

Where are all the new antibiotics? The new antibiotic paradox

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At the beginning of the 20th century, illnesses caused by infectious agents ranked among the most common causes of death in North America and, indeed, worldwide. By the middle of the century, dramatic advances in the diagnosis, management and prevention of infectious diseases had occurred, and hopes were raised that many infectious diseases would be eliminated by the end of the 20th century. Much of this success in the management of infectious diseases was related to a continuous new armamentarium of antibiotics. The discovery of penicillin by Fleming in 1928 followed by the discovery and clinical use of sulphonamides in the 1930s heralded the age of modern antibiotherapy (1,2). Penicillin came into widespread use during the early 1940s. By the 1950s, the 'golden era' of antibiotic development and use was well underway, and multiple new classes of antibiotics were introduced over the next two decades (Table 1) (3).

These new antibiotics garnered such enthusiasm during the late 1960s and 1970s that some experts believed that infectious diseases would be conquered. Unfortunately, since the early 1990s, humankind has been confronted with an unprecedented number of resurgent and 'new' infectious diseases on a global scale. The threat of bioterrorism, particularly with genetically engineered pathogens such as *Bacillus anthracis*, has added a new dimension to resurgent infectious diseases, in part because genetic engineering of pathogens could render them resistant to currently available antimicrobials (4,5). It is interesting to note that despite the advances in antimicrobial and vaccine development, infectious diseases still remain as the third-leading cause of death in the United States (6) and the second-leading cause of death worldwide (7). Among the many resurgent and 'new' infectious diseases, antimicrobial resistance represents one of the most significant threats to human health (8-11). The problem of antibiotic resistance, although not new, has increased dramatically during the past 10 to 15 years. It now poses a serious threat to the treatment of infection.

Despite this increase in antimicrobial resistance, the development of new antimicrobial agents is declining. Several scientific articles, monographs and popular press articles have been published over the past few years pointing out the emerging paradox of a pressing need for new antimicrobial agents juxtaposed against the declining interest in the discovery and introduction of new antimicrobial agents by the world's major pharmaceutical companies. Spellberg et al (12) recently examined the number of new antibacterial agents approved from 1980 to 2003 as well as the number of new antiviral, antifungal

and antiparasitic agents approved from 1998 to 2003 by searching United States Food and Drug Administration (FDA) databases. They also examined the research and development programs of 15 major pharmaceutical companies and seven major biotechnology companies via their Internet listings to document trends in the development of new antimicrobial agents. Their findings revealed that FDA approval of new antibacterial agents had decreased by 56% over the past 20 years (1998 to 2002 versus 1983 to 1987). Of the 225 total new entities approved by the FDA from January 1998 to December 2002, only seven (3%) were new antibacterial agents (12). No new antibacterial agents were approved in 2002. On April 7 and September 12 of 2003, gemifloxacin and daptomycin were approved, respectively. Of the nine new antibacterial agents approved since January 1998, two (linezolid [approved in April 2000] and daptomycin) have novel mechanisms of action. Spellberg et al (12) also examined the development programs of the world's seven largest biotechnology companies in an effort to determine whether biotechnology companies were filling the gap in antibacterial development. They found only one new antibacterial agent in development (12). When they examined the data supporting future development of new antibacterial agents in the developmental programs of the largest pharmaceutical and biotechnology companies, six of 506 drugs were disclosed.

TABLE 1
History of introduction of new classes of antibiotics

Year introduced	Class of drug
1935	Sulphonamides
1941	Penicillins
1944	Aminoglycosides
1945	Cephalosporins
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides/lincosamides/streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitroimidazoles
1962	Quinolones
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides

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Spellberg et al argued that the decline in antibacterial research and development is at least one decade old, based on an average period of eight years to bring a drug from phase I clinical testing to product launch and the diminishing number of approvals of new antibacterial agents over the previous five years. Since the submission of Spellberg et al's article (12), telithromycin has been approved by the FDA (13), though it was not considered to be a new agent. Spellberg et al suggested that current antimicrobial drug development is insufficient to meet society's needs and that a solution is to establish a continuum of development of novel antibacterial agents and engage the FDA in the process, similar to an approach used in the development of anticancer drugs (12).

The reasons for this declining interest by the pharmaceutical industry are multifactorial and have been outlined in a recent monograph published by the Infectious Diseases Society of America (IDSA) (3). Bringing a new drug to market requires an average investment of US\$800 million and 10 years or longer. As well, pharmaceutical companies have to support the relatively large research costs of medications that do not make it to market. Furthermore, the risks of postapproval adverse events must also be taken into consideration. A recent example was the liver toxicity experienced by trovafloxacin patients within a year after its release (14). Clinical trials and studies on more than 7000 patients had suggested that the antibiotic was equivalent or potentially superior to potential competitors in multiple indications. However, the significance of the hepatic toxicity only became apparent after its release, and the FDA recommended that it be reserved for very select settings (14). At about the same time, another major pharmaceutical company introduced the first vaccine to prevent severe rotavirus diarrhea. At postapproval, after the vaccine had been extensively administered in clinical trials, 15 children developed intussusception. With an estimated risk of one case per 2500 to 9500 children immunized, the company withdrew the vaccine from the market (15).

Another factor that may play a role in the reduced interest in antibacterial development is the current focus on medications for the treatment of chronic diseases. Unlike medications used to treat chronic diseases, most antibiotic treatments are given for five to 14 days and then discontinued.

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Anti-infectives are intended to quickly eliminate the need for their use. In addition, novel breakthrough antimicrobials often become the agents of last resort, as clinicians and policy makers tend to hold them in reserve, hoping to slow the inevitable emergence of resistance. A recent IDSA monograph (3) pointed out that because antibiotics work so well and so fast, they produce a low return on investment for manufacturers.

The IDSA called attention to the new paradox in the battle against antibiotic resistance and stated that the "pharmaceutical pipeline is drying up" (3). They also suggested a number of potential solutions and recommendations: legislative solutions to fuel innovation (establishing a commission to prioritize the discovery of new antimicrobials, supplemental intellectual property protections and statutory incentives); modifications to existing FDA policies and procedures with respect to the process of antimicrobial development; enhancing the role of the National Institute of Allergy and Infectious Diseases in the research and development process; and new funding models including an increase in public funding for public agencies and public/private collaborative research efforts to combat antibiotic resistance (3).

The IDSA has provided a number of laudable suggestions. However, the decline in new antimicrobial agents and the need to manage an increasingly complex health care environment may require even more robust activity and innovative solutions. Other specific management strategies that may offer promise include improved point-of-care molecular diagnostics to allow for greater precision in the treatment modalities employed for viral, bacterial or fungal infections, the use of pharmacogenomics to gauge the host response to the anti-infective or biological agents used in an individual patient, the development of novel targets such as agents that block quorum sensing, the selective use of probiotics and prebiotics, the use of bacterial interference, and the deliberate refocus on narrow-spectrum as opposed to broad-spectrum antibiotics in clinical practice. Given the significant lag time between the discovery and introduction of new anti-infective agents and the need for new discovery of alternative solutions, it behooves all physicians to refocus their efforts on the appropriate and judicious use of antibiotics in any clinical setting in which they are used.