

Fighting Superbugs

Are disease-resistant bacteria becoming unstoppable?

Antibiotics — the wonder drugs of the 20th century — are gradually losing their clout. Bacteria naturally develop resistance to antimicrobial drugs. In recent years, however, overuse of antibiotics has caused a growing number of staphylococcus bacteria to evolve into disease-causing “superbugs” resistant to drugs like methicillin. Hospital patients with MRSA — a potent antibiotic-resistant staph infection — are four times as likely to die as other patients. Moreover, while most superbugs once thrived only in hospitals, new strains outside health facilities are killing healthy people. Adding to the concerns of public-health officials, drug companies are developing few new antimicrobials. Some activists urge strong curbs on all antimicrobial use, including to promote fast growth in farm animals. Others oppose legal requirements for animal or human antibiotics, arguing that voluntary efforts are better able to keep pace with the fast-evolving world of microbes.



Bryce Smith, a youngster from Santee, Calif., almost died after contracting what doctors belatedly identified as the MRSA superbug. He recovered after 49 days in intensive care.

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Fighting Superbugs

BY MARCIA CLEMMITT

THE ISSUES

In late January, 12-year-old Carlos Don — a sixth-grader in Ramona, Calif., who loved playing football and racing motorcycles — returned from several days at a school-sponsored trip with flulike symptoms. The local urgent-care center diagnosed pneumonia and assured his parents he'd be fine once antibiotics kicked in.

But within days Carlos was hospitalized and breathing with the aid of a ventilator. On Feb. 4, with his heart, lungs and other organs too damaged to function, he was taken off the ventilator. The cause of death was an often-fatal bacteria widely known as MRSA (methicillin-resistant staphylococcus aureus).¹

Staph infections were once easily treatable with antibiotics. Over the past few decades, however, more staph bacteria and other pathogens — microbes that make us sick — have evolved into bacteria that are resistant to antibiotics like methicillin and cephalosporin — dubbed superbugs.

Until recently, MRSA mainly infected hospital patients. Today, however, many resistant bacteria are acquired outside hospitals, like the staph infection Carlos contracted. Known as CA-MRSA (community-acquired MRSA), it seems to be even more dangerous than its hospital-acquired cousin, HA-MRSA.

An antibiotic is designed to kill specific bacteria, but they can mutate and become resistant to the drug. Over time, such antibiotic-resistant bacteria can survive and multiply, producing an entire population of bugs that are difficult or impossible to kill with ex-



Infectious Disease Society of America

Doctors diagnosed pneumonia when 12-year-old Carlos Don, of Ramona, Calif., became ill in late January, but his flulike symptoms actually were caused by the antibiotic-resistant staph infection known as MRSA, and he died on Feb. 4. Once easily treated, staph infections have become drug resistant. A resistant pathogen that often afflicts wounded soldiers in Iraq has forced many infected limbs to be amputated.

isting antibiotics, especially frequently used antibiotics. * (To reduce the chance that bacteria will become resistant, doctors urge patients to take all the antibiotics they are prescribed, even after an infection has been cleared up, because not using all the prescribed pills tends to kill off just the weaker bugs, leaving behind the stronger, more resistant bacteria.)

Shortly after antibiotics came into use in the 1940s, scientists and doctors observed that some bugs developed resistance, but only now are they

* Antibiotics kill bacteria but not viruses, such as the common cold, flu and HIV/AIDS.

beginning to understand the true scope of the danger from superbugs. Each antibiotic is “like a tank of gasoline,” good for only so many uses, says John H. Powers, former lead medical officer for Antimicrobial Drug Development and Resistance Initiatives at the Food and Drug Administration (FDA).

“When it runs out, it runs out,” says Powers, now senior medical scientist at Maryland-based SAIC Frederick, Inc., a research contractor for the National Institute of Allergy and Infectious Diseases.

Community-acquired MRSA may be the most frightening of the newly resistant pathogens, as Dee Dee Wallace, a 47-year-old mother of two in Mahotah, Wis., discovered late last year when she developed several skin infections. Her doctors thought they were minor, but after a “little red bump” on Wallace’s knee “turned into white blisters,” then “deep bone pain,” doctors cultured her infection and discovered drug-resistant “flesh-eating” staph, she says.

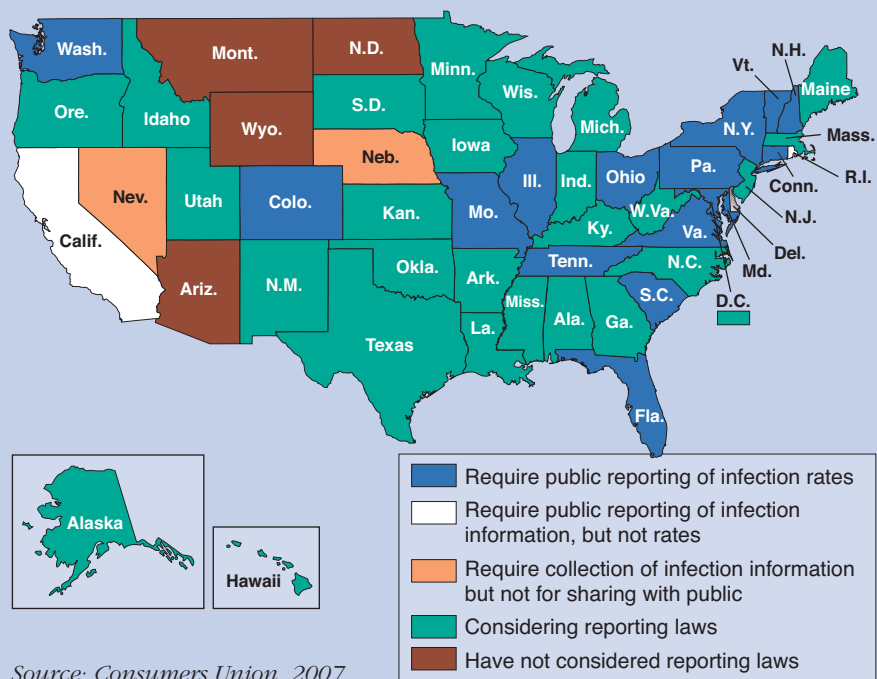
Even the surgery that removed a chunk of her abscessed flesh — “down to where my husband could see the muscle lying on the bone” — didn’t end Wallace’s troubles. The bug lingered, eventually becoming resistant to vancomycin, the main antibiotic used to treat MRSA today, and it was months before she fully recovered.

A pediatrician’s similar lack of awareness of CA-MRSA last year nearly claimed the life of a toddler from Santee, Calif., a San Diego suburb. The one-and-a-half-year-old, who’d never even had a cold, grew bloated and lethargic, his nostrils flaring as he struggled for breath, recalls his father, Scott Smith.

Few States Require Hospital Infection Reports

Only 17 states require hospitals to report infection rates or infection information. Twenty-seven states and Washington, D.C., have similar legislation pending. With the rise of “superbugs,” patient-safety advocates say it’s more important than ever for patients to pressure hospitals to control the spread of infections.

State Requirements for Reporting Hospital Infection Rates



Source: Consumers Union, 2007

“We felt something was terribly wrong,” but Bryce’s pediatrician “said we were typical new parents” and repeatedly advised that they take the baby home and stop worrying, Smith says. Early on New Year’s Day, with Bryce’s condition worsening, his parents took him to the emergency room, where staff immediately suspected MRSA.

After a 55-day hospital stay — and surgery to remove part of his lung, through which the infection had eaten a hole — Bryce went home. He had to be given methadone to wean him from the narcotics he’d been sedated with during his long hospital stay, which included 49 days in intensive care.

The Smiths have switched doctors, and “our new pediatrician says she sees a case [of CA-MRSA] almost weekly,” Smith says.

Hospital-acquired MRSA is also on the rise. According to a 2007 study by the Association for Professionals in Infection Control and Epidemiology, 34 out of every 1,000 hospital patients (3.4 percent) have active HA-MRSA infections; another 12 patients are “colonized” with the bug, which means they could contract or spread the disease. That amounts to up to 1.2 million patients infected annually and between 48,000 and 119,000 deaths — far more than epidemiologists previously thought. A study released in

2005 by the U.S. Centers for Disease Control and Prevention (CDC) found that only 3.9 of every 1,000 patients (0.39 percent) had active MRSA infections.² At a minimum, treating HA-MRSA costs the United States between \$3 billion and \$4 billion annually.³

In fact, all bacteria — not just MRSA — and other microbes like viruses and fungi are becoming resistant to antimicrobial drugs. But antibiotic-resistant bacteria are causing the most concern, because most have been successfully treated with antibiotics for decades, while treating other kinds of microbes has been less successful.

Among other dangerous bacteria showing resistance, *klebsiella pneumoniae* can cause several kinds of urinary-tract and wound infections in hospitalized people, says Michael Feldgarden, research director of the Boston-based Alliance for the Prudent Use of Antibiotics. And if *klebsiella* develops resistance, Feldgarden explains, “a whole bunch of other organisms” will begin developing resistance as well.

Another hospital-based resistant pathogen, *acinetobacter*, has afflicted many soldiers wounded in the Iraq War, often forcing infected limbs to be amputated.⁴ “It’s totally resistant to all antibiotics but doesn’t have the virulence of MRSA,” says Harold Standiford, medical director of infection control and antimicrobial effectiveness at the University of Maryland Medical Center in Baltimore.

And tuberculosis (TB) — which kills 2 million worldwide a year, more than any other infectious disease — is becoming increasingly resistant. In the five years from 2000 to 2005, multi-drug-resistant TB (MDR-TB) increased from 275,000 cases to at least 460,000, mostly in Russia, China and India.⁵

Inadequately treated MDR-TB may evolve further into “extensively drug-resistant” TB (XDR-TB), which is impervious to almost all drugs. It was the initial diagnosis given to Atlanta lawyer Andrew Speaker, who made

headlines around the world in May for sneaking back into the United States after learning of his diagnosis — potentially exposing his fellow airline passengers to TB. Speaker claimed he feared he would die if he stayed in Europe, where he had honeymooned against doctors' advice.

Only 30 to 50 percent of patients with XDR-TB recover from the deadly illness.⁶ Speaker was later found to have MDR-TB, not the lethal XDR variety.⁷

Not long ago, it was widely assumed that when a drug lost its potency, another would soon be available to replace it. But today “there are so few new drugs in the pipeline that if we don't act to prolong the effectiveness of the drugs we've got, then we're in trouble,” says Robert Guidos, director of policy and government relations at the Infectious Disease Society of America.

Although doctors know that overuse of antibiotics promotes resistance, controlling excessive antibiotic use has proven difficult. In many developing countries, for example, access to antibiotics is unregulated, says John McGowan, a professor of epidemiology at Emory University's Rollins School of Public Health in Atlanta. “You can walk into a pharmacy and get whatever you want” without a prescription.

Moreover, he says, countries like the United States promote resistance by creating “an artificial division” between individual care and the care given by public-health agencies. Private physicians often feel compelled to dose patients with the strongest, newest antibiotics, he explains, while public-health agencies want doctors to reserve such drugs for the toughest cases in order to prevent resistance from increasing.

Curbing the spread of infections through careful hygiene and isolation of the sick is crucial to slowing the spread of resistant microbes. But there

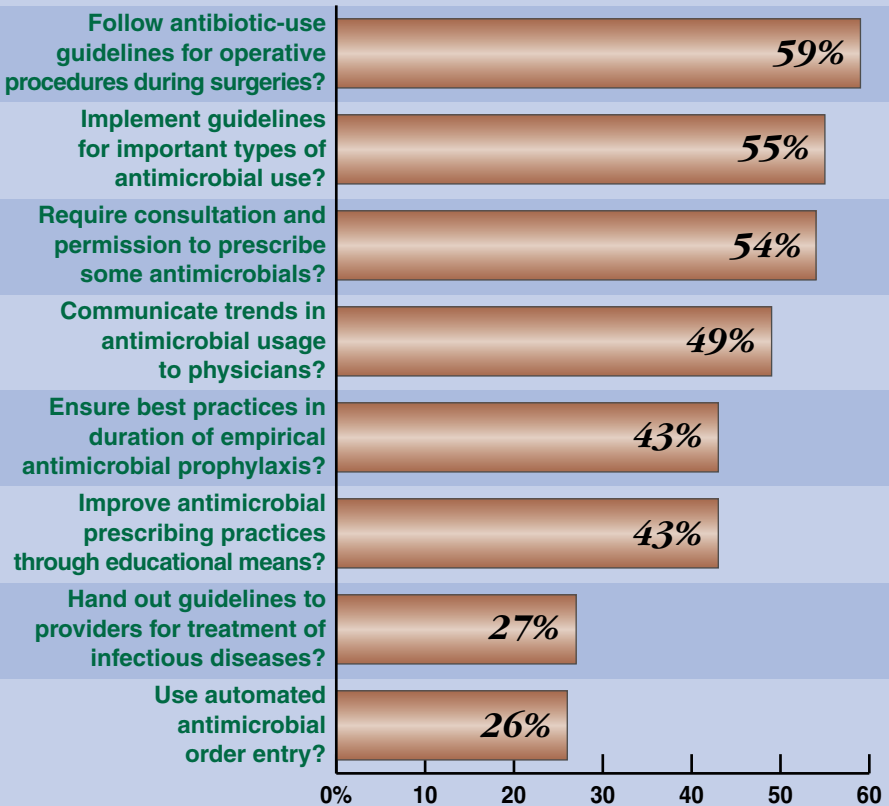
Fighting Drug Resistance in Hospitals

Fewer than 60 percent of U.S. hospitals follow recommended guidelines for antimicrobial use, according to a recent survey of infection-control personnel. And only 27 percent hand out guidelines for treatment of infectious diseases.

Control of Antimicrobial Use in U.S. Hospitals to Prevent or Control Drug Resistance

To what extent does your hospital:

Percentage who answered “great” or “very great”



Source: Alan J. Zillich, et al., “Antimicrobial Use Control Measures to Prevent and Control Antimicrobial Resistance in US Hospitals,” *Infection Control and Hospital Epidemiology*, October 2006; 448 infection-control practitioners responded.

is little consensus about what, if any, infection-control measures public-health agencies should impose.

“It's tough to make rules when everybody is not in agreement,” says Standiford. For example, while he says it is important to screen at least some incoming hospital patients for MRSA — even if they show no signs of infection — he's unsure exactly who

should be screened — surgical intensive-care patients, all intensive-care patients or some other group?

Antibiotics are also widely used on farms, not only to treat diseases that can spread to humans but also to increase animal growth rates, keep infection from breaking out in crowded barns and prevent crops from developing infections.⁸

How to Avoid Drug-Resistant Bugs

Hand washing is crucial

As antibiotics grow less effective, hygiene once again assumes a key role in protecting health.

Raised in an age before antibiotics, “Our grandparents told us, ‘Wash your hands. Period. Wash before you eat. Wash after you go to the bathroom,’” says Stuart Levy, a professor of microbiology at Tufts University School of Medicine in Boston. Now, as the ability of antibiotics to treat infections wanes, those days are back, he says. “In developing countries, that means giving people clean water. For us, it means ‘Wash.’”

Here are some other tips for staying healthy:

- Be especially careful about hygiene in moist, sweaty environments, like gyms. Athletic locker rooms, including in major-league professional sports, have become breeding grounds for dangerous bugs like methicillin-resistant staphylococcus aureus (MRSA). “You shouldn’t be sharing clothes or towels or personal items like razors,” says Jane D. Siegel, a pediatric infectious-disease specialist at the University of Texas’ Southwestern Medical Center in Dallas.
- Avoid sharing personal objects like cell phones, too. Alla Lulu, a sophomore biology major at the University of Arizona (UA), picked up a nasty face rash after borrowing a friend’s phone, said Charles Gerba, a professor of environmental microbiology at UA and Lulu’s uncle. The phone carried staph bacteria.¹
- Avoid products like special soaps and detergents that contain antibacterials like the chemical triclosan. “There’s no benefit to it over plain, old soap, and it drives resistance, so we need to be careful,” says Allison Aiello, assistant professor of epidemiology at the University of Michigan School of Public Health. These antibacterials, which are hard to avoid, leave residues that continue killing at a low rate, thus driving bacteria to become resistant. In a recent survey 76 percent of liquid soaps contained triclosan, and 30 percent of bar soaps contained triclocarban, according to the Alliance for the Prudent Use of Antibiotics.² For tough cleanups, traditional antiseptics like alcohol, peroxide and bleach are the better choice. They kill quickly and leave no residue, so they’re unlikely to increase resistance. Antibacterials like triclosan do have legitimate uses in health-care situations.
- Don’t demand that your doctor give you an antibiotic, but if one is prescribed, take it for as long as directed. Otherwise, partly resistant bacteria still in your body can multiply and grow more resistant.³
- Don’t take anyone else’s antibiotic. It may not be appropriate for your illness and will kill off beneficial bacteria in your body.⁴ “You’ve got hundreds of millions of bacteria in your intestines, and they ain’t bothering you,” says John H. Powers, former lead medical officer for the Food and Drug Administration’s Antimicrobial Drug Development and Resistance Initiatives. In fact, many carry out important jobs, such as synthesizing vitamins like Vitamin K, used in blood clotting, he says. “Bugs get a bad rap. They’re only bad if they get in the wrong place.”
- If you’re hospitalized, have someone there with you, especially on weekends and at night, says Lisa McGiffert, director of the Stop Hospital Infections project at Consumers Union. Hospital staff members might wash their hands and then touch the bed or a tray before touching you, but that shouldn’t happen, says McGiffert. “You want them to go straight from the hand gel to you,” she says. Health-care workers “know that and they mean to do it right, so they won’t mind being reminded.”
- When you have surgery scheduled, don’t be afraid to ask the surgeon about the hospital’s infection rate, says William Schaffner, chair of preventive medicine at the Vanderbilt University School of Medicine. Hospitals should also be able to tell you their hand-hygiene compliance rate, and you should ask, he says. “It is important to have a conversation with your surgeon,” says McGiffert. “Just ask, ‘Can you tell me what you do to prevent infections?’ You should get a number of answers,” including these: give antibiotics within 60 minutes of surgery; use the right antibiotic for the surgery; clip rather than shave the body pre-operation; keep the body warm during surgery and stop antibiotics within 24 hours of the surgery.

“You have to be your own advocate,” says Dee Dee Wallace, a 47-year-old Wisconsin mom who had a life-threatening brush with a resistant skin infection this year that doctors responded to slowly. “You have to say, ‘I don’t think this is right.’ You know your own body. Stick up for yourself. Don’t let them say, ‘Go home, you’ll be fine.’”

¹ Quoted in Yusra Tekbali, *Arizona Daily Wildcat*, University of Arizona, “University Wire,” Aug. 1, 2007.

² “Antibacterial Agents,” APUA, www.tufts.edu/med/apua/Q&A_antibacterials.html.

³ “When and How to Take Antibiotics,” Alliance for the Prudent Use of Antibiotics, www.tufts.edu/med/apua/Patients/How2Take.html.

⁴ *Ibid.*

But the amount of antibiotics used in agriculture is heavily disputed, primarily because no government agency collects the data. While most experts

agree farms use many more antibiotics than humans do, debate rages over how seriously farm antibiotics affect human health. And while foodborne

bacteria can grow resistant, few foodborne diseases are as virulent as MRSA. Moreover, benign resistant bacteria can transfer their resistance to

pathogens, but there is no clear evidence that agricultural antibiotics have accelerated drug resistance among human pathogens like MRSA.

Several bills pending in Congress address resistance, as does at least one major bill in the works but not yet introduced. The proposals include incentives for drug companies to discover new antibiotics, stricter limits on farm use of antibiotics, a strengthened federal role in studying resistant infections and programs to combat them. Democratic leaders of the House and Senate health committees hope at least some of the provisions will be enacted this year, but action on the measures stalled during the summer while Congress debated other issues, including expansion of children's health insurance.

As lawmakers and infectious-disease specialists confront the rising tide of drug resistance, here are some of the questions being asked:

Should government agencies do more to combat superbugs?

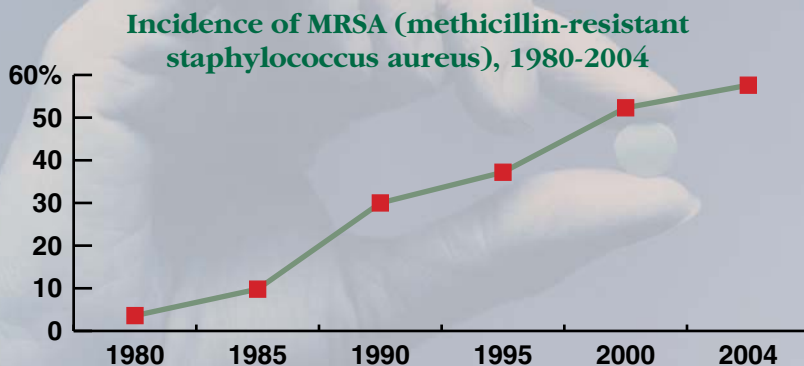
With antibiotic-resistant bacteria on the rise — hospital-acquired MRSA, for example, soared from about 3 percent of hospital staph infections in 1980 to nearly 60 percent in 2004 — most experts agree the government should spend more on disease-surveillance and anti-resistance efforts. Moreover, they say hospitals, doctors and the drug industry aren't doing enough to stem the tide of resistance. But debate rages over whether they should be required to do more.

Ideally, Congress should establish an antibiotic-resistance coordinator who reports directly to the secretary of Health and Human Services (HHS), says Guidos of the infectious disease society. A direct line to the Cabinet is vital, he says, because other departments — including Defense, Veterans Affairs and Agriculture — also have roles to play.

Most other industrialized countries keep stricter tabs on how antibiotics are used — both for humans and agriculture — says Feldgarden of the Al-

Incidence of MRSA Rose Steadily

The percentage of staph infections resistant to methicillin and other antibiotics has increased from less than 4 percent to nearly 60 percent in 2004.



Source: "Bad Bugs, No Drugs As Antibiotic Discovery Stagnates . . . A Public Health Crisis Brews," Infectious Disease Society of America, 2007

liance for the Prudent Use of Antibiotics. Without knowing exactly what's being used and how, it's difficult to trace the cause and effect for microbes developing resistance or to issue accurate guidelines and alerts to hospitals and doctors, he says.

The U.S. data-gathering effort — the National Antibiotic Resistance Monitoring System (NARMS) — is "run on a shoestring" by three agencies, Feldgarden says, and data in some of their reports "are three years behind," so scientists can't get a real handle on how resistance is developing today. In addition, the agencies don't have authority to collect some of the data that would be most useful, he says.

"There are a lot of stakeholders with conflicting interests," he says, such as antibiotics manufacturers, who are unwilling to see their sales data made public.

But Neil Fishman, an associate professor of medicine at the University of Pennsylvania School of Medicine, says the government could gather much more information without compromising business secrets. "I don't care what Dr. Smith prescribes," he says. "I just need his state's use."

States also should be required to report incidents of MRSA, says Brian Currie, senior medical director of the Montefiore Medical Center at the Albert Einstein College of Medicine in Bronx, N.Y. "There's mandatory reporting for other communicable diseases in every state," he says, and MRSA should be on the list.

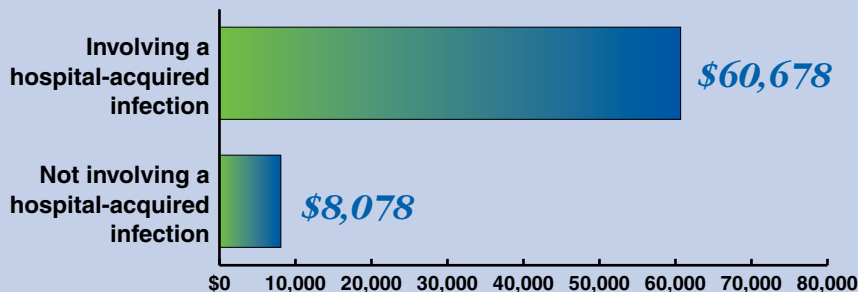
The private sector has not shown that it's able or willing to control infections or head off antibiotic resistance on its own, says Feldgarden. "We've got slightly more staph, and MRSA is going through the roof," he says, yet there has been no "forceful government intervention," such as shutting down hospitals. "The idea has been, 'Let doctors practice medicine.' But at some point, you have to say, 'You guys don't get to call the shots any more.'"

Yet, he warns, regulations would need to avoid unfairly scapegoating some hospitals. "If you're a hospital with an elderly population, you'll have a lot of MRSA even if you're doing a good job," he says. "So you can't just set a percentage level and tell people, 'Above that, and you're in trouble.'"

The High Cost of Hospital Infections

The cost to treat a patient with a hospital-acquired infection in Pennsylvania in 2004 was \$60,678 — more than seven times the cost of treating an uninfected patient.

Average 2004 commercial insurance payment in Pennsylvania for hospitalizations . . .



Source: "Hospital-acquired Infections in Pennsylvania," PHC4 Research Briefs, Pennsylvania Health Care Cost Containment Council, March 2006

The Netherlands, for instance, has instituted "search and destroy" tactics in MRSA cases, says Feldgarden. Patients infected with MRSA are isolated, MRSA-colonized health-care employees are furloughed with pay and their families and pets are also checked and treated. The country's MRSA rate has dropped to 1 percent of its hospital-based staph infections, "while ours is 50 percent," he says.

However, the CDC doesn't have the authority to do what the Netherlands did, Feldgarden says.

Traditionally, states are the primary regulators of health care in the United States, but that approach can fail, says Feldgarden. "In the many tri-state areas, infections jump state lines," he says.

Whether or not they envision a stronger government role in fighting resistance, many analysts concede that private institutions aren't making much headway. For example, medical education has not focused much on resistance prevention, says Elaine Larson, associate dean of research at the Columbia University School of Nursing in New York City and director of

the Center for Interdisciplinary Research on Antimicrobial Resistance.

Still, she and others remain skeptical of government efforts to force change.

Given Americans' predominantly private health system and their love affair with high-tech solutions, it's been difficult to develop a national policy that dissuades doctors from prescribing the most expensive, newest antibiotic first, says Larson. "I don't think a change is going to happen voluntarily," she says. Nevertheless, she's "not a big proponent" of legislating solutions because "it can take forever to change laws while microbes mutate very fast."

Even Fishman says the data do not yet support mandatory universal screening for MRSA. Universal screening "is the right strategy in some settings," he says, such as in academic medical centers that see the sickest patients. "But it might not be the correct strategy for a community hospital with low MRSA rates."

In addition, neither the Society for Healthcare Epidemiology of America nor the Association for Professionals in Infection Control and Epidemiology supports mandatory screening of

patients showing no symptoms of active infection with MRSA or other antimicrobial-resistant pathogens. They fear any legislation would be written too narrowly and would not be flexible enough to apply to a newly developing resistance.

"Legislation in general is not sufficiently flexible to permit rapid response to local epidemiological trends," the groups maintain.⁹

Should the government make it easier for drug companies to bring new antibiotics to market?

With few if any new antibiotics being developed, some infectious-disease experts say the government should ease drug companies' path to creating new products. But other drug analysts argue that safety and public-health priorities must not be compromised.

"There are no drugs coming through the pipeline," says Guidos at the infectious disease society. With diseases like MRSA spreading, the government should consider major monetary incentives for companies to develop new antimicrobials, he says. For example, companies could be given a "wild card" patent extension — additional time to exclusively market some other lucrative drug they've developed — in exchange for developing the less profitable antibiotic. Drug patents run for 20 years from the date a patent application is filed.

From drug companies' standpoint, curbing antibiotic overuse makes drug development economically risky in the anti-infective field, says William Schaffner, chairman of preventive medicine at the Vanderbilt University School of Medicine in Nashville, Tenn. "As soon as one is developed, we immediately tell doctors, 'Don't use it, you dopes,'" he says. "We don't do that with Fords. I know of no other new product for which people say out in chorus, 'Don't use it.'"

Antibiotic development is further complicated by its heavy dependence

on small producers, says Michael Bonney, CEO of Cubist Pharmaceuticals in Lexington, Mass. And unlike big pharmaceutical companies, smaller firms depend on the capital markets for borrowing funds for research and development, says Bonney, whose small company specializes in antibiotics for hospital-based infections.

“Lenders aren’t devoted to antibacterials” and will put their dollars elsewhere if they don’t see the promise of good returns, he says. “They pay a lot of attention to what’s happening in Washington.” Few small companies will be able to obtain cash to develop antibiotics if the law doesn’t assure lenders they’ll eventually make money, he says.

The federal government could buy and stockpile a new drug until resistance appears, Bonney says. But stockpiling “would have to work in concert with extending [the developer’s] market exclusivity” for more years, so the company — not a generic competitor — would make money once the drug was in demand.

To offset the low profitability of so-called orphan drugs — which target serious diseases affecting fewer than 200,000 people — Congress in 1983 created development incentives for drugmakers. The law could be tweaked to help spur antibiotic development, says Michael Kurilla, director of the office of biodefense research affairs and associate director of biodefense product development at the National Institute of Allergy and Infectious Diseases.

Today, drugs for illnesses that affect populations just above the orphan-drug cutoff get no breaks, says Kurilla. “If you’re at 250,000 patients or 10 million, it’s all the same.” A “sliding scale” of incentives might support antibiotic development, he says.

Some pharmaceutical scientists argue the FDA is more concerned about safety today than in the 1950s and ’60s — the golden age of antibiotic develop-

ment — making the discovery of new drugs more challenging. The FDA should give more weight during the approval process to the potential benefits of new antibiotics instead of nixing those that show modest safety risks, says Jeffrey D. Alder, vice president of drug discovery and evaluation at Cubist.

“Some infectious diseases have a very high kill rate” — as high as 70 to 90 percent for staph aureus in the blood, for example — says Alder. “In those cases, almost everyone would say they’d want to be treated, even if it meant nausea” or some other side effect.

But some infectious-disease experts are wary of suggesting that companies don’t have enough financial incentives, or that the FDA should make it easier to get antibiotics approved.

SAIC Fredericks’ Powers, the former FDA infectious-disease officer, argues against offering financial carrots unless they’re carefully targeted at companies developing antibiotics for virulent resistant infections like MRSA, not for self-resolving conditions like sinusitis. “The places where we need new antibiotics are very specific situations,” he says.

He’s skeptical of incentives because the FDA earlier had tried hard to make it easier for companies to develop antibiotics, but rather than stimulating development of drugs to treat more serious diseases, most companies focused on relatively minor problems like sinusitis, ear infections and bronchitis — most of which clear up on their own.

Some drug analysts also question the wisdom of further easing any FDA standards to help companies bring antibiotics to market.

For instance, in 2004 the agency approved the antibiotic Ketek — manufactured by the French firm Sanofi-Aventis — as a drug that might head off resistance in treating pneumonia, bronchitis and sinusitis. The company had tested the drug using FDA clinical-trial guidelines designed to speed approvals of new antibiotics.

The agency abandoned the guidelines as inadequate before Ketek received its final approval, but the drug was approved anyway because the agency felt it needed “to stand by prior agreements with industry,” said David B. Ross, a clinical assistant professor at George Washington University School of Medicine and Health Sciences in Washington and a former FDA physician who helped in reviewing Ketek.¹⁰

In 2006, the drug was linked to severe liver damage and failure in a small number of patients, but the agency was reluctant to react too strongly for fear of discouraging antibiotic development. For example, after a Ketek user died of liver failure, the FDA’s only formal response was a few paragraphs in “an internal safety review written months later,” said Ross. The FDA didn’t re-label the drug to warn about liver damage until 16 months after the first report and didn’t withdraw approval until Feb. 12, 2007 — a day before congressional hearings on Ketek’s safety were to be held, he said.

The Ketek case suggests the agency, at least in some cases, has paid too little attention to antibiotics’ downsides, said Ross.¹¹

Powers says that rather than paying too much attention to the adverse effects of antibiotics — such as allergic reactions — the FDA and the medical community focus too much on the “inferred benefits” of antibiotics, which Powers says are often unproven. One pediatrician told Powers that he “will treat a million kids for ear infections to prevent one case of meningitis,” Powers says. “I said, ‘And you’ll kill 10 with allergic reactions.’”

Powers also rejects drug company claims that testing is too costly. An antibiotic trial, he points out, only requires about 200 subjects, while a trial for a cardiac drug requires 10,000. “People say the FDA should lower the [testing] standards. But they already have.”

Should Congress limit the use of antibiotics in farming?

Debate is fierce over antibiotic use in farming.

Because food animals like cows and chickens largely are raised today crammed into tight quarters rather than in open fields or pastures, antibiotics are used both to treat and to prevent communicable diseases.¹² Animals also get low doses of antibiotics to promote faster growth, and many crops are sprayed with antibiotics to kill bacteria. Consequently, most food — from milk to potatoes to beef — is likely to contain at least traces of the drugs. Food produced organically is prohibited from containing antibiotics.¹³

Advocates of stricter limits on farm use of antibiotics argue that, to slow development of antibiotic resistance among human pathogens, antibiotic use should be cut back. Farm animals can become reservoirs of resistant bacteria, they point out, and non-pathogenic bacteria can pass their resistance to bacteria that do make people sick.

But veterinary-drug manufacturers and farmers say there are few proven links between antibiotics used in farming and life-threatening drug-resistant infections in humans and that clamping down would lead to more foodborne illness. Epidemiological studies don't show that antibiotic-resistant bacteria in farm animals increase resistance in dangerous human diseases, says Michael Doyle, director of the Center for Food Safety at the University of Georgia.

Even if the illnesses humans sometimes pick up from food were to become antibiotic resistant, they are far less serious than other resistant pathogens like MRSA, he adds. "How many people have had untreatable foodborne illnesses? You can count them on two hands," he says. "You may have seen more hospitalizations, but you don't have deaths. I'm just not seeing the data to tell me that this is a public-health hazard like MRSA."

However, scientists at the National

Institutes of Health's Fogarty International Center, which studies global health issues, say farm use of antibiotics can contribute significantly to drug-resistant disease in humans, even if the illness isn't life-threatening.

In a 2005 paper, infectious-disease ecologist David L. Smith and his colleagues compared the incidence of VRE — vancomycin-resistant *enterococci* — in humans in Europe and in the United States. They found that in the late 1990s in Europe — where vancomycin was used in hospitals and the related antibiotic avoparcin was used on farms — VRE rates outside the hospitals ranged from 2 to 12 percent of all enterococcus infections. Meanwhile, in the United States — where vancomycin was heavily used in hospitals but no avoparcin was used on farms — community VRE rates were below 1 percent. And community rates of VRE declined after the European Union banned avoparcin, demonstrating that agricultural antibiotics did contribute to VRE showing up in humans, said Smith.¹⁴

Europe has restricted use of agricultural antibiotics for the past decade. "We are never willing to accept that you first have to create a lot of dead people before you intervene," said Henrik C. Wegner, director of both the World Health Organization's Collaborating Centre for Antimicrobial Research and Foodborne Pathogens and the Danish Institute for Food and Veterinary Research. "From our perspective, this is first and foremost a preventive action. It is not acceptable to sit and wait for the next MRSA."¹⁵

Moreover, he added, Denmark has had "fewer healthy people in the community who carry VRE in their guts since we stopped using growth promoters" on farms.

Many infectious-disease experts want the United States to follow Europe's lead in banning much antibiotic use on farms. "It's embarrassing that we're way behind Europe," says Columbia University's Larson.

Others complain the impact of agricultural antibiotics on resistance gets an undeserved pass in the United States. "Agribusiness is off the public radar screen," says Currie of Montefiore Medical Center. "We've had antibiotics developed where the resistance was high before the drug was [even] released," he says, because related drugs were already being used in agriculture.

At the very least, agricultural antibiotic users should release data on what drugs farms are using and how, says Guidos of the infectious disease society. "The animal-drug industry says [various] reported volume-of-use numbers are inflated," he says, "but we say, 'Prove it.' We want to see what is really going on."

Agriculture analysts say, however, that limiting antibiotics in farming would drive up the rate of foodborne illnesses, outweighing any so-far-undiscovered benefits for limiting their use. "When the European Union cut off some of the antibiotics used as growth promoters, more animals got sick," and the infected animals could pass the illnesses to consumers, says the University of Georgia's Doyle.

Indeed, some farm advocates and scientists say not enough attention is paid to the value of antibiotics on farms. "Antibiotics help farmers keep animals healthy with less strain on the environment," according to the Animal Health Institute, an association of animal-drug manufacturers. "More meat can be raised [on less land] with fewer animals because of the growth-promoting qualities of antibiotics."¹⁶

Ian Phillips, a professor of biological and chemical sciences at the University of London, says research suggests the added risk to human health caused by antibiotics being used as growth promoters "is small." But "the benefit to human health from their use, hitherto largely ignored, might

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Chronology

1940s-1950s

Penicillin becomes the first widely available antibiotic, used to treat soldiers in World War II whose infected wounds would otherwise be deadly. By the mid-1940s, the first penicillin-resistant staph bacteria are found.

1940

Oxford University pathologist Howard Florey isolates pure penicillin and demonstrates that it kills a wide range of pathogens, including strep and gonorrhea.

1943

Drug companies begin to mass-produce penicillin.

1958

American molecular geneticist Joshua Lederberg wins Nobel Prize in medicine for demonstrating bacteria's ability to exchange genetic material, which helps spread resistance.

1960s *Fast-developing resistance to antibiotics like tetracycline is spotted, but a large number of new antibiotics enter the market.*

1960

Methicillin is introduced in Great Britain.

1961

The first methicillin-resistant staph aureus infection (MRSA) turns up in a British hospital.

1963

MRSA appears in Denmark.

1967

Penicillin-resistant strep pneumonia is found in New Guinea.

1970s-1980s

Antibiotics are routinely prescribed for cold-like illnesses, even when they aren't bacterial. U.S. soldiers return from the Vietnam War with penicillin-resistant gonorrhea. People increasingly have weakened immune systems and need stronger antibiotics as more cancer patients are successfully treated, organ transplants increase and HIV/AIDS appears.

1977

South African doctor Michael Jacobs finds a strep *pneumoniae* bacterium that resists every available drug.

1983

The first hospital-acquired intestinal infection becomes penicillin resistant. . . . Eighteen people in the Midwest are hospitalized with multi-drug-resistant salmonella food poisoning after eating beef from cows given antibiotics.

1986

Sweden bans use of antibiotics to make farm animals grow faster.

1990s *Big drug firms pull resources away from infectious-disease research. MRSA turns up outside hospitals.*

1992

Antibiotic-resistant bacterial infections kill record 13,000 hospital patients.

1998

Denmark taxes antibiotics used as animal-growth promoters. . . . European Union bans use of antibiotic used in humans for animal growth.

1999

Federal Interagency Task Force on Antimicrobial Resistance is launched.

2000s *More microbes become resistant, but public-health efforts to combat resistance lag.*

2000

Congress reauthorizes Public Health Services Act, enabling federal government to take stronger steps to combat resistance, but the measure is never funded.

2001

Terrorism-related anthrax scare leads some Americans to take the high-powered antibiotic Cipro "just in case" and stockpile it in their homes.

2003

Drug-resistant *acinetobacter* infects Iraq War wounded in military hospitals, leading to many amputations.

2005

France bans 12 sore-throat medications containing topical antibiotics.

2006

European Union bans using any antibiotic to promote animal growth. . . . Ketek, an antibiotic to treat bronchitis, pneumonia and sinusitis, is linked to severe liver damage.

2007

Cases of multiple-drug-resistant tuberculosis (TB) quadruple in South Africa's Western Cape Province. . . . World Health Organization launches plan to fight drug-resistant TB. . . . Scientists find avian-flu virus is naturally evolving resistance to anti-flu drugs. . . . Study finds 10 times as many MRSA cases in U.S. hospitals as previously thought. . . . Food and Drug Administration mulls approval of a new antibiotic for respiratory disease in cows, although infectious-disease experts argue the drug could create more resistant pathogens since similar antibiotics are used in human medicine.

Doctors Turning to Ancient Remedies for Infections

Honey and copper doorknobs are said to work wonders

With superbugs developing resistance to many antibiotic drugs, doctors are trying out some old anti-infective remedies in hopes of finding additional tools to fight infection. Meanwhile, the search for new antibiotics goes on, with some scientists hoping to exploit the millions of microbial species — many in remote environments like hot springs or the sea bottom — for new kinds of antibiotic action.

Most future anti-infective drugs are likely to bypass killing bacteria, antibiotic-style, in favor of blocking their sickness-inducing properties. Microbes would be less likely to develop resistance to such drugs.

Honey was known to have anti-infective properties as far back as the ancient Mesopotamian kingdom of Sumer, 5,000 years ago. Today some doctors are using it again.

Jennifer Eddy, an assistant professor of family medicine at the University of Wisconsin School of Medicine, dressed an elderly diabetic man's ulcerated foot in honey-soaked gauze after the sore was attacked by drug-resistant bacteria, and amputation seemed the only option. In two weeks, the blackened foot began to heal, and a year later, the man was walking again. "I've used honey in a dozen cases since then," said Eddy. "I've yet to have one that didn't improve."¹ Some research suggests that bacteria are unlikely to become resistant to honey.

Another ancient antibacterial remedy — copper — is getting a trial in a British hospital. Healers in ancient Egypt, Greece and Rome all recognized copper's infection-killing properties and used it to treat wounds. Despite its history of discouraging the growth of germs, however, little copper is found in modern hospitals, which gleam with stainless steel, even though

germs can remain active on steel for days.

Now the Selly Oak Hospital in Birmingham, England, is testing whether replacing stainless steel fittings like door handles, bathtub faucets, toilet flush handles and grab bars with copper can help cut the spread of infections. The hospital was chosen for the trial in part because soldiers wounded in Iraq had become infected with MRSA while being treated in the facility.²

In the early 20th century, biologists discovered a way to treat infections using bacteriophages — viruses that invade certain species of bacterial cells and cause them to burst and die. The therapy was pioneered at Paris' Pasteur Institute and the Institute of Microbiology in Tbilisi, capital of the Soviet Republic of Georgia, home of George Eliava, one of the scientists who discovered bacteriophages. Eliava discovered the tiny killers when he returned after three days to look at a microscope slide of river water that had contained cholera bacteria and found the slide bacteria-free.³

In World War II, Soviet military medics used the viruses to treat infected wounds on the battlefield, and German Gen. Erwin Rommel's troops used phage therapy against infections in hot North Africa, where infection-causing bacteria thrive.

But as antibiotics came into wide use after the war, bacteriophage therapy was largely forgotten. Georgian scientists and doctors continued studying and even treating patients with phages, but lack of money gradually crippled their research. Today, however, phage research is making a comeback, as superbugs strip traditional antibiotics of their power.

For example, researchers at the Massachusetts Institute of Technology and Boston University are using DNA technology

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more than counterbalance this." For instance, Phillips said, banning farm antibiotics except to treat sick animals has put more unhealthy animals into the human food chain in Europe.¹⁷

In another assessment, Phillips and other epidemiologists found the risk of increased antibiotic resistance related to antibiotic use in chickens "is small" compared to the increase in human foodborne illnesses that would result if the chickens' antibiotics were cut.

"Immediately following the removal of the antibiotic, animal illness levels might be expected to increase," they said, potentially making more people who ate the chicken sick.¹⁸ ■

BACKGROUND

Bacterial World

Almost as soon as antibiotics came into use, microbes began developing resistance to them.¹⁹

In the 1940s and '50s, when penicillin was first used, it could kill most bacteria. But as early as 1945, the drug's discoverer, British bacteriologist Alexander Fleming, warned in a *New York Times* interview that misusing penicillin could quickly lead to the evolution of

mutant bacterial strains not susceptible to the medicine, an outcome he'd already verified.

In the 1960s, when the antibiotic tetracycline was routinely prescribed for teenagers' acne, resistant bacteria turned up in patients "within a few weeks," says Columbia University's Larson.

That resistance develops quickly among microbes isn't surprising. The world is chock full of bacteria — and other microscopic organisms like fungi — "all fighting for their environmental niche," says SAIC Fredericks' Powers, the former lead infectious-disease officer at FDA. In fact, virtually all antibiotics today were derived from organisms that evolved to have bacteria-killing or bacteria-growth-

to alter bacteriophages to produce enzymes that can kill specific infectious bacteria like *e. coli*.⁴ The Food and Drug Administration also recently approved a bacteriophage product for food-processing companies to use to eliminate the dangerous foodborne microbe *listeria*.⁵

Meanwhile, new antibiotics still lurk in nature, waiting to be discovered, says Jeffrey D. Alder, vice president of drug discovery and evaluation at Cubist Pharmaceuticals in Lexington, Mass.

Only one in 100,000,000,000,000,000,000,000 (1 in 10 to the 25th power) of the world's microbes has been screened for antibiotic action, says Alder. Most of the vast number remaining grow in airless environments, in a narrow temperature range, or in difficult-to-access places. Earth's more remote and unusual environments could be the source for new antibiotic discoveries, some scientists believe.

The University of Hawaii, for example, hopes to set up a drug-discovery center "to take advantage of their unique isolated environment" that's home to hordes of unstudied microbes in hot springs, ocean thermal vents and the like, says Alder. DNA techniques make it possible to discover antibiotic and other microbial properties more easily than in the past, he says.

But most future anti-infective drugs will be developed according to a new paradigm, says Michael Kurilla, director of the office of biodefense research affairs at the National Institute of Allergy and Infectious Diseases. Lost in medicine's long love affair with antibiotics is the fact that "you're really interested in curing a disease, not killing an organism," Kurilla says.

Shifting the focus from killing bugs to blocking their sickness-causing toxins — as a tetanus shot or anthrax vaccine do — may be the best approach for future drug discovery.

"If we take care of the toxin," and your immune system is strong, "your body can clear" the bacteria on its own, says Kurilla.

Paratek Pharmaceuticals, a small Boston-based company started by Stuart B. Levy, a microbiology professor at Tufts University School of Medicine, takes such an approach. Paratek focuses on a protein that can inactivate the process by which bacteria cause illness. "The bacteria doesn't need it to live and grow, so because you aren't inhibiting the bacteria's survival, you're not selecting against it," and resistance is much less likely to develop, Levy says.

But so far, financial backers are hard to come by for novel approaches, Levy says. "Everybody loves the story. But when it comes to plunking the money down, they go to the guy next door who has an antibiotic."

¹ Quoted in Brandon Keim, "Honey Remedy Could Save Limbs," *Wired*, Nov. 11, 2006.

² Philippe Naughton, "Hospital Gets Copper Fittings in MRSA Trial," *The Times online*, March 13, 2007, www.timesonline.co.uk/tol/news/uk/article1509513.ece.

³ For background, see Richard Martin, "How Ravenous Soviet Viruses Will Save the World," *Wired*, October 2003, www.wired.com/wired/archive/11.10/phages_pr.html.

⁴ Brandon Klein, "Scientists Build Bacteria-Killing Organisms From Scratch," *Wired Science*, Wired Blog Network, July 10, 2007.

⁵ "FDA Extends GRAS Approval LISTEX to All Food Products," *Food Ingredients First*, May 7, 2007, www.foodingredientsfirst.com.

inhibiting properties. "The bugs actually invented the antibiotics" in their evolutionary struggle for survival, Powers says.

Microbes abound in the environment, and they multiply quickly. "When we are born, 100 percent of our cells are mammalian," says Barry I. Eisenstein, senior vice president for medical affairs at Cubist Pharmaceuticals. "By the time we are 1 month old, only 10 percent [of our cells] are." That's because most of the cells in and on the body are bacterial — hundreds of trillions of them.

And, under optimal conditions, a single bacterium can produce a billion offspring in a single day. Furthermore, "out of a million bacteria,

every one will have a mutation," any one of which might allow that cell and its offspring to survive exposure to an antibiotic, says N. Kent Peters, program officer for antibacterial resistance at the National Institute of Allergy and Infectious Diseases (NIAID).

Doctors' Orders

The good news is that, "everywhere you measure, there's been improvement in antibiotic use," says Schaffner, Vanderbilt's preventive medicine chairman. But while the message is getting through, and many doctors

are becoming warier prescribers, "it's not enough," he says. "We are not going to get a stream of antibiotics that will rescue us."²⁰

New antibiotics aren't forthcoming, in part, because the easy-to-find ones were discovered long ago. Today's huge pharmaceutical companies increasingly are focused on high-profit drugs that patients take for chronic conditions, while small firms have trouble funding drug development at all and thus tend to seek more specialized niches.

"Why should we be investing in anti-infectives when people take them for seven to 10 days, while they'll take chronic-disease drugs" — such

FIGHTING SUPERBUGS

as antidepressants or cholesterol drugs — “for the rest of their lives?” an executive at the large pharmaceutical company Eli Lilly once asked Cubist’s Eisenstein, who directed infectious-disease research at Lilly in the early 1990s.

Ironically, systematic technical improvements in the drug-development process also act as a barrier to finding new antibiotics.

Chemists find new drugs by testing compounds from pharmaceutical companies’ vast libraries of chemicals, explains Kurilla, the director of biodefense research affairs at NIAID. But as companies have refined their collections, “they’ve evolved a series of ideas about what makes a compound ‘druggable’ ” — meaning that it is absorbable and capable of penetrating human cells or entering the brain, he says.

“If you asked a chemist today if [the antibiotic chemicals] tetracycline or cephalosporin could be drugs, he’d say no,” says Kurilla, because today’s pharmaceutical chemists focus almost entirely on compounds that show potential for creating drugs that interact with human cells, such as the cholesterol-reducing drug Lipitor or the antihistamine Claritin. Chemicals with the potential to interact with bacteria — as antibiotics must — have been weeded out of the drug-discovery labs to make screening chemicals for drug potential more efficient, he says.

The U.S. medical system also has built-in barriers to reducing the use of



Simon Macario appeared to have a minor throat infection, but one morning he awoke screaming with pain. “By 10 that night he was dead” from MRSA, which was attacking his organs, says his mother. Until recently, MRSA mainly infected hospital patients. Today, however, many resistant bacteria are acquired outside hospitals and seem more dangerous than hospital-acquired infections.

antibiotics. For instance, patients know antibiotics are wonder drugs and ask for them — even when their infections are viral, and antibiotics won’t work. “It takes longer for a physician to explain why an antibiotic isn’t a good idea” than to simply prescribe one, even if it’s not indicated, says Larson, the associate dean of research at Columbia.

As a result, about 28 percent of doctors say they would order an antibiotic if a patient had a chest cold — a viral illness — says Feldgarden of the Alliance for the Prudent Use of

Antibiotics, and the percentage doubles in the case of bronchitis. Furthermore, prescribing habits inexplicably worsen as doctors-in-training advance through their medical education, he says.

Indeed, a study in the late 1990s showed that one of five U.S. prescriptions is for an antimicrobial drug, and 95 percent of them are unnecessary, Feldgarden says. Another study showed that doctors prescribe antibiotics for children’s colds and earaches 65 percent of the time if they believe that parents expect them to, but only 12 percent if they don’t.²¹

“Prescribing practices are difficult to change, so we need an array of interventions,” says Vanderbilt’s Schaffner.

Funds have been lacking for “social-marketing” campaigns to help change public attitudes. For instance, the Centers for Disease Control and Prevention (CDC) has developed a consumer-awareness program dubbed “Get Smart” but doesn’t have enough money to

launch it, says Ralph Gonzales, a professor of medicine, epidemiology and biostatistics at the University of California, San Francisco.

Gonzales tested a similar advertising campaign in Denver that raised public awareness by about 10 percent and cost about \$150,000 to implement. The dent in attitudes is significant enough to lower antibiotic use, which would save money for insurance companies and Medicare and improve public health, says Gonzales. But only a few private insurers and cities have expressed interest.

Infectious Disease Society of America

The University of Pennsylvania's Fishman says the lack of quick, cheap diagnostic tests to identify what's making a patient sick is also a problem. "It's 2007, and we can only determine the cause of pneumonia 50 percent of the time, if we're lucky," he says. Thus, doctors often have to guess at the cause of an infection and use broad-spectrum antibiotics that kill multiple kinds of bacteria rather than an antibiotic narrowly targeting one bacteria. But broad-spectrum antibiotics should be reserved for resistant cases, Fishman says.

Technical hurdles have bedeviled development of quick, accurate diagnostics, such as the difficulty — or sometimes the impossibility — of growing some bacteria and viruses in the lab. The National Institute of Allergy and Infectious Diseases (NIAID) is pushing for development of diagnostics as fast as it can, "but cost is still an issue" in implementing them, says NIAID program officer Peters.

"Even when diagnostic tests work, though, many physicians are reluctant to narrow the therapy" once they get a diagnosis if they've already started treatment with another antibiotic, Fishman says. "In America, we tend not to stop the treatment."

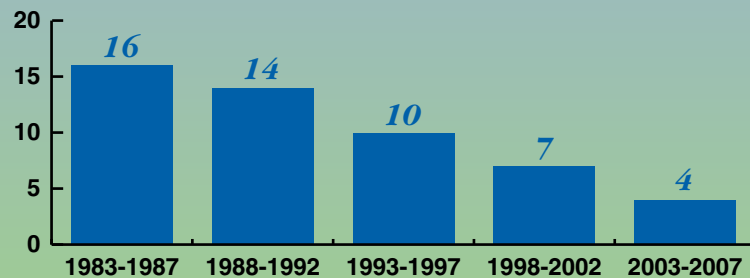
"Education alone doesn't work" in changing prescribing behavior, says Donald Goldmann, a professor of infectious diseases at the Harvard School of Public Health and senior vice president of the Institute for Healthcare Improvement, which supports quality-improvement initiatives for health-care institutions. In fact, he says, physicians "will fudge" even when systems exist to warn doctors away from some drugs. One study found an "epidemic" of pneumonia at a hospital where doctors discovered they could prescribe a certain drug only if they "checked a box for pneumonia" on a prescription order form, he says.

The best intervention is "strong decision support" — good, specific in-

Development of Antibacterials on the Decline

The number of antibiotic drugs approved in the United States has steadily declined in the past quarter-century, reflecting lack of interest by drug firms and the fact that many key drugs already have been developed.

Number of Approved Antibacterials in the U.S., 1983-2007



Source: "Bad Bugs, No Drugs As Antibiotic Discovery Stagnates . . . A Public Health Crisis Brews," *Infectious Diseases Society of America*, 2007

formation provided at the time and place of prescribing — and "tough feedback" showing doctors how they're doing compared to other physicians, Goldmann says.

U.S. doctors who treat patients outside of hospitals, however, are tied into few if any systems offering feedback, Schaffner says, making it even more difficult to mold non-hospital physician behavior. Some health-maintenance organizations and a few fledgling state Medicaid efforts, however, have made headway, he says. "Physicians really need to know what the standard of practice is and how they measure up to it," says Schaffner. "When they do, a light goes on."

Drug companies' "gross overpromotion" of the latest antibiotics exacerbates the problem, says Sidney Wolfe, director of the Health Research Group at the consumer organization Public Citizen. For example, after CDC guidelines declared that azithromycin (trade name Zithromax) should not be either a first- or a second-choice treatment for ear infections, the drug's manufacturer, Pfizer, "brought in academics to subvert the guide-

line," says Wolfe, who obtained and publicized an internal Pfizer memo about the policy.

The company's heavy promotion, including sponsoring the children's television program "Sesame Street" — "brought to you by the letter Z as in Zithromax" — made the drug the fifth most commonly prescribed in the United States by 2003. Nineteen states sued Pfizer to stop the promotion, but the \$6 million in fines Pfizer paid was dwarfed by the \$1.5 billion it earned in 2003 from Zithromax sales alone.²²

At the federal level, the FDA has no authority to levy fines for overpromotion and can't regulate prescription-writing, but Wolfe says health-care payers, especially Medicare and Medicaid, should crack down on doctors' unjustified use of overhyped new antibiotics.

"I've been urging FDA to do more education" on prescribing, but not much has happened, says Wolfe. "CDC and the Centers for Medicare and Medicaid Services do some, but it is inadequate to counterbalance the vast amounts of advertising."

How Superbugs Develop Resistance Quickly

Speed and flexibility help them mutate

Bacteria can become resistant to antibiotics even if they have never come in contact with a human-made antibiotic. (Antibiotic drugs are derived from naturally occurring microbes that excrete substances that can kill bacteria or interfere with some of their vital natural processes.)

For example, wild animals in Australia have little or no exposure to antibiotics, but a study of *e. coli* bacteria from kangaroos and wombats found that 3 percent were resistant to the antibiotic amoxicillin. And hospital patients in India, Turkey and Poland were infected with methicillin-resistant *staphylococcus aureus* — MRSA — even before the antibiotic methicillin had been used in those countries.¹

Large numbers of resistant bacteria usually don't evolve, however, until after the bacteria come in contact with the antibiotic. And over the years, scientists have discovered some traits that allow bacteria to evolve into a resistant population quickly, such as:

- **Speed.** Bacteria can evolve quickly partly because they reproduce so quickly. A human population can double about every 20 years. “For bacteria, it’s every 20 minutes,” says Barry I. Eisenstein senior vice president for medical affairs at Cubist Pharmaceuticals, in Lexington, Mass.
- **Exchangeability.** Many resistant bacteria can pass on their resistance genes to other bacteria, even if they’re of different species. Humans’ guts are filled with harmless bacteria that can block antibiotics. That’s no problem unless a disease-causing bug enters the gut. Then the harmless but resistant bugs may pass their resistance to the dan-

gerous bacteria, making them resistant, too. Often what’s transferred is a “plasmid” — a hunk of DNA that isn’t part of the bug’s regular DNA — and some plasmids can carry resistance genes for several kinds of antibiotics. A bacterium that picks them up becomes a “superbug,” resistant to more than one drug. A potential route to new antibiotic treatments would be drugs that block plasmid transfer, says N. Kent Peters, program officer for antibacterial resistance at the National Institute for Allergy and Infectious Diseases (NIAID).

- **Tendency to mutate.** In nature’s ongoing war among microbes, mutant offspring with better ways to survive allow a species to evolve to overcome enemies. In recent years, scientists have found that something even more complicated occurs. When some bacteria are under pressure, such as from a dose of antibiotics, their offspring actually have more genetic mutations than usual, thus increasing the species’ chance of evolving a means to survive, says Michael Kurilla, director of the office of biodefense research affairs at NIAID. A few researchers are exploring ways to block mutations, Kurilla says. When bacteria are under attack from an antibiotic that doesn’t kill them, they “don’t sit on their duffs,” says Eisenstein. “They become more promiscuous,” exchanging more genes with other nearby bacteria, which ups the chance they’ll produce resistant offspring that can survive.

¹ Peter J. Collignon, “Antibiotic Resistance,” *Medical Journal of Australia*, Sept. 16, 2002, p. 325, www.mja.com.au/public/issues/177_06_160902/co110836_fm.html.

Ounce of Prevention

Since fewer antibiotics will be prescribed if fewer people get sick, curtailing the spread of infectious disease is key in fighting antibiotic resistance.²³

In the past, resistant pathogens spread mainly in hospitals. But today an especially virulent strain of MRSA has emerged outside of hospitals, making infection control even tougher.

“Every hospital in the country has a policy for handling MRSA,” but “we have failed dismally” in getting a handle on it, says Montefiore Medical Center’s Currie. “A lot of the

guidance on infection control is not data-based.”

The University of Maryland’s medical center now screens everyone checking into its nine intensive-care units for MRSA, whether the patient shows signs of infection or not. “There’s debate in the United States over whether [such] ‘active surveillance’ works,” says medical director Standiford. “I believe it does and that it saves money in the long run” by identifying the “reservoirs of infection” — non-symptomatic patients who can spread the bug. “Every time you get MRSA in the bloodstream, it costs the hospital \$20,000 at least” because the patient’s stay is so much longer.

In hospitals, the confining of infected patients once halted the spread of contagion, but with the number of infections growing, many hospitals don’t have enough separate areas to confine patients, says Allison Aiello, an assistant professor of epidemiology at the University of Michigan School of Public Health.

And with the new, highly virulent strain of MRSA popping up in the community, infection control becomes even harder. More patients already have a resistant infection when they enter a hospital, and no one knows how the CA-MRSA strain spreads, says Robert Daum, a professor of pediatrics at the University of Chicago.

During the past decade, the federal government has taken stabs at attacking the antimicrobial-resistance problem but hasn't sustained its support. In 1999 the CDC established a Federal Interagency Task Force to Combat Microbial Resistance, which issued an action plan in 2001.²⁴ The inadequately funded panel, however, has the tools to do little "but issue an annual laundry list of uncoordinated activities," says Guidos of the Infectious Disease Society of America.

In 2000, Sen. Edward M. Kennedy, D-Mass., and former Sen. Majority Leader Bill Frist, R-Tenn., a cardiac surgeon, authorized \$40 million in annual funding for resistance research and federal initiatives like the task force. But Congress never appropriated any funds, says Guidos. In 2001, for example, then-Rep. Sherrod Brown, D-Ohio — now a senator — and Sen. Orrin Hatch, R-Utah, sponsored legislation to fund the programs, "but no funding ever came," Guidos says.

Moreover, jurisdictional struggles between the CDC and the states makes surveillance of resistance difficult, says Feldgarden at the Alliance for the Prudent Use of Antibiotics. Too often, "there's a one-way highway for information. It goes up to the CDC and then doesn't get back to the states," he says. And states don't always hold up their end of the reporting bargain, he adds. "Unless they get money, states don't want to play nice with the CDC."

The CDC and state public-health agencies already issue many disease-surveillance reports, and "diseases don't go away. So if you want to add something" — such as resistance — "you need to add money," Feldgarden explains. But in recent years states haven't been adding money for public health.

"It's ridiculous that CVS [pharmacy] knows more about the [birthday] cards I send to my mother" than health agencies know about developing infectious outbreaks, says Feldgarden. "Real-time reporting is essential, be-

cause once you're beyond the anecdote stage, look out."

In any case, the states, the federal government and private organizations are unlikely to do much to institute anti-resistance measures until they get clear proof that they can save both lives and money, says Stuart B. Levy, a professor of microbiology at Tufts University School of Medicine in Boston. The Massachusetts Department of Public Health, for instance, is "very receptive" and is launching its own surveillance system, but doing it "on a shoestring," he says,

The Alliance for the Prudent Use of Antibiotics, which Levy founded, is mining hospital records for what it says will be the first solid statistics on the dollar cost of resistant infections. The CDC's current cost data "are all wrong" because the agency did not have access to the hospital cost information that tells the real story, says Christopher Spivey, the alliance's manager for business development and communications. The real costs are "quite breathtaking, much bigger than we thought," he says. He could not predict exactly when the data will be available. ■

CURRENT SITUATION

Under the Radar

Unlike in previous decades, MRSA is now invading facilities such as sports locker rooms, jails and day-care centers and threatens even healthy people, says University of Chicago pediatric professor Daum, and it's more potent than hospital-acquired MRSA. After first turning up in a handful of cases, community-acquired (CA)

MRSA has seen "an explosive increase over the past 10 years in city after city," he says, beginning in the Midwest and Texas, then spreading to the West Coast and finally in the East. "And when it comes, it doesn't leave."

Today "perfectly healthy people are coming in with MRSA infections," he says, whereas in the past they developed only in hospitalized patients.

And many times the victims have never heard of the disease. "When we got the cause of [our son's] death, I had never heard of MRSA," recalls Everly Macario, a public-health researcher and writer in Chicago whose year-and-a-half-old son Simon died of CA-MRSA in 2004. The child, who had appeared to have a minor throat infection, awoke screaming with pain one morning. Doctors later discovered that toxins from the bacteria were attacking his organs. "By 10 that night he was dead," Macario says.

While hospitals still have a tough time containing traditional, hospital-acquired MRSA in their facilities, containing the community-acquired version — which causes more severe illness and appears to be more contagious — presents a more daunting challenge, says Daum. And CA-MRSA is beginning to spread to hospitals.

State public-health agencies didn't immediately realize that the new MRSA was a public-health problem, because they thought it was hospital-related, says Daum. But the "CDC is now really on board with the idea that this is something new," he says.

And as Macario found, no one is safe. "My parents are scientists, so I'm anal about washing hands," she says. "In my own home I want everything to be immaculate. I had breast fed Simon for a year, and he was up to date on all his inoculations."

Scientists don't know how CA-MRSA is spread, says Daum. For example, "I don't know what the role of inanimate objects is," such as whether the bacteria can survive and spread to other

people if a person with an abscess, for example, sits on a doctor's table, he says.

"Staph is an amazing foe," Daum says. Some bacteria are easy to fight because they have limited ways to carry out certain functions, such as adhering to human cells. If the immune system counters that method, it can neutralize the bug. But staph has multiple means of accomplishing some basic functions, making it much more formidable, he points out. And while vaccines usually stimulate the immune system to produce a key antibody that can stop a microbe, he says, "staph is not going to yield to an approach like that."

Legislation Uncertain

Efforts to shore up the federal response to drug resistance are moving forward in Congress, but it's not clear how much legislation — if any — will be enacted this year.

Both the House and the Senate have passed FDA-overhaul measures that also provide incentives for developing antibiotics. The bills would make orphan drugs eligible for special federal grants and contracts and offer longer periods for companies to retain exclusive rights to market their new antibiotics before they can be sold by generic-drug makers.

House and Senate lawmakers must still reconcile differences between the two versions, but a joint conference panel has yet to be appointed, partly because a bitter fight over children's health insurance has stalled progress of health legislation.²⁵

Bills also are pending that would ban many uses of agricultural antibiotics, an especially contentious issue.

Finally, Rep. John Matheson, D-Utah, plans to introduce a measure establishing initiatives to jump-start federal efforts to combat resistance. Among other provisions, the bill would give

the CDC task force greater authority; establish a surveillance network covering several geographic regions; provide incentives for development of new antimicrobials and require drug companies marketing new antibiotics to explain whether the drugs would increase resistance and if so, what steps would be taken to retard the spread of resistance.

Many infectious-disease experts — and especially the Infectious Disease Society of America (IDSA) — have pressed Congress to strengthen the federal government's anti-resistance efforts and offered suggestions to Matheson and others about what legislation should contain. "I have a lot of hope for the Matheson bill," says the University of Pennsylvania's Fishman, who chairs IDSA's Antibiotic Resistance Working Group. "There's a need to coordinate and oversee research, and a need for increased funding in all areas related to resistance, and it's critical to do it now."

To ease the bill's passage, Matheson probably will not make many specific demands on the private sector. Even so, the bill's introduction has been stalled for months.

The Democratic leaders of the two health committees hope to discuss both the farm-antibiotics measure and Matheson's bill, possibly in connection with the yet-to-be-held conference on the FDA bills. But the FDA bills' slow movement leaves the fate of the antibiotic legislation unclear.

Meanwhile, many states are moving to require hospitals to publicly report how many of their patients contract infections in hospitals.

Consumers Union has pushed for such laws over the past three-and-a-half years, and the effort is working, says Lisa McGiffert, director of the group's Stop Hospital Infections project. Hospital-related infections, including resistant ones, have been going on for decades "because there hasn't been a public outcry," she says.

To date, bills have been filed in 45 states, 17 of which require hospitals to report information about what infections their patients contract in their facilities, McGiffert says. Other states have voluntary reporting systems, but she prefers mandatory systems because they can be standardized so consumers can understand what the data mean. Four states — Pennsylvania, Missouri, Florida and Vermont — publish their reports online.

But most of the reporting requirements don't yet include antibiotic-resistant infections. "Data on resistant strains will come next," she says, as states perfect their systems. ■

OUTLOOK

Beyond Antibiotics

Without decisive action, drug resistance can only get worse, warn infectious-disease experts.

The drug-resistance issue "is at a tipping point right now, and I see it escalating dramatically and exponentially," says Associate Professor of Medicine Fishman at the University of Pennsylvania.

Despite her young son's death, public-health researcher Macario is optimistic but still wary about the future. "There are campaigns to urge prudent prescribing," she says, so "sometimes I think: 'There's hope. We can all rally together.'" But humans have a defense mechanism in which they say to themselves, " 'It won't happen to me.' "

"Without aggressive collaboration, we may be faced with a public-health crisis and return to the pre-antibiotic era," warns the Alliance for Prudent Use of Antibiotics in a paper laying out guidelines for medical practitioners.²⁶

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At Issue:

Should tighter restrictions be placed on antibiotics in animals?



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WRITTEN FOR *CQ RESEARCHER*, AUGUST 2007

the overprescription and overuse of antibiotics has produced an increasingly widespread number of resistant microbes. Current global trends, including urbanization and global travel and trade, have increased the demand for antibiotics worldwide. That, in turn, has increased the opportunities for antibiotic misuse. Additionally, although more and more bacteria have become resistant to the limited availability of treatments, research and development of new antibiotics has been scarce.

Antibiotic resistance already has been labeled a top concern by the Centers for Disease Control and Prevention and a “crisis” by the World Health Organization. Bacterial infections resistant to existing treatments increase health-care costs by \$4 billion to \$5 billion each year. Two million Americans acquire a bacterial infection annually during stays at hospitals. Seventy percent of the infections they contract are resistant to the drugs prescribed for treatment, and 38 patients die every day as a result.

As a microbiologist, I have always been concerned that our nation’s health policies have done little to deter microbial drug resistance. The question of how we can preserve the effectiveness of existing antibiotics is complex but demands an immediate response.

One area in which it is both feasible and logical to limit antibiotic overuse is in production of food animals. In North America and Europe, an estimated 50 percent of all antibiotics are used in food-producing animals and poultry. Much of this is not for treating sick animals but for preventing disease and promoting growth. As a result, huge numbers of animals are regularly exposed to subtherapeutic concentrations of antibiotics, with disastrous results.

To address this problem, I am the proud sponsor of the Preservation of Antibiotics for Medical Treatment Act, which would phase out antibiotics use in livestock for growth or preventative purposes unless manufacturers could prove such uses don’t endanger public health. It would also provide federal funds to help farmers adopt other approaches to preventing illness among their herds, such as cleaner housing and natural supplements. This bill would not restrict the use of antibiotics to treat sick pets or other animals not used for food.

Options exist to combat the growing public-health threat from drug-resistant bacteria. We must reevaluate how we use antibiotics, beginning with situations we can control. Our ultimate goal should be the elimination of practices that threaten the health and well-being of our citizens. The lessons of the past are plain for all to see. If we ignore them, we will risk making antibiotic treatments a thing of the past.



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bans on antibiotics used to keep animals healthy have proven to be counterproductive. The United States should not risk animal health and human health by repeating these mistakes.

Following Denmark’s ban on using antibiotics for growth promotion, the increase in animal illness and death in that country required veterinarians to nearly double their use of antibiotics to treat diseases.

The current U.S. regulatory system provides many layers of protection to ensure the safest possible use of antibiotics to keep animals healthy:

- The pre-market review process used by the Food and Drug Administration (FDA) to review antibiotics is arguably more stringent than the review of antibiotics for humans. Sponsors must demonstrate safety for both animals and the humans who consume the meat from treated animals. Also, measures imposed in 2003 require sponsors, prior to product approval, to assess the risk of resistant bacteria being transferred from animals to humans.
- Post-approval risk assessments that have been conducted and published by FDA, sponsors and researchers.
- Food-safety monitoring programs that have been established by government agencies and sponsors to track the development of antibiotic-resistant bacteria.
- Responsible-use programs that are specific to the different livestock species give veterinarians and producers specific guidelines to safely and properly use antibiotics in their health management systems.
- Pathogen-reduction programs that have successfully led to documented reductions in pathogens on meat, contributing to decreased foodborne illness.

Recent literature demonstrates the benefits of using antibiotics to keep animals healthy and the risks of letting politicians ban uses. These papers show that when antibiotics are removed without a careful assessment of the consequences, there is an increased risk of meat containing the kinds of pathogens that make people sick. Allowing producers to carefully use antibiotics to keep their animals healthy is important to our food safety system.

The FDA has in place a rigorous, science-based process for the approval of new animal drugs. This review process, combined with post-approval monitoring, risk assessments and adherence to proper-use principles, allows producers to use antibiotics to keep animals healthy, contribute to a safe food supply and minimize the risk of resistant bacteria transferring from animals to humans.

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Nevertheless, a Chicken-Little-sky-is-falling attitude isn't warranted, since 20th- and 21st-century medicine has already developed many more tools besides antibiotics to combat infectious disease, says former FDA infectious-disease officer Powers. Despite headlines declaring the contrary, "we won't go back to the pre-antibiotic era," he says. Evidence for this comes from the fact that better public health and health care had already made many infectious diseases more tractable, even before the discovery of antibiotics, he says. For example, between 1935 and 1945 — before the public introduction of penicillin — mortality from pneumonia in industrialized countries had already dropped from 70 percent to 40 percent, and medical progress in non-antibiotic areas will continue, he says.

Meanwhile, researchers continue to seek new antibiotics, exploring for undiscovered, natural antimicrobial excretions from microbes in remote environments like the Amazon jungle, deserts and the ocean floor. They also are using genetic technology to screen for more "targets" within bacteria to attack with drugs. And some researchers are using DNA techniques to explore the antibiotic effects of microbes that can't be grown in the lab, by transferring genetic material from microbes that don't grow in the lab into other microbes that can be grown and

studied there, says Kurilla, of the National Institute of Allergy and Infectious Diseases.

Future infectious-disease drugs may act on the human host rather than on the microbes, says Kurilla. Today's scientists hope someday to be able to identify host targets in human cells that will block the ability of a bacterium to complete its life cycle and produce an infection, he says.

Some small companies already are researching this area, while "big pharma" is watching from the sidelines," he says. If the research pans out, large pharmaceutical companies' chemical libraries — which primarily contain chemicals suitable for interacting with human cells — would become a richer resource for anti-infective drugs, he says.

Focusing on the host would "side-step resistance," because bacteria would have a harder time producing the complex group of mutations needed to bypass a change in their human host, Kurilla says.

Up to now, infectious-disease medicine has focused too much on throwing antibiotics at infections, then depending on pharmaceutical companies to develop a new antibiotic when resistance and new infectious ills pop up, says Montefiore Medical Center's Currie. But with new antibiotics harder and harder to find, in the future that paradigm must change, he says.

"We should have a five- or 10-year goal of learning to pry ourselves" from the antibiotic-resistance treadmill, "kind of the equivalent of the Manhattan Project to build an atom bomb in five years," Currie says. ■

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Sample formats for citing these reports in a bibliography include the ones listed below. Preferred styles and formats vary, so please check with your instructor or professor.

MLA STYLE

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