Why It Is Important To Continue Antibacterial Drug Discovery

Combating resistance, improving safety, and preserving R&D teams are among reasons for persevering

Karen Bush

Antibiotic resistance is a fact of life that we must accept and confront. Consequently, modern pharmaceutical companies have faced repeated crises when new forms of antibiotic resistance emerged in previously susceptible pathogens. In each of these crises, the industry has rallied to bring forward new therapeutic approaches. During the past 30 years, I have been directly involved in several of these efforts as the pharmaceutical industry responded to emerging medical needs. I have also experienced the rise and wane of research efforts to meet those changing needs. We must hope that the current impending crisis of multidrug-resistant, or pan-resistant, pathogenic bacteria will serve as yet another impetus for allocating additional resources toward the discovery and development of new antibacterial agents.

Resistance is a growing menace to a world that expects to have effective drugs available for every disease

Pharmaceutical companies have been creative in their efforts to combat pathogenic organisms responsible for worldwide morbidity and mortality, but sometimes the companies have fallen short. Despite these continuing efforts, antibiotic resistance continues to increase. Not only do bacteria possess the uncanny ability to thrive under pressure from natural antibiotics in diverse natural environments, but they must also endure the added insults from both broad-spectrum and targeted pharmaceutical agents. Hence, resistance has become a growing menace to a world that expects to have effective drugs available for every disease. This expectation is no longer being fully met by the marketed anti-infective agents. Therefore, resistance remains an important driving force for antibiotic drug discovery efforts.

Karen Bush is a Distinguished Research Fellow and Biology Team Leader for Antimicrobial Agents Drug Discovery at Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, N.J.

First Report of Antibiotic Resistance Predates Widespread Use

Edward Abraham and Ernest Chain at Oxford University in the United Kingdom provided an early warning in 1940 about intrinsic antibiotic resistance when they described an enzyme in an *Escherichia coli* extract that could destroy the antibacterial effects of penicillin even before this drug was being used clinically. Soon after penicillin came into clinical use, additional bacteria were identified with a similar ability to hydrolyze this "wonder drug" that saved so many lives during World War II.

The pharmaceutical companies that combined resources to optimize penicillin production during the war subsequently became fragmented while they established competing programs to identify better antimicrobial agents with greater stability and broader activity. During the next several decades, such efforts led to the discovery and development of many antibiotics, including streptomycin, tetracyclines, aminoglycosides, glycopeptides, cephalosporins, carbapenems, β-lactamase inhibitors, and monobactams, all identified from natural products as agents with improved, or differentiated, properties compared to penicillin.

Synthetic chemists also contributed thousands of analogs that eventually led to the penicillinase-stable penicillins, the 2nd-, 3rd-, and 4th-generation cephalosporins, improved macrolides, tetracyclines, glycopeptides, and aminoglycosides. All these efforts were based on the assumption that the newer drugs would counteract innate resistance mechanisms being found in pathogenic bacteria.

Table 1. Rapid development of resistance to newly introduced antibacterial agents.

Agent	Year of FDA approval	First reported resistance
Penicillin	1943	1940
Streptomycin	1947	1947
Tetracycline	1952	1956
Methicillin	1960	1961
Nalidixic acid	1964	1966
Gentamicin	1967	1969
Vancomycin	1972	1987
Cefotaxime	1981	1981 (AmpC β-lactamase) 1983 (ESBL)[a]
Linezolid	2000	1999

[a]Extended-spectrum β-lactamase.

Increased Resistance Accompanies New Antibacterial Agents

Despite these efforts to provide new or improved antibiotics, bacteria continue to evolve in response to the new antimicrobial agents that they encounter. The resulting drug resistance occurs in pathogens with selected chromosomal mutations or those with acquired extrachromosomal determinants that allow otherwise susceptible bacteria to survive exposure to antibiotic agents.

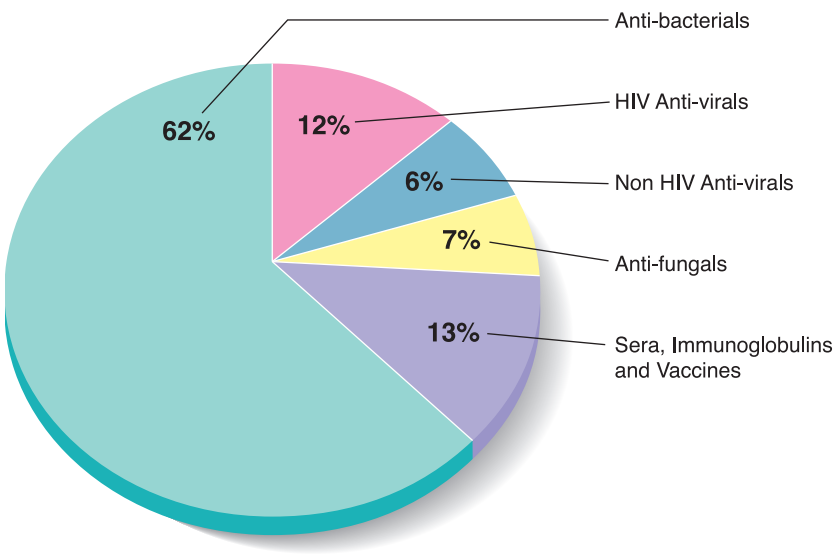
In general, resistance for most classes of antibiotics or antibacterial agents typically has been identified within four years following FDA approval of an agent (Table 1). The exception is vancomycin, a drug that was used infrequently for treating patients until methicillin-resistant *Staphylococcus aureus* (MRSA) emerged and spread. In many cases, resistance was already present in the environment before the agent was formally approved for clinical use. When resistance determinants began to appear as part of

Table 2. Major resistance mechanisms reported and subsequent development activities

Observed resistance	Approximate Date	Drugs developed to counteract resistance (drugs in development)
Penicillinase production in *S. aureus*	1945	Oxacillin and related penicillinase-stable penicillins (methicillin, cloxacillin, dicloxacillin) 1st and 2nd generation cephalosporins (cefaclor, cephradine, cephalexin)
Tetracycline resistance	1952	Minocycline, doxycycline
Gentamicin resistance	1970	Tobramycin, amikacin
Nalidixic acid	1966	Norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin
Plasmid-encoded TEM-1 β-lactamase and tetracycline resistance in *Neisseria gonorrhea* followed by increase in plasmid-mediated multidrug resistance in gram-negative rods	1976–1980	3rd and 4th generation cephalosporins (cefoperazone, cefotaxime, ceftazidime, ceftriaxone, cefepime) Monobactams (aztreonam) Carbapenems (imipenem) β-Lactamase inhibitors (clavulanic acid, sulbactam, tazobactam)
MecA (penicillin-binding protein 2a) production in *S. aureus* leading to β-lactam resistance	1961	Quinupristin-dalfopristin, linezolid, daptomycin (oritavancin[a], dalbavancin[a], ramoplanin[a], tigecycline[a], BAL5788[a])
Extended-spectrum β-lactamases (ESBLs)	1983	Carbapenems (meropenem, ertapenem, tigecycline)
VanA and VanB leading to vancomycin resistance in enterococci	1987	Quinupristin-dalfopristin, linezolid (oritavancin, tigecycline)

[a] Investigational drugs

FIGURE 1



Worldwide anti-infective market.

mobile elements that are easily transferred on plasmids, multidrug-resistant organisms began to appear.

Hence, from a clinical standpoint, we are facing a crisis when dealing with pathogens such as *Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and *Acinetobacter* spp. Particularly in cases involving patients who are being cared for in intensive care units (ICUs), these pathogens are proving to be increasingly multidrug resistant (MDR) to at least three classes of antibiotics. For example, a large percentage of *S. maltophilia* isolates from Singapore in 2000–2001 were not susceptible to the cephalosporin ceftazidime (47%), the monobactam aztreonam (95%), the carbapenem imipenem (96%), the fluoroquinolone ciprofloxacin (36%), the aminoglycosides gentamicin and amikacin (80%), and chloramphenicol (46%), according to Fu Wang and colleagues at Fudan University in Shanghai, China.

Because of the decreased susceptibility to single agents in these organisms, combination antibiotic therapy is required more frequently. In some cases, physicians are resorting to toxic polymyxins to treat patients infected with MDR pseudomonads and *Acinetobacter* spp., resulting in clinical outcomes that may be unsatisfactory due to decreased clinical cure rates and poorly tolerated drug regimens. These limited therapeutic options emphasize the need for new, alternative agents for treating MDR pathogens.

Companies Historically Met Successive Drug Resistance Challenges

Soon after each major resistance mechanism was identified, pharmaceutical companies in the United States, Western Europe, and Japan increased efforts leading to products for counteracting or circumventing those resistances (Table 2). When faced with unmet medical needs or emerging diseases, drug discovery and development programs either were expanded or new programs were instituted.

However, as each resistance crisis was perceived to have been met, some companies curtailed their antibacterial research programs. Following the major influx of new β-lactams in the early to mid-1980s, several companies, including Lilly, Roche, and Schering, decreased their respective antibacterial research and development (R&D) programs. Meanwhile, several other major companies, including GlaxoSmithKline, Squibb, and Schering, emphasized antiviral and antifungal research instead of traditional antibacterial programs, particularly in response to concerns over HIV.

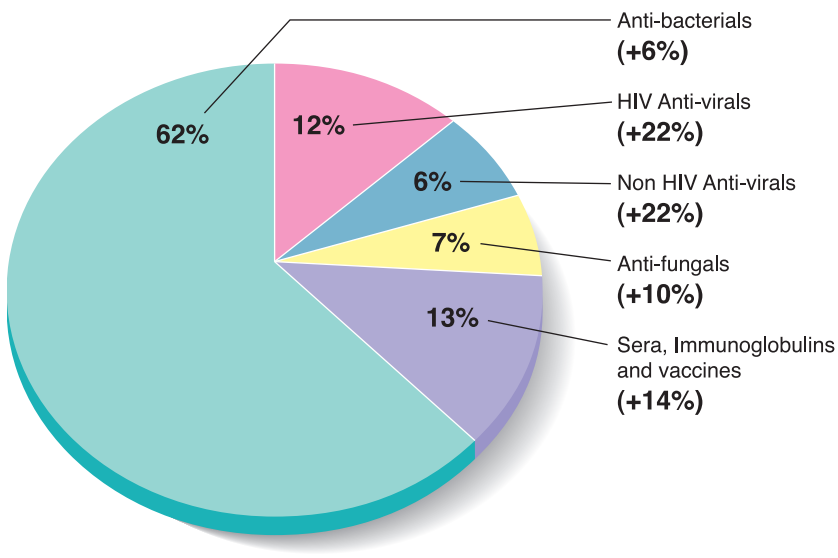
However, by 1990, the increasing incidence of MRSA and vancomycin-resistant enterococci (VRE) led several companies to expand or reinstitute their efforts to identify new antibacterial agents to treat these emerging threats from gram-positive pathogens. By the mid-1990s, bacterial genomic information was aiding these efforts.

Antibiotic R&D Programs Meet Other Medical Needs Such as Safety

Historically, companies have continued their efforts to develop new anti-infective agents because they were seeking to address other medical needs. For example, patient safety remains a primary concern in the development and use for any pharmaceutical agent, including antibiotics. Even though antibacterial agents are usually

administered to patients for relatively short periods of less than two weeks, these drugs are being administered to broad segments of the population, typically in hundreds of milligrams per day. Oral agents in particular are frequently distributed empirically with no follow-up. Thus, antibiotics need to have very good safety profiles. For instance, when a company can identify a second-generation agent whose use leads to fewer adverse events than does the current standard of care, the company is medically justified in supporting development of the new agent.

FIGURE 2



Growth of anti-infective market by sector.

Research and Development Advantages Aid Antibiotic R&D Efforts

As new anti-infective drugs enter the pipeline, it is important for large companies to continue their efforts in antibacterial research and development. Many of the companies remaining in this field have built extensive histories while discovering and developing anti-infective drugs. Moreover, such companies also typically have considerable microbiological and medicinal chemistry expertise that is available to determine whether a compound has the potential for becoming a commercially viable drug or is merely a nonspecific membrane disruptive agent.

Such companies typically also retain experts in chemical and clinical development who understand the importance of chemical properties, formulation, pharmacokinetics for anti-infectives, and clinical design issues. They also have experts who know how to deal with regulatory agencies and to complete new drug filings appropriately.

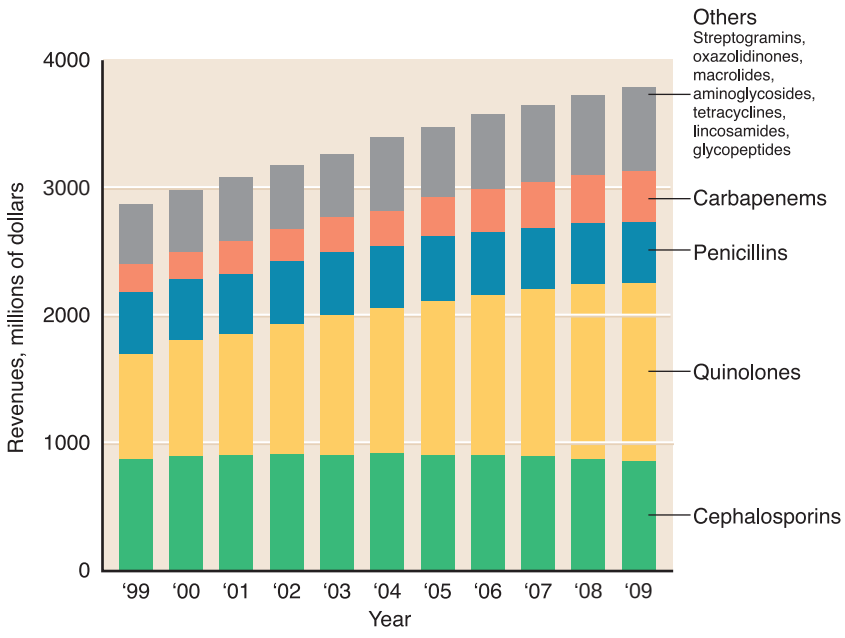
One important reason companies could respond to the resistance issues relatively rapidly in the past was that they maintained the infrastructure needed to address these distinctive challenges. These resources are extremely expensive for small companies to establish and maintain, suggesting that most large-scale drug development efforts will continue to be conducted with large pharmaceutical partners.

Another reason pharmaceutical companies continued sponsoring anti-infective drug development is because it tended to be lower risk than other therapeutic areas. Success rates—measured in terms of the percentage of compounds approved for marketing as they progress from discovery through clinical trials—are highest for anti-infective drugs compared to drugs targeting either the cardiovascular system, central nervous system (CNS), or cancer, according to a recent study from Joseph DiMasi and colleagues from Tufts University, Boston, Mass. This higher rate of success for anti-infective products partly reflects the predictive nature of preclinical data both from in vitro microbiological testing and from in vivo efficacy models that mimic the diseases that will ultimately be treated in clinical settings.

Commercial Interests Remain Attractive for Anti-Infective Agents

Even while considering such developmental advantages and also while trying to meet public health needs, pharmaceutical companies are constantly weighing the commercial implications of their antibacterial product development programs. From a commercial standpoint, anti-infective drugs rank third in terms of overall worldwide sales of both prescription and over-the-counter medications, following drugs that target the cardiovascular system and the CNS, according to the IMS Health World Review, a

FIGURE 3



Growth of anti-infective market by sector. Base year for calculation is 2002 (Data provided by Frost and Sullivan.)

company based in Fairfield, Conn., that tracks marketing trends in the pharmaceutical industry.

Estimated worldwide sales for all anti-infective products in 2002 were $45 billion (Fig. 1), of which antibacterial agents represented 62% at $28 billion, followed by biologicals at 13% at $5.9 billion, and HIV antivirals at 12% of the market, or $5.4 billion. Although growth of antibacterial drug sales is not projected to increase as rapidly as other segments of the anti-infective market (Fig. 2), 6% growth per year of $28 billion is growth of $1.7 billion per annum, compared to the projected growth in the HIV sector of 22%, or $1.2 billion. Continued growth in the antibacterial segment is expected in the United States critical care market (Fig. 3), as the population continues to age and to require additional hospital visits.

Even though the antibacterial market is fragmented among a number of companies, there are fewer companies in the business than 10 years ago, due to downsizing of programs or consolidations through mergers and acquisitions. Thus, commercial opportunities remain. None of these forecasts takes into account emerging infectious diseases or an increase in MDR strains that may evolve rapidly in the near future, making these projections artificially low.

Therefore, there are both sound scientific and medical reasons, as well as commercial opportunities, for companies to continue identifying new antibiotics. As in the past, resistance to available drugs will continue to fuel our efforts to identify alternative products. Importantly, pharmaceutical companies have a social responsibility to support anti-infective drug research. Unless we act now, and continue to maintain active programs, we may soon forfeit opportunities for controlling antibiotic-resistant infections. Antibiotic resistance is not going to disappear.

An even larger concern is that we might enter a period much like the earlier "pre-antibiotic" era during which bacterial infections could mean a rapid death sentence because effective treatments were not available. However, if pharmaceutical companies continue to engage in antibacterial research and explore new ways of confronting MDR pathogens that are proliferating worldwide, we may be spared this fate. Hence, those companies that recently halted or curtailed their antibiotic R&D efforts should reconsider those decisions. Moreover, because drug discovery is not an easy exercise, we need contributions on as many fronts as possible to maintain our assault on the continuously evolving pathogenic bacteria that surround us.

SUGGESTED READING

Abraham, E. P., and E. Chain. 1940. An enzyme from bacteria able to destroy penicillin. Nature **146:**837.

Davies, J. E. 1997. Origins, acquisition and dissemination of antibiotic resistance determinants. Ciba Foundation Symp. **207:**15–27; discussion 27–35.

DiMasi, J.A. 2001. Risks in new drug development: approval success rates for investigational drugs. Clin. Pharmacol. Ther. **69:**297–307.

Fu, W., Z. Demei, W. Shi, H. Fupin, and Z. Yingyuan. 2003. The susceptibility of non-fermentative Gram-negative bacilli to cefperazone and sulbactam compared with other antibacterial agents. Int. J. Antimicrob. Agents. **22:**444–448.

Hiramatsu, K., L. Cui, M. Kuroda, and T. Ito. 2001. The emergence and evolution of methicillin-resistant Staphylococcus aureus. Trends Microbiol. **9:**486–493.
Hoban, D. J., S. K. Bouchillon, J. L. Johnson, G. G. Zhanel, D. L. Butler, K. A. Saunders, L. A. Miller, J. A. Poupard, and G. Surveillance Study Research. 2003. Comparative in vitro potency of amoxycillin-clavulanic acid and four oral agents against recent North American clinical isolates from a global surveillance study. Int. J. Antimicrob. Agents. **21:**425–433.
Karlowsky, J. A., D. C. Draghi, M. E. Jones, C. Thornsberry, I. R. Friedland, and D. F. Sahm. 2003. Surveillance for antimicrobial susceptibility among clinical isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* from hospitalized patients in the United States, 1998 to 2001. Antimicrob. Agents Chemother. **47:**1681–1688.
Keim, K. L., J. Calcagno, S. M. Leventer, and H. W. Harris. 2003. Unlocking the value of failed CNS trials. Curr. Drug Discovery **3:**29–33.
Levin, A. S., A. A. Barone, J. Penco, M. V. Santos, I. S. Marinho, E. A. Arruda, E. I. Manrique, and S. F. Costa. 1999. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clin. Infect. Dis. **28:**1008–1011.
Mazel, D., and J. Davies. 1999. Antibiotic resistance in microbes. Cell. Mol. Life Sci. **56:**742–754.
Saiman, L., Y. Chen, P. S. Gabriel, and C. Knirsch. 2002. Synergistic activities of macrolide antibiotics against *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Alcaligenes xylosoxidans* isolated from patients with cystic fibrosis. Antimicrob. Agents Chemother. **46:**1105–1107.

The discovery of novel small-molecule antibacterial drugs has been stalled for many years. The purpose of this review is to underscore and illustrate those scientific problems unique to the discovery and optimization of novel antibacterial agents that have adversely affected the output of the effort.Â Dates indicated are those of reported initial discovery or patent. It is due in large part to this discovery void that Big Pharma has been withdrawing from research in the area, even though there has certainly been recognition of the continuing need for new antibacterials to combat the rise of resistant organisms. Class Modifications versus Novel ClassesThe antibacterial product pipeline has not been empty during this time but has been filled with improved versions of previously registered classes. This discovery drastically reduced its use and it is now recommended only for those cases where it is truely needed and other antimicrobials are likely to be ineffective. Chloramphenicol did not lead to the development of a large family of drugs, although a few derivatives are now available or being tested.Â It is important to realize that the means by which organisms become resistant, that is, how they acquire the ability to resist antimicrobials is different from the biochemical mechanism of the resistance itself. BE SURE TO NOTE THIS DIFFERENCE on examination questions.Â Why is it believed by some authorities that knowledge of categories of drugs, e.g., aminoglycosides or sulfonamides, is of value? Medecine and Drugs Unit 12 Learn with flashcards, games and more â€” for free.Â The general structure of penicillin, an antibacterial, is given below.a) With reference to the structure above, state what the letter R represents and discuss how penicillins can be made more resistant to the penicillinase enzyme. (2). side chain/alkyl group; Accept hydrocarbon chain.Â b) Explain why it is important to continue to develop semi-synthetic penicillins. (2). to overcome the resistance that bacteria develop to existing antibiotics / increases resistance to penicillinase enzyme / OWTTE; Do not accept "over prescription".