

How staph became drug-resistant threat

94,000 infections a year, many occurring outside of hospitals

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The evolutionary path of the bacterium called MRSA wound around the globe for decades before a pair of Chicago doctors in 1996 noticed the bug had taken an ominous turn.

Before then, the germ's resistance to antibiotics was of concern mainly in hospitals, where steadily growing numbers of patients were contending with the stubborn staph infection. Reports of healthy people who contracted MRSA outside of a hospital were rare and isolated, the stuff of obscure medical journal articles.



Tribune photo by Zbigniew Bzdak

New strains of methicillin-resistant *Staphylococcus aureus* bacteria occur outside hospitals with increasing frequency.

But the bacterium, formally known as methicillin-resistant *Staphylococcus aureus*, was beginning to depart from the habits it had settled into during years of adaptation to human hosts.

At the University of Chicago Medical Center, pediatric specialists Dr. Robert Daum and Dr. Betsy Herold held an impromptu meeting to discuss a dramatic increase in young patients showing up at the hospital with MRSA infections they'd gotten in the community. Dozens of children were sickened by the resistant bacteria without having contact with hospitals—an unprecedented outbreak.

"We just looked at each other and said, 'What's going on here?'" said Daum, chief of pediatric infectious diseases at the U. of C.

They were witnessing a pivotal episode in the biography of a bacterial family that is now found widely in hospitals and among the public at large, causing 94,000 severe infections each year with 19,000 deaths, according to a recent federal estimate. From its humble birth at hospitals in Britain, MRSA has transformed itself into a menacing microbe with fewer weaknesses and perhaps more lethal power than its ancestors had.

The germ's years of adaptation did not make it an invulnerable superbug. Some antibiotics still work reliably against MRSA and even severe cases of illness can be treated. But many doctors still do not know how to recognize and properly treat the infection, and experts are concerned potent strains will continue spreading in the community.

The bug's erratic evolutionary story became clear only in the last few years as scientists

decoded the full genomes of at least 12 separate staph varieties, making the bacteria among the most intensely studied pathogens in recent memory. Genetic sleuthing has revealed MRSA's family ties and some potential gaps in its armor, as well as the darker corridors of its private life.

Like most successful germs, MRSA has triumphed by constantly changing and adapting to new environments. MRSA does this mostly through an uncanny talent for weird bacterial sex.

It's not sex as humans understand the term, but the effect is the same: a blending of genes from unrelated individuals. MRSA does it with the aid of viruses that siphon DNA from an individual germ and inject it into the next, like microscopic mosquitoes. The bacterium also has the ghoulish ability to suck up genetic material from germs that have died and dissolved.

"This isn't like human biology at all—after we're born we're stuck with the genes we've got," said MRSA researcher Dr. Henry Chambers, chief of infectious diseases at San Francisco General Hospital. "Staph can take on new genes and share them with friends."

The bacterial ancestors of MRSA have probably stalked humans throughout history. Staph is an ancient, ball-shaped germ that caused skin inflammation and battlefield wound infections long before it encountered the antibiotics that helped spawn MRSA. Scientists identified *Staphylococcus aureus* as a species in the late 19th Century.

Staph felt the sting of antibiotics before any other bacteria, when British researcher Anthony Fleming discovered penicillin

stopped the germ's growth. By the 1950s, however, the bacterium had adapted by making an enzyme that could slice through penicillin. The need for more antibiotics led to a new wave of drugs, including the debut of methicillin in 1959.

Just one year after methicillin hit the market, a young English bacteriologist named Patricia Jevons was testing thousands of bacterial samples and found three strains were resistant to the new drug. Reporting her findings in the *British Medical Journal* in 1961, Jevons noted calmly, "The fact that the occasional resistant strain does exist should be borne in mind."

No newspaper headlines heralded the birth of MRSA, perhaps because experts already knew it was only a matter of time before staph figured out the new drug. Antibiotics shove bacteria into an evolutionary corner, weeding out the vulnerable varieties and offering an opportunity to strains that have picked up key defensive traits.

"We can always expect antibiotic resistance to follow antibiotic use, as surely as night follows day," said Dr. John Jernigan, a medical epidemiologist with the federal Centers for Disease Control and Prevention.

Evolution's answer to methicillin was a gene called *mecA* that allowed MRSA to evade the antibiotic's molecular weaponry. Scientists searching for its origins have found different versions of the gene in a form of staph that infects rats, as well as in a relatively harmless type of staph that can be found virtually everywhere.

The resistance gene likely hopped repeatedly from one staph species to another, perhaps using the bacterial viruses called phages as its taxi service. The gene "wasn't very common, but it was there in the

background, waiting to be amplified," Chambers said.

Landing in the U.S.

MRSA spent its youth in the '60s lurking in the shadows, slowly spreading and gathering force. The bacteria got its U.S. passport in 1968, when the first American cases showed up in Boston. Methicillin fell out of use as a drug because it was toxic to some patients, but MRSA was still resistant to the similar drugs that replaced it.

Then as today, doctors could still stop the bug with a more powerful antibiotic, vancomycin. But if an infection is not recognized as MRSA, the patient's condition can get dangerously worse while a physician tries to treat it with weaker antibiotics. Doctors typically do not reach first for vancomycin because routine use of the drug could help bacteria build resistance to it as well.

As of 1974 the resistant bug still accounted for only 2 percent of all hospital staph infections. The problem in hospitals grew more quickly in the 1980s before flattening out. MRSA took off first in big-city teaching hospitals, which brought together large numbers of the sickest patients from around the world. Once the bug gained a foothold, it seemed almost impossible to eradicate.

"It's not as though we can point to one organism at one location and say everything emanated from here in logical fashion," said Fred Tenover, acting director of the CDC's office of antimicrobial resistance. "We had progressions, fallbacks; then the bacteria reached a critical mass, got a foothold, and from there you got larger and larger epidemics."

Scattered cases of MRSA cropped up outside of hospitals in Michigan and parts of

Australia. But before the 1990s, resistant staph never quite caught on in the community.

Pressures of evolution

The reason may go back to the selective pressures of evolution. Drug resistance doesn't always help bacteria survive. It's vital for germs in a hospital, where the constant use of antibiotics slowly weeds out any bacteria that lack such defenses. But in the community, resistance genes may become a drag.

"Having this extra baggage can take away from the bacteria's fitness, so it's better for the bug not to have it," said **Susan Boyle-Vavra, a staph researcher at the University of Chicago.**

That's one reason the U. of C. finding of a spike in community-acquired MRSA cases came as such a shock when Daum's team published its results in 1998. Another was that no one had seen this strain of MRSA before. Among other clues, the U. of C. strain could be treated with drugs such as clindamycin, which the common forms of hospital MRSA had learned to resist long before.

Daum began sounding an alarm about the new form of community MRSA, but few people in the media or in the research community took his concern seriously. Community MRSA still seemed rare, and the hospital variety was a bigger problem. Jernigan was one of many experts who argued the new bug had merely escaped from hospitals and posed no unique threat.

"Early on I wondered if MRSA in the community had its origins in the health-care setting," Jernigan said. "That was wrong. It definitely has its own foothold in the community."

The unusual properties of MRSA's new form have emerged since 2000 as scientists intensely studied the bug.

Troubling toxin

One of the strain's most potentially troubling features is a gene for a toxin called PVL, which hopped a ride into the staph genome on a bacterial phage. The toxin's role has spurred debate, as some researchers think it's merely a benign passenger. But some studies suggest MRSA with PVL can cause more serious forms of disease, including a severe form of pneumonia.

"If you have bad staph pneumonia, you're likely to have a strain with PVL," Daum said. "It's a convergence of drug resistance and virulence."

An even newer strain of community MRSA has swept the country in the last few years and now accounts for nearly all cases. The latest variety appropriated yet another gene from a mostly harmless type of staph that may be helping the new strain spread.

"It can survive inside the cells the body normally uses to kill it," Tenover said. In the latest twist to the story, scientists say the community strain now has begun infecting hospital patients, who may be more vulnerable to it.

Genetic studies of MRSA have brought some good news. Last year **researchers from the U. of C.** and Rockefeller University in New York reported a successful test in mice of a vaccine that would protect against several forms of MRSA, including one of the community varieties.

It may even be possible to make old antibiotics work against MRSA. Daum's lab

has focused on disabling a system of proteins in the bacteria that sense when antibiotics are nearby. Turning off that system makes the bug blind to the drugs that can kill it.

If successful, the approach one day could allow doctors to use standard antibiotics even against germs that possess the resistance gene. For once, MRSA's long evolutionary march could take a welcome step backward.

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Avoiding infection

Good hygiene is the best way to avoid infection with MRSA. This staph infection sometimes first appears on the skin as a red, swollen pimple or boil that may be painful or have pus. It can be spread by close, skin-to-skin contact or by touching surfaces contaminated with the germ. The federal Centers for Disease Control and Prevention advises:

- * Keep your hands clean by washing thoroughly with soap and water or using an alcohol-based hand cleaner.
- * Keep cuts and scrapes clean and covered with a bandage until healed.
- * Avoid contact with other people's wounds or bandages.
- * Avoid sharing personal items such as towels or razors.

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Tracking MRSA in hospitals and communities

Resistant strains of *Staphylococcus aureus* have evolved steadily over the years and acquired the ability to spread through the

community. Today about 2.3 million Americans carry MRSA in their nose or on their skin.

TIMELINE OF MRSA

Methicillin-resistant *Staphylococcus aureus*

1959: Methicillin is introduced as an antibiotic.

1961: Bacteriologist Patricia Jevons discovers first methicillin-resistant *Staphylococcus aureus* (MRSA) in England hospitals.

1968: First report of MRSA in American hospitals in Boston.

1974: MRSA accounts for 2% of hospital staph infections in U.S.

1981: First reports of MRSA acquired in the community, while MRSA in hospitals rises steadily.

1997: MRSA accounts for 50% of hospital staph infections.

1998: University of Chicago researchers report a 25-fold increase in community-acquired MRSA from 1993 to 1995. During the same period, 35 kids in Chicago are hospitalized with community-acquired MRSA.

1999: CDC reports deaths of four otherwise healthy children from community-acquired MRSA.

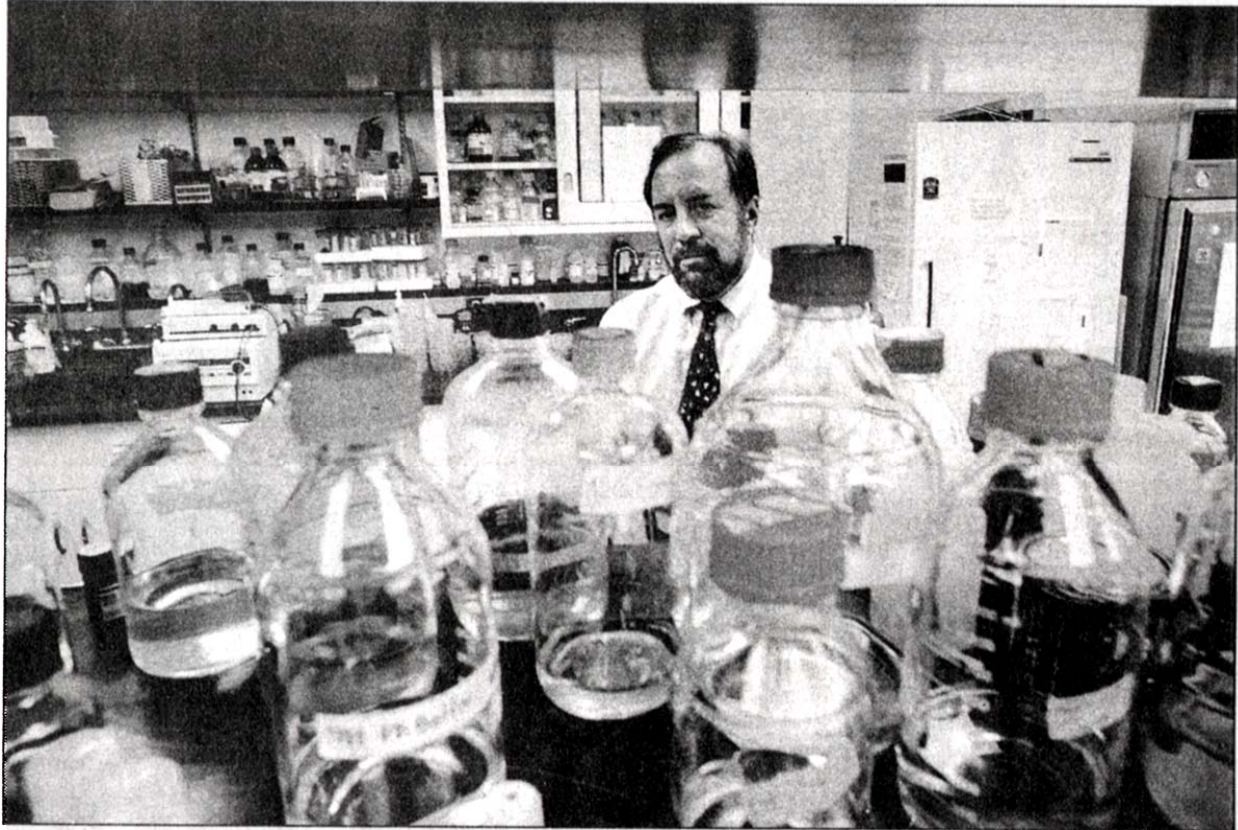
2002: U. of C. team finds that new cases of community-acquired MRSA are genetically distinct from hospital strains.

2007: CDC estimates that MRSA causes 94,000 severe infections each year, killing 19,000.

Sources: CDC, University of Chicago, Barry Kreiswirth for The Public Health Research Institute Center

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Robert Daum, a pediatric specialist at the University of Chicago Medical Center, helped identify a new strain of MRSA that was developing in the community instead of in hospitals.