A fact sheet from THE PEW CHARITABLE TRUSTS | June 2016

A Scientific Roadmap for Antibiotic Discovery

A sustained and robust pipeline of new antibacterial drugs and therapies is critical to preserve public health

Overview

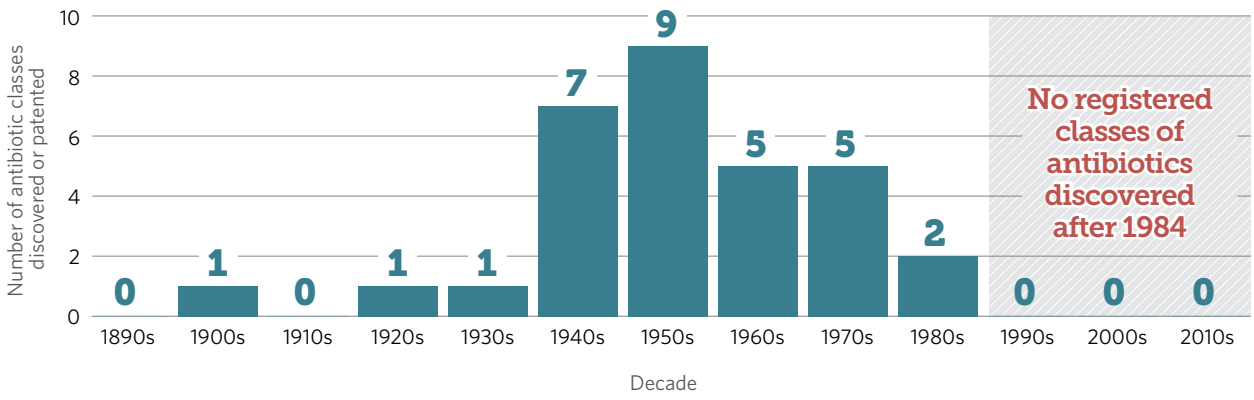
Every year, more than 2 million people in the United States contract a drug-resistant bacterial infection, and 23,000 die as a result. Yet, there are too few new antibiotics in development to meet patient needs. Underpinning the problem are fundamental gaps in scientific research that hinder drug discovery.

State of the field

Antibiotic discovery peaked in the 1950s, but then dropped precipitously from the 1980s onward. (See Figure 1.)[1] Every antibiotic in clinical use today is based on a discovery made more than 30 years ago.[2]

Figure 1

More Than 30-Year Void in Discovery of New Types of Antibiotics



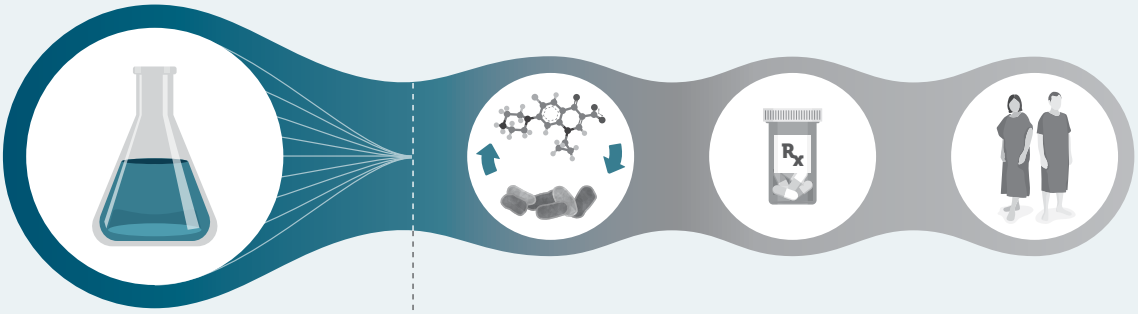
Source: Adapted from Lynn L. Silver, "Challenges of Antibacterial Discovery," *Clinical Microbiology Reviews* 24, no. 1 (2011): 71–109, doi: 10.1128/CMR.00030-10.

Why Do We Need New Classes of Antibiotics?

Antibiotics can be categorized based on similarities in their chemical structures (i.e. antibiotic classes). Resistance to one antibiotic often leads to resistance to multiple antibiotics within the same class.

Most large pharmaceutical companies are no longer actively searching for new antibiotics. Neither the small companies that continue to develop new drugs nor the academic researchers focused on this problem are well positioned to tackle the scientific challenges facing the field as a whole. (See Figure 2.)

Figure 2
Scientific Barriers Impede Antibiotic Discovery



Basic research
Scientists build on biological and chemical understanding

Scientific barriers

Discovery research
Scientists search for or design compounds that could eventually become approved medicines

Development
The process of bringing a new drug to the market

Delivery
Patient care

- **Drug discovery:** the process of finding or designing new molecules that could someday lead to candidate drugs.
- **Drug development:** the process of rigorously testing a drug candidate for safety and efficacy in order to bring a new drug to market.

Scientific barriers to antibiotic discovery

There are three key scientific barriers to the discovery of new antibiotics and the advancement of novel therapies.

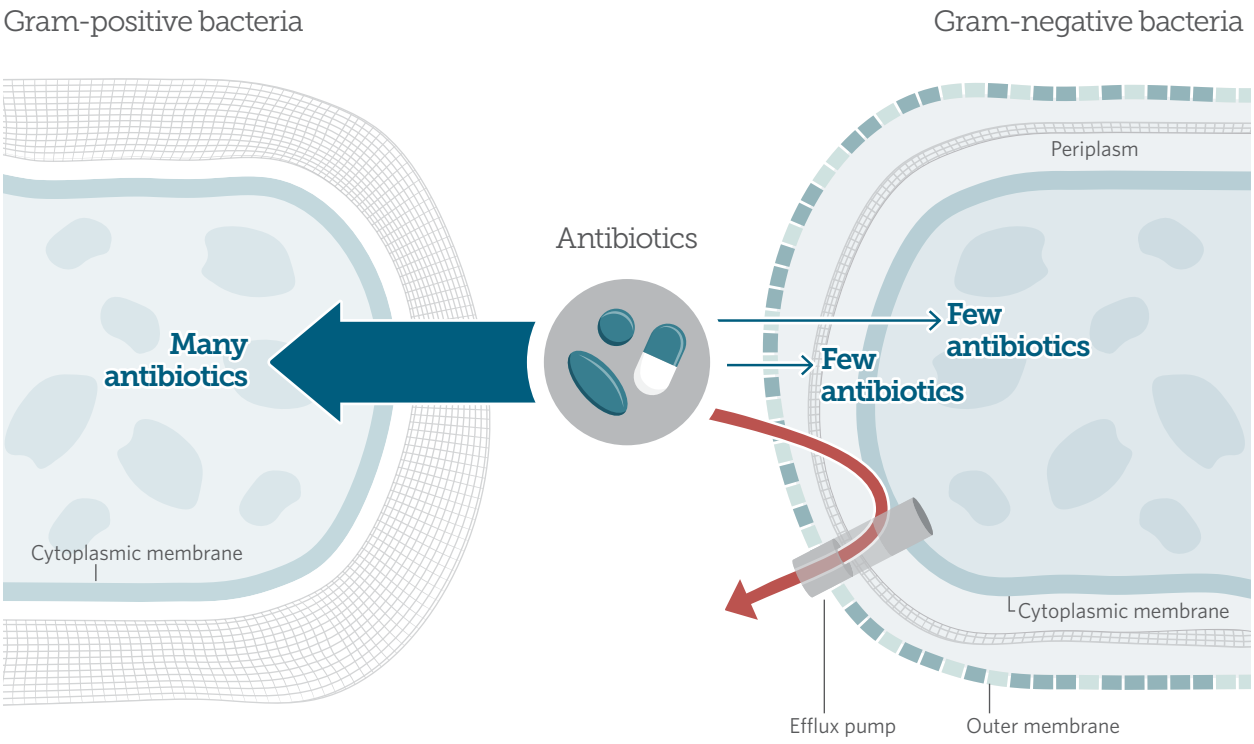
The first is the need to overcome the multiple defenses of drug-resistant Gram-negative pathogens, bacteria which cause some of the most deadly infections.[3] Gram-negative bacteria have two membranes and protein "pumps" that actively expel drugs from the cell—built-in defense mechanisms against many antibiotics. (See Figure 3.) This is only one of the critical challenges that scientists must address to better find and design starting points for new drugs.

Second, of the millions of molecules available in existing chemical collections, few have the properties needed to enter and stay inside Gram-negative bacteria; finding a molecule that may lead to a potential antibiotic is astonishingly difficult. To increase the odds of success, scientists need to experiment to figure out which types of molecules can get into the bacterial cell and which cannot, in order to create guidelines for finding the molecules that work. This would allow for the creation of collections of promising molecules that researchers everywhere could use to more effectively search for new antibiotics.

Finally, entirely new approaches to treating infections must be studied. Biologics, immunotherapies, and anti-virulence therapies have shown promise as alternatives to traditional antibiotic therapy. But there is a need for more standard tools with which to assess these methods, such as new proof-of-concept studies and experimental models to predict whether these novel approaches might work in the clinic.

Figure 3

Barriers to Antibiotic Entry Into Gram-Negative Bacteria



Why Are There So Few Antibiotics to Treat Gram-Negative Infections?

Bacteria have evolved ways to prevent the entry of unwanted or toxic compounds such as antibiotics. Gram-positive bacteria have a membrane barrier that is relatively easy to penetrate, so many types of antibiotics get into the cell. Gram-negative bacteria have a double membrane along with a variety of efflux pumps that expel drugs from the cell, making it difficult to design new antibiotics that target Gram-negative pathogens.

Pew's roadmap for antibiotic discovery

To overcome the barriers to antibiotic discovery, The Pew Charitable Trusts has proposed a strategy to fund research tackling the key questions outlined above. It draws on input from leading antibiotic discovery experts in industry, academia, government, and the nonprofit sector.

In addition, the roadmap highlights growing concern that valuable institutional knowledge and expertise are at risk of being lost as industry teams are downsized or shuttered, and antibiotic scientists retire or shift to different biomedical areas. Collating the existing body of research, and making it available to scientists who need this information, would promote knowledge-sharing and help reinvigorate the research landscape.

Pew's *Scientific Roadmap for Antibiotic Discovery* report seeks to build a sustainable and robust foundation for the discovery of new antibiotics over the decades to come. The roadmap recognizes the need for full-time scientific leadership and identifies a concrete, targeted approach to tackle the basic scientific barriers impeding antibiotic discovery—which includes better understanding how to overcome the defenses of Gram-negative bacteria, developing tools and technologies for scientists to generate new molecules tailored for antibiotic discovery, evaluating promising alternatives to traditional antibiotic use, and establishing a framework for sharing information, expertise, and materials across the antibiotic research community. These are critical next steps to fostering innovation and spurring the discovery of new antibiotics.

Endnotes

1 Adapted from Lynn L. Silver, "Challenges of Antibacterial Discovery," *Clinical Microbiology Reviews* 24, no. 1 (2011): 71–109, doi: 10.1128/CMR.00030-10.

2 Cynthia C. Knapp and John A. Washington, "Antistaphylococcal Activity of a Cyclic Peptide, LY146032, and Vancomycin," *Antimicrobial Agents and Chemotherapy* 30, no. 6 (1986): 938–39, doi:10.1128/AAC.30.6.938.

3 U.S. Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States*, 2013 (2013), http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

For further information, please visit:

pewtrusts.org/antibiotic-discovery

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