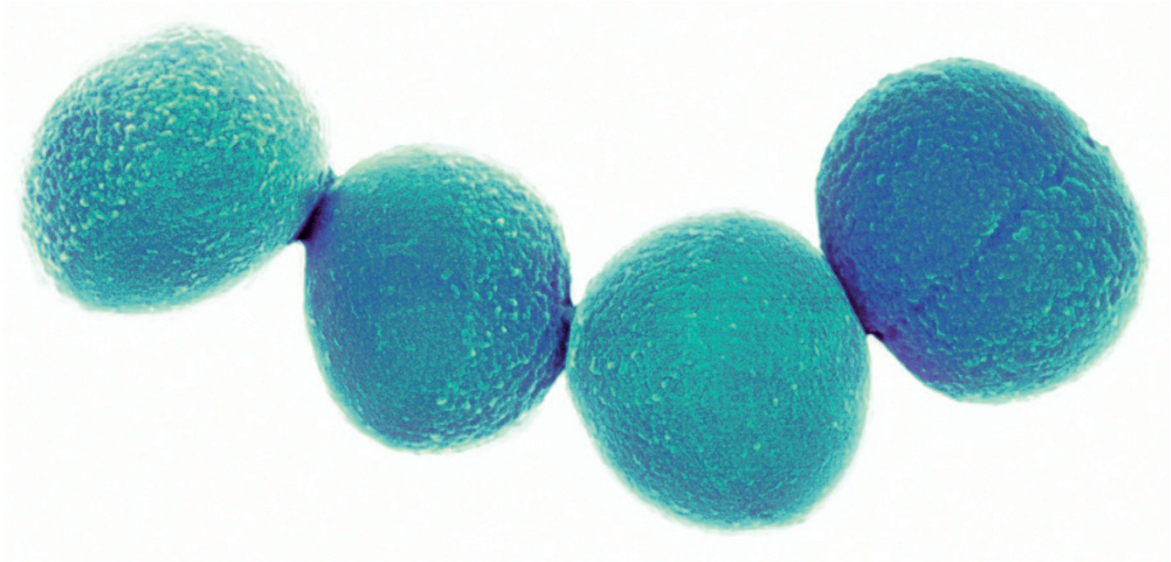

Man vs MRSA

For decades, Robert Daum has studied the havoc wreaked by methicillin-resistant Staphylococcus aureus. *Now he thinks he can stop it for good.*

BY MARYN MCKENNA

Over the years, Robert Daum has learned to respect his adversary. In 1995, he and his co-workers at the University of Chicago children's hospital in Illinois were investigating infections that had affected two dozen children in their emergency department. Three children had fast-moving pneumonia. A fourth had an abscess the size of his fist buried in the muscle of one buttock. In a fifth, the bacterium had infiltrated the bones of one foot. The infections were resistant to many common antibiotics, including methicillin. To Daum's surprise, the culprit was MRSA — methicillin-resistant *Staphylococcus aureus* — a bacterium that was thought to spread only among hospital inpatients. But none of these kids had been to the hospital for months before becoming ill.

Few researchers were willing to accept the implications. Daum wrangled for 18 months with editors at the *Journal of the American Medical Association* over a paper reporting the cases and showing that this strain was dangerous, acquired in the community and differed genetically from hospital strains. His article[1] was eventually published in 1998 and is now widely considered to be the early warning of an epidemic that currently results in millions of visits to doctors and hospitals a year[2].

Daum, a paediatric infectious-disease physician and founder of the University of Chicago's MRSA Research Center, is still raising the alarm about the epidemic. He sees the fight as more urgent than ever, and now thinks he knows how to win it. A few days before Christmas, he and Brad Spellberg, a physician who conducts vaccine research at the University of California, Los Angeles, published an article[3] calling for a vaccine that would vanquish *S. aureus*. "We can't treat this," Daum says. "We have to prevent it."

This time, Daum's views have more support. Over the past 10 years, as MRSA has become resistant even to last-resort antibiotics, several pharmaceutical companies have launched research programmes for vaccines, some with Daum's input. But Daum contends that they underestimate the enemy by relying on the standard immunological approach of triggering the production of protective antibodies. Instead, he advocates a strategy that stimulates T cells, part of a different branch of the immune system. It is an ambitious proposal and not all infectious-disease specialists are convinced that it will work.

The MRSA bacterium (pictured) is resistant to almost all antibiotics.

SPL

"It is a provocative idea," says Gerald Pier, a microbiologist at Harvard Medical School in Boston, Massachusetts, who also works on *S. aureus* vaccines. "But it is still too early to know how applicable this component of immunity would be to vaccine development."

EVIDENCE FOR AN EPIDEMIC

It took a while for the field to agree with Daum that a new epidemic had begun. Attitudes began to shift around 18 months after his seminal paper, when investigators for the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, reported that four children in Minnesota and North Dakota had died from infections similar to those in Daum's hospital. After that, the CDC and hospitals found clusters of community-associated infections in jails and prisons, then in sports teams, then in unusually high numbers of patients in emergency departments. Physicians, too, were reporting unexpected cases of grave illness — necrotizing pneumonia and flesh-eating disease — all caused by the community-associated strain.

From there, the epidemic grew. By one estimate, community-acquired MRSA accounts for half of the more than 14 million skin and soft-tissue infections that send people to doctors and emergency departments in the United States every year[2]. MRSA also causes around

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100,000 serious blood infections and more than 15,000 deaths a year. Meanwhile, pharmaceutical manufacturers are backing away from making new antibiotics, arguing that resistance is undermining compounds too quickly for them to recoup their costs.

A study by staff at the CDC's Division of Healthcare Quality Promotion estimates that an *S. aureus* vaccine given to vulnerable groups could reduce the number of serious MRSA infections by 24,000–34,000 cases per year[4]. Researchers familiar with vaccine development say that manufacturers have recognized the potential market. "You can see it within the industry now. They are all interested," says Jean Lee, an *S. aureus* vaccine researcher at Harvard Medical School. "Ten years ago, that wasn't the case." But getting from interest to a viable formula is proving a formidable challenge.

SHOT IN A DIFFERENT ARM

Since Edward Jenner first scratched cowpox virus into a boy's arm 216 years ago, vaccination has mostly proceeded along variations of one strategy: introducing into the body an antigen, such as a weakened disease organism or a fragment of an organism. The immune system responds by producing an antibody, a protein that recognizes the antigen and triggers an immune attack on the organism. For years, the presence of antibodies has been taken as a sign that a person will be immune to later infection.

The first attempt at making a *S. aureus* vaccine was modelled on successful vaccines for *Streptococcus pneumoniae* and *Haemophilus influenzae*. Like them, it used antigens consisting of carbohydrate molecules from the sticky capsule surrounding the bacterium, attached to a protein produced by another bacterium. But the formula, called StaphVax and developed by Nabi Biopharmaceuticals in the late 1990s, was unsuccessful. When the company tested it in 1998–99 in a phase III trial[5], the recipients made antibodies, but then developed *S. aureus* infections in their blood at the same rate as those who received placebo. The programme was suspended in 2005 and sold to GlaxoSmithKline in 2009. Merck, meanwhile, created a formula that used a cell-surface protein involved in the bacterium's ability to take up iron. It cancelled late-phase clinical trials in June last year because of negative results.

In retrospect, Daum says, no one should have expected an *S. aureus* vaccine to be that easy. "This organism has multiple strategies for accomplishing all its tasks, from invading the blood stream to elaborating toxins to causing local skin abscesses," he says. "Targeting a vaccine against just one of them merely eggs the bug on."

> *"This is a universal epidemic, and there should be a universal vaccine."*

Unlike most pathogens, *S. aureus* is a commensal organism; it lives on the skin and in the nostrils of up to one-third of humans, mostly without causing disease. This benign but continual occupation means that much of the population already has antibodies to the bacterium. And unlike many infections, having it once is no guarantee of protection; roughly one in four people who have one *S. aureus* infection will go on to develop another. So vaccine developers don't really know what characterizes an immune individual. "We're working without any information as to what constitutes high-level immunity to *S. aureus* infection," says Pier.

Still, some companies are attempting to build immunity using an all-out antibody attack: Pfizer, Novartis and GlaxoSmithKline are testing formulas packed with four or five antigens, hoping to elicit an array of antibodies that will overwhelm the bacterium's defences. Several other companies are trying passive immunization — delivering antibodies harvested from people — but none has yet achieved results better than placebo.

The team that may have edged closest to success is actually on Daum's own campus. Microbiologist Olaf Schneewind, who is not affiliated with Daum's group, has developed a formula that incorporates a mutated version of a cell-wall component of *S. aureus* called protein A. Under normal circumstances, protein A binds to antibodies, protecting the bacterium from attack by the immune system; the mutant version, however, is unable to bind. So far, the formula has been tested only in mice[6].

Daum is familiar with the failed-vaccine landscape, not just from his consulting work with pharmaceutical companies, but also from serving on the US Food and Drug Administration's Vaccine and Related Biological Products Advisory Committee. At the same time, his research into how *S. aureus* is able to cause disease in so many tissues and its bristling array of defences against the immune system convinced him that a new approach was needed.

When Daum discusses *S. aureus*, he is blunt about the challenges and impatient to move ahead. "I don't think multiple antigens are enough," he says, sitting in the old hospital building where he spotted the first community-acquired MRSA cases, now transformed into overcrowded offices stacked with piles of journals. "I think we need multiple immunological mechanisms. And I think the central one should be something that has been considered heresy up to now."

LUCKY BREAK

The heretical approach was inspired, in part, by a patient. As part of an ongoing project to root out the causes of recurring infections, in 2009 two of Daum's team members went to the home of a toddler who had recently been in the emergency department. But the girl wasn't there; she was in the hospital's intensive-care unit with a new infection. When Daum tracked her down, he noticed something odd in her records. She had had unusually frequent abscesses and repeated bouts of pneumonia.

Acting on a hunch, Daum teamed up with Steven Holland, chief of the clinical infectious diseases laboratory at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, to carry out a detailed genetic analysis. Daum's hunch was right: the girl had a mutation that Holland had recently linked to a rare immunodeficiency called Job's syndrome[7]. People with the syndrome have persistent, smouldering *S. aureus* infections, owing to an inability to make a type of lymphocyte, or immune cell, called a T_H17 cell.

These cells, which make a proinflammatory protein called interleukin-17, have become a hot topic in vaccine research. They are produced by a different branch of the immune system from the one that makes antibodies, yet they still seem to be involved in the body's memory of exposures to pathogens.

Daum believes that T_H17 cells are the key to an *S. aureus* vaccine. "It looks like T cells are very important in staphylococcal immunity," he says. Spellberg demonstrated in 2009 that a vaccine that stimulated production of interleukin 17 could protect mice against infections of *S. aureus* and *Candida albicans*[8]. (That vaccine is now being developed by NovaDigm Therapeutics as NDV3.)

Daum and Spellberg have now joined forces and formed a cross-disciplinary team to see whether boosting the activity of T_H17 cells can prevent S. *aureus* infections in humans. The team includes an intensive-care specialist who has developed animal models to study these infections; an epidemiologist; two immunologists; and a biomedical engineer.

They have begun by selecting current and former patients with MRSA from the University of Chicago's hospitals and comparing

JIM NEWBERRY FOR *NATURE*

Robert Daum has shown that MRSA is not confined to hospitals — and is determined to find a vaccine that will fight the bacterium.

their immunological activity with that of people who have never had MRSA. In a second phase, they will test how lymphocytes harvested from the patients react to a number of infectious organisms, including MRSA.

The project will face significant challenges, Spellberg points out. "One of the reasons the vaccine world has always been so focused on antibodies is because it's so easy to measure antibodies," he says. "There is no high-throughput T-cell assay. It takes a lot of work."

FAR FROM FINAL

If the team can succeed in boosting T-cell activity, it will still be only part of a solution. The group has to consider whether to include a traditional antibody-stimulating antigen in a vaccine, and whether to add a third component, such as protein A. The researchers must also work out whether one vaccine formula can stop *S. aureus* from invading many types of tissue. "We want a vaccine that prevents invasive disease, we want a vaccine that prevents pneumonia and we want a vaccine that prevents skin infections," Daum says. "Can one vaccine solve three separate clinical problems?"

The researchers will have to manoeuvre around *S. aureus*'s dual role as pathogen and commensal bacterium. If they wipe out the body's benign staph occupiers, a more harmful organism might take their place.

Daum and his collaborators will also have to face down scepticism from other staph researchers, who view the T_H17 idea as intriguing but impractical. Schneewind points out that the US Food and Drug Administration's rules require a vaccine to demonstrate antibody production to win licensure. "I am not aware of any vaccine licence where the correlate of protective immunity is IL-17 response," he says. But given the surge of interest in T_H17 cells, he adds, "people will try it, and we'll see how far they get".

Perhaps the most difficult question to answer is: who should get an *S. aureus* vaccine? Because community-acquired MRSA is so widespread, the maximum benefits might come only if the vaccine is administered to everyone. But with a great deal of suspicion of vaccines in the United States and elsewhere, an addition to the routine immunization schedule is likely to be met with resistance.

Mention these concerns to Daum, and the trademark impatience break through. "This is a universal epidemic, and there should be a universal vaccine," he says. "I think we should put this into the paediatric vaccine schedule in the first year of life. And if it happened to work on all MRSA syndromes, like the skin infections that flood our emergency room, then we would have something wonderful on our hands." ■

Maryn McKenna *is a science journalist in Atlanta, Georgia, and author of the book* Superbug: the Fatal Menace of MRSA.

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