Miracle Drugs vs. Superbugs

Preserving The Usefulness Of Antibiotics

by Tamar Nordenberg

The historical scourge known as the bubonic plague killed up to one-third of Europe's population in the 1300s. But in modern times, it has been controlled handily with the help of antibiotic drugs such as streptomycin, gentamicin and chloramphenical.

That is, until 1995, when a plague infection in a 16-year-old boy from Madagascar failed to respond to the usual antibiotic treatments. This first documented case of an antibiotic-resistant plague, reported in the September 1997 *New England Journal of Medicine*, eventually succumbed to another antibiotic.

In the United States and globally, many other infectious germs, including those that cause pneumonia, ear infections, acne, gonorrhea, urinary tract infections, meningitis, and tuberculosis, can now outwit some of the most commonly used antibiotics and their synthetic counterparts, antimicrobials. According to the Mayo Clinic in Rochester, Minn., drug resistance may have contributed to the 58 percent rise in infectious disease deaths among Americans between 1980 and 1992.

Antibiotic resistance isn't a new problem; resistant disease strains began emerging not long after the discovery of antibiotics more than 50 years ago. Penicillin and other antibiotics, which were initially viewed as miracle drugs for their ability to cure such serious and often life-threatening diseases as bacterial meningitis, typhoid fever, and rheumatic fever, soon were challenged by some defiant strains.

"What's different now," explains David Bell, M.D., an expert on antimicrobial resistance with the national Centers for Disease Control and Prevention, "is that we've reached a situation where it's no longer an isolated problem of this bug or that bug; virtually all important human pathogens treatable with antibiotics have developed some resistance."

Despite the frightening trend, most people aren't likely to encounter a "superbug" that can outsmart all antibiotics, says Mark Goldberger, M.D., director of the Food and Drug Administration's division of special pathogen and immunologic drug products. "For the average person walking around on the street, the risk at the moment remains low."

Still, as one antibiotic's effectiveness wanes, doctors are forced in many cases to rely on more expensive and toxic drugs. Resistance is "a big problem and growing," says Linda Tollefson, director of surveillance and compliance in FDA's Center for Veterinary Medicine. "You're dealing with living microbes that have shown an incredible ability to accommodate antibiotics and come out winning. We have no idea what they are going to do next. Our fear is that we're seeing the tip of the iceberg."

To stop infectious germs from gaining ground, experts the world over, including doctors and scientists from FDA, CDC, and the World Health Organization, have been focusing since 1995 on finding ways to prolong the lives of antibiotics and to encourage drug companies to develop new "miracle drugs."

Survival of the Fittest

Every time a patient takes penicillin or another antibiotic for a bacterial infection, the drug may kill most of the bacteria. But a few tenacious germs may survive by mutating or acquiring resistance genes from other bacteria. These surviving genes can multiply quickly, creating drug-resistant strains. The presence of these strains may mean that the patient's next infection will not respond to the first-choice antibiotic therapy. Also, the resistant bacteria may be transmitted to others in the patient's community.

Experts say the risk is greatest, but still not high, for those in hospitals, nursing homes, and other settings where

© Culver Pictures, 1995

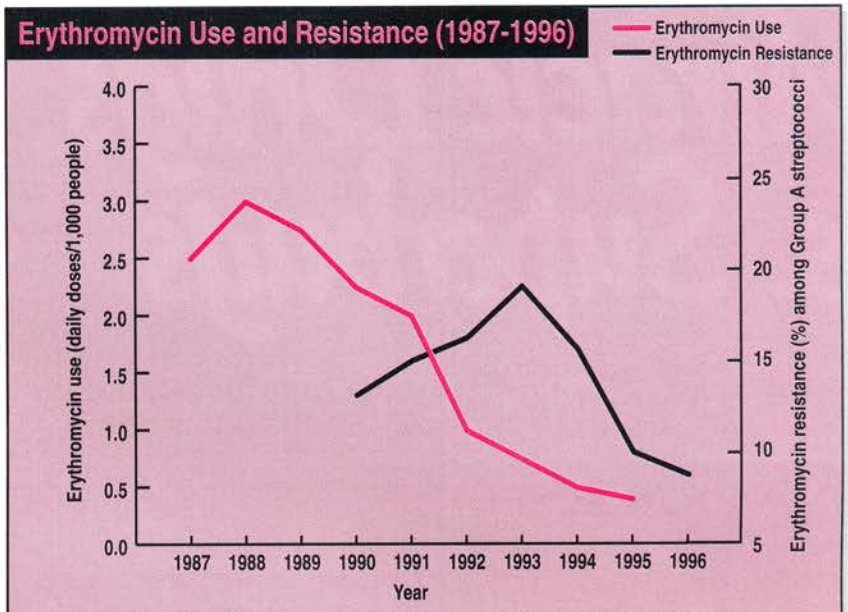
Sir Alexander Fleming's discovery in 1928 of the first antibiotic, penicillin, meant a cure for such dangerous and sometimes-fatal diseases as typhoid fever and rheumatic fever.

ILLUSTRATION BY JACK PARDUE

people tend to be sick often. In these environments, people may be taking an array of antibiotics (one researcher estimates that 25 to 40 percent of hospital patients get intravenous antibiotics), increasing the chance of a resistant germ originating within their own bodies. Also, hospitalized patients are surrounded by others whose infectious diseases may spread, and their immune systems may be weakened and incapable of beating the infectious bugs.

Organisms that have already developed defenses against antibiotic attack include:

• *Staphylococcus aureus.* This bacterium, which is the biggest cause of infections in patients in U.S. hospitals, can infect burns, skin, and surgical wounds. Since 1996, at least four patients—three in the United States and one in Japan—reportedly were infected with a strain that was partially resistant to normal doses of the powerful, last-resort anti-



These data from Finland suggest that as fewer doses (measured in units called "defined daily doses" per 1,000 inhabitants per day) of the antibiotic erythromycin were taken to treat group A streptococci, a decrease in resistance followed several years later.

(Source: Centers for Disease Control and Prevention CAUSE newsletter, October 1997)

Animal Use: Medicine and More

While the numbers have not been established with certainty, drug resistance expert Stuart Levy, M.D., has estimated that, of the 50 million pounds of antibiotics produced in the United States, over 40 percent are used not to treat human disease but for farm animals and agricultural crops.

Writing in the May 7, 1998, *New England Journal of Medicine,* Levy states that some 20 percent of this amount is used in therapeutic doses to treat sick animals. The rest is used in lower doses to promote food animals' growth, prevent disease in an entire herd or flock, or protect crops from disease.

Scientists fear that certain bacteria that develop resistance in animals can then infect people who eat meat or other animal products. It is difficult to measure precisely the impact on human health of the use of antibiotics in farm animals, but experts believe that, already, resistant strains of *Salmonella*, *Campylobacter*, *Enterococcus*, and *E. coli* have been transmitted from animals to people.

But farmers count on antibiotics to keep their animals healthy, and healthy animals, experts point out, may translate into a safer and more abundant U.S. food supply. Keeping in mind the vital protective role of antibiotics in the food chain, FDA's Center for Veterinary Medicine, the World Health Organization, the Centers for Disease Control and Prevention, and the animal industry are seeking ways to prevent the overuse and misuse of antibiotics in animals, while not interfering with necessary uses. FDA's Center for Veterinary Medicine and CDC are working with the American Veterinary Medical Association to develop recommendations and an educational campaign on the judicious veterinary use of antimicrobials.

One issue that is receiving ongoing attention is the use of fluoroquinolones in food animals. The agency approved drugs in this class of antibiotics in 1995 to treat disease in poultry and in July 1998 to treat disease in cattle. The agency has banned other, unapproved uses of fluoroquinolones. At a WHO meeting in Geneva earlier this year, which included FDA representatives, participants urged further research into the public health impact of fluoroquinolone use in animals.

For any animal drug that raises a public health concern, FDA may begin to require evidence before approval that it will not create drug-resistant food-borne pathogens that can harm human health. But drug resistance may be difficult to predict based solely on preapproval studies, says Sharon Thompson of the agency's Center for Veterinary Medicine, so the agency may also require companies to monitor their animal antimicrobials for drug resistance once they are on the market. FDA plans to have a public meeting as early as this fall to discuss whether the agency should require drug sponsors to conduct such studies.

In addition to information collected by the drug company, FDA, CDC, and the U.S. Department of Agriculture look for trends toward resistance in humans and animals through the National Antimicrobial Resistance Monitoring System. Under this key part of FDA's strategy to address antibiotic resistance, scientists collect *Salmonella*, *E. coli,* and *Campylobacter* from sick animals and humans, healthy farm animals, and animal carcasses, and check if the bacteria are becoming less susceptible to any of 17 antimicrobial drugs. ■

—T.N.

biotic vancomycin. Some strains of *S. aureus* have already shown resistance to all antibiotics other than vancomycin, raising the fear that an invincible strain is near at hand.

- *Enterococcus.* This organism can cause everything from urinary tract to heart valve infections. Some strains can outmatch many previously effective antibiotics.
- *Streptococcus pneumoniae.* Up to 30 percent of the strains of this bacterium, which can cause pneumonia, meningitis, and ear infections, are at least partially resistant to antibiotics in the penicillin family, according to the Mayo Clinic.

Other germs that have grown resistant to formerly reliable antibiotics include *Neisseria gonorrhoeae,* the cause of the sexually transmitted disease gonorrhea; the food poisoners *Salmonella, Escherichia coli (E. coli)* and other Enterobacteriaceae; and *Mycobacterium tuberculosis,* which causes TB.

Luckily, Goldberger says, there is a renewed interest among U.S. drug companies in developing new antibiotics to target organisms that are developing resistance. Earlier this year, an FDA advisory panel recommended approval for the antibiotic Synercid. If approved, it could be used to treat such hospital-acquired infections as pneumonia and some vancomycin-resistant infections of the bloodstream.

Too Much of a Good Thing

Experts say that doctors are sometimes quick to prescribe antibiotics for all sorts of symptoms, even though antibiotics work only against bacterial infections, not viruses such as the flu or the common cold. More than 50 million of the 150 million antibiotic prescriptions written each year for patients outside of hospitals are unnecessary, according to a recent CDC study. (See chart.)

Sometimes, doctors lack knowledge about the symptoms and natural course of respiratory illnesses, which contributes to overuse, according to a CDC editorial in the Sept. 17, 1997, *Journal of the American Medical Association.* Also, many doctors have told CDC they sometimes write prescriptions simply to meet patient demands.

Patients therefore must take some of the responsibility for the overprescribing problem, according to Stuart Levy, M.D., director of Tufts University's Center for Adaptation Genetics and Drug Resistance. "Patients have been left out of the formula. Overuse of antibiotics was felt to be a physicians' problem when it is really as much a patient problem."

Patients can do their part to help curb resistance:

- Don't demand an antibiotic when the health-care provider determines one isn't appropriate.
- Finish each prescription. Even when the symptoms of an illness have disappeared, some bacteria may still survive and reproduce if the patient doesn't complete the course of treatment.
- Don't take leftover antibiotics or antibiotics prescribed for someone else. These antibiotics may not be appropriate for the current symptoms, and taking the wrong medicine could delay getting appropriate treatment and allow bacteria to multiply.

For more tips on the proper use of antibiotics, visit the Website of the Alliance for the Prudent Use of Antibiotics (*www.healthsci.tufts.edu/apua/patient.htm*).

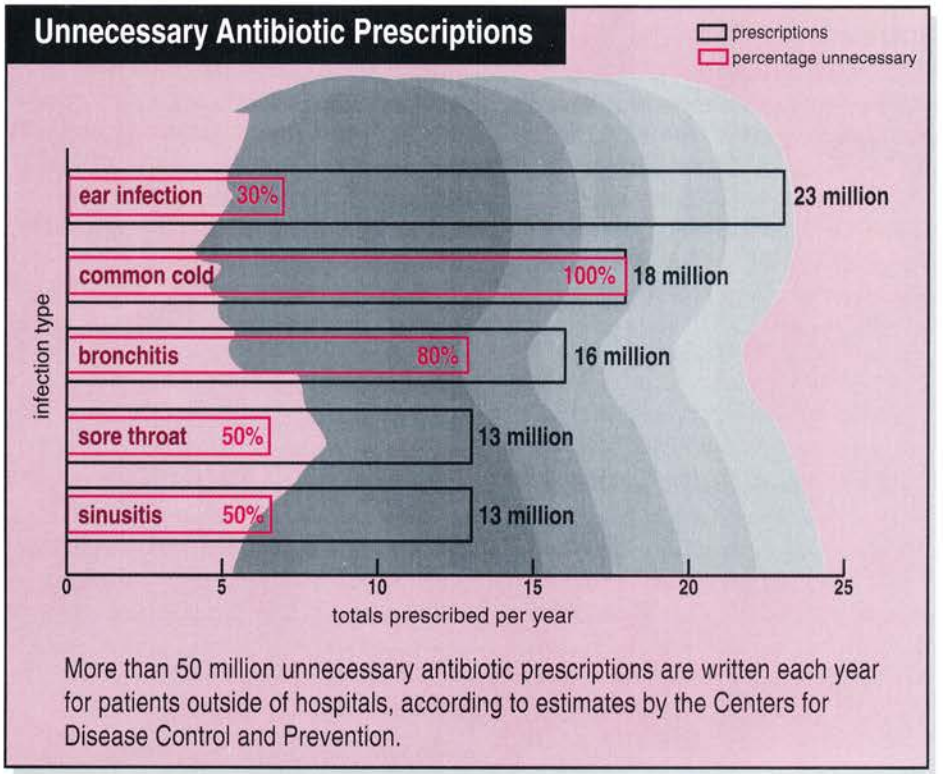
Even when used carefully, all organisms can devèlop some resistance to antibiotics over time. "It is a perfectly natural phenomenon for a living organism to develop the means of survival in a hostile environment," wrote French microbiologist Jacques Acar in a 1997 article in *World Health.*

Preventing infection in the first place may therefore be the best defense against an antibiotic-resistant infection.

Frequent and thorough hand washing is one key to preventing the spread of infection. Good kitchen habits, such as storing foods at the proper temperature, washing fruits and vegetables thoroughly, and cooking foods completely, can also reduce the chance of getting a food-borne illness. (See "Can Your Kitchen Pass the Food Safety Test?" in the October 1995 *FDA Consumer.*)

"Take your basic precautions," Bell advises. "That means practicing common hygiene, as well as food safety in your kitchen." ■

Tamar Nordenberg is a staff writer for FDA Consumer.



More than 50 million unnecessary antibiotic prescriptions are written each year for patients outside of hospitals, according to estimates by the Centers for Disease Control and Prevention.