Infectious Diseases," WHO, accessed August 19, 2019, http://www.who.int/topics/infectious_diseases/factsheets/en/; "Introduction to Infectious Diseases," Baylor College of Medicine, accessed August 19, 2019, https://www.bcm.edu/departments/molecular-virology-and-microbiology/emerging-infections-and-biodefense/introduction-to-infectious-diseases; "Bacterial Infections 101: Types, Symptoms, and Treatments," OnHealth, accessed August 19, 2019, https://www.onhealth.com/content/1/bacterial_infections; R. M. Krause, "Syphilis during 1900-1910: Similarities to Present-Day AIDS," *Allergy Proceedings: The Official Journal of Regional and State Allergy Societies* 12, no. 2 (April 1991): 127–32; "CDC Fact Sheet: Antibiotic Treatment of Gonorrhea," 2011, 3.

[3] "Generations" of antibiotics vary depending on the composition of the side chains. Greenwood, *Antimicrobial Drugs*; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; "Bacterial Infections 101." Penicillin and cephalosporin have some molecular structures in common, making them more closely related than other antibiotics. They are sometimes referred to as belonging to the large "Beta lactams" family or class.

[4] Ciprofloxacin is considered "broad spectrum" but is effective against many gram-negative bacteria (with a protective outer membrane) and only a few gram-positive bacteria (without a protective membrane).

[5] Bacteria that lack a protective outer membrane are known as "gram positive" bacteria. Bacteria with a protective outer membrane are known as "gram negative" bacteria.

[6] Greenwood, *Antimicrobial Drugs*; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; "Bacterial Infections 101"; "Third-generation antibiotics enter the fray." *Chemical Week*. August 19, 1981.

[7] Rustam I. Aminov, "A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future," *Frontiers in Microbiology* 1 (December 8, 2010), https://doi.org/10.3389/fmicb.2010.00134. "SECURING NEW DRUGS FOR FUTURE GENERATIONS FINAL WEB_0.Pdf." Accessed December 13, 2019. https://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf. "Modelling the Antibiotic Development Process.Pdf." Accessed December 13, 2019. https://amr-review.org/sites/default/files/Modelling%20the%20antibiotic%20development%20process.pdf.

[8] Basil Achilladelis, "The Dynamics of Technological Innovation: The Sector of Antibacterial Medicines," *Research Policy* 22, no. 4 (August 1, 1993): 279–308, https://doi.org/10.1016/0048-7333(93)90001-X; Basil Achilladelis and Nicholas Antonakis, "The Dynamics of Technological Innovation: The Case of the Pharmaceutical Industry," *Research Policy* 30, no. 4 (April 1, 2001): 535–88, https://doi.org/10.1016/S0048-7333(00)00093-7; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; Peter M. Wright, Ian B. Seiple, and Andrew G. Myers, "The Evolving Role of Chemical Synthesis in Antibacterial Drug Discovery," *Angewandte Chemie (International Ed. in English)* 53, no. 34 (August 18, 2014): 8840–69, https://doi.org/10.1002/anie.201310843.

[9] Bacteria evolve extremely rapidly--some reproduce in just twenty minutes. The rapid rate of reproduction increases the chances that a mutation will occur that helps the bacteria develop resistance. "Bacterial Infections 101"; "Understanding Genetics," accessed August 19, 2019, https://genetics.thetech.org/ask/ask202.

[10] Meng Zhang et al., "Research and Development of Antibiotics: Insights from Patents and Citation Network," *Expert Opinion on Therapeutic Patents* 26, no. 5 (May 2016): 617–27, https://doi.org/10.1517/13543776.2016.1167877; United States. Congress. Office of

Technology Assessment, *Impacts of Antibiotic-Resistant Bacteria* (Washington, DC: Office of Technology Assessment, Congress of the US: For sale by the USGPO, Suptof Docs, 1995); Nancy Gallini, "Do Patents Work? Thickets, Trolls and Antibiotic Resistance," *Canadian Journal of Economics/Revue Canadienne d'économique* 50, no. 4 (2017): 893–926, https://doi.org/10.1111/caje.12312; Martin L Katz et al., "Where Have All the Antibiotic Patents Gone?," *Nature Biotechnology* 24, no. 12 (December 2006): 1529–31, https://doi.org/10.1038/nbt1206-1529; Ramanan Laxminarayan, "How Broad Should the Scope of Antibiotics Patents Be?," *American Journal of Agricultural Economics* 84, no. 5 (2002): 1287–92; Jessica P. Schulman, "Patents and Public Health: The Problems with Using Patent Law Proposals to Combat Antibiotic Resistance," 2014.

[11] Aminov, "A Brief History of the Antibiotic Era."

[12] They had also given the compound the name "arsphenamine."

[13] Up until the nineteenth century, most medicines had a botanical source, however, many of these sources were scarce. In the nineteenth-century, chemists sought to surpass the effectiveness of herbs and medicinal plants with drugs made from widely-available lab chemicals. In the testing phase, Ehrlich and his team produced and dispensed 65,000 free samples to syphilis patients at several German university hospitals. Ehrlich studied the human body's immune system, which he understood to form antitoxins to fight the toxins that cause disease. He then developed a theory that "magic bullet" drugs could like the body's antitoxins in targeting toxic causes of disease (like bacteria), thereby helping the body cure itself. Fèlix Bosch and Laia Rosich, "The Contributions of Paul Ehrlich to Pharmacology: A Tribute on the Occasion of the Centenary of His Nobel Prize," *Pharmacology* 82, no. 3 (2008): 171–79, https://doi.org/10.1159/000149583; Anna Piro et al., "Paul Ehrlich: The Nobel Prize in Physiology or Medicine 1908," *International Reviews of Immunology* 27, no. 1–2 (April 2008): 1–17, https://doi.org/10.1080/08830180701848995; Christoph Gradmann, "Magic Bullets and Moving Targets: Antibiotic Resistance and Experimental Chemotherapy, 1900-1940," *Dynamis* 31, no. 2 (2011): 305–21, https://doi.org/10.4321/S0211-95362011000200003; Wright, Seiple, and Myers, "The Evolving Role of Chemical Synthesis in Antibacterial Drug Discovery"; Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; RUDOLPH H. Kampmeier, "Introduction of Salvarsan," *Sexually Transmitted Diseases* 4, no. 2 (June 1977): 66–68; Wilhelm Wechselmann, *The Treatment of Syphilis with Salvarsan*, Open Collections Program at Harvard University. Contagion (New York: Rebman, 1911), http://nrs.harvard.edu/urn-3:HMS.COUNT:1074952; "The Nobel Prize in Physiology or Medicine 1908," NobelPrize.org, accessed August 20, 2019, https://www.nobelprize.org/prizes/medicine/1908/ehrlich/biographical/; Steven Riethmiller, "From Atoxyl to Salvarsan: Searching for the Magic Bullet," *Chemotherapy* 51, no. 5 (2005): 234–42, https://doi.org/10.1159/000087453; Amanda Yarnell, "Salvarsan: Purpose Antisyphilitic." *Chemical & Engineering News.* 83: 25 (June 20, 2005); Rustam I. Aminov, "A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the Future," *Frontiers in Microbiology* 1 (December 8, 2010), https://doi.org/10.3389/fmicb.2010.00134.

[14] The tragedy prompted the passage of the 1938 U.S. Food, Drug, and Cosmetic Act, which authorized the Food and Drug Administration to require safety testing of drugs before marketing.

[15] Aminov. "Vital Signs: Improving Antibiotic Use Among Hospitalized Patients." John E. Lesch, *The First Miracle Drugs : How the Sulfa Drugs Transformed Medicine* (Oxford: Oxford University Press, 2007), http://ezp-prod1.hul.harvard.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=nlebk&AN=167671&site=ehost-live&scope=site; William Stork, "PRONTOSIL," *Chemical & Engineering News* 83, no. 25 (2005): 102, https://doi.org/10.1021/cen-v083n025.p102; "Prontosil," News, Nature, accessed December 16, 2019, https://doi.org/10.1038/142533a0; Basil Achilladelis, "The Dynamics of Technological Innovation: The Sector of Antibacterial Medicines," *Research Policy* 22, no. 4 (August 1, 1993): 279–308, https://doi.org/10.1016/0048-7333(93)90001-X.

[16] Alexander Fleming, "On the Specific Antibacterial Properties of Penicillin and Potassium Tellurite. Incorporating a Method of Demonstrating Some Bacterial Antagonisms," *The Journal of Pathology and Bacteriology* 35, no. 6 (1932): 831–42, https://doi.org/10.1002/path.1700350603; Alexander Fleming, "On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of B. Influenzae," *Reviews of Infectious Diseases* 2, no. 1 (1980): 129–39; Fleming A, "On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of '"B. Influenzæ"'.," *Br J Exp Pathol* 10, no. 31 (1929): 226–36; "The Nobel Prize in Physiology or Medicine 1945," NobelPrize.org, accessed October 22, 2019, https://www.nobelprize.org/prizes/medicine/1945/fleming/biographical/; "The Nobel Prize in Physiology or Medicine 1945," NobelPrize.org, accessed October 22, 2019, https://www.nobelprize.org/prizes/medicine/1945/florey/biographical/; "The Elixir Tragedy, 1937," The Scientist Magazine®, accessed December 19, 2019, https://www.the-scientist.com/foundations/the-elixir-tragedy-1937-39231.

[17] E. Chain et al., "PENICILLIN AS A CHEMOTHERAPEUTIC AGENT," *The Lancet*, Originally published as Volume 2, Issue 6104, 236, no. 6104 (August 24, 1940): 226–28, https://doi.org/10.1016/S0140-6736(01)08728-1; E. P. Abraham et al., "FURTHER OBSERVATIONS ON PENICILLIN," *The Lancet*, Originally published as Volume 2, Issue 6155, 238, no. 6155 (August 16, 1941): 177–89, https://doi.org/10.1016/S0140-6736(00)72122-2; D Crowfoot, "X-Ray Crystallographic Studies of Compounds of Biochemical Interest," *Annual Review of Biochemistry* 17, no. 1 (June 1948): 115–46, https://doi.org/10.1146/annurev.bi.17.070148.000555; Charles M. Grossman, "The First Use of Penicillin in the United States," *Annals of Internal Medicine* 149, no. 2 (July 15, 2008): 135, https://doi.org/10.7326/0003-4819-149-2-200807150-00009; Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; "PENICILLIN PURIFIED," *The Lancet*, Originally published as Volume 2, Issue 6207, 240, no. 6207 (August 15, 1942): 189–90, https://doi.org/10.1016/S0140-6736(00)41481-9; Greenwood, *Antimicrobial Drugs*; C. P. Kurtzman, "The ARS Culture Collection: Present Status and New Directions," *Enzyme and Microbial Technology* 8, no. 6 (June 1, 1986): 328–33, https://doi.org/10.1016/0141-0229(86)90130-4; "The Nobel Prize in Physiology or Medicine 1945"; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf; Aminov, "A Brief History of the Antibiotic Era"; Robert A. Kyle, David P. Steensma, and Marc A. Shampo, "Howard Walter Florey—Production of Penicillin," *Mayo Clinic Proceedings* 90, no. 6 (June 1, 2015): e63–64, https://doi.org/10.1016/j.mayocp.2014.12.028.

[18] Kyle, Steensma, and Shampo, "Howard Walter Florey—Production of Penicillin"; John Warren Henderson, "The Yellow Brick Road to Penicillin: A Story of Serendipity," *Mayo Clinic Proceedings* 72, no. 7 (July 1, 1997): 683–87, https://doi.org/10.4065/72.7.683; David P. Adams, "The Penicillin Mystique and the Popular Press (1935-1950)," *Pharmacy in History* 26, no. 3 (1984): 134–42; see also Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; Greenwood, *Antimicrobial Drugs*; Wright, Seiple, and Myers, "The Evolving Role of Chemical Synthesis in Antibacterial Drug Discovery"; David P. Adams, "The Penicillin Mystique and the Popular Press (1935-1950)," *Pharmacy in History* 26, no. 3 (1984): 134–42; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; Achilladelis, "The Dynamics of Technological Innovation"; "The Nobel Prize in Physiology or Medicine 1952," NobelPrize.org, accessed July 3, 2019, https://www.nobelprize.org/prizes/medicine/1952/waksman/biographical/; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf.

[19] That same year, Fleming, Florey, and Chain were awarded the Nobel Prize for Physiology and Medicine. Kyle, Steensma, and Shampo, "Howard Walter Florey—Production of Penicillin"; Katrina T. Forest and Ann M. Stock, "Classic Spotlight: Crowd Sourcing Provided Penicillium Strains for the War Effort," *Journal of Bacteriology* 198, no. 6 (March 15, 2016): 877–877, https://doi.org/10.1128/JB.00903-15. E. Chain et al., "PENICILLIN AS A CHEMOTHERAPEUTIC AGENT," *The Lancet*, Originally published as Volume 2, Issue 6104, 236, no. 6104 (August 24, 1940): 226–28, https://doi.org/10.1016/S0140-6736(01)08728-1; E. P. Abraham et al., "FURTHER OBSERVATIONS ON PENICILLIN," *The Lancet*, Originally published as Volume 2, Issue 6155, 238, no. 6155 (August 16, 1941): 177–89, https://doi.org/10.1016/S0140-6736(00)72122-2; D Crowfoot, "X-Ray Crystallographic Studies of Compounds of Biochemical Interest," *Annual Review of Biochemistry* 17, no. 1 (June 1948): 115–46, https://doi.org/10.1146/annurev.bi.17.070148.000555; Charles M. Grossman, "The First Use of Penicillin in the United States," *Annals of Internal Medicine* 149, no. 2 (July 15, 2008): 135, https://doi.org/10.7326/0003-4819-149-2-200807150-00009; Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; "PENICILLIN PURIFIED," *The Lancet*, Originally published as Volume 2, Issue 6207, 240, no. 6207 (August 15, 1942): 189–90, https://doi.org/10.1016/S0140-6736(00)41481-9; Greenwood, *Antimicrobial Drugs*; C. P. Kurtzman, "The ARS Culture Collection: Present Status and New Directions," *Enzyme and Microbial Technology* 8, no. 6 (June 1, 1986): 328–33, https://doi.org/10.1016/0141-0229(86)90130-4; "The Nobel Prize in Physiology or Medicine 1945"; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf.

[20] Henry Welch, "Certification of Antibiotics," *Public Health Reports (1896-1970)* 71, no. 6 (1956): 594–99, https://doi.org/10.2307/4589475.

[21] The law provided for the FDA to select batches for testing, rather than testing all batches produced. As civilian production ramped up, testing of select batches became automated. Amendments added in the late 1940s and 1950s extended the regulations to cover streptomycin and later antibiotics. These regulations were unusual: the FDA had only recently been authorized to require basic safety testing of drugs in 1938 and would not be authorized to require tests of effectiveness of all other drugs until 1962. Henry Welch, "Certification of Antibiotics," *Public Health Reports (1896-1970)* 71, no. 6 (1956): 594–99, https://doi.org/10.2307/4589475; Office of the Commissioner, "Milestones in U.S. Food and Drug Law History," *FDA*, March 12, 2019, http://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/milestones-us-food-and-drug-law-history; "Federal Food, Drug, and Cosmetic Act Penicillin Amendment," Pub. L. No. PL79-139 (1945), https://congressional.proquest.com/legisinsight?id=PL79-139FT&type=PUBLIC_LAW. See also Adams, "The Penicillin Mystique and the Popular Press (1935-1950)."

[22] Botanist Benjamin Duggar led the Lederle team. He had retired from teaching and research at the University of Wisconsin, but had been hired as a consultant for Lederle. After Waksman gave a conference paper on streptomycin, the president of Lederle had urged Duggar to search for a similar molecule in soil bacteria. Duggar was nominated for a Nobel Prize during the same period as Waksman but did not win. Selman Waksman later faced accusations of having stolen credit for the discovery of streptomycin from his Ph.D. student, Albert Schatz. Jukes, Thomas H. "Some Historical Notes on Chlortetracycline" *Reviews of Infectious Diseases*. 7:5 (Septemner-October 1985); Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; Greenwood, *Antimicrobial Drugs*; Achilladelis, "The Dynamics of Technological Innovation"; "The Nobel Prize in Physiology or Medicine 1945"; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf

[23] Cephalosporium acremonium has now been reclassified as *Acremonium chrysogenum*. "Acremonium Chrysogenum - an Overview | ScienceDirect Topics."

[24] Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; G. Bo, "Giuseppe Brotzu and the Discovery of Cephalosporins," *Clinical Microbiology and Infection* 6 (January 1, 2000): 6–8, https://doi.org/10.1111/j.1469-0691.2000.tb02032.x; E. P. Abraham, "A Glimpse of the Early History of the Cephalosporins," *Reviews of Infectious Diseases* 1, no. 1 (1979): 99–105; "AJPH.13.8.Pdf." Accessed September 22, 2019. https://ajph.aphapublications.org/doi/pdf/10.2105/AJPH.13.8.660; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf.

[25] Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; Bo, "Giuseppe Brotzu and the Discovery of Cephalosporins"; Abraham, "A Glimpse of the Early History of the Cephalosporins"; Greenwood, *Antimicrobial Drugs*; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*.

[26] In lab tests, Cephalosporin C appeared to be effective against bacteria with or without a protective outer membrane. This attribute, combined with its ability to overcome common mechanisms of bacterial resistance, suggested cephalosporin drugs could be used to both complement and substitute for penicillin. Zaffiri, Gardner, and Toledo-Pereyra, "History of Antibiotics. From Salvarsan to Cephalosporins"; Abraham, "A Glimpse of the Early History of the Cephalosporins"; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; Greenwood, *Antimicrobial Drugs*; W. F. Bynum, *History of Medicine: A Very Short Introduction*, Very Short Introductions 191 (Oxford ; New York: Oxford University Press, 2008), http://nrs.harvard.edu/urn-3:hul.ebookbatch.GEN_batch:VSI038820150414.

[27] At the time, Oxford University had no policies, protocol, or structure in place to catalyze development of researchers' discoveries. "Development of Inventions Act 1948 (Hansard)," accessed July 9, 2019, https://api.parliament.uk/historic-hansard/acts/development-of-inventions-act-1948; Achilladelis, "The Dynamics of Technological Innovation"; Robert Bud and Philip Gummett, *Cold War, Hot Science: Applied Research in Britain's Defence Laboratories, 1945-1990* (Science Museum, 2002); Takuji Hara, *Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development* (Edward Elgar Publishing, 2003); Greenwood, *Antimicrobial Drugs*; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/; "NATIONAL RESEARCH DEVELOPMENT CORPORATION (NRDC) (BRITISH TECHNOLOGY GROUP)," n.d. ABRAHAM/C/4. Oxford University: Bodleian Library, Special Collections.

[28] Greenwood, *Antimicrobial Drugs*; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/; "NATIONAL RESEARCH DEVELOPMENT CORPORATION (NRDC) (BRITISH TECHNOLOGY GROUP)," n.d. ABRAHAM/C/4. Oxford University: Bodleian Library, Special Collections; "Building Brands: 1919 – 1949 | GSK," accessed August 13, 2019, https://www.gsk.com/en-gb/about-us/our-history/building-brands-1919-1949/; "Milestones of Lilly Caring and Discovery," accessed August 13, 2019, https://www.lilly.com/interactive-header/milestones-of-lilly-caring-and-discovery; HannahBlake, "A History of... Eli Lilly & Co," Pharmaphorum, July 29, 2013, https://pharmaphorum.com/views-and-analysis/a-history-of-eli-lilly-co/.

[29] Richard S. Griffith and Henry R. Black, "Cephalothin—A New Antibiotic: Preliminary Clinical and Laboratory Studies," *JAMA* 189, no. 11 (September 14, 1964): 823–28, https://doi.org/10.1001/jama.1964.03070110025005. "Second Cephalosporin Antibiotic Emerges," n.d., 2; Abraham, "A Glimpse of the Early History of the Cephalosporins" Greenwood, *Antimicrobial Drugs*; Achilladelis, "The Dynamics of Technological Innovation"; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/.

[30] Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; Greenwood, *Antimicrobial Drugs*; Achilladelis, "The Dynamics of Technological Innovation"; "Second Cephalosporin Antibiotic Emerges"; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf.

[31] "Makers of Certain Antibiotics Are StudiedBy FTC for Possible Antitrust Violations," *Wall Street Journal (1923 - Current File); New York, N.Y.*, July 29, 1975, sec. 1; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; Greenwood, *Antimicrobial Drugs*; Achilladelis, "The Dynamics of Technological Innovation"; "Second Cephalosporin Antibiotic Emerges"; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf.

[32] Annetine Gelijns et al., *The Changing Economics of Medical Technology*, Medical Innovation at the Crossroads ; v. 2 (Washington, DC: National Academy Press, 1991); Joichi Kumazawa and Morimasa Yagisawa, "The History of Antibiotics: The Japanese Story," *Journal of Infection and Chemotherapy* 8, no. 2 (January 1, 2002): 125–33, https://doi.org/10.1007/s101560200022; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf; "Antibiotics business is destined to expand to Y1,000 bil. market" *The Japan Economic Journal*. October 14, 1980.

[33] Aaron Eli Glatt, "Second-Generation Cephalosporins," *Hospital Practice* 21, no. 3 (March 15, 1986): 158A-158L, https://doi.org/10.1080/21548331.1986.11704945; Greenwood, *Antimicrobial Drugs*; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development;* Achilladelis, "The Dynamics of Technological Innovation"; Verbist, "The Cephalosporins"; Neu, "Antibiotics in the Second Half of the 1980s"; "Third-generation antibiotics join the fray." *Chemical Week,* August 19, 1981..

[34] "Third-generation antibiotics join the fray." *Chemical Week,* August 19, 1981; "Lilly on the offensive." *Forbes.* February 15, 1982. "The Product That Made SmithKline Red Hot." *Forbes.* December 15, 1976. "No Headline In Original" ("Eli Lilly and Company today announced a 19-percent sales increase…") *PR Newswire.* February 6, 1980.

L. Verbist, "The Cephalosporins: Past And Future," *Acta Clinica Belgica* 34, no. 3 (January 1, 1979): 165–78, https://doi.org/10.1080/22953337.1979.11718683; Glatt, "Second-Generation Cephalosporins"; "An Emerging Consensus on Bundled Discounts under Section 2 of the Sherman Act?," accessed September 15, 2019, http://link.galegroup.com/apps/doc/A206110317/LT?sid=lms; Achilladelis, "The Dynamics of Technological Innovation"; Harold C. Neu, "Antibiotics in the Second Half of the 1980s: Areas of Future Development and the Effect of New Agents on Aminoglycoside Use," *The American Journal of Medicine*, Aminoglycoside Therapy The New Decade: A Worldwide Perspective, 80, no. 6, Supplement 2 (June 30, 1986): 195–203, https://doi.org/10.1016/0002-9343(86)90501-2.

[35] Aaron Eli Glatt, "Second-Generation Cephalosporins," *Hospital Practice* 21, no. 3 (March 15, 1986): 158A-158L, https://doi.org/10.1080/21548331.1986.11704945; H. H. Hutchinson, "Cephalosporins and Cost Containment," *Journal of the Medical Association of the State of Alabama* 52, no. 12 (1983): 7, 44; Steven E. Schonberg, "Cost of Antibiotics," *JAMA: The Journal of the American Medical Association* 250, no. 13 (October 7, 1983): 1693, https://doi.org/10.1001/jama.1983.03340130023012; Mervyn Shapiro et al., "Benefit-Cost Analysis of Antimicrobial Prophylaxis in Abdominal and Vaginal Hysterectomy," *JAMA* 249, no. 10 (March 11, 1983): 1290–94, https://doi.org/10.1001/jama.1983.03330340032026.

[36] All cephalosporin producers came under the scrutiny of the Federal Trade Commission in the mid-1970s for possible violations of U.S. antitrust law; however, regulators chose to take no action against the companies. See "Makers of Certain Antibiotics Are StudiedBy FTC for Possible Antitrust Violations," *Wall Street Journal (1923 - Current File); New York, N.Y.*, July 29, 1975, sec. 1. "Third-generation antibiotics join the fray." *Chemical Week,* August 19, 1981; "Lilly on the offensive." *Forbes.* February 15, 1982. "The Product That Made SmithKline Red Hot." *Forbes.* December 15, 1976. "No Headline In Original" ("Eli Lilly and Company today announced a 19-percent sales increase…") *PR Newswire.* February 6, 1980.

L. Verbist, "The Cephalosporins: Past And Future," *Acta Clinica Belgica* 34, no. 3 (January 1, 1979): 165–78, https://doi.org/10.1080/22953337.1979.11718683; Glatt, "Second-Generation Cephalosporins"; "An Emerging Consensus on Bundled Discounts under Section 2 of the Sherman Act?," accessed September 15, 2019, http://link.galegroup.com/apps/doc/A206110317/LT?sid=lms; Achilladelis, "The Dynamics of Technological Innovation"; Harold C. Neu, "Antibiotics in the Second Half of the 1980s: Areas of Future Development and the Effect of New Agents on Aminoglycoside Use," *The American Journal of Medicine*, Aminoglycoside Therapy The New Decade: A Worldwide Perspective, 80, no. 6, Supplement 2 (June 30, 1986): 195–203, https://doi.org/10.1016/0002-9343(86)90501-2.

[37] Achilladelis, "The Dynamics of Technological Innovation"; Gelijns et al., *The Changing Economics of Medical Technology*; Ragnar Norrby, "New Aspects of Cephalosporins: A Symposium of Glaxo, Sweden: Skövde, October 28–29 1977," *Scandinavian Journal of Infectious Diseases* 10, no. sup13 (May 1978): 1–99, https://doi.org/10.3109/inf.1978.10.suppl-13.01; John Henahan, "High Hopes for 'third Generation' Cephalosporins," *JAMA* 246, no. 13 (1981): 1398–1399, https://doi.org/10.1001/jama.1981.03320130008004.

[38] Third-generation cephalosporins also attacked porous bacteria that rapidly ejected all types of antibiotics (*Pseudomonas* bacteria). Robert C. Moellering, "Can the Third-Generation Cephalosporins Eliminate the Need for Antimicrobial Combinations?," *The American Journal of Medicine*, Advances in Cephalosphorin Therapy Beyond the Third Generation, 79, no. 2, Supplement 1 (August 9, 1985): 104–9, https://doi.org/10.1016/0002-9343(85)90269-4; Lionel A. Mandell et al., "Once-Daily Therapy with Ceftriaxone Compared with Daily Multiple-Dose Therapy with Cefotaxime for Serious Bacterial Infections: A Randomized, Double-Blind Study," *The Journal of Infectious Diseases* 160, no. 3 (1989): 433–41; Verbist, "The Cephalosporins"; Henahan, "High Hopes for 'third Generation' Cephalosporins"; S. L. Barriere and J. F. Flaherty, "Third-Generation Cephalosporins: A Critical Evaluation," *Clinical Pharmacy* 3, no. 4 (August 1984): 351–73; L. S. Young, "Ceftazidime: Summary of the First International Symposium," *Journal of Antimicrobial Chemotherapy* 8, no. suppl_B (January 1, 1981): 349–52, https://doi.org/10.1093/jac/8.suppl_B.349; Norrby, "New Aspects of Cephalosporins"; Norberto J. Palleroni, "The Pseudomonas Story," *Environmental Microbiology* 12, no. 6 (2010): 1377–83, https://doi.org/10.1111/j.1462-2920.2009.02041.x; Gelijns et al., *The Changing Economics of Medical Technology*; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; Greenwood, *Antimicrobial Drugs*. "Third-generation antibiotics join the fray." *Chemical Week*. August 19, 1981; "A stitch in time." *Forbes*. November 22, 1982; "INTENSE BATTLE FOR ANTIBIOTICS." *The New York Times*. June 13, 1983, Monday, Late City Final Edition; "Fujisawa is in final stage of new antibiotics development." *The Japan Economic Journal*. September 20, 1983. "Research seeks to increase the power of antibiotics." *The Globe and Mail* (Canada). April 20, 1984 Friday; "List of Third Generation Cephalosporins + Uses, Types & Side Effects." Drugs.com. Accessed July 31, 2019. https://www.drugs.com/drug-class/third-generation-cephalosporins.html. "List of Fourth Generation Cephalosporins." Drugs.com. Accessed July 31, 2019. https://www.drugs.com/drug-class/fourth-generation-cephalosporins.html.

[39] Third-generation cephalosporins also attacked porous bacteria that rapidly ejected all types of antibiotics (*Pseudomonas* bacteria). Robert C. Moellering, "Can the Third-Generation Cephalosporins Eliminate the Need for Antimicrobial Combinations?," *The American Journal of Medicine*, Advances in Cephalosphorin Therapy Beyond the Third Generation, 79, no. 2, Supplement 1 (August 9, 1985): 104–9, https://doi.org/10.1016/0002-9343(85)90269-4; Lionel A. Mandell et al., "Once-Daily Therapy with Ceftriaxone Compared with Daily Multiple-Dose Therapy with Cefotaxime for Serious Bacterial Infections: A Randomized, Double-Blind Study," *The Journal of Infectious Diseases* 160, no. 3 (1989): 433–41; Verbist, "The Cephalosporins"; Henahan, "High Hopes for 'third Generation' Cephalosporins"; S. L. Barriere and J. F. Flaherty, "Third-Generation Cephalosporins: A Critical Evaluation," *Clinical Pharmacy* 3, no. 4 (August 1984): 351–73; L. S. Young, "Ceftazidime: Summary of the First International Symposium," *Journal of Antimicrobial Chemotherapy* 8, no. suppl_B (January 1, 1981): 349–52, https://doi.org/10.1093/jac/8.suppl_B.349; Norrby, "New Aspects of Cephalosporins"; Norberto J. Palleroni, "The Pseudomonas Story," *Environmental Microbiology* 12, no. 6 (2010): 1377–83, https://doi.org/10.1111/j.1462-2920.2009.02041.x; Gelijns et al., *The Changing Economics of Medical Technology*; Thomas Dougherty and Michael J. Pucci, *Antibiotic Discovery and Development*; Greenwood, *Antimicrobial Drugs*. "Third-generation antibiotics join the fray." *Chemical Week*. August 19, 1981; "A stitch in time." *Forbes*. November 22, 1982; "INTENSE BATTLE FOR ANTIBIOTICS." *The New York Times*. June 13, 1983, Monday, Late City Final Edition; "Fujisawa is in final stage of new antibiotics development." *The Japan Economic Journal*. September 20, 1983. "Research seeks to increase the power of antibiotics." *The Globe and Mail* (Canada). April 20, 1984 Friday; "List of Third Generation Cephalosporins + Uses, Types & Side Effects." Drugs.com. Accessed July 31, 2019. https://www.drugs.com/drug-class/third-generation-cephalosporins.html. "List of Fourth Generation Cephalosporins." Drugs.com. Accessed July 31, 2019. https://www.drugs.com/drug-class/fourth-generation-cephalosporins.html.

[40] Gelijns et al., *The Changing Economics of Medical Technology*; Kumazawa and Yagisawa, "The History of Antibiotics"; "Wit6.Pdf." Accessed July 7, 2019. http://discovery.ucl.ac.uk/2074/1/wit6.pdf; "Third-generation antibiotics join the fray." *Chemical Week*. August 19, 1981; "Japanese drug groups maintain growth despite drop in prices." *Financial Times* (London, England). March 18, 1982, Thursday; "An injectable cephalosporin." *Chemical Week*. July 28, 1982; "A stitch in time." *Forbes*. November 22, 1982; "INTENSE BATTLE FOR ANTIBIOTICS." *The New York Times*. June 13, 1983, Monday, Late City Final Edition; "Japanese boost germs' defenses to screen antibiotics." *McGraw-Hill's Biotechnology Newswatch*. September 5, 1983; "Fujisawa is in final stage of new antibiotics development." *The Japan Economic Journal*. September 20, 1983; "Research seeks to increase the power of antibiotics." *The Globe and Mail* (Canada). April 20, 1984 Friday; "Japanese Drug Firms Flourish." *The Washington Post*. April 22, 1984, Sunday, Final Edition.

[41] Helga Tilton, "New Generations; the Antibiotic Market Is Back to Square One as the Top Seller Comes off Patent, and a Host of New Products Enter the Scene. (Pharmaceuticals '93: Antibiotics)(Includes Related Article)," *Chemical Marketing Reporter* 243, no. 10 (1993): SR40; Helga Tilton, "Pharmaceuticals '93: Antibiotics - New Generations," *Chemical Marketing Reporter* 243, no. 10 (1993): SR40; Achilladelis, "The Dynamics of Technological Innovation"; Achilladelis and Antonakis, "The Dynamics of Technological Innovation"; Michael R. Reich, "Why the Japanese Don't Export More Pharmaceutical: Health Policy as Industrial Policy," *California Management Review; Berkeley, Calif.* 32, no. 2 (Winter 1990): 124–150; Aki Yoshikawa, "The Other Drug War: U.S.-Japan Trade in Pharmaceutical," *California Management Review; Berkeley, Calif.* 31, no. 2 (Winter 1989): 76–90; "Cephalosporins Set for Decline In Market Value, Study Reports." *Chemical Market Reporter.* August 5, 1996; "Japan Drugmakers' Foreign Sales Still Low." *Pharma Marketletter*. July 26, 1993; later in the 1990s, however, the boom in Japan ended as the government tightened prices: Anonymous. "Japan's Sickly Drug Firms." *The Economist; London*, October 19, 1996.

[42] Young, "Ceftazidime," 349.

[43] Stephen T. Chambers, David R. Murdoch, and Malcolm J. Pearce, "Clinical and Economic Considerations in the Use of Third-Generation Oral Cephalosporins:," *PharmacoEconomics* 7, no. 5 (May 1995): 416–27, https://doi.org/10.2165/00019053-199507050-00006; John S. Czachor and Richard A. Gleckman, "Third-Generation Cephalosporins: A Plea to Save Them for Specific Infections," *Postgraduate Medicine* 85, no. 4 (1989): 169–176, https://doi.org/10.1080/00325481.1989.11700624; Jack D. McCue, *Cost-Conscious Use of the Cephalosporins: A Guide to Empiric Therapy*, 2nd ed. (New York, N.Y.: Raven Health Care Communications, 1986); H. Hutchinson, "Cephalosporins and Cost Containment," *Journal of the Medical Association of the State of Alabama* 52, no. 12 (1983): 7, 44; Mervyn Shapiro et al., "Benefit-Cost Analysis of Antimicrobial Prophylaxis in Abdominal and Vaginal Hysterectomy," *JAMA* 249, no. 10 (March 11, 1983): 1290–94, https://doi.org/10.1001/jama.1983.03330340032026; Steven E. Schonberg, "Cost of Antibiotics," *JAMA: The Journal of the American Medical Association* 250, no. 13 (October 7, 1983): 1693, https://doi.org/10.1001/jama.1983.03340130023012; Norrby, "New Aspects of Cephalosporins"; Verbist, "The Cephalosporins"; Henahan, "High Hopes for 'third Generation' Cephalosporins"; Young, "Ceftazidime"; Barriere and Flaherty, "Third-Generation Cephalosporins"; Stephen T. Chambers, David R. Murdoch, and Malcolm J. Pearce, "Clinical and Economic Considerations in the Use of Third-Generation Oral Cephalosporins:," *PharmacoEconomics* 7, no. 5 (May 1995): 416–27, https://doi.org/10.2165/00019053-199507050-00006.; See also Frost & Sullivan (2003) *U.S. Critical Care Antibiotics Markets.*

[44] Penicillin had been effective against staph infections when first introduced in the 1940s. However, some strains of staph bacteria had developed resistance to it in the 1960s, as well as to subsequent antibiotics. These strains had proliferated in hospitals in the ensuing decades.

[45] C. Lee Ventola, "The Antibiotic Resistance Crisis," Pharmacy and Therapeutics 40, no. 4 (April 2015): 277–83. David M. Shlaes and Jr. Robert C. Moellering, "The United States Food and Drug Administration and the End of Antibiotics," Clinical Infectious Diseases 34, no. 3 (2002): 420–22. FDA rules governing trial design became stricter in the mid-2000s. In 2006, a newly-approved antibiotic, telithromycin was found to cause liver failure in some patients. After one patient required a liver transplant and four died as a result of being treated with telithromycin, the U.S. Congress held hearings into the approval process, the FDA issued a warning about the drug, and authorities charged the researchers and producers with fraud. The makers, Sanofi-Aventis, withdrew the drug from the U.S. market shortly after. According to David Shlaes, et al: "In the aftermath of telithromycin, FDA rules governing trial conduct became increasingly stringent to the point of making antibacterial trials infeasible, nonsensical, or both." David M. Shlaes et al., "The FDA Reboot of Antibiotic Development," *Antimicrobial Agents and Chemotherapy* 57, no. 10 (October 2013): 4605–7, https://doi.org/10.1128/AAC.01277-13; Brad Spellberg, "The Future of Antibiotics," *Critical Care* 18, no. 3 (June 27, 2014): 228, https://doi.org/10.1186/cc13948.Matthew A. Cooper and David Shlaes, "Fix the Antibiotics Pipeline," *Nature* 472, no. 7341 (2011): 32–32, http://dx.doi.org.ezp-prod1.hul.harvard.edu/10.1038/472032a; Achilladelis, "The Dynamics of Technological Innovation"; Achilladelis and Antonakis, "The Dynamics of Technological Innovation"; Bridget Kuehn, "Proposals Seek to Reduce Resistance, Boost Development of New Antibiotics," *JAMA* 305, no. 18 (2011): 1845–6, https://doi.org/10.1001/jama.2011.598; Steven J Projan, "Why Is Big Pharma Getting out of Antibacterial Drug Discovery?," *Current Opinion in Microbiology* 6, no. 5 (October 1, 2003): 427–30, https://doi.org/10.1016/j.mib.2003.08.003; ://www.pharmaceutical-journal.com/news-and-analysis/features/why-are-there-so-few-antibiotics-in-the-research-and-development-pipeline/11130209.article; "Illiad.Pdf." Accessed July 29, 2019. https://illiad-hul-harvard-edu.ezp-prod1.hul.harvard.edu/illiad/HLS/illiad.dll?Action=10&Form=75&Value=5378217; "Basilea Pharmaceutica Announces Discontinuation of Sale of Ceftobiprole by Janssen-Cilag AG, a Johnson & Johnson Company, In Switzerland," BioSpace, accessed December 18, 2019, https://www.biospace.com/article/basilea-pharmaceutica-announces-discontinuation-of-sale-of-ceftobiprole-by-janssen-cilag-ag-a-johnson-and-johnson-company-in-switzerland-/; Peter Mansell, "FDA Warns J&J over Ceftobiprole Trial Violations," text, PharmaTimes, August 19, 2009, http://www.pharmatimes.com/news/fda_warns_j_and_j_over_ceftobiprole_trial_violations_983792; "FDA Issues Complete Response Letter for Ceftobiprole for Treatment of Complicated Skin Infections," Johnson & Johnson, accessed December 18, 2019, https://johnsonandjohnson.gcs-web.com/news-releases/news-release-details/fda-issues-complete-response-letter-ceftobiprole-treatment; "Recent FDA Antibiotic Approvals: Good News and Bad News," Center for Disease Dynamics, Economics & Policy (CDDEP), June 24, 2017, https://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news/; "FDA Approves Ceftaroline Fosamil for Bacterial Infections," accessed December 16, 2019, https://www.healio.com/infectious-disease/emerging-diseases/news/print/infectious-disease-news/{cc17050d-3fd6-48ae-a080-4300a04ab43c}/fda-approves-ceftaroline-fosamil-for-bacterial-infections; Infectious Disease News et al., "Ceftaroline Fosamil: A New FDA-Approved Anti-MRSA Cephalosporin Antibiotic," accessed July 29, 2019, https://www.healio.com/infectious-disease/vaccine-preventable-diseases/news/print/infectious-disease-news/{82e25871-ce14-43f9-8eab-d66aa4a85570}/ceftaroline-fosamil-a-new-fda-approved-anti-mrsa-cephalosporin-antibiotic.

[46] Cephalosporins were popular in low income countries because their variable production costs were low and they did not require much less skill and infrastructure to dispense (unlike sophisticated operations, such as coronary artery bypass surgery and device innovations (such as magnetic resonance imaging machines). Sources: Thomas P Van Boeckel et al., "Global Antibiotic Consumption 2000 to 2010: An Analysis of National Pharmaceutical Sales Data," *The Lancet Infectious Diseases* 14, no. 8 (August 2014): 742–50, https://doi.org/10.1016/S1473-3099(14)70780-7; Thomas Van Boeckel and Ramanan Laxminarayan, "Correction to Global Antibiotic Consumption Data," *The Lancet Infectious Diseases* 17, no. 5 (May 2017): 476–77, https://doi.org/10.1016/S1473-3099(17)30187-1; Note: even though consumption doubled, prices continued to fall and the overall value of the market remained essentially the same. According to: "Overcoming Antibiotic-Resistant Bacteria." *GEN - Genetic Engineering and Biotechnology News* (blog), September 1, 2010. https://www.genengnews.com/magazine/139/overcoming-antibiotic-resistant-bacteria/, the value of the world antibiotics market was $42billion in 2009, 23% of which was attributed to sales of cephalosporin drugs, making the cephalosporin market around $9.66 billion, or similar to its size in the mid-1990s; See also: Calvin M. Kunin, "Use of Antimicrobial Drugs in Developing Countries," *International Journal of Antimicrobial Agents* 5, no. 2 (April 1, 1995): 107–13, https://doi.org/10.1016/0924-8579(94)00039-W; "Focus Report: Pharmaceuticals 98: Anti-infective Drugs on the Mark." *Chemical Market Reporter*. November 23, 1998; "Cephalosporin Market Drives Orchid's Move into China." *IHS Global Insight*. July 16, 2004; "BCC Library - Report View - PHM209A," accessed August 20, 2019, https://www-bccresearch-com.ezp-prod1.hul.harvard.edu/market-research/pharmaceuticals/antibiotics-global-markets.html.