

# Arsenal Of Antibiotics Not Being Restocked

BY TRINE TSOUDEROS  
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CHICAGO — Nobody knows where Simon Sparrow picked up the bug that killed him.

One sunny April morning six years ago, the curly-haired toddler woke up with flu-like symptoms; by afternoon he was struggling for breath. He went into septic shock. Doctors at the hospital gave him intravenous antibiotics, but the drugs failed.

By the next afternoon, Simon was dead at 18 months old, the victim of a highly drug-resistant bacterium, methicillin-resistant *Staphylococcus aureus*. The day before, on the way to the hospital, he had learned the word "flower."

"I was insane for a year," said his mother, Everly Macario of Chicago. "You feel like you are in a dream. You feel like you will wake up sometime."

We have come to expect that modern medicine can cure just about any infection. But bacteria are finding ways to evade, one by one, the drugs in our arsenal, and that arsenal is not being replenished with new antibiotics.

Drug companies are abandoning the antibacterial business, citing high development costs, low return on investment and, increasingly, a nearly decade-long stalemate with the Food and Drug Administration over how to bring new antibiotics to market.

Soon, doctors fear, we could be defenseless against bacteria that can resist all existing antibiotics, which would mean more victims like Simon, dead from a staph infection that drugs used to conquer easily.

Dr. Brad Spellberg, an expert on antibiotic resistance, called the situation "catastrophic."

At the core of the problem is a regulatory impasse over whether drug companies seeking FDA approval for antibiotics should be required to run much more stringent clinical trials.

The FDA says yes, citing advances in the science of clinical trial design and a series of humiliations involving trials for drugs the agency had approved, including the antibiotic Ketek.

"We don't want to approve products that don't work," Dr. Joshua Sharfstein, principal deputy commissioner of the FDA, told physicians and scientists gathered for a workshop on antibiotics and clinical trials in late July.

But the pharmaceutical industry and some infectious-disease doctors say the proposed rules will make it so difficult and expensive to gain approval for new antibiotics that the few remaining companies will abandon the field altogether.

The debate over setting new guidelines for antibiotic clinical trials has lasted almost a decade. In two years there have been at least nine meetings among the FDA, pharmaceutical industry scientists and physicians, academics and infectious-disease doctors, but the group has agreed on little besides the dire need for new antibiotics.

At times the debate has been so heated that the acting chairman of an FDA committee opened a 2009 meeting by warning that he didn't want to read the next day about police "having to arrest scientists for breaking shop windows and turning over cars."

"I fear the conversation may be beyond all hope," said infectious-disease specialist Spellberg, who has been involved in the meetings. "We've hashed and re-hashed the same things over and over."

Dr. Edward Cox, director of the FDA's Office of Antimicrobial Products, said there has been some progress, pointing to recently issued draft rules for antibiotic trials involving sinus infections, ear infections, a type of bronchitis, skin infections and community-acquired pneumonia.

However, Spellberg said, "The end result is exactly the same: No drugs."

For years, new antibiotics often were approved based on clinical trials that didn't have to show the new drug was better than an old one. Instead it had to fall within an acceptable margin of efficacy, which meant it could test somewhat worse and still be considered a success.

Just how much worse is OK with the FDA lies at the heart of the debate. The FDA wants the margins for these "non-inferiority trials" to be scientifically justified, and that may result in margins much tighter than before.

This type of trial has pitfalls, the FDA has said. If the definition of success is too loose, you might not be measuring efficacy at all.

The FDA is now proposing that antibiotics used to treat non-lethal infections which often resolve on their own, such as sinusitis, ear infections and bronchitis, be tested under different methods: superiority trials or placebo-based trials.

But showing one antibiotic is superior to another is hard because many antibiotics work so well, Spellberg said.

Cox of the FDA said clinical trials that show an experimental drug is significantly better than a current drug would provide clear evidence that the experimental drug works. He also acknowledged it may be difficult to show that an experimental antibacterial drug is better than a current drug.

Placebo trials, in which the drug is tested against a look-alike but useless pill or injection, are also unrealistic, according to some experts. It's nearly impossible to persuade patients with a painful sinus infection to enroll in a study with a 50 percent chance of getting a sugar pill and not a drug, they said.

Dr. David Shlaes, who worked in pharmaceutical antibiotic development for decades and is now a consultant to the industry, said it is absurd to be, in effect, questioning if antibiotics work.

"This is like asking how do I know para-

chutes work? ...

Those of us in infectious disease, we are all scratching our heads wondering: What the hell they are talking about?" said Shlaes, whose book, "Antibiotics: The Perfect Storm," will be published this fall. "It is like proving gravity all over again."

In the case of life-threatening infections such as community-acquired pneumonia, the FDA is discussing whether to require much stricter non-inferiority trials.

That, several experts said, would create new obstacles in a field where already there are few financial incentives to bring antibiotics to market.

Physicians use new antibiotics only sparingly because they want to keep bacteria from developing resistance. And people take the drugs only for a short time — a week, maybe two or three. By contrast, a blockbuster cholesterol drug does not need to be conserved, doesn't lose potency and may be prescribed for a person's entire life.

In 1980, 36 U.S. and European companies were in the antibiotic business, said Dr. Karen Bush, an Indiana University professor who recently left antibacterial development at Johnson & Johnson. "Today there are somewhere between four and seven large companies, depending on how you count," she said.

Bush, Spellberg and Powers all consult for pharmaceutical companies.

Dr. Barry Eisenstein, senior vice president for scientific affairs at Cubist Pharmaceuticals, a Lexington, Mass.-based biotech company that makes the antibiotic CUBICIN, said that without clear FDA guidance, companies and investors will not want to pursue these types of trials.

Some are suggesting that for community-acquired pneumonia, antibiotics trials might require as many as 10,000 patients at a cost of about \$50,000 a patient, or \$500 million. "Cubist barely makes that much a year," he said.

"Nobody can run those trials," said Shlaes. "They live in a different world. Their world is numbers and logic. It is not patients and life."

In an e-mail, Sharfstein wrote: "We are hearing the concerns and are working to make sure the pathway is realistic."

A few days after an FDA meeting on clinical trials in December 2009, Tom Dukes felt a familiar pain in his abdomen. He thought it was just his diverticulitis again, and that a day or two of antibiotics would have him feeling fine.

He was right about the diagnosis, but this time the inflamed pouch in his colon was infected with drug-resistant *E. coli*. Oral antibiotics failed and he became deathly ill, requiring emergency surgery. "I still have dreams about those last 10 seconds before they were going to knock me out," said Dukes, of Lomita, Calif. "I remember thinking, 'I wish I had one more day. I wish I had one more day.'"

Doctors threaded a thin tube into his heart to deliver the more exotic antibiotic ertapenem. It worked. Dukes lost 8 inches of his colon, wore a colostomy bag for months, was out of work for five months and lost 20 pounds off his fit, 52-year-old frame, but he lived.

Without effective antibiotics, the whole medical system falls apart, experts say. Simple problems like diverticulitis turn into life-threatening medical crises. Surgery becomes much riskier without antibiotics that can keep infection at bay.

"People have to understand how much of our medical way of life is completely dependent on antibiotics," said infectious disease physician and scientist Dr. Lou Rice, vice chairman of the Department of Medicine at the University Hospitals of Cleveland. Rice also sits on two pharmaceutical company boards.

"We would have no transplants without antibiotics," Rice said. "Much of cancer we are able to treat because of antibiotics. ... This is a big problem that will alter our way of life."

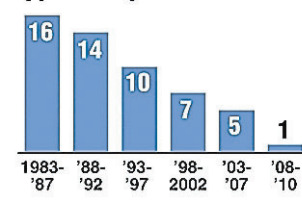
Macario, who lost her toddler son, Simon, to a MRSA infection, said his death reminded her of tragedies suffered long ago, from a time before antibiotics.

"Before Simon died I thought that infectious diseases were a thing of the past," said Macario, who helped found the MRSA Research Center at the University of Chicago. "Losing my son made me appreciate the profound and habitual pain and grief families a half of a century ago experienced."

## Fewer new drugs, more resistance

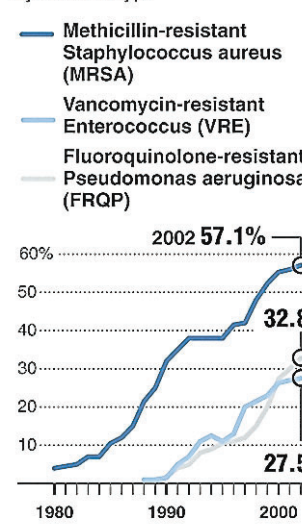
Hospitals report seeing more drug-resistant strains of some infections while fewer new drugs are coming on the market to fight them.

New antibiotics approved by the FDA



## Incidence of drug-resistance

By infection type



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Source: Brad Spellberg, associate professor of medicine, Gillies School of Medicine at UCLA; Infectious Diseases Society of America  
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