The Bacteria Fight Back

In their ongoing war against antibiotics, the bacteria seem to be winning, and the drug pipeline is verging on empty

MAYBE IT WAS JUST A BAD MONTH—AN unfortunate statistical fluctuation. Maybe not. As Vance Fowler, an infectious-disease specialist at Duke University Medical Center in Durham, North Carolina, tells it, the first case appeared in early spring 2008: a 13-year-old girl whose bout with the flu evolved into a life-and-death struggle, still ongoing, with necrotizing pneumonia and a particularly pernicious strain of bacteria known as methicillin-resistant Staphylococcus aureus (MRSA). Should the girl survive, her life will be “forever changed,” says Fowler, from pulmonary disease caused by the death of the lung tissue. The next case, a week or so later, was a research technician from Fowler’s laboratory, admitted to the hospital with a facial abscess that showed no signs of healing. Again, MRSA was the cause. A week or so after that, the victims were a husband and wife. “Both were admitted with life-threatening acute MRSA infections out of nowhere,” he says. “Multiple surgeries. Life- and limb-threatening infections.” Neither one worked in a hospital or a long-term care facility, the kind of environments in which such bacteria might commonly be found. Nor had they visited one recently. So how did they get it? “Bad luck, bad genes, a bad bug, or all three,” says Fowler.

The last decade has seen the inexorable proliferation of a host of antibiotic-resistant bacteria, or bad bugs, not just MRSA but other insidious players as well, including Acinetobacter baumannii, Enterococcus faecium, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Enterobacter species. The problem was predictable—“resistance happens,” as Karen Bush, an anti-infectives researcher at Johnson and Johnson (J&J) in Raritan, New Jersey, puts it—but that doesn’t make it any easier to deal with. In 2002, the U.S. Centers for Disease Control and Prevention (CDC) estimated that at least 90,000 deaths a year in the United States could be attributed to bacterial infections, more than half caused by bugs resistant to at least one commonly used antibiotic. Last October, CDC reported in the Journal of the American Medical Association that the number of serious infections caused by MRSA alone was close to 100,000 a year, with almost 19,000 related fatalities—a number, an accompanying editorial observed, that is larger than the U.S. death toll attributed to HIV/AIDS in the same year.

So far these outbreaks have been concentrated in hospitals, where the environment is particularly conducive to the acquisition and spread of drug-resistant bugs. But the big worry, for Fowler and others, is that they will spread to the wider community—a nightmare scenario, he says. MRSA is particularly worrisome, but so is another class of bacteria, called Gram-negative bacteria, that are even tougher to defeat. These include A. baumannii, which has plagued injured soldiers returning from Iraq. For these bacteria, the pipeline of new antibiotics is verging on empty. “What do you do when you’re faced with an
infection, with a very sick patient, and you get a lab report back and every single drug is listed as resistant?” asks Fred Tenover of CDC. “This is a major blooming public health crisis.”

Right bug, wrong place
One of the many misconceptions about bacterial infections is that the bugs involved are not native to the human body or are particularly pernicious to begin with. Virtually all bacteria are capable of causing serious infections, at least in immunocompromised patients, although most do not. In hospitalized patients, many infections arise from the patient’s own bacterial flora, flourishing where they’re not supposed to be. Pneumonia, for instance, can be caused when bacteria from the mouth are aspirated to the lungs. Just as *Escherichia coli* is a normal inhabitant of the gut, *S. aureus* colonizes the skin and mucosal surfaces in the nose in 30% of the population. When it sets up shop somewhere else, *S. aureus* can cause a host of infections, including skin abscesses, necrotizing pneumonia, joint infections, and heart valve infections known as endocarditis. Similarly, *S. epidermidis* normally colonizes the human skin, but when it gets into the bloodstream, it can cause sepsis and endocarditis, as well as infections involving prosthetic devices such as pacemakers and artificial joints. The risk of acquiring one of these serious infections is highest in hospitals and health-care facilities simply because these environments offer the greatest opportunities for bacteria to enter the bloodstream or infect open wounds.

Treating a bacterial infection with antibiotics is the obvious first step. But in the 65 years since the first widespread use of penicillin during World War II, infectious-disease specialists have been treated to an ongoing tutorial in the many ways bacteria can acquire and spread resistance to these drugs. Unlike tuberculosis and other bacteria, in which antibiotic therapy simply selects for rare resistance-bestowing mutants, the bacterial strains that are so insidious in hospitals employ far more diverse techniques, says Louis Rice of Case Western Reserve University and the Louis Stokes Cleveland VA Medical Center in Ohio. *S. aureus* and *Enterococcus*, for instance, can acquire resistance by exchanging entire genes or multiple genes with other bacteria, either through plasmids—loops of DNA that are independent of the bacterial chromosomal DNA—or so-called gene cassettes or transposable elements that can be inserted directly into the chromosomal DNA.

Penicillin and all penicillin-like antibiotics are ringlike molecular structures, known technically as β-lactams. They work by attacking a particular cell wall enzyme in the bacteria. The first strains of penicillin-resistant *S. aureus*, which arose within a few years of penicillin’s introduction, were strains that have a survival advantage because they naturally produce an enzyme—penicillinase, one of a class of enzymes known as β-lactamases—that destroys the ring structure of penicillin. Within a decade, the effectiveness of penicillin against hospital-acquired staph infections was “virtually annulled,” says microbiologist Alexander Tomasz of Rockefeller University in New York City, by “plasmid epidemics” that then spread the penicillinase gene through the entire species of *S. aureus*.

The pharmaceutical industry responded in the 1950s with a host of semisynthetic penicillins designed to be resistant to penicillins. Methicillin, introduced in 1959, was believed to be the most effective. As Graham Ayliffe, a veteran hospital infection expert at the University of Birmingham in the U.K., recalled, “this was [supposed to be] the end of the resistant staphylococcus.” Within 2 years, however, hospitals in Europe were identifying strains of *S. aureus* that were resistant to methicillin: the first MRSA strains.

Researchers later realized that these strains had taken a different route to acquiring resistance. Rather than generating new or different β-lactamases, which could attack the antibiotic directly, they had acquired a new gene entirely, called mecA, that coded for a variant of the antibiotic’s target: the penicillin-binding protein. When the antibiotics attack the original penicillin-binding protein, explains Tomasz, this “surrogate” binding protein “takes over the task of cell wall synthesis” and works to keep the antibiotic at bay. The mecA gene itself, says Tomasz, appears to derive from a common bacterium on the skin of domestic and wild animals known as *S. sciuri*.

How *S. aureus* came to acquire the gene is a mystery, but since it did, it passes it on by exchanging entire gene cassettes with the mecA gene on them.

Breaking out
Through the 1970s and 1980s, MRSA remained little more than a nuisance bug, although occasional hospital outbreaks would have to be reined in with strict isolation and control programs. In the mid-1980s, typically only 1% to 5% of all *S. aureus* isolates were methicillin-resistant, says Henry Chambers, an infectious-disease specialist at the University of California, San Francisco. Around that time, *S. aureus* began to acquire genes that confer resistance to other common antibiotics,
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apparently from methicillin-resistant *S. epidermidis* and carried on the same mobile cassettes as mecA. The result was a bug that was both far more difficult to treat and, as Chambers says, “pretty adaptive to surviving in hospitals.” Today, 60% to 70% of all *S. aureus* strains found in hospitals are multidrug-resistant MRSA.

Worries intensified when MRSA appeared a decade ago as a community-acquired infection rather than one exclusive to health-care settings. In 1999, CDC reported on four deaths in Minnesota and North Dakota, all children, all caused by MRSA infections that could not be traced back to hospitalizations by either the patients or family members. Somehow the mecA gene had emerged in *S. aureus* strains outside hospitals or health-care facilities. “This was a real biological success story,” says CDC’s Tenover. “And it all back to hospitalizations by either the patients or family members. Somehow the mecA gene had emerged in *S. aureus* strains outside hospitals or health-care facilities. “This was a real biological success story,” says CDC’s Tenover. “And it all happened off our radar screens.” MRSA isolates then began to appear in a range of unexpected community settings: children in day-care centers, army recruits, athletes in contact sports, native Americans living on reservations, prison populations, intravenous drug users, and among men who have sex with men.

The possibility that these MRSA strains were simply hospital strains that had migrated out into the community was refuted by analysis of the gene cassettes carrying the resistance. In hospital strains, these cassettes are relatively large and carry multiple resistance-bestowing genes, explains Tomasz. The “oddball” cassettes carrying the mecA gene in the early community-acquired isolates were small and contained only the one gene. In the last few years, however, MRSA strains in the community have begun to acquire multidrug resistance, suggesting that they’ve been intermingling with the hospital strains.

A half-dozen community-acquired MRSA clones have now spread around the world as their prevalence in the community has continued to increase; in San Francisco, for instance, up to 50% of all *S. aureus* isolates outside health-care settings are now methicillin-resistant. “These methicillin-resistant strains seem to be replacing the susceptible strains of *S. aureus* in the general population,” says Mark Enright, an infectious-disease specialist at Imperial College London (ICL), “which means people are carrying strains of MRSA in their nose in the community. Now when they get infections, ones that were formerly treatable are going to be replaced with difficult-to-treat infections.”

The public health anxiety increased still further in 2002 with the detection of isolates of MRSA that were fully resistant to the antibiotic vancomycin, traditionally considered the last resort for treating resistant staphylococcal infections. These *S. aureus* isolates seem to have acquired a gene for vancomycin resistance—vanA—from enterococci, and specifically *E. faecalis*, which are part of the natural flora of the intestinal tract and can cause serious infections in hospitalized patients. When the enterococci developed resistance to common antibiotics in the 1980s, physicians had responded by using vancomycin to treat them. Vancomycin-resistant *Enterococcus* (VRE) was first reported in 1986, and the vanA gene soon spread throughout the species. Because enterococci readily exchange genetic information with other bacterial species, says Tenover, he and other experts assumed that it would soon pass vanA and vancomycin resistance to MRSA. “Everybody was waiting for the shoe to drop,” says Tenover. In 2002 it did, when the Michigan Department of Community Health reported the first isolate of MRSA that had vanA-mediated resistance to vancomycin. The patient was a 40-year-old diabetic who had recently been given an extended course of vancomycin for a foot ulcer.

Fortunately, vancomycin-resistant MRSA—now known as VRSA—has not developed into the nightmare researchers feared. Only nine isolates have been detected worldwide in 6 years, seven from the same region in Michigan, which suggests that *S. aureus*, unlike *Enterococcus*,

![Drug Resistance timeline](https://www.sciencemag.org)
loses the ability to compete in the broader environment when it takes on the vanA gene. That only one of these infections was life-threatening suggests that the vancomycin-resistant bug also loses its virulence.

A paltry pipeline

Although MRSA and other Gram-positive bacteria remain a major threat, a half-dozen new antibiotics have either just been approved or are in the pipeline that should work well against them—at least until the bugs evolve more resistance. This is not the case, however, for Gram-negative bacteria, such as *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae*. These bacteria have both an inner and outer cell membrane, as opposed to the single cell membrane of Gram-positive bugs like MRSA. (The name comes from how these bacteria stain on a Gram stain test.) The pipeline for antibiotics against Gram-negative bacteria, says Bush of J&J, is limited to development programs in a few small companies; only one drug has made it through phase 1 clinical trials.

Prompted by the emergence of MRSA and VRE in the late 1980s, pharmaceutical companies focused their attention on Gram-positive bugs. Meanwhile, many Gram-negative bugs became resistant to virtually every known antibiotic, or at least every antibiotic that isn’t toxic. “These organisms may well start to spread into the community,” says Tenover, “and then we really will be in trouble. We have drugs to fall back on in a few small companies; only one drug has made it through phase 1 clinical trials.”

One reason for the dearth of drug candidates is that Gram-negative bacteria are simply harder to kill. First, they have the extra cell membrane the drug has to penetrate. Then they have other defense mechanisms that Gram-positives lack, such as the ability to activate pumps or close down protein channels in the membranes that let these antibiotics in. “They can have three or four mechanisms working at once,” says Case Western’s Rice. “Even if you develop a new drug entirely, these bacteria may be just as likely to be resistant to new drugs as old ones. It’s just really hard.”

The problem has been exacerbated by the gradual exodus of pharmaceutical companies from antibiotic development—a trend that began in the 1980s and has accelerated since 2000, in large part because the market is iffy and the chances of success are slim. Of the 15 major pharmaceutical companies that once had flourishing antibiotic discovery programs, eight have left the field entirely, and two others had flourishing antibiotic discovery programs, eight have left the field entirely, and two others have reduced their efforts significantly. That only one of these infections was life-threatening suggests that the vancomycin-resistant bug also loses its virulence.

Even though the market for antibiotics is in the neighborhood of $25 billion a year, says Steve Projan, vice president of biological technologies at Wyeth Research in Cambridge, Massachusetts, other drugs, such as antidepressants or antihypertensives, offer a greater bang for the buck because they are often taken for years or decades rather than just a 7- to 14-day course. Resistance only compounds the problem: A drug that takes a decade to develop might be useful clinically for only a handful of years.

What’s more, the better the antibiotic, the less health experts want to see it used to avoid the development of resistance. “It’s probably the only area of medicine where a drug company can invest all this money to develop a drug, come up with a good one, and then the so-called thought leaders in the field, like myself, will tell people not to use it,” says Rice. “We say it’s such a good drug that we should save it.”

As a result, virtually all the new antibiotics and all those in the pipeline for Gram-positive bacteria are second-generation drugs, that is, incremental improvements on existing classes. The one conspicuous exception—daptomycin, developed for *S. aureus* by the late Frank Tally at Cubist in Lexington, Massachusetts—was first identified 20 years ago by Eli Lilly and Co. and then shelved because it had toxicity problems at high doses.

To the surprise of many, the recent sequencing of more than 650 bacterial genomes has been a “dismal failure” when...
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it comes to drug development, says ICL’s Enright. Although genome sequences were expected to yield a “treasure trove of new targets for entirely new classes of antibiotics,” as David Pompliano and colleagues at GlaxoSmithKline in Collegeville, Pennsylvania, recently wrote, this simply hasn’t panned out. At GlaxoSmithKline, Pompliano and his colleagues spent 7 years and more than $70 million evaluating more than 300 “canonical” bacterial genes that they thought were essential to the viability of the bacteria. The result was just five leads, a success rate, they estimated, that was four- to fivefold lower than for other areas of therapeutics.

Genomics is simply not a good paradigm for discovering new antibiotics, suggests Pompliano. The genetic approach assumes that a candidate drug can knock out a single gene in the bacterium to render it unfit for survival. But the drugs don’t knock out a gene’s activity entirely, he says; instead they modulate activity. “As we found out in oncology,” says Projan, “sometimes leaving even 5% activity is enough for the tumor to grow. The same thing is true for bacteria.” Projan. The genetic approach assumes that a

Collateral Damage: The Rise of Resistant *C. difficile*

In April 2002, Mark Miller, an infectious-disease specialist and microbiologist working at Jewish General Hospital in Montreal, Canada, began to suspect that he had an outbreak on his hands. He was used to dealing with the bacteria *Clostridium difficile*, which can cause severe diarrhea in debilitated patients and had been a common problem in hospitals for more than 30 years. But now the number of cases had started to climb, as did their severity. “One of the first indications that we knew we had a problem,” says Miller, “was when one of the colorectal surgeons called me and said, ‘I just took out my second colon in a month on a *C. difficile* patient.’ When we started looking at the numbers, they were absolutely horrendous.” At the peak of the outbreak, says Miller, there were 50 new cases of *C. difficile* diarrhea every month in their 600-bed hospital. “Of those, about one in six was dying or going for a colectomy. That’s kind of staggering.”

Resistance to antibiotics makes for bacteria that are harder to kill, but it can also bestow on a bacterial strain the advantage it needs to spread through the hospital environment and perhaps around the world—a kind of collateral damage in the escalating war between man and microbes. *C. difficile* is an unfortunate case in point. The bacterium has currently been linked to at least 5000 deaths a year in the United States; at the height of the Quebec epidemic it caused more than 7000 serious infections and 1200 deaths in a single year. In many hospitals, *C. difficile* constitutes a greater risk to patients than methicillin-resistant *Staphylococcus aureus* or any other bacteria.

The symptoms of a *C. difficile* infection range from mild diarrhea to severe colitis, and the elderly bear the brunt of the disease. One in four patients will have a recurrence or multiple recurrences. “It’s a horrible problem,” says Dale Gerding, an infectious-disease specialist at Hines Veterans Administration Hospital and Loyola University in Chicago, Illinois. Patients have to be treated almost constantly with oral vancomycin to prevent recurrences, he says.

*C. difficile* diarrhea first appeared in the medical literature in the 1970s, mistaken for a side effect of the antibiotic clindamycin. In 1978, physicians realized that the diarrhea was induced by toxins from clindamycin-resistant *C. difficile*, which had colonized the victim’s colon after their normal gut flora had been decimated by the clindamycin treatment. *C. difficile* has remained a common hospital infection ever since because the bacteria produce heat-resistant spores that are exceedingly difficult to kill. They’re very resistant to detergents and cleaning agents,” says Gerding. “Really, the only thing that destroys them is bleach or hydrogen peroxide.”

Through the 1990s, however, *C. difficile* wasn’t considered a major threat because the bacteria were susceptible to two antibiotics, vancomycin and metronidazole, the latter of which is inexpensive. As many as 40% of all hospitalized patients are colonized with *C. difficile*, but most tolerate it without symptoms. A series of hospital outbreaks in six U.S. states, beginning around 2000 and capped by the severe Quebec outbreak in a dozen hospitals, suggested that a new, hypervirulent strain of *C. difficile* was circulating.

Since then, the same offending strain has been identified in hospitals in 38 states and has also been linked to outbreaks in Western Europe. What sets it apart from its predecessors, say Gerding and Miller, is its high resistance to the newer fluoroquinolone antibiotics, such as levofloxacin and moxifloxacin. These antibiotics began to be used widely in the late 1980s, and usage has increased steadily ever since. Why this strain induces more severe disease—

The battle escalates. A hypervirulent strain of *C. difficile*, resistant to two of the newer, last-resort antibiotics, has triggered outbreaks across the United States and in Western Europe.
and others suggest that the only route to a new antibiotic—short of pure luck—will be through more fundamental research on the basic biology of the bacteria.

Cutting back

Barring the discovery of miracle antibiotics to which bacteria cannot evolve resistance—a “laughable” notion, says one expert—the only foreseeable route to curbing antibiotic resistance will be to rein in the use of antibiotics. One obvious way is to lower the risk of acquiring resistant bugs in the hospital. Countries that have mandated rigorous infection control in hospitals, such as Denmark, the Netherlands, and Finland, have been able to keep MRSA infection rates low. These infection-control procedures, however, go far beyond physicians and nurses wearing gloves and protective masks and washing their hands before and after patient contacts, essential as those are. These nations employ a technique known as “active detection and isolation,” or “search and destroy,” as it’s called in the Netherlands. Patients considered at high risk of carrying MRSA and other antibiotic-resistant bugs are cultured when they’re admitted to the hospital, and periodic cultures are taken of all patients, particularly those in high-risk wards. The greater the prevalence of pathogens and risk factors, the more frequent this surveillance. Patients who are infected or are carriers are isolated. Health-care workers who are colonized with resistant bacteria can be “decolonized,” using skin washes and nasal ointments.

Whether U.S. hospitals should be required to implement active detection and isolation is a long-running controversy. Some specialists—led by University of Virginia epidemiologist Barry Farr, an expert on controlling VRE and MRSA—have argued that it’s the only proven method to control hospital MRSA infections. Others have questioned the technique’s cost-effectiveness and viability, particularly when rates of MRSA in the community are beginning to rival those in many hospitals.

Vaccines against antibiotic-resistant bacteria would also go a long way to reining in resistance, but only one such vaccine candidate, against S. aureus, has ever made it through phase III clinical trials: StaphVAX, licensed by Nabi Biopharmaceuticals. Although patients who received the vaccine had significantly lower rates of S. aureus infections at 40 weeks compared to controls, this apparent protection was lost at 54 weeks. A follow-up trial also failed to demonstrate efficacy. Several more vaccines are in development, including a new-generation StaphVAX. Even temporary protection could be useful, argue some experts, either for health-care workers, who could be vaccinated regularly, or for patients who are about to be hospitalized to undergo a procedure.

Ultimately, physicians will have to be persuaded to reduce their use of antibiotics, although that will be a hard sell. One step, for instance, would be to persuade physicians outside hospitals to treat only those patients who are truly infected. A 2001 study from the University of Colorado Health Sciences Center estimated that 55% of all antibiotics prescribed in the United States for upper respiratory infections were unnecessary. This is what Rice describes as the “get-a-little-sniffle-get-a-little-Levaquin” problem. “The patients want it,” he says, and “the doctor wants to get the patient out of the office, and the quickest way to do it is to write a prescription.” But the societal problem of antibiotic resistance should outweigh whatever personal peace of mind comes from the indiscriminate use of antibiotics, says Tenover (see sidebar on p. 360).

Similarly, many times physicians prescribe combination “broad-spectrum” antibiotics when a single “narrow-spectrum” antibiotic would do the trick. Understandably, says Rice, physicians are unwilling to wait to treat serious infections until the bug is cultured and they learn to which antibiotics it’s still susceptible. But once the crisis is over, usually 1 to 3 days after starting therapy, physicians could switch their patients to the appropriate narrow-spectrum antibiotic.

What the field desperately needs, these experts say, are randomized, controlled trials to establish how long antibiotic therapy should be prescribed for different infections. The data are scarce, and misconceptions abound. The ubiquitous advice in the field—from physicians, patients, and even CDC—is that patients should continue the full course of antibiotics even after they feel better. Because antibiotics tend to have few side effects, physicians consider a longer course to be a no-lose proposition.

But from the perspective of preventing antibiotic resistance, says Rice, “this is totally wrong-headed.” In patients with healthy immune systems, he explains, most antibiotics merely stun the bacteria sufficiently to make it easier for the host immune system to do its job. “You can take tetracycline until the cows come home,” Rice says, and “all it does is stop most bacteria from growing. It doesn’t kill them.” Extending the course of the antibiotic unnecessarily increases the likelihood that the patient’s normal flora will be inhibited to the point that bacteria resistant to the antibiotic will fill the void.

The few existing studies on the necessary length of therapy have suggested that it is often surprisingly short. Urinary tract infections in young women can be treated with 1- to 3-day courses of antibiotics. The Infectious Diseases Society of America recommends a 3-day treatment for traveler’s diarrhea, while acknowledging that 1 day appears to be equally effective. Studies from the 1940s suggested that the “vast majority” of patients with pneumonia get better after 2 or 3 days, says Rice: “Somewhere along the line, that morphed into 7 days, 10 days, 21 days, with no real reason other than making the doctor more comfortable.” In May, the U.S. National Institute of Allergy and Infectious Diseases responded to the expert demand and put out a request for proposals for clinical studies that would determine the optimal use of antibiotics, including the optimal duration of therapy. “I think most physicians would respond to compelling data from a well-done trial,” says Rice.

One beneficial side effect to curbing antibiotic use is that it may serve to rehabilitate those antibiotics that have lost their effectiveness. “Many of these were wonderful new drugs just 20 years ago, able to treat a wide variety of bugs, both inside and outside the hospital,” says Rice. “Now we’re at a point where some of them are next to useless, because they’ve been used for everything.”

—GARY TAUBES