SUPERBUGS DODGE SUPERDRUGS

AS ANTIBIOTIC RESISTANCE SPREADS

By Karen L. Brooks

STORY SUMMARY

- Once viewed as wonder drugs, antibiotics are losing effectiveness, and drug-resistant infections are on the rise.
- Excessive use of antibiotics in both humans and farm animals has intensified the problem.
- Pharmaceutical companies lack incentives to develop new antibiotics, and the pipeline is running dry.
- Efforts to control the spread of infection, enforce proper use of antibiotics and encourage new drug development are essential to curb resistance.

Terrorism. Climate change. Civil unrest. A skinned knee.

One of these things is not like the others, but experts say in the future, minor cuts and scrapes could rank among more obvious threats to global human safety as antibiotic resistance spreads and even simple infections become untreatable.

Once heralded as medical miracles, antibiotics are losing clout. The number of deaths triggered annually worldwide by drug-resistant organisms already surpasses the number caused by terrorist attacks and natural disasters. The U.S. Centers for Disease Control and Prevention estimates that bacteria resistant to antibiotics infect 2 million Americans and kill 23,000 every year.

"We had a pre-antibiotic era, we're in the antibiotic era and I don't think it's an understatement to say we're heading toward a post-antibiotic era," says Randi S. Silibovsky, MD, assistant professor of medicine and antibiotic stewardship clinician in Jefferson's Division of Infectious Diseases. "Today, if you scratch yourself and get an infection, you can treat it. But in the future, we may have no treatment left, and that infection could become deadly."

In A World Without Antibiotics... What Could Kill You?

- **A simple scratch** (before penicillin, one in nine skin infections killed)
- **Insect bites** (scratching opens wounds, exposing them to microbes from under your fingernails)
- **Minor burns**
- **A cold or the flu** (pneumonia can strike if a virus compromises your immune system, and one-third of pneumonia cases kill without antibiotics)
- **Any kind of surgery** (even minimally invasive procedures bring risk of infection)
- **Giving birth** (natural childbirth killed five mothers out of every 1,000 before antibiotics — and cesarean sections, obviously, are a surgery)
- **Treatments like dialysis or a blood transfusion**
- **Being hooked up to a ventilator**
- **Catheter insertion**
- **Implantation of any kind of medical device** (new joints, new heart valves, pacemakers)
- **Getting a tattoo**

How Resistance Happens

Bacteria are survivors. Some are naturally impervious to certain antibiotics; when drugs kill off susceptible bacteria, the resistant strains left behind are free to multiply and share their survival strategies with other bacteria. Bacteria can also grow resistant through mutation, their genetic code changing to enable them to rebuff an antibiotic. The wrong medications — or those taken in inadequate doses or stopped too early — will not destroy the altered microbes.

Although resistance develops inevitably over time, its spread has been expedited by a preventable phenomenon: improper use of antibiotics. Physicians have been over-prescribing the drugs since mass production of penicillin began in the early 1940s. About half of all antibiotics prescribed are unnecessary — and the more often antibiotics are used, the more opportunities bacteria have to outsmart them.

A recent study in *JAMA Internal Medicine* found that physicians prescribe antibiotics in 60 percent of all sore throat cases, even though only about 10 percent involve strep, the specific bug requiring antibiotics. Another study found physicians prescribe antibiotics in 73 percent of bronchitis cases, even though the vast majority are viral. Broad-spectrum agents, which act against a wide range of bacteria including the "good" kind, are the most overused, potentially setting patients up for more serious infections with resistant bacteria later on.

Physicians should know better than to write superfluous prescriptions, right? Unfortunately, say infectious disease experts, many patients demand antibiotics whenever they feel sick — and physicians comply to appease them.

"A doctor once told me, 'I'm on the phone for 30 seconds if I agree to prescribe an antibiotic. But if I explain to the patient why they don't need it, I'm on the phone for 20 minutes.' That was very telling. Patients want medication, and doctors give in," Silibovsky says.

William R. Short, MD, assistant professor of medicine in the Division of Infectious Diseases and infection control officer at Methodist Hospital, contrasts his peers' reaction to his large outpatient HIV practice with their reaction to his work promoting antibiotic stewardship, saying the difference reveals a lot about healthcare culture.

"Other healthcare professionals constantly say to me, 'Oh, caring for HIV patients must be so sad.' Why is it sad? We have a remarkable 29 drugs available, and regimens are simpler than ever. I put someone on the right medication, and they can live a long, normal life with HIV. It's not 1980 anymore," he says.

"But when these same people see someone with a drug-resistant infection, they never say, 'Wow, that's sad.' Physicians don't see the urgency unless they are infectious disease specialists. We look at the community from a big-picture public health perspective, whereas other practitioners usually focus on individual cases. That's why they are comfortable overprescribing antibiotics."

The Trouble with Farms

Excessive antibiotic use on farms — to prevent and treat infections among animals but even more so to accelerate growth and weight gain — has also empowered drug-resistant organisms.

Eighty percent of all antibiotics sold in the United States are used in meat and poultry production. The Food and Drug Administration has approved nearly 700 drugs for supplementing animal feed but, recognizing resistance as a growing threat, announced new guidelines in December 2013 to discourage their misuse. The guidelines ask animal drug manufacturers to change their labeling to prohibit the drugs' "non-therapeutic" use to help livestock grow and require licensed veterinarians to approve certain drugs' use on farms. Critics say the policies contain obvious loopholes; the label adjustments are voluntary, and the line between "therapeutic" and "non-therapeutic" use is blurry.

"It's not well documented yet that the widespread use of antibiotics in animal industry is driving antibiotic resistance, but there is a lot of speculation and new evidence showing that's the case. Further FDA efforts to revise policies are important, because anywhere antibiotics are used extensively, we will see resistance," says Kathleen E. Squires, MD, the W. Paul and Ida H. Havens Professor and Director of Infectious Diseases at Jefferson.

Many bills have proposed an absolute ban on antibiotic use in animals, but farmers and pharmaceutical companies

have been able to deflect them. As far back as 1977, the FDA warned that excessive use of penicillin and tetracycline in livestock could promote new superbugs — but industry lobbyists crushed a recommended prohibition, and the FDA hasn't pushed another ban since.

Threats and Consequences

Patients are already dying from antibiotic-resistant infections, and resistant organisms are spreading at a rapid rate, even crossing international boundaries with ease.

"We're having to recycle old drugs that may have severe adverse effects or use different pharmacokinetic principles of the drugs to overcome resistance, and in some cases we are only left with one or two last-line antibiotics that are very toxic to the kidneys. Patients cannot tolerate them. Plus, they are intravenous, and putting in a central line brings its own set of complications. It's madness," Short says.

The biggest "superbug" threat, experts say, is from multi-drug-resistant gram-negative bacteria such as Enterobacteriaceae — a family that includes *Salmonella* and *E. coli* and is resistant to carbapenems, once the strongest group of antibiotics we had. According to the CDC, about 9,000 drug-resistant infections from these germs occurred last year. In 1998, there was just one case.

Another top concern is the highly contagious *Clostridium difficile*, which causes life-threatening diarrhea and kills more than 14,000 Americans a year. Although there are still drugs that work against *C. difficile*, the bacteria are resistant to many antibiotics.

"People who are what I call 'health-care experienced' are at the greatest risk of these infections: patients residing in nursing homes or other long-term care facilities, patients on hemodialysis, patients who have been hospitalized frequently or for a long time," says Bryan D. Hess, MD '06, a clinician in Jefferson's Division of Infectious Diseases. "But healthy people could be susceptible, too."

Short predicts a trend toward resistant bugs infecting more healthy individuals.

"A good example of the change that's occurring is MRSA (methicillin-resistant *Staphylococcus aureus*), which back in the 1980s was strictly a hospital-associated bug. Over the past decade, MRSA has spread out into the community, which was unheard of in the past. This shows the bug's evolution and puts into perspective how it's spilling out into community. I think it's where we're going with many superbugs," he says.

In addition to threatening lives, drug-resistant infections add significant costs to the U.S. healthcare system, requiring expensive and prolonged treatments and extended hospital stays. The exact economic burden is difficult to gauge, but estimates have reached $20 billion annually in direct healthcare costs, with additional societal costs from lost productivity as high as $35 billion.

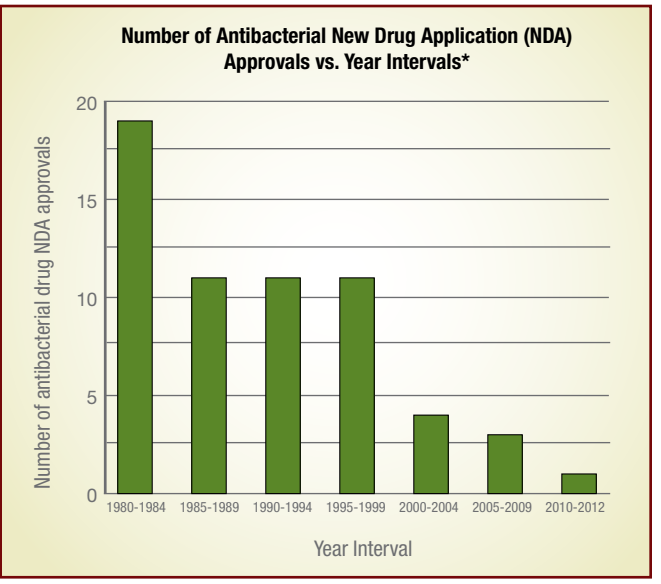
Can't We Just Make New Drugs?

Complicating resistance's spread is the disturbingly low number of new antibiotics in the pipeline. FDA approvals of new antibiotics have dropped nearly 90 percent over the last 30 years. In the past 15 years, just 15 antibiotics have been approved — whereas in the preceding 15 years, there were 40.

Since resistance builds naturally over time, new antibiotics must continually replace old ones. But pharmaceutical companies' efforts to develop new antibiotics decreased rapidly in the 1990s, when they started focusing more on drugs for chronic diseases, which are taken long term and promise greater profit. Companies spend between $800 million and $1.7 billion on every new drug — a hefty expense for drugs that are taken for just weeks at a time and will eventually lose effectiveness.

Tomorrow's Antibiotics: The Drug Pipeline

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.



*Intervals from 1980 to 2009 are five-year intervals; 2010-2012 is a three-year interval. Drugs are limited to systemic agents.
Data courtesy of the FDA's Center for Drug Evaluation and Research.

"The pharmaceutical industry is not incentivized to develop antibiotics. These are for-profit companies looking for disease areas in which they can be first, second or third in developing a new kind of specialized drug and dominate the market," Squires says.

Resistance has accelerated over time as antibiotics have become cheaper and more broadly prescribed. Signs of resistance against two newer antibiotics — linezolid, introduced in 2000, and daptomycin, introduced in 2003 — appeared within a few years.

Harnessing the Problem

Fighting drug-resistant organisms requires preventing their spread and improving the use of antibiotics we already have — initiatives heavily promoted at Jefferson, where an antibiotic stewardship team supervises inpatient antibiotic administration, ensuring the drugs are used in the right circumstances, at the right doses and for the right duration.

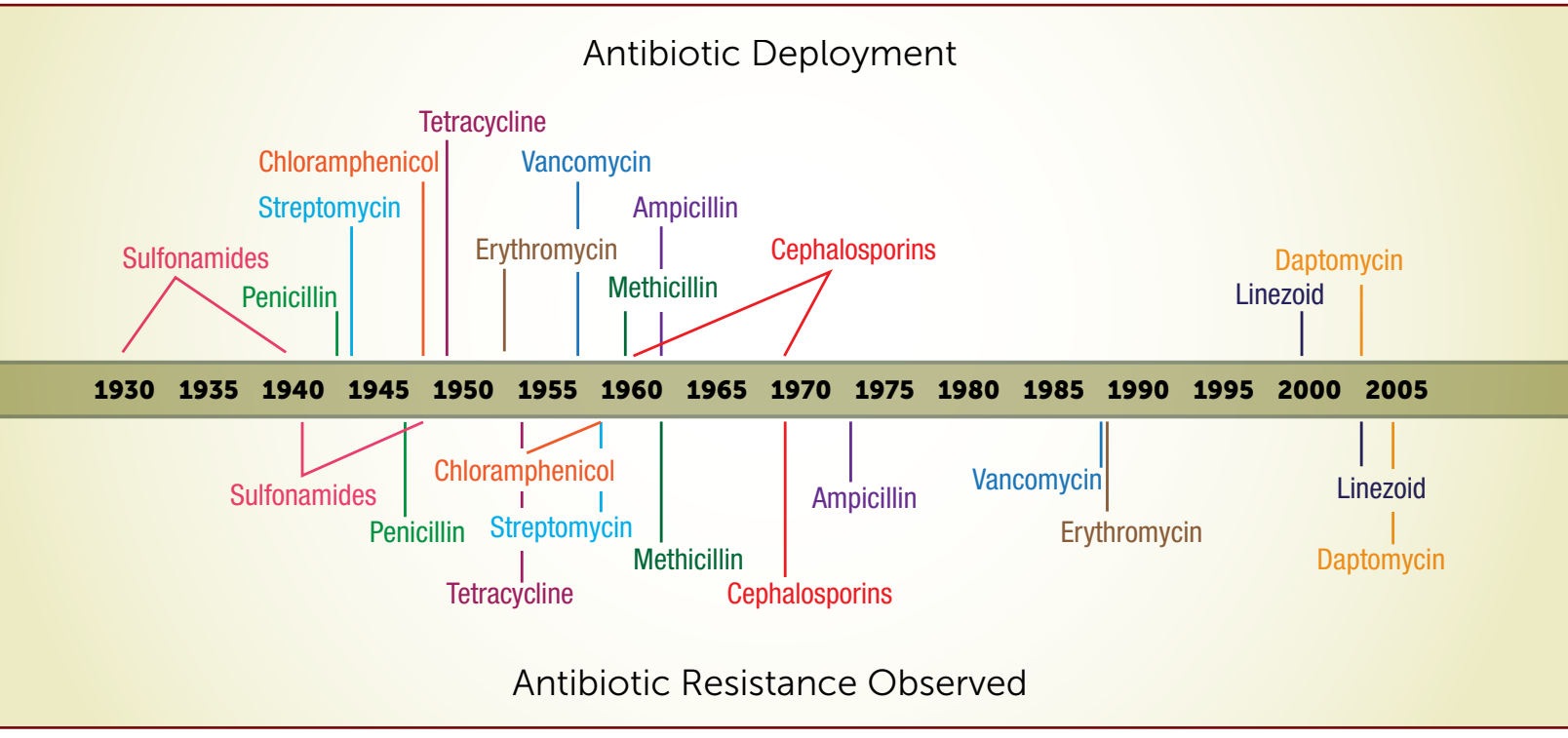
"There's always been an infectious disease pharmacy specialist whose job was to monitor antibiotic use, but now we have an infectious disease physician leader. Physicians don't want to take orders from pharmacists; they listen better to their peers," says Phyllis R. Flomenberg, MD, associate professor of medicine and infection control officer.

Flomenberg stresses the importance of enforcing hand hygiene protocols in the hospital. "We have an anonymous task force observing and reporting people who don't wash their hands properly. It's an effective system for physicians — nobody wants to be on the 'bad list,'" she says.

Hess emphasizes the precautions taken when a patient has a known drug-resistant organism. "Person-to-person spread is a big concern. Any patient identified as a carrier of a one of these organisms is placed on contact isolation and only approached by people wearing gowns and gloves," he says.

In January 2014, the Society for Healthcare Epidemiology of America, whose mission is to prevent infections in healthcare environments, issued new recommendations on what caregivers should wear. Although no one has found a concrete connection between hospital uniforms and infections, studies have detected bugs on the sleeves and pockets of coats and scrubs. One study found that a third of physicians' neckties grew *Staphylococcus aureus* in the lab and determined the germs were drug resistant. As a result, the new guidelines advise short sleeves, bare hands and white coats that are laundered at least once a week — and taken off during physical exams — as well as the removal of ties, watches and rings.

"Wearing the appropriate protection is not just important for clinicians. A critical piece is educating family members,



The year each antibiotic was deployed is depicted above the timeline; the year resistance was observed is depicted below. The appearance of resistance does not necessarily indicate that a given antibiotic has lost all clinical utility.

What Bacteria Present the Greatest Threat?

The Centers for Disease Control and Prevention has classified drug-resistant bacteria into three categories: urgent, serious and concerning.

Urgent Threats

Carbapenem-resistant *Enterobacteriaceae* (CRE)
Clostridium difficile (C. diff)
Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

Multidrug-resistant *Acinetobacter*
Drug-resistant *Campylobacter*
Fluconazole-resistant Candida (a fungus)
Extended spectrum ß-lactamase-producing *Enterobacteriaceae* (ESBL)
Vancomycin-resistant *Enterecoccus* (VRE)
Multidrug-resistant *Pseudomonas aeruginosa*
Drug-resistant non-typhoidal *Salmonella*
Drug-resistant *Salmonella typhi*
Drug-resistant *Shigella*
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Drug-resistant *Streptococcus pneumonia*
Drug-resistant tuberculosis

Concerning Threats

Vancomycin-resistant *Staphylococcus aureus* (VRSA)
Erythromycin-resistant Group A *Streptococcus*
Clindamycin-resistant Group B *Streptococcus*

Estimated number of illnesses and deaths in America caused by antibiotic resistance every year:

2,049,442 illnesses
23,000 deaths

who never want to wear gowns when visiting and don't understand that it's for the benefit of the greater community," Short says.

Scientists are testing new methods of fighting superbugs, such as combining substances like silver with antibiotics to make them more powerful. Other researchers are using genetic sequencing of bacteria to help develop new germ-killing drugs, and some aren't looking to kill the bugs at all, but rather to make them less harmful. Since bacteria only cause infections when their population has grown to a certain level, called a quorum, scientists are trying to disrupt the chemical signals the germs use to communicate.

Entities such as the U.S. Biodefense Advanced Research and Development Agency, the National Institutes of Allergy and Infectious Diseases and the Department of Defense are encouraging the development of new antibiotics by offering funding opportunities. In July 2012, President Barack Obama signed the Generating Antibiotic Incentives Now, or GAIN, Act, which extends by five years the exclusivity period during which certain antibiotics can be sold without generic competition. And in December 2013, bipartisan House of Representatives members introduced a bill to provide a fast-track route to FDA approval for promising new antibiotics. The bill would allow the FDA to approve antibiotics needed for life-threatening infections based on data from smaller clinical trials — an incentive that could save companies a lot of money.

"Bacteria are not going to go away and are actually an important part of our lives. We need bacteria on our skin to protect us from the environment and inside our bodies to assist our metabolic processes," Squires says. "But if we get to the point where we have dangerous bacteria that are resistant to all the antibiotics we have, people will simply keep dying. We need to find new ways to treat them." ■