





MEDICINE

The Enemy Within

A new pattern of antibiotic resistance that is spreading around the globe may soon leave us defenseless against a frighteningly wide range of dangerous bacterial infections

By Maryn McKenna

Maryn McKenna is an independent science journalist and a blogger for *Wired*. She has reported from the scene of disease outbreaks on most of the continents. She is author of *Superbug: The Fatal Menace of MRSA* (Free Press, 2010) and *Beating Back the Devil: On the Front Lines with the Disease Detectives of the Epidemic Intelligence Service* (Free Press, 2004).



IN EARLY SUMMER 2008 TIMOTHY WALSH OF CARDIFF UNIVERSITY IN WALES GOT AN e-mail from Christian Giske, an acquaintance who is a physician on the faculty of Sweden's Karolinska Institute. Giske had been treating a 59-year-old man hospitalized that past January in Örebro, a small city about 100 miles from Stockholm. The man had lived with diabetes for many years, suffered several strokes and had lately developed deep bedsores. But those were not the subject of Giske's message. Instead he was worried about a bacterium that a routine culture had unexpectedly revealed in the man's urine. Would Walsh, who runs a lab that unravels the genetics of antibacterial resistance, be willing to take a look at the bug?

Walsh agreed and put the isolate through more than a dozen assays. It was *Klebsiella pneumoniae*, a bacterium that in hospitalized patients is one of the most frequent causes of pneumonia and bloodstream infection. This strain, though, contained something new, a gene that Walsh had never seen before. It rendered the *Klebsiella*, which was already resistant to many antibiotics used in critical care medicine, insensitive to the only remaining group that worked reliably and safely—the carbapenems, the so-called drugs of last resort. The one medication the investigators found that had any effect on the resistant strain was colistin, a drug that had been out of general use for years because of its toxic effects on the kidneys. Walsh named the enzyme that this gene produced New Delhi metallo-beta-lactamase, or NDM-1, for the city where the man acquired the infection just before he returned home to Sweden.

If there was one such case, Walsh thought, there were likely to be others—and he, Giske and a team of collaborators went in search of them. In August 2010 they published their results in *Lancet Infectious Diseases*: they had found 180 instances of patients carrying the gene. NDM-1 was widely distributed in *Klebsiella* in India and Pakistan and had already traveled to the U.K. via residents who had traveled to South Asia for medical care or to visit friends and family. Worse, it had spread in a few cases into a different bacterial genus—from *Klebsiella* into *Escherichia coli*, which lives in the gut of every warm-blooded being and is ubiquitous in our environment. That transfer raised the prospect that

the gene would not stay confined to hospitals and hospital infections but would begin moving silently through the everyday world, carried in bacteria

in the intestines of average people, advancing without detection via handshakes and kisses and doorknobs.

It raised another possibility as well: that the delicate, seesawing balance between bugs and drugs, set into motion in 1928 with the discovery of penicillin, was about to come down for good on the side of the bacteria. If so, many lethal infections that antibiotics have held at bay for decades might soon return with a vengeance.

A NEW PATTERN OF RESISTANCE

THE END of the antibiotic miracle is not a new theme. For as long as there have been antibiotics, there has been antibiotic resistance: the first penicillin-resistant bacteria surfaced before penicillin was even released to the marketplace in the 1940s. And for almost that long, doctors have raised the alarm over running out of drugs, sparked by the global spread of penicillin-resistant organisms in the 1950s and followed by methicillin resistance in the 1980s and vancomycin resistance in the 1990s.

This time, though, the prediction of postantibiotic doom comes from a different part of the microbial world. The genes that confer carbapenem resistance—not just NDM-1, but an alphabet soup of others—have appeared over the past decade or so in a particularly challenging grouping of bacteria called gram-negatives. That designation, which borrows the name of a Danish 19th-century scientist, superficially indicates the response to a stain that illuminates the cell membrane. What it connotes is

IN BRIEF

A new pattern of resistance has emerged among a particularly challenging group of bacteria called the gram-negatives; it threatens to make many common infections untreatable.

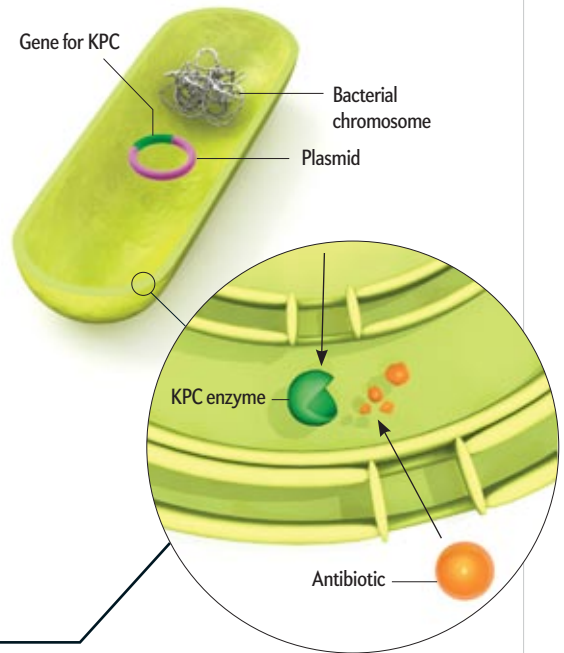
The bacterial genes responsible confer resistance to the carbapenems, a group of so-called last-resort antibiotics. Two of the most important resistance genes are dubbed NDM-1 and KPC.

Carbapenem resistance in gram-negative bacteria is especially worrisome because these germs are ubiquitous and share genes easily. Plus, no new drugs for these bugs are being developed.

This confluence of factors means many people in hospitals and in the wider community could die of newly untreatable infections of the urinary tract, blood and other tissues.

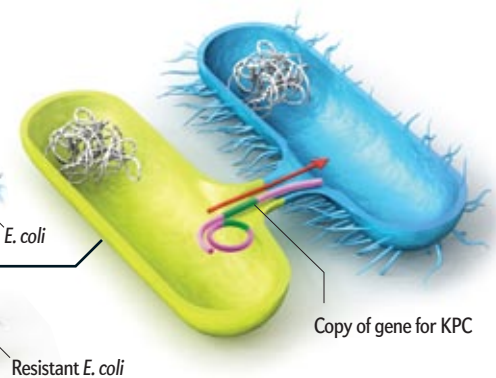
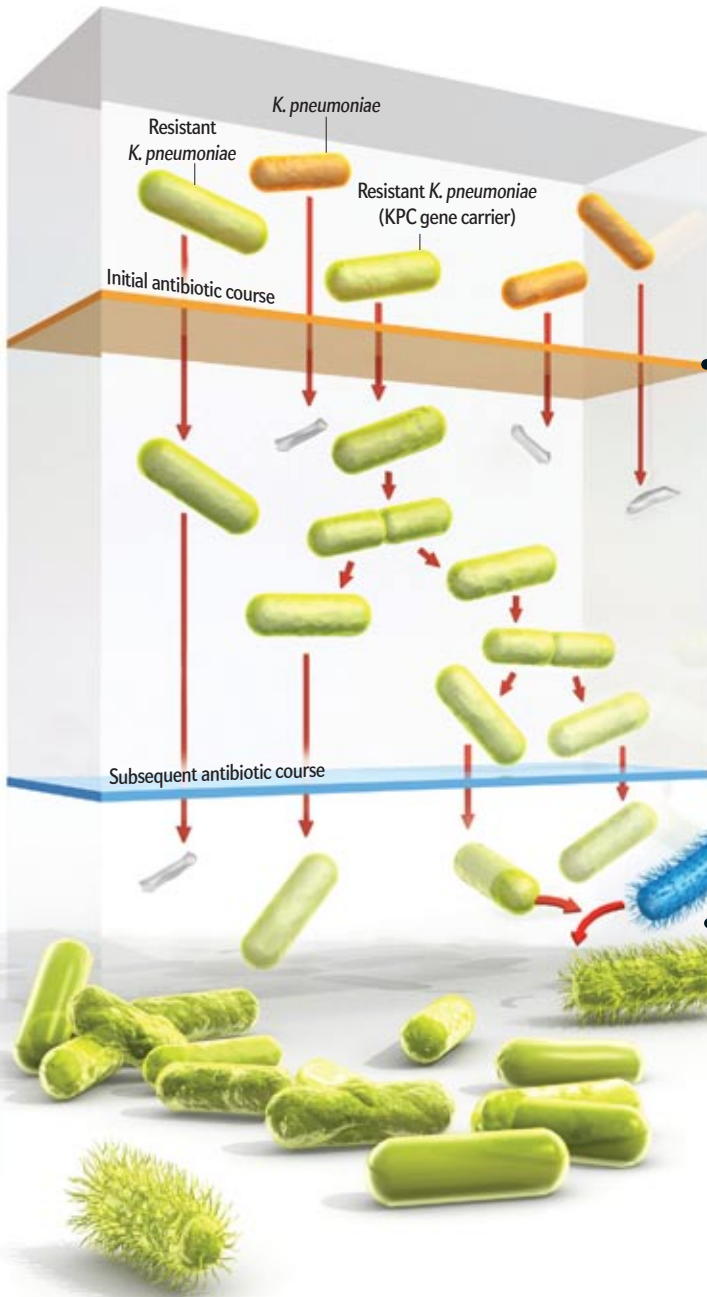
Resistance Roulette

The constant use of antibiotics, which helps to foster drug resistance across bacterial species, has produced a deadly new threat. The new strain, depicted below, began with a few *Klebsiella* bacteria that happened to carry the KPC gene, which rendered them insensitive to antibiotics known as carbapenems. Multiple rounds of ineffective treatment cleared the way for the KPC-bearing bacteria to proliferate. Even more worrisome, as shown on the right, *Klebsiella* and other gram-negative bacteria easily share KPC- and other resistance genes across species, which could make them impermeable to all drugs.



Extensive Treatment Favors Resistant Strains

In an environment awash with antibiotics, such as intensive care units, only those germs with genes that confer resistance survive and then multiply. In the closeup shown above, the KPC gene has coded for an enzyme (green) that sweeps in to attack the carbapenem medication (orange) before the drug even has a chance to make it past the germ's double-membrane outer layer.



Resistance Spreads to Other Bacterial Species

The KPC-resistance gene is found on loops of DNA called plasmids, which are present outside the bacterial cell's chromosome. During conjugation (bacterial sex), two cells form a bridge between them, allowing the plasmid to transfer its genes from one cell to the other. Gram-negative bacteria are particularly adept at this type of transfer, which in turn allows cells that have never been treated by antibiotics to become drug-resistant. The KPC-resistance pattern grows ever more dangerous as it spreads from *Klebsiella* to *E. coli* to other gram-negative germs that cause common infections.

much more complex. Gram-negative bacteria are promiscuous: they easily exchange bits of DNA, so that a resistance gene that arises in *Klebsiella*, for example, quickly migrates to *E. coli*, *Acinetobacter* and other gram-negative species. (In contrast, resistance genes in gram-positives are more likely to cluster within species.) Gram-negative germs are also harder to kill with antibiotics because they have a double-layered membrane that even powerful drugs struggle to penetrate and possess certain internal cellular defenses as well. In addition, fewer options exist for treating them. Pharmaceutical firms are making few new antibiotics of any type these days. Against the protean, stubborn gram-negatives, they have no new compounds in the pipeline at all. All told, this unlucky confluence of elements could easily export disaster from medical centers to the wider community.

Resistance to the carbapenem class of antibiotics has already brought hospital-acquired infections, such as the *Klebsiella* that infected that original Swedish patient, to the brink of untreatability. Beyond the carbapenems, there remain only a few drugs that doctors are loathe to prescribe, either because they cannot reach all the hiding places in the body where bacteria dwell or they make patients so sick as to be unsafe.

Even if health care-related infections are difficult to cure, they are usually detected because the patients in whom they occur—elderly, debilitated, confined to an intensive care unit—are usually under close watch. What keeps health authorities awake at night is the possibility that carbapenem-resistance genes will propagate, undetected, beyond the hospital inside of organisms that cause everyday maladies—such as *E. coli*, which is responsible for most of the millions of urinary tract infections in the U.S. every year. Walsh, NDM-1's discoverer, proffers the example of a woman dropping in to see her primary care doctor with what looks like uncomplicated cystitis. With no reason to suspect resistance, the physician would prescribe drugs that no longer work, while the infection spread unimpeded up her urinary tract, into her kidneys and, devastatingly, into her blood. "There would be nothing to treat her with," he concludes.

LOSING THE ANTIBIOTIC MIRACLE

THE 83-YEAR BATTLE between bacteria and the drugs created to kill them falls somewhere between a carnival game of Whack-a-Mole and a nuclear strategy of Mutually Assured Destruction. For almost every antibiotic developed to date, bacteria have evolved a resistance factor that protects them from the drug's attack. For almost every resistance factor, pharmaceutical companies have produced a tougher drug—until now.

Over the decades the battle has gradually tilted to the side of the organisms, like a seesaw slowly shifting out of balance. Bacteria, after all, have evolution on their side. It takes them 20 minutes to produce a new generation. It takes a decade or more to research and develop a new drug. Furthermore, any use—even reasonable use—of antibiotics drives the emergence of resistance by exerting what is known as selective pressure. Typically a few bacteria with random fortunate mutations survive an antibiotic's attack. They reproduce, filling in the living space that the antibiotic cleared for them by killing their susceptible brethren and passing on the genes that protected them. (That is why it is so important to take a full course of antibiotics: to kill all the bacteria causing an infection, not just the most susceptible ones.) But resistance does not spread only via inheritance. By exchanging pieces of DNA, bacteria can acquire resistance without

ever having been exposed to the drug the genes protect against.

You can see that pattern of resistance trumping drug trumping resistance in the evolution of *Staphylococcus aureus*, a gram-positive (single-membrane) organism: indifferent first to penicillin, then the synthetic penicillins—including methicillin, earning it the name MRSA—then the cephalosporins such as Keflex, and then vancomycin, the last line of defense against MRSA. Gram-negatives followed a similar pattern, disabling penicillins, cephalosporins, macro-

With no new medications in the pipeline capable of dispatching these latest superbugs, we may have to live with the risk of untreatable infections for an uncomfortably long time.

lides (erythromycin and azithromycin, or Zithromax) and lincosamides (clindamycin). But until very recently, the carbapenems could safely and reliably dispatch even the most persistent infections, making them the last resort for gram-negative bacteria, the final barrier between treatable and nontreatable infections. They were inexpensive, dependable, broad-spectrum—meaning they worked against many organisms—and very, very strong.

We might be able to research our way out of this dilemma with yet another new class of antibiotics—at least until the bacteria catch up once again. But with no

new medications in the 10-year pipeline capable of dispatching these latest superbugs, we may have to live with the risk of many kinds of untreatable infections for an uncomfortably long time.

"It has been hard to discover new compounds that work against gram-negatives and are not toxic to people," says David Shlaes, a physician and drug-development consultant and author of *Antibiotics: The Perfect Storm* (Springer, 2010). "When you think about it, what you are trying to do with an antibiotic is trying to kill something within us, without hurting us. It is challenging." The last new antibiotic licensed for gram-negative infections was doripenem, a carbapenem that was approved by the Food and Drug Administration in 2007.

The situation would be grave enough if it were limited to the few hundred cases that feature the NDM-1 gene so far. But for the past five years another gene conferring similar resistance—dubbed KPC for *Klebsiella pneumoniae* carbapenemase—has moved swiftly across the globe. And it appears to be following the pattern set in the 1950s by penicillin-resistant organisms and in the 1990s by MRSA: first sparking epidemics among vulnerable hospital patients and then spreading into the community at large.

UNCOVERING A HIDDEN THREAT

WHEN WALSH AND GISKE published their NDM-1 results in *Lancet Infectious Diseases* last summer, their paper sparked an immediate international furor. Indian health officials cried foul, charging that the Western doctors were enviously trying to undermine the subcontinent's booming medical-tourism industry.

The first sighting of KPC provoked none of that uproar. It arrived quietly, in one of hundreds of bacterial samples collected during 1996 from hospitals in 18 U.S. states. The project that

Global Threat

For four years after the KPC gene was first isolated from an unidentified hospital in North Carolina, no one could find any evidence of its spread. But once the KPC-bearing bacteria gave rise to outbreaks in several New York City hospitals, the assault was on. The tough-to-kill germs quickly traveled to France, Colombia, Canada, Greece and China. An outbreak in Israel spread to England, Norway and several other European countries.



- North Carolina, 1996
- New York, 2000
- Paris, 2005
- Subsequent cases
- States with confirmed KPC-related resistance by 2010 (37 total)

requested them, called ICARE, was a joint effort of the Atlanta-based Centers for Disease Control and Prevention and Emory University next door. (ICARE stands for Project Intensive Care Antimicrobial Resistance Epidemiology.) The program’s goal was to monitor how antibiotics were being used in intensive care units and other hospital departments, in hopes of gauging where the next resistant organism might emerge.

One isolate, sent from a North Carolina hospital that has never been publicly identified, turned out to be *Klebsiella*. That was not unusual. It is a common hospital infection, an almost unavoidable consequence of its use as a treatment in intensive care: high doses of broad-spectrum antibiotics disrupt the ecology of the intestinal tract and cause diarrhea, which contaminates the environment around patients and the hands of the health care workers who treat them. “If you think of a patient in an ICU, sedated, on a ventilator, they can’t get up and go to a bathroom,” says Arjun Srinivasan, the CDC’s associate director for health care-associated infection-prevention programs. “If they are incontinent, the health care staff will have to clean them up. There is lots of equipment close to the patient, and there are lots of surfaces that could become contaminated.”

If becoming infected with *Klebsiella* in an ICU was not a surprise, the results of its analysis were. As expected, the North Carolina isolate was resistant to a laundry list of antibiotics, including penicillin and some other related drugs. But the sample was also resistant to two carbapenems—imipenem and meropenem—to which *Klebsiella* had always responded. The sample was not completely resistant, but test results at the CDC indicated that unusually high doses of carbapenems would be needed to treat any infection that it caused. The enzyme that provided that resistance attacked the carbapenem drugs before they could even cross the inner membrane of the bacterial wall.

No one had ever seen a resistance pattern like KPC before. It made the epidemiologists working it up uneasy—as though they were sensing, just at the edge of their hearing, the ring of a distant alarm. “It was a new kind of resistance, but when there is just a single isolate, you don’t know how common it is going to be,” says Jean B. Patel, deputy director of the CDC’s office of antimicrobial resistance. “And for a long time, there were no other isolates like it.”

OUTBREAK IN NEW YORK

FOR SEVERAL YEARS the North Carolina *Klebsiella* sample remained a worrisome fluke. Then, in mid-2000, patients in four intensive care units at Tisch Hospital, part of New York University’s Langone Medical Center on the east side of Manhattan, began developing unusually tough *Klebsiella* infections that were resistant to almost all the drug classes that an intensive care physician would want to use. It was the first time physicians at N.Y.U. had ever seen infections resistant to carbapenems. Fourteen patients developed highly drug-resistant pneumonia, surgical infections and bloodstream infections, and another 10 were carrying the KPC bug without symptoms. Eight of the 24 died. On analysis, the hospital discovered that their *Klebsiella* strain carried the same key KPC gene as the original North Carolina sample.

The hospital would also soon learn how hard containing the resistant microbe could be. With so many drugs found to be ineffective, the only option was to enforce the old-fashioned tool of rigorous cleanliness, to make sure the resistant bacterium did not travel further on the hands of unknowing health care workers. Langone Medical Center put infected patients into isolation, required anyone going into their rooms to wear gowns and gloves and policed hand-washing and hand-sanitizer use. When those were not enough, they changed the cleaning

Exacting Protocol

Health care workers are often unwitting carriers of bacterial resistance. Hospitals that have controlled outbreaks of carbapenem-resistant infection were forced to adopt rigorous hygiene and surveillance measures.



Identify

To avoid missing any potential cases, hospitals in France use rectal swabs to test incoming patients with a history of previous multidrug-resistant infection.

Sterilize

Doctors and nurses must routinely wash hands and wear gloves. Patients are wiped down with antiseptics every day. All surfaces in their room are sanitized, including any computer keyboards.

Review

Laboratory specimens are continually tested and infection-control measures adjusted until multidrug-resistant germs are eliminated.

solutions used in the intensive care units. When infections still rebounded, they zoomed in on the care of the infected patients and discovered that some of them with urinary tract infections were getting splashed when their urine-collection bags were changed—splashes that contaminated the health care workers and the environment as well. It took a year to bring the outbreak under control.

Two years later the same highly resistant bug somehow appeared in hospitals in Brooklyn, further reinforcing how difficult it can be to contain *Klebsiella* harboring the KPC gene. One hospital found two infected patients in August 2003, put them in isolation, immediately ramped up its infection-control practices, and yet by the end of February 2004, 30 more diagnosed cases were scattered through the hospital. Another identified one patient in December 2003 and found two more in February 2004 and 24 additional patients by the end of May, all of them infected in-house despite aggressive efforts to block the microbe's spread.

KPC-bearing bacteria showed up in Harlem Hospital, where they caused an outbreak of seven bloodstream infections in spring 2005; only two patients survived. They also surfaced at Mount Sinai Medical Center on the Upper East Side, where researchers began testing all the patients admitted to three ICUs in hopes of getting a handle on the rapidly spreading epidemic. What they found helped to explain why the bacteria were becoming such a problem: 2 percent of all of the ICU patients were carrying the resistant strain—not showing symptoms but posing a risk of infection to others.

New York City hospitals had become a breeding ground for the resistant germs, something that federal numbers confirmed. In 2007 21 percent of *Klebsiella* samples collected in New York City carried the KPC gene, compared with 5 percent in the rest of the country. In 2008 one New York hospital reported its KPC rate had risen to 38 percent.

Patients in ICUs are seriously ill by definition—they suffer from trauma, cancer, failure of major organs—so their deaths can be complex to sort out, with no single cause. But in certain cases involving KPC, there is no question as to the cause, says John Quale, an associate professor of medicine at S.U.N.Y./Downstate Medical Center in Brooklyn who treated some of the earliest cases in New York. “Clearly, there have been instances where treatment has failed despite every effort,” he says. “And patients have died.”

GLOBAL SPREAD

FROM NEW YORK CITY, KPC *Klebsiella* spread. It was found first in places that New Yorkers frequently travel to and from—New Jersey, Arizona and Florida—and then much farther away.

Carbapenem resistance is not a reportable disease, meaning that a clinical laboratory that detects its presence is not required to notify public health authorities. So the full extent of the KPC gene's distribution is not known. In 2009, however, half of Chicago hospitals had discovered the KPC gene in at least some of their patients. A year later the proportion of Chicago hospitals reporting the presence of KPC had gone up to 65 percent. By the end of 2010 KPC bacteria had gravely sickened hospital patients

in 37 U.S. states. Once the CDC began tracking the bug, officials discovered that hospitals were not prepared for its arrival. “We saw over and over again that an isolate sent to us would end up not being the first in a hospital,” says the CDC's Patel. “When they looked back in their data, they would find earlier ones that just had not sparked anybody's attention.”

In February 2005 an 80-year-old man who had been living for five years with prostate cancer sought emergency treatment near where he lived in Paris. After he was admitted, doctors found he had brought *Klebsiella* bearing KPC into the hospital, probably from an operation in New York City a few months before. It was the first known move of KPC from the U.S. to another country, but not the last. Soon KPC organisms from New York were found in patients in Colombia, Canada, China and Greece. They caused a 45-person outbreak in a Tel Aviv hospital that traveled via patients and health care workers to England, Norway, Sweden, Poland, Finland, Brazil and Italy.

WHAT NEXT?

HEALTH AUTHORITIES now view the global dissemination of carbapenem resistance—from KPC, NDM-1 and other genes—as a “public health event of international concern,” as the World Health Organization put it last November. (The international agency has named “antimicrobial resistance and its global spread” the theme of its annual World Health Day on April 7.) That declaration is in part because so little can be done to stop carbapenem-resistant organisms: only a few antibiotics still work against them, and the drugs are far from perfect.

Most of these infections still respond to tigecycline, a newer drug, and colistin, the decades-old one. Tigecycline, released in 2005, was the first of a new antibiotics class called glycylcyclines; because bacteria had never experienced its mechanism of action before, they have been slow to develop resistance to it. But tigecycline does not diffuse well through the blood or in the

bladder, rendering it ineffective for bloodstream and urinary tract infections caused by KPC and NDM-1. (Plus, the FDA last year updated tigecycline's label, adding a warning that some patients with severe infections face an unexplained increased risk of death.) Colistin, on the other hand, is one of a small class of drugs called polymyxins that dates back to the 1940s. It has its own issues: in addition to its long-standing reputation for damaging the kidneys, it does not penetrate well into tissues. Those problems kept it from being widely used for decades, and that may be what preserved its usefulness this long—as colistin use has increased in recent years, resistance to it has increased as well.

Beyond tigecycline and colistin, we have almost nothing. Between 1998 and 2008 the FDA approved 13 new antibiotics. Only three had new mechanisms of action, something to which bacteria do not already possess resistance. In 2009 the Infectious Diseases Society of America counted up research efforts on new antibiotics. Out of the hundreds of new drug applications submitted every year to the FDA, they found only 16 antibiotics at any stage of development. Eight of them were intended to treat gram-negative bacteria, but the number that could be used against highly resistant gram-negatives such as KPC and NDM-1 bacteria was zero.

Those statistics make the case: without explicitly saying so, most of the pharmaceutical industry has decided that drugs to treat carbapenem-resistant infections are so challenging to develop and can be used for so short a period before resistance arises, that they are not worth research and development time. “We are getting to the stage now where we need to seriously start investing rather a lot of money into novel compounds—something that we haven't seen before and, more important, that the bacteria haven't seen before,” Walsh says. “And we don't need just one or two. We need 10 or 20.”

The expanding epidemic has forced hospitals to reassess the efficacy of their infection-control measures. Institutions that have been able to curb the bacteria say that the effort requires ferocious focus. Their protocols include washing down patients with antiseptics every day and cleaning the surfaces in patients' rooms, down to the smallest joints and nooks on monitors and computers, as frequently as every 12 hours. “I worry about disinfection of surfaces. It is where hospitals typically fall down,” says Michael Phillips, who is head of infection control at the Langone Medical Center, site of the sentinel outbreak in New York. Phillips helped to develop a novel “Clean Team” project that pairs infection-control experts with the hospital's building-service workers; the team cut the occurrence of several health care infections in its first six months.

The newest KPC reports show just how obsessive health workers must be about cleanliness. Last year 28 patients in two French hospitals were infected with resistant *Klebsiella* by endoscopes, flexible fiber-optic viewers that are threaded down the throat and into the digestive tract. The hospitals thought they had sterilized their equipment, but KPC slipped through.

Health care teams are also boosting surveillance, hoping to identify patients who are carriers so they can be isolated before they infect others. France, for instance, has instituted mandatory testing using rectal swabs of all hospital patients who were hospitalized in other countries for a multidrug-resistant infection on the first day of their subsequent admission at a French

hospital. “In my own hospital, we had a transfer from Morocco of a patient who was a carrier” of carbapenem resistance, says Patrice Nordmann, chief of the departments of bacteriology and virology at the Bicêtre Hospital in Paris, who treated the first French KPC case in 2005. “We isolated the patient; we rang the alarm. We avoided an outbreak.”

In 2009 the CDC published extensive guidelines to help hospitals control carbapenem-resistant bacteria. The agency did not recommend the French strategy of testing every patient before admitting them to the hospital, however, saying the bacteria are still too unevenly distributed across the country to justify the cost and staff time.

Keeping carbapenem-resistant organisms out of hospitals is important not only for controlling outbreaks among debilitated patients. It is also vital for preventing spread to health care workers. Quale and others who documented KPC's movement through New York speculate that some of it may have been unknowingly transported by physicians, nurses and midlevel staff who held jobs in several institutions. And it is even more important for keeping KPC-bearing bacteria from sharing their resistance genes with other bacterial species, such as *E. coli*, that are present in the hospital but also flourish outside it. Such a KPC-fortified *E. coli* could escape the hospital, passing out of reach of any surveillance scheme.

In at least one case, that escape has happened. In 2008 Israeli physicians treated an elderly man who came into their hospital very sick but with no sign of carbapenem resistance. In his first week in the hospital, he became infected with KPC bacteria. Within a month the KPC gene moved from the *Klebsiella* infection to an *E. coli* residing in the man's own intestines, creating a strain that was very resistant but did still respond to high doses of antibiotics. That transfer of genes happened in the hospital, under the evolutionary pressure of the drugs the man was receiving. But in January of this year researchers in Hong Kong reported that it was happening in the outside world as well. A patient who came to a local outpatient clinic there was revealed to be silently carrying *E. coli* that had acquired NDM-1. There was no record of the man ever having been hospitalized.

Looking ahead, researchers envision the emergence of completely resistant strains of gram-negative bacteria, arriving long before the drugs that could treat them. Some do not have to imagine that happening; they have seen it come true. Three years ago doctors at St. Vincent's Hospital in Manhattan treated two cases of *Klebsiella* that were resistant to everything in their arsenal. One patient survived. One died. “It is a rarity for a physician in the developed world to have a patient die of an overwhelming infection for which there are no therapeutic options,” they wrote in a medical journal. “We had no effective treatment to offer.” Unless bacterial evolution slows or drug development accelerates, such cases may soon become far too commonplace. ■

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