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Germ Warfare

Robert Langreth and Matthew Herper 06.19.06

Drug-resistant infections kill more Americans than AIDS and breast cancer combined. Biotech is fighting back. So far, the superbugs are winning.

Eight-year-old Jewaun Smith of Chicago fell off his bicycle and skinned his knee one Sunday last fall. When he complained of severe pain, his mom, Kansonja Love, took him to the emergency room at three different hospitals in four days but was told not to worry: It was just a sprain.

The next day Jewaun woke up with yellow eyes and with strange spots on his forehead. He was rushed to a fourth hospital, where doctors said his lungs, liver and kidneys were failing--and they had no idea why. That night, his mom recalls, "We were in intensive care, he was getting worse and worse, with vomiting and diarrhea. The doctors were freaking out."

Jewaun was transferred to the children's hospital at the University of Chicago, where doctors discovered that a frighteningly virulent staph infection--impervious to standard antibiotics--had begun at the knee and spread through the body. The last three children with similar infections they had treated in recent months had all died; Jewaun, they said, could go next.

Then a miracle happened: On Christmas Day 2005, after Jewaun had spent two months in an induced coma hooked up to a ventilator as doctors flooded his body with a potent, last-resort antibiotic combo, he woke up. Jewaun celebrated his ninth birthday on Jan. 31; he returned home on Mar. 10 and has recovered almost fully.

Johanna Daly was not so lucky. The Brooklyn resident checked into New York's Hospital for Joint Diseases in January 2004 for routine surgery to repair a broken shoulder. Five days after leaving the hospital, she woke up in excruciating pain; a staph infection had spread from her surgical wound to her bloodstream and lungs. She spent four months in two hospitals and a rehab center, but no antibiotic worked for long. The infections ate away her nerves and paralyzed her from the neck down.

She died May 23, 2004 at age 64. "We never dreamt she would end up being killed by her care," says her daughter, Maureen Daly. The hospital says privacy laws prevent it from discussing the case and that its infection rate is "very low."

Drug-resistant bugs are out of control. The epicenter of this epidemic lies inside the hospital. Each year, estimates the u.s. Centers for Disease Control & Prevention, 100,000 Americans die of hospital-bred infections, a higher toll than deaths from breast cancer and AIDS combined. Nearly 2 million patients get hospital infections (of a total 35 million stays), and two-thirds of them have infections that resist at least one drug. This crisis costs us \$30 billion a year.

Frighteningly lethal and insidiously efficient, these bacteria replicate and mutate prodigiously, turning out variants that elude most of the chemical weapons--antibiotics--that medicine has invented over the past century. Even more alarming, resistant bacteria are breaking out to infect healthy people outside the hospital ward.

While Johanna Daly likely died from a hospital staph infection, the staph superstrain that almost killed young Jewaun Smith didn't come from a hospital visit at all, doctors believe. He probably picked it up beforehand, and it was even more virulent than the hospital version. This same staph bug has rippled through the National Football League, infecting muscular limbs skinned by artificial turf. Another resistant bacterium has tormented hundreds of wounded soldiers brought home from Iraq.

Some doctors paint a scary worst-case scenario: A flu pandemic breaks out and beats down the immune systems of millions of people, and then staphylococci--the hospital strain and the nastier variant in the community--run wild on a killing spree.

"We really are in a desperate situation. We need more bullets, and we need them yesterday," says John Quale, who treats drug-resistant infections at the State University of New York Downstate Medical Center in Brooklyn. "The bacteria are winning right now," adds Paul Miller, who directs antibiotic research at Pfizer. Robert Moellering, an infectious-disease specialist at Harvard Medical School, issues this alarm: "More and more bugs are becoming dangerously close to untreatable."

But Big Pharma, rather than riding to the rescue, has largely abandoned antibiotic research, a low-ticket business, for more lucrative pursuits. Only 7 new antibiotics have won federal approval since 2000, compared with 30 in the decade ending 1992. Bristol-Myers Squibb, Eli Lilly, Roche and, most recently, Bayer have bailed out of antibiotic research. "The scientific hurdles were such that we had no confidence we could develop a sustainable pipeline," says Arthur Higgins, Bayer HealthCare chief.

Some help is on the way, not from the drug giants but from a coterie of obscure biotech boutiques. "Small companies like ours realized we have to do it ourselves," says Stuart Levy of Tufts University, who has been warning about emerging resistance for decades. He cofounded Paratek Pharmaceuticals in Boston and is testing an improved version of tetracycline that zaps resistant strains. Other small companies are testing compounds cast off by reluctant giants. Basilea Pharmaceutica in Switzerland, spun off by Roche in 2000, works on a potent successor to Rocephin, Roche's big seller for hospitals.

Often the new firms are manned by grayheads from the old-line drug industry. "Much of the expertise has retired, and young people coming into the industry are attracted to other targets," says P. Roy Vagelos, the retired chief executive of Merck. He developed two big antibiotics at Merck in the 1980s and now is chairman of biotech Theravance in South San Francisco. Its new technology lets chemists mash together fragments of old drugs to create more potent versions. It now is running clinical trials of a compound that aims to improve on vancomycin, an old drug that is the antibiotic of last resort for many tough infections. Results are expected in a few months.

Encouraging, but it remains likely that hundreds of thousands more Americans will die of antibiotic-resistant infections before we see a truly effective breakthrough. Only ten antibiotics are in final-stage trials--and just two are truly novel, says the Infectious Diseases Society of America. Meantime, superbugs are getting harder to kill--and growing ever more lethal themselves, fed by overuse of antibiotics, the research cutbacks and spotty practices in infection control at hospitals nationwide (*see Clean Hands*).

Half a dozen species have variants that resist all but the most powerful antibiotics. Standard antibiotics fail to quell almost 60% of hospital staph infections, up from just 2% in 1974. Several bugs once regarded as a nuisance have mutated into killers, including an intestinal bacterium called *Clostridium difficile*. A new version circulating in hospitals and clinics in North America produces 20 times as much toxin and can destroy the colon in less than a week. One recent outbreak at hospitals in Quebec infected 1,700 patients and killed 117 of them; the germ was so destructive that 33 patients had to have their colons removed.

"Antibiotic resistance and virulence have converged," says physician Robert Daum, who treated Jewaun Smith at Comer Children's Hospital in Chicago. In 1998 Daum spotted one of the first strains of antibiotic-resistant staphylococcus bacteria outside of hospitals; since then staph infections have emerged as the most feared killer bug.

In some staph cases the bacteria penetrate deep into the lungs or other internal organs and kill within days. At the Virginia Commonwealth University Medical Center last year staph spawned toxins that carved a hundred holes in

the brain of a 38-year-old man in 24 hours; he soon died. In a case that terrified doctors at Harvard's Beth Israel Deaconess Medical Center staph solidified both lungs of a previously healthy 28-year-old; in an autopsy they looked like solid hunks of liver. Doctors at Comer have treated 14 children with severe staph infections; 7 have died.

"Staph is generating resistance to every available antibiotic," frets Vance G. Fowler, an infectious-disease expert at Duke University. "The problem is bad and getting worse."

Bacteria have been around for 3 billion years--simple, single-cell organisms supremely adapted to survive in a harsh environment. These microbes are found just about everywhere--in the soil, at the bottom of the ocean, inside our bodies. Most do little harm, and some are helpful; humans carry ten times as many bacterial cells as human cells.

The link between germs and disease was first shown by Louis Pasteur in the 1860s. In 1900 infectious diseases were the most common cause of death in the U.S.; that year the death toll from tuberculosis was three times that of cancer. Mortality plummeted with the advent of sewers, protected water supplies, vaccines and penicillin. The scientist Alexander Fleming famously found penicillin in mold in 1928; it was commercialized in the early 1940s.

In the heyday of antibiotic discovery, from the 1940s to the early 1960s, drug firms launched dozens of powerful new microbe fighters, many first found in bacteria in the soil. They included streptomycin, tetracycline and erythromycin, antibiotics still in use today, though they easily get outflanked by resistant bacterial strains.

Some bacteria had already become resistant to penicillin by the mid-1940s, but it wasn't a big problem because so many new antibiotics were emerging from the lab. In the 1950s antibiotics spread to animal feed as growth promoters and for disease prevention. After criticism agricultural use is down from its peak but is still at 13.5 million pounds a year, says a 2001 estimate from the Union of Concerned Scientists.

In the early 1960s a penicillin sibling was introduced, methicillin. Strains that sidestepped it emerged in Europe several years later. Around this time scientists gained chilling new insights into how killer bugs work--and how they shrewdly pass on their most lethally effective traits to one another and even to bugs of other species. An early infection holds thousands of bacteria, and in the body each one divides into two daughter cells every few hours. Each split provides a shot at a random mutation that defies drug attack, and all bugs possess sly mechanisms for trading DNA among differing species, letting them perpetuate and multiply resistant techniques. They may even use harmless bacteria as a transport link to arm other harmful bugs that pass by.

Thus bacteria have developed molecular pumps to expel antibiotics and the ability to produce enzymes that chew them up. "They have the sheer power of simple mutations," says Francis Tally, chief scientist at Cubist Pharmaceuticals in Lexington, Mass.

By the 1970s antibiotics were routinely prescribed even for nonbacterial infections. The rampant overuse bred ever stronger resistance by wiping out weaker strains that otherwise might compete with the drug-resistant variants, leaving only the balkiest bugs to take hold. Researchers began finding bacteria that defied assaults by a number of antibiotic drugs.

In 1977 a 28-year-old doctor in South Africa, Michael Jacobs, found a strep pneumoniae bacterium that resisted every drug then available; it was only the second time a strep multidrug resistor had been cornered. Today such strains show up in the U.S., and current pneumococcal vaccines may not stop them, says Jacobs, now an infectious-disease specialist at Case Western Reserve University.

In 1981 Stuart Levy, the Tufts professor, along with 200 other scientists and public health officials in numerous countries, issued one of the first dire public warnings about the misuse of antibiotics and the risks of killer bugs resistant to them. The warning made good headlines but had little impact on the medical establishment. "There were deaf ears for a long time," he says. Levy later wrote a book on the problem, *The Antibiotic Paradox*.

By the late 1980s enterococcus bacteria started becoming resistant to even the last line of defense, vancomycin. In the early 1990s forms of tuberculosis immune to an array of antibiotics emerged in New York and also became a persistent problem in eastern Europe and Asia.

Yet despite this worsening picture, doctors continued using antibiotics in a willy-nilly style. In 1997 a study in the *Journal of the American Medical Association* found that half of patients with a common cold were given antibiotics, even though antibiotics work only against bacteria and a cold is caused by a virus. Today more than 60% of all antibiotic use is unnecessary, New York University infectious-disease specialist Dr. Philip M. Tierno estimates.

In the mid-1990s drug firms touted gene sequencing as the solution to the resistance problem. By decoding microbial DNA, drug researchers hoped to pinpoint key proteins that could be gummed up with novel druglike chemicals. In 1996 SmithKline Beecham vowed to discover two new antibiotic classes by 2003. But when SmithKline researchers screened their compound collection against the novel proteins from staph and strep bacteria, they found few good leads.

"It was incredibly disappointing," laments retired SmithKline executive Martin Rosenberg, who led the effort. Bacteria genome efforts elsewhere also have yielded little. "We found the easy stuff in the '40s, '50s and '60s," says Wyeth Vice President Steven Projan. "What happened with genomics was a degree of irrational exuberance. It didn't work."

Big drugmakers started pulling back on antibiotic research in the late 1990s. Wyeth has cut its antibiotic research staff from 80 in 2003 to 15 currently. Other efforts to devise new ways of killing the killer bugs fizzled. In 1999 Pfizer had to severely limit use of Trovan, a potent antibiotic aimed at many bugs, after it was linked to a dozen cases of liver failure. This year Bristol-Myers Squibb vowed to stop selling another antibiotic, Tequin, which has been linked to dangerously high blood-sugar levels. More recently two vaccines against staph infection, made by nabi Biopharmaceuticals and Inhibitex, failed in big trials.

"It's very discouraging. They work in the rabbit, but they don't work in people," says Duke University staph expert Dr. G. Ralph Corey.

Companies still in pursuit are turning back to old-fashioned chemical tinkering and screening natural products to unearth new antibiotics. In May Merck published details of a new antibiotic gleaned from a soil sample from South Africa after screening 250,000 natural extracts. This very early work, however, may fail to yield a drug.

Pfizer is further along. One of the few giants that have kept at it in antibiotics, it has one fast-growing resistance fighter, Zyvox, with expected sales of \$780 million this year. It has deployed 150 scientists and hopes to have six new antibiotics in three chemical classes in human trials by year's end. GlaxoSmithKline is also testing several new bug bashers.

But much of the new effort comes from small biotech firms and Big Pharma defectors. At Theravance, Merck alum Roy Vagelos lured former Merck chemist Burton Christensen, co-inventor of three antibiotics at Merck, to come out of retirement in 1998 to help create new antibiotics. He has designed a drug, telavancin, that may work three times as fast as vancomycin, which can take nine days or more to quell a staph infection.

Theravance's drug grips the bacterial membrane more tightly than vancomycin, enabling it to kill faster. In a middle-stage trial of 195 patients with staph skin infections, it cured 96% of the patients; vancomycin had a 90% cure rate. Two final-stage trials, each covering a thousand patients with staph skin infections, aim to clinch a more definitive difference, with results due this summer. Two other trials target pneumonia in hospitals.

"We think we can score," says Vagelos. "These are lifesaving drugs."

At Cubist Pharmaceuticals outside Boston, Wyeth veteran Francis Tally rescued a novel antibiotic abandoned by Eli Lilly. His company acquired it for \$1 million plus royalties in 1997. The drug had caused muscle toxicity in earlier tests, but Tally's team changed the dosage and minimized the problem. The drug, Cubicin, hit the market in 2003 and is only the second totally new antibiotic class in 40 years; sales will hit \$200 million this year. A downside is that it doesn't work for pneumonia; the firm is crafting a second version that does. Meanwhile, Roche spinoff Basilea, developing a successor to Rocephin, touts its new drug, ceftobiprole, against drug-resistant staph

infections.

Other outfits sidestep antibiotics altogether, hoping to treat infections without breeding more resistance. The new killer bug *C. difficile* has flourished because older antibiotics killed off the healthy bacteria that normally live in the intestine, clearing the way for toxic *C. difficile* to take over. New strains are far more deadly than old ones.

"Ironically, you have an antibiotic-induced disease being treated with more antibiotics," says David Davidson, medical director at Genzyme. Ditching that approach, his firm is testing an indigestible polymer called tolevamer that binds the bacterial toxins causing *C. difficile*'s symptoms; it aims to resolve the disease without killing the bacteria directly. A midstage study of 289 patients found it comparable in power to vancomycin; a final-stage trial could yield results next year.

Meanwhile, ViroPharma in Exton, Pa. hopes to launch clinical trials of a more radical approach: preventing outbreaks by infecting high-risk patients with innocuous strains to prevent toxic strains from taking hold. This concept comes from infection specialist Dale N. Gerding at the Hines va Hospital in Chicago. He showed in 2002 that feeding hamsters nontoxic bacteria was 90% effective at holding off the bad *C. difficile* strains.

One doctor group, the Infectious Diseases Society of America, calls for new incentives to lure big pharmaceutical companies back into the field. A patent "wild card" would let a drugmaker add six months to any drug patent if it introduces a new antibiotic; or makers could get longer exclusivity for antibiotics themselves. Congress is considering extra tax credits. None of this, however, will quell killer bugs for now. Give your kids kneepads.

Limited Arsenal

In recent years the number of new antibiotics hitting the market has declined, a trend that has infectious disease doctors worried. Here are some of the more prominent examples.

DRUG/MAKER	APPROVED	HISTORY	PROJECTED 2006 SALES
Zyvox Pfizer	April 2000	At the time, first new antibiotic class in 35 years; hits hospital infections hard	\$780 million
Cubicin Cubist Pharmaceuticals	Sept. 2003	Second new class; abandoned Eli Lilly drug; fastest antibiotic launch ever.	\$200 million
Ketek Sanofi-aventis	April 2004	Touted as new class; many experts disagree	Not available
GTygacil Wyeth	June 2005	Shelved for years; now useful against broad range of bugs	\$90 million

Sources: Prudential Securities; Sanford C. Bernstein; Lazard; FDA; company statements.

New Weapons

Biotech firms are now behind many new antibiotics in testing.

DRUG NAME	MAKER	HISTORY	DEVELOPMENT STAGE
Telavancin	Theravance	Super-vancomycin developed by former Merck exec	Late-stage trials
Tolevamer	Genzyme	Polymer used to absorb toxins from <i>C. difficile</i>	Late-stage trials
Ceftobiprole	Basilea Pharmaceutica; Johnson & Johnson	A super version of Roche bestseller Rocephin is being developed by a Roche spinoff	Late-stage trials
Lysostaphin	Biosynexus	Enzyme cuts through staph cell walls	Preclinical trials
PTK 0796	Paratek Pharmaceuticals; Merck	Uses new chemistry to improve upon tetracycline	Early-stage trials
Zeven	Pfizer	Another vancomycin-style drug	Awaiting approval

Sources: Companies.

Medical Technology



Antibiotics kill bacteria by blocking necessary enzymes (see 1, above). But bacteria ply sly mechanisms for evading attack. They spew out enzymes to slice apart the antibiotic (2). They close off the cell wall to prevent penetration (3). They pump out the antibiotic before it can kill (4) or change the targeted enzyme to disable the drug (5). And they easily pass on the best tools to still other bugs.

Sidebars:

[Bad Bugs](#)
[Clean Hands](#)
[War Wounds](#)

In Pictures:

Six Strains Of Killer Bacteria