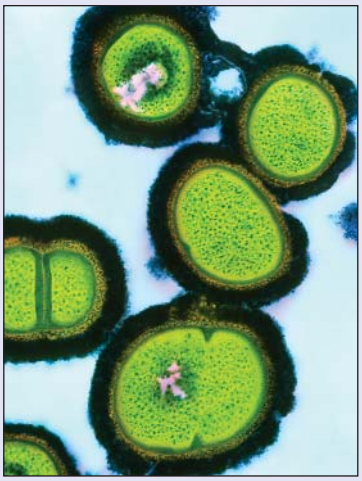
Orphan Drugs of the Future?

Eli Lilly pioneered the development of penicillin, vancomycin, and erythromycin a half-century ago, building an empire on their ability to stop bacterial infections. But in 2002 the company decided to refocus its infectious-disease research on more lucrative targets: fighting viruses and boosting the body's own immune defenses. And the Indianapolis, Indiana–based Lilly isn't the only one that's retreating from the battle against bacteria; so are Abbott Laboratories of suburban Chicago, Aventis of Strasbourg, France, and others.

The trend is part of an industry-wide hunt for bigger and better prizes. Larger financial returns are needed, companies say, because new products must overcome staggeringly high testing costs to prove that they are safe and effective. For a variety of reasons, the barriers are worse for antibiotics, which are rapidly becoming the stepchild of the pharmaceutical industry. And infectious-disease specialists are sounding an alarm.

"There is an increasing number of [antibiotic] resistant organisms and a decreasing number of drugs in the pipeline," says David Gilbert, a clinician at Portland Providence Medical Center and the Oregon Health & Science University in Portland and the past president of the Infectious Disease Society of America (IDSA). Gilbert says the combination could be brewing up a "perfect storm."



Resistance. Antibiotics are losing effectiveness against *S. aureus* (*above*) and other organisms.

Since their discovery in the 1940s, antibiotics have saved millions of lives. But as antibiotic use has grown, the bugs they were designed to kill have grown more resistant. Just a few years ago, for example, a commonly acquired bug known as *Staphylococcus aureus* was quickly felled by a penicillin relative called methicillin; today over 50% of hospital-acquired staph infections are methicillin resistant. Other top-selling antimicrobials such as the fluoroquinolones and vancomycin are also now facing increasing resistance.

Although the need for new drugs is on the rise, the number of successful new antibiotics has been on the wane in recent years. According to John Powers, an infectious-diseases specialist at the U.S. Food and Drug Administration (FDA), 16 new antibacterials were approved by FDA from 1983 to 1987, whereas just nine passed approval from 1998 to 2003. And according to IDSA, only two of the compounds developed in the last 5 years had a novel mode of action, which helps evade resistance. Mark Goldberger, the acting deputy director of FDA's Center for Drug Evaluation and Research in Rockville, Maryland, agrees that there is "a concern that we are not seeing as many innovative compounds as we would like."

The picture's not likely to improve anytime soon. IDSA's recent survey of 11 of the largest pharmaceutical companies found that of the estimated 400 compounds the companies have in development, only five are antibacterials. And if companies continue to scrap research programs, they will have a "big problem" trying to make up the lost ground later, Gilbert says: "Discovery is not an easy or quick process. There is a huge start-up phase." Goldberger adds, "If you wait until there is a significant problem" with resistance, it will be "too late."

Industry analysts give several reasons for the declining interest in antibiotics R&D; all boil down to money. First, it's a highly competitive market, filled with products that are typically cheap and effective, says Frank Douglas, chief scientific officer of Aventis in Frankfurt, Germany. Targeting a drug to a resistant organism may not improve its chances. It's a "tough sell because of the limited market size," Goldberger says.

Second, there's a built-in brake on success. Doctors and public health officials are reluctant to use new compounds; they want to save them as a last line of defense against resistant organisms. "Drug companies have to spend a lot of money generating a drug that the medical community wants to hold in abeyance," says Peter Traber, who became the president of Baylor College of Medicine in Houston, Texas, last year after serving as the chief medical officer for GlaxoSmithKline, the world's second largest pharmaceutical company.

Antibiotics also buck another trend: They treat acute conditions and work quickly, whereas companies have become more interested in compounds that treat long-term, chronic conditions, such as obesity and high cholesterol. "As a consumer, you want a drug you don't have to take very long and works very well," Goldberger says. But that isn't the most profitable type of drug. He adds that "in some cases the economics and the public health imperative do not match up."

Drug Resistance in Hospital-Acquired Infections

Drug/pathogen	Resistance (%)
Vancomycin/enterococci	24.7
Methicillin/*S. aureus*	53.6
Methicillin/Coag.-neg. *S. aureus*	88.2
3rd-gen. cephalosporin/*E. coli*	3.9
3rd-gen. ceph./*K. pneumoniae*	10.4
Imipenem/*P. aeruginosa*	16.4
Quinolone/*P. aeruginosa*	23.0
3rd-gen. ceph./*P. aeruginosa*	20.6
3rd-gen. ceph./*Enterobacter*	33.1

The problem is getting some attention. Last month, IDSA leaders met with FDA Commissioner Mark McClellan in an effort to make the field more attractive to industry. Goldberger, who attended the meeting, says FDA is looking at ways to streamline the drug-approval process for antibiotics and allow companies to track a compound's effect on biomarkers linked to disease, a move that should simplify clinical trials and reduce their cost.

But such changes, even if they are adopted, may not improve the underlying economics. IDSA is pushing more sweeping ideas. One proposal would ask FDA to develop a priority list of antimicrobial drugs that need to be developed. One proposal would ask companies to invest in products on the list and get in return extended-life patents on these or other products. This would require congressional authorization, and no such bill has yet been introduced. But if such a bill were to pass, it could mean billions of dollars in extra revenues—and possibly a new R&D boom—for antibiotic developers.

Consumers might view this sort of award for drugmakers as bitter medicine, Gilbert acknowledges. But he thinks it may be necessary medicine all the same. **–R.F.S.**

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