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WHO CAN STOP SUPERBUGS?

WHY A LITTLE-KNOWN NONPROFIT MIGHT BE OUR BEST HOPE TO CONTAIN ANTIBIOTIC-RESISTANT BACTERIA.

BY MARYN MCKENNA

A 1975 BATTLE FOR CIVIL RIGHTS ON CARSON BEACH

CORONAVIRUS AND THE RISE OF DIY CULTURE

RECIPES: 3 WAYS TO MAKE THE MOST OF TOMATO SEASON

Boston University law professor Kevin Outterson founded nonprofit CARB-X to keep antibiotic development alive.

No Time to Wait

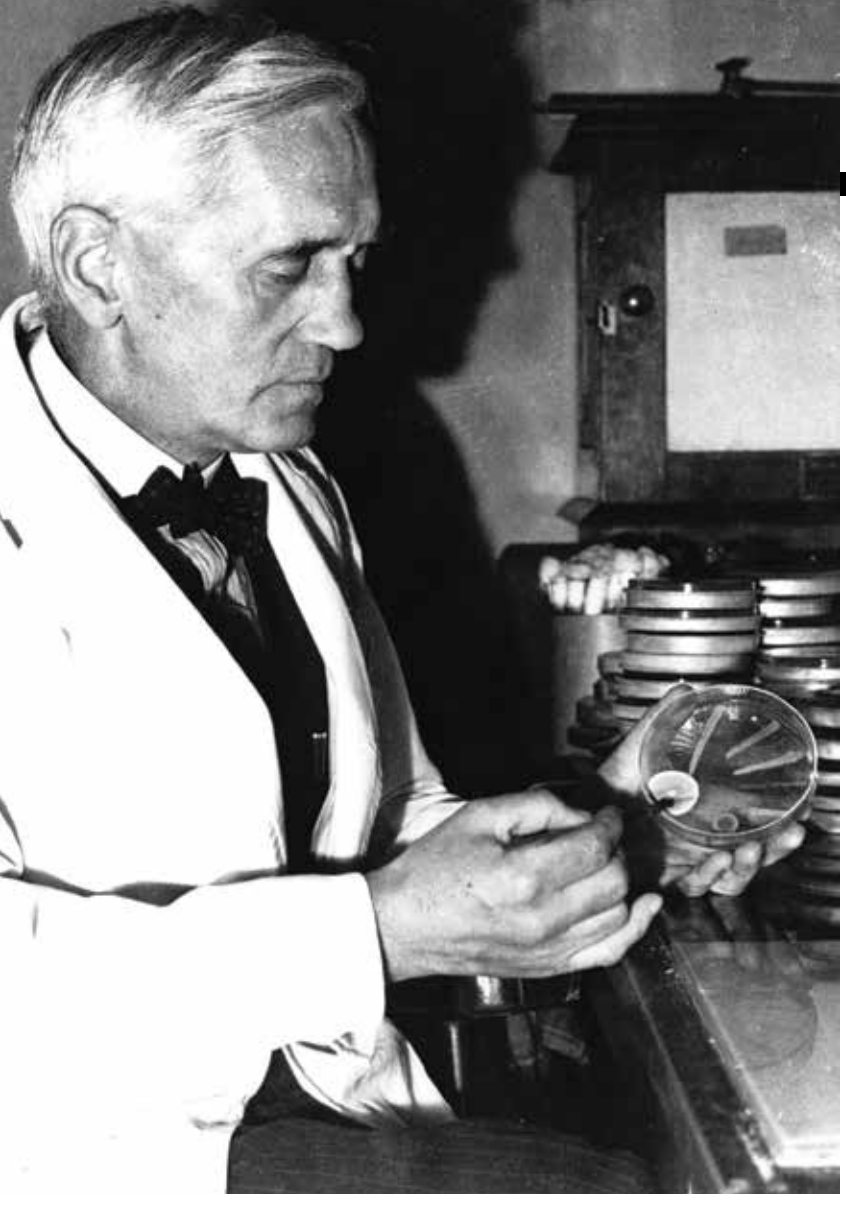
ANTIBIOTIC-RESISTANT SUPERBUGS KILL AN ESTIMATED 700,000 PEOPLE WORLDWIDE EACH YEAR. CAN A LITTLE KNOWN BOSTON NONPROFIT LAUNCH THE NEW DRUGS WE NEED TO DEFEAT THEM?

BY MARYN MCKENNA

Alexander Fleming launched the antibiotic era in 1928 with the discovery that the blue-green mold *Penicillium notatum* had contaminated culture dishes in his London laboratory and was excreting a compound that killed staph bacteria growing on the dish. It wasn't until 13 years later that a drug based on Fleming's original insight was given to a human being, a British constable hospitalized for an infection. He made what seemed a miraculous recovery—until the supply of penicillin ran out, and he relapsed and died. But its brief success showed that bacterial infections, the leading cause of death for as long as people had been keeping track, could be defeated by science. That recognition ignited a half-century-long fervor for antibiotics—one which has been almost completely lost.

If you graphed the discovery of all the antibiotics that have come to market since Fleming first recognized penicillin, the curve would look like a

OUTTERSON PHOTOGRAPH BY WEBB CHAPPELL, BACTERIA FROM ADOBE STOCK



Alexander Fleming, who discovered penicillin in 1928 and shared a Nobel Prize for the work, in his London laboratory.

waterslide: a quick climb up to a peak, a fast skid down, and then a long, slow bottoming out. Between the 1920s and the 1970s, 28 classes of antibiotics with novel mechanisms of action—methods of attack that pathogens have never experienced before and cannot defend against—were brought to market. In the 1980s, two classes were achieved. In the past three decades, there has been one.

Meanwhile, the popularity of the miracle drugs came with a price: the evolution of superbugs. Over the decades, bacteria accumulated self-defense mechanisms, mutations that protected them against antibiotics' attack. Over time we learned that any deployment of an antibiotic triggered a paradox: It would save the patient it was given to, but its use would risk the development of resistance that would imperil future patients. Today, it's estimated superbugs kill almost three-quarters of a million people around the globe annually; by 2050 that could grow to 10 million every year if the trend isn't slowed.

And that has brought us to a crisis that nests inside the larger catastrophe of the COVID-19 pandemic: The world needs new antibiotics more than ever—for resistant infections, and now also for coronavirus patients developing pneumonia and other infections as they endure long hospital stays. Yet the problem of how to pay for the development of a new antibiotic—which can cost about $1 billion—has deprived us of the drugs just when we need them most.

"Antibiotics are like fire extinguishers," says Dr. John Rex, a longtime antibiotic developer who is now the chief medical officer of UK biotech firm F2G Ltd. "You want to have it available and not use it. But you would be crazy to not have it available. And you can't wait until you have a fire to buy the fire extinguisher."

Years before the world need that fire extinguisher for Covid complications, big pharma began walking away from antibiotic development, toward the more reliable income to be found in cancer chemotherapy, cardiovascular treatments, and everyday conditions from allergies to heartburn. The historic centers of antibiotic research in the United States—San Francisco's Bay Area, New York, and New Jersey—receded in importance. Ever since, the biotech hub of Boston has been rising.

A key player in that rise: a little-known nonprofit called CARB-X, based at Boston University, that has quietly become one of the largest funders of early antibiotic development in the world.

We know now that on February 26, the Biogen conference in Boston became the first COVID superspreader event on the East Coast, seeding more than 100 cases throughout the United States. But on the same day, an effort was marshaling against a different threat—the world's slow-moving epidemic of antibiotic resistance.

On the 5th floor of BU's Law Tower, 13 nascent companies faced a panel of 15 drug-development experts. The lightning-round presentations and interrogations they were about to endure—like a *Shark Tank* on steroids—would determine whether the companies received millions of dollars in funding, and with it the chance to create products that could save lives and maybe change the world.

The research groups were appearing before the advisory board for CARB-X, the acronym for Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. Outside the room, Kevin Outterson — CARB-X's founder and executive director, a BU law professor and N. Neal Pike Scholar in Health and Disability Law—waited to hear what his advisory board would

THE LONG ROAD TO DRUG DEVELOPMENT

$20 billion
Annual health care costs in US in 2013 from infections resistant to antibiotics

314
Estimated number of research groups worldwide conducting antibiotic innovation

10
Minimum years to develop a new antibiotic, gain FDA approval, and begin treating patients

$1 billion
Approximate cost to develop a new antibiotic

15
Number of new antibiotics approved by the FDA since 2010

PHOTOGRAPH FROM AP

THE PROBLEM OF HOW TO PAY FOR THE DEVELOPMENT OF A NEW ANTIBIOTIC — WHICH CAN COST ABOUT $1 BILLION — HAS DEPRIVED US OF THE DRUGS JUST WHEN WE NEED THEM MOST.

recommend. "When we started this four years ago, we had some concerns that we'd run out of hearing good ideas," Outterson says. "We have not. We're very encouraged by what there is to invest in."

There's a lot about CARB-X that's unexpected. With half a billion dollars in funding, it has millions to give away, but its staff of 26 occupies a modest basement office, with a view of ankles and bike wheels. Outterson is a lawyer, not a physician or a microbiologist or a chemist. And, it all started with a footnote.

Outterson began his career at major law firms in Chicago and Nashville, handling part of the 1990s wave of transactions in which entrepreneurial groups of doctors broke off from big hospitals to form independent companies. A decade later, he was ready for a change, and moved to England with his wife and four young daughters to spend a year at the University of Cambridge. He returned stateside to join the law faculty at West Virginia University.

Outterson was at the start of his academic career, but he was already tackling the problem of how to fund research that would keep new antibiotics arriving to defeat the constant recurrence of resistance. In one of his first law review articles, he examined the 20-year patents given to new pharmaceuticals, a protection of intellectual property meant to compensate for the immense costs of developing a new drug. The arrangement is based on an assumption that a drug is still clinically valuable when its patent ends and it enters the public domain.

"I dropped in a footnote saying this wouldn't be true if the value of the drug degraded over time, which is what happens with antibiotics," he recalls. "And then I went on with my life. But that footnote bugged the hell out of me. I realized that all the theoretical foundations of how drug innovation works might not be correct." Outterson had stumbled on a key challenge: Antibiotics begin losing their usefulness as soon as they debut, because bacteria adapt to them.

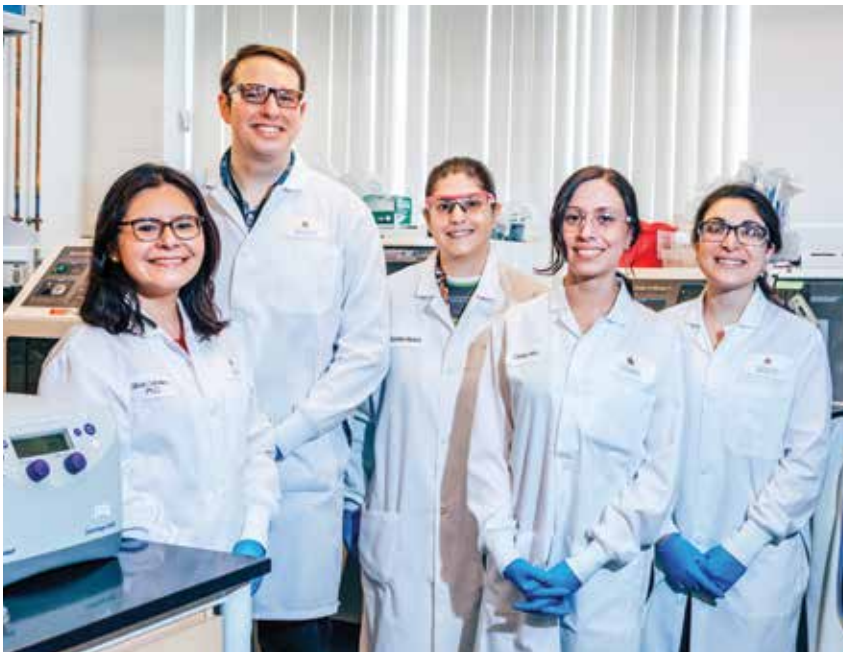
The problem still nagged at him in 2007 when he came to BU, eager to be in a city where biotech was flourishing. Then, late in 2013, the Centers for Disease Control and Prevention published its first threat assessment of how antibiotic resistance harms Americans, estimating that each year at least 2 million people are infected and at least 23,000 die, costing the country as much as $20 billion per year in health care costs, and an additional $35 billion in lost productivity. (The CDC has since revised that to more than 2.8 million infections and 48,700 deaths annually, from resistant infections or *C. difficile*, which is enabled by antibiotic overuse; one academic estimate puts the toll north of 160,000.) The Obama administration took on the problem, issuing an executive order in 2014 and creating a national strategy in 2015. The following year, the administration published a call for proposals to help solve the punishing economics of antibiotic production. Outterson applied, recruiting the Wellcome Trust, a British philanthropy built out of a pharmaceutical fortune, as his partner.

They won a five-year contract, awarded in July 2016, and Outterson quickly put together $350 million in funding from the Wellcome and the US government's Biomedical Advanced Research and Development Authority and National Institute of Allergy and Infectious Diseases; later he brought in the Bill & Melinda Gates Foundation, and the governments of Germany and the United Kingdom. The new group moved fast, launching a call for proposals before Labor Day and making its first awards the next spring to 11 companies and research groups, for a collective $24 million upfront and $24 million more over three years, if they met milestones.

Outterson had very specific parameters for CARB-X: It would fund preclinical and early clinical development, for which there is no other support. It would aim for creative proposals that would be more likely to yield innovative results, though they might have a high likelihood of failure. Overall, it would escort small new companies, not yet earning revenue, through what pharma people call the valley of death, the difficult-to-fund gap between promising discovery and first human trial. That practical focus has not changed. Since 2017, CARB-X has granted $240 million to 67 companies and research groups in 10 countries. Five drugs or diagnostics have gone into early human trials.

"We are not just a science organization," Outterson says. "We are not just a research funder. We are trying to actually move products to the market."

No other organization in the world has amassed so much money to support preclinical antibiotic research. "They are the most important," says Aleks Engel, director of REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund belonging to the Danish Novo Nordisk Foundation. Engel, who works out of an office in Copley Square, knows the landscape well—with $165 million to invest, REPAIR is the world's largest private funder of preclinical projects. "They have a great set of individuals," he says, "and a great approach—and they are based here in Boston, which is becoming the biotech hub of the world."



Silvia Caballero, lead researcher for multidrug-resistant organisms at Vedanta Biosciences, and her team.

PHOTOGRAPH: BEARWALK CINEMA

"WHEN WE STARTED THIS FOUR YEARS AGO, WE HAD SOME CONCERNS THAT WE'D RUN OUT OF HEARING GOOD IDEAS," OUTTERSON SAYS. "WE HAVE NOT. WE'RE VERY ENCOURAGED BY WHAT THERE IS TO INVEST IN."

CARB-X's influence and the Boston area's preeminence in life sciences are linked in an intriguing way. It isn't just that both have risen; it's that other places have fallen off.

The first antibiotics were relatively easy to discover: They were products of inquiries into the natural world that no one had made before. That initial burst of innovation tapped what bacteria had been amassing for millennia: natural chemical weapons that fungi and soil organisms developed to compete for living space and food. Those were found quickly, but also exhausted quickly. By the 1960s, the pharmaceutical companies that dominated the market thanks to the first antibiotics apparently became convinced that soil's promise was exhausted. Taking the compounds they'd found into the laboratory, they began basing their searches for new versions on increasingly complex—and expensive—methods of screening and synthesizing.

But because bacterial pathogens can adapt to the drugs sent against them, making antibiotics began to feel like the Red Queen in Lewis Carroll's *Through the Looking-Glass*: running as hard as possible, just to stay in the same place. About 20 years ago, companies began dropping their antibiotic discovery programs in favor of more lucrative drugs. Among the more than 30 firms that once led the space were household names: Eli Lilly & Co., Bristol-Myers Squibb, Wyeth, Novartis, Pfizer, and Merck. But barely a handful of such companies conduct antibiotic research now.

Yet antibiotic resistance was growing more dire, not less, lengthening hospital stays, padding bills, and imperiling treatment of even simple, well known infections. The most common bacterial cause of pneumonia on the East Coast can be resistant to the drug best suited to treating it in more than half of the cases. That ought to seem like a guaranteed market. But at the same time as the need rose, society collectively decided to pay less for antibiotics. The reasons why are complex: the cost of developing a new drug—at least 10 years and about $1 billion dollars—balanced against competition from generics; pressure not to use a new drug to keep from creating superbugs; and low rates of federal reimbursement when antibiotics are used in hospitals.

The collective effect: Even companies that want to make antibiotics find the financials insuperable. In the past 18 months, four small companies that had gotten new antibiotics through FDA approval — Achaogen, Aradigm, Melinta Therapeutics, and Tetraphase Pharmaceuticals of Watertown — have all declared bankruptcy, left the market, or put themselves up for sale. Those actions have removed from the market five of the 15 new antibiotics approved by the FDA since 2010.

The historic business model was that antibiotics were developed in-house by big companies, which possessed deep benches of research staff and multiple product lines that kept income flowing. The second version of that model, small companies discovering drugs and then being bought out by big ones, pushed the initial research costs onto small biotechs but compensated them with assistance and funds once a deal was made. Now those companies must exist entirely on their own, emerging from academic research into a landscape that requires them to ask friends and family or venture capital for money, or take the risk of going public very early. Outterson estimates that the majority of antibiotic innovation worldwide is being conducted by fewer than 314 research groups, most with no more than 25 employees.

With CARB-X, Outterson essentially turned back the clock to when small biotechs routinely received outside support. His nascent organization gives small companies what they need to make it to market: funds *and* access to experts with decades in the business. Many of the advisers he calls on are former employees of the pharma giants whose research programs have shut down. "These people can look at a proposal and say, 'You're going to need six chemists for six months. Lab space, you budgeted for $2 million, there's no way it should cost that much,'" Outterson says. "Or, conversely, 'We know you're trying to be frugal, but this one is really worth doing it right.'"

CARB-X grants and the implicit endorsement that accompanies them have been critical to some companies' survival. One example is San Diego-based Forge Therapeutics, which is trying to create a new class of drugs using a method that no one has tried before: targeting a particular class of enzymes present in some of the most dangerous resistant bacteria. To an investor, that would be high risk—but CARB-X has given it $8.8 million for a novel antibiotic to treat resistant urinary tract infections, and a second grant, of $11.1 million, for a drug to treat resistant lung infections.

The CARB-X examiners take a broad view of what counts as an antibiotic. Vedanta Biosciences in Cambridge analyzes the gut microbiome to identify commensal bacteria—ones that live quiescently in our bodies—that might regulate the immune system and help combat resistant bacteria. The $11.2 million CARB-X has awarded Vedanta so far supported two critical infectious-disease research programs, says Silvia Caballero, Vedanta's lead researcher for multidrug-resistant organisms. "There just is not a lot of money that goes toward infectious-disease research right now," she says.

It might seem that antibiotics, which kill only bacteria, would have no relevance to a worldwide pandemic of viral disease. But the novel coronavirus has highlighted how critically needed antibiotics remain. Case reports from multiple countries have recorded bacterial pneumonias

THE DEADLY TOLL OF SUPERBUGS

48,700-160,000
Estimated deaths in the US from antibiotic resistance per year

700,000
Estimated deaths worldwide per year

10 million
Projected number of deaths per year by 2050 if antibiotic resistance cannot be slowed

SOURCES: CENTERS FOR DISEASE CONTROL;CARB-X; PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA; TRANSLATIONAL RESEARCH; THE SOCIETY FOR HEALTHCARE EPIDEMIOLOGY OF AMERICA; REVIEW ON ANTIMICROBIAL RESISTANCE

occurring in gravely ill COVID-19 victims, taking hold in lung tissue roughed up by viral inflammation. Stephen Ubl, president and CEO of the trade group Pharmaceutical Research and Manufacturers of America, estimated at an industry event in July that bacterial infections occur in 1 out of every 7 patients hospitalized with COVID-19, and that half of the patients who develop those pneumonias die.

That makes the underlying paradox of how to develop and pay for antibiotics even more urgent. Because antibiotics stimulate the emergence of resistance as soon as they're used, it's both a natural impulse and careful medicine to use a new one as little as possible, to preserve it for when it's really needed. But fewer uses equal fewer sales and less income for a developer once its product debuts. "These companies spend a huge amount of money to develop their drugs," says physician David Shlaes, a former pharmaceutical executive who authored *Antibiotics: The Perfect Storm*. "When they come out after approval, they have marketing costs and post-approval obligations. That costs them more money. And because there's no market, there's no way they can make up their investment, much less make a profit."

President Obama and his administration created a national strategy in 2015 to tackle the economic challenge of developing new antibiotics.

CARB-X's spending focuses on the earliest end of the drug development timeline, up through the point where a new drug is first given to a human being. As substantial as CARB-X grants are, they don't help with the costs of the later-phase trials that prove a new compound is efficacious and safe. Part of the challenge of reviving antibiotics has been finding other entities to stand beside CARB-X to support those parts of the process.

But last month, one stepped forward. On July 9, a coalition of 20 large pharma companies, including ones that had long ago left antibiotic research, announced a joint $1 billion investment in a new fund that aims to usher at least two and possibly as many as four new antibiotics through development and approval in the next decade. The new group, which calls itself the AMR Action Fund, plans to help companies seeking funding for human clinical trials—the development phase that comes after the one that CARB-X and REPAIR support.

The AMR Action Fund's launch event included a splashy series of webinars that kicked off in Washington, D.C., and continued in Berlin and Tokyo. Outterson, who is not involved in the fund, was one of the speakers. In an interview afterward, he was characteristically blunt: "If we don't change the basic economics, this is the last private money we'll ever see in antibiotic development. This is one last chance for governments to get the rest of it right."

That's a candid assessment, and it's not wrong. Studies done in the United States, Britain, and the European Union have all concluded that supporting the post-approval phase of antibiotic development, the point where Watertown's Tetraphase and others failed, requires so much money that it has to be a government task. But exactly what governments ought to do has been debated. Proposals range from granting pharma companies longer patents for other drugs they make to creating "market entry rewards," which hand successful antibiotic makers a lump sum of a billion dollars or more. But there is little indication that such incentives are gaining traction in the United States. Another proposal, contained in legislation called the DISARM Act, was added as a rider to the coronavirus stimulus bill passed in March. It would have changed the way that Medicare pays hospitals back after inpatients are given antibiotics, creating a two-tier reimbursement that would pay more for newer antibiotics and discourage physicians from sticking with cheaper but less effective ones. The proposed legislation was pulled from the stimulus bill before the final vote.

In the many years that resistance has been growing worse and antibiotics have been falling behind, physicians and researchers have said privately that what they most feared was the moment when all the available antibiotics ran out. At that point, they'd say, the public would be forced to confront what medicine already knew: that it takes at least a decade to produce a new antibiotic, and that neglecting to pay for them would leave us vulnerable to deadly infections until funding and research caught up.

With the coronavirus pandemic, that envisioned crisis has come very close. Antibiotics are the foundation of modern medicine, protecting us from infections stemming from injuries and childhood maladies, and making surgery, transplants, and chemotherapy safer. They are also now the last defense against the worst complications of COVID-19. Yet we let their development languish. In the midst of a global conflagration, we have opened the cupboard to find we have no fire extinguishers.

Outterson hoped, when he launched the accelerator, that enough other entities would arrive to help solve the problem. That hasn't yet happened. Recently, he started discussions with his funders about justifying a second five-year round. "But I would be extremely happy," he says, "to work myself out of a job." ■

Science journalist Maryn McKenna is a senior fellow of the Center for the Study of Human Health at Emory University. Her latest book is Big Chicken: The Incredible Story of How Antibiotics Created Modern Agriculture and Changed the Way the World Eats. *Send comments to magazine@globe.com.*