New antibiotics are urgently needed, but economics stand in the way

In the wake of Achaogen's bankruptcy, experts discussed ways to ensure new treatments are available to combat drug-resistant bacteria that threaten a post-antibiotic world.

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On March 10, 2017, shares of antibiotic developer Achaogen traded at $27 on the Nasdaq.

Two years later, it has become a penny stock trading at around 9 cents per share after the company filed for bankruptcy under Chapter 11, on April 15, as anemic sales of its drug failed to keep pace with operational costs.

Achaogen's journey from promise to penury illustrates the Herculean task the biopharma industry faces: Fulfill a growing need for antibiotics while facing economic realities that make doing so unprofitable.

As is apparent from the proliferation of apocalyptic stories about a future "post-antibiotic era" of drug-resistant superbugs, the need for new treatments is dire.

But what are the economic hurdles and how can the industry overcome them?

Unlike cholesterol drugs taken by millions of people for their entire lives, or $100,000 cancer drugs designed to prolong life, antibiotics are short-term drugs with limited shelf lives.

"Antibiotics are not valued by society as a high-value product, so they're not priced very high," said Gregory Frank, director of infectious disease policy at the Biotechnology Innovation Organization, in a phone interview.

A 2014 paper by Dr. Brad Spellberg, chief medical officer of the Los Angeles County-University of Southern California Medical Center and expert on antimicrobial resistance, is illustrative of the economic challenges. Spellberg cited a London School of Economics study showing that while a new arthritis drug's net present value – a measure of a drug's net value over the ensuing decades – would be $1 billion, that of a new antibiotic would be negative $50 million.

"To invest in an antibiotic based on that data from five years ago would be like throwing money into a paper shredder," said Kevin Outterson, executive director of CARB-X, a nonprofit group focused on providing funding for new antibiotics, in a phone interview. And the market has gotten worse, he added, pointing to Achaogen as an example of a company that was supposed to be successful, but instead went bankrupt.

Indeed, Achaogen suffered a bad case of basic math with its drug, Zemdri (plazomicin), which the Food and Drug Administration approved June 25, 2018 to treat carbapenem-resistant enterobacteriaceae (CRE). According to its fiscal year 2018 annual report, released April 1, Zemdri's sales for the year were only $783,000, while the company reported losses from operations of more than $189 million.

"We have had difficulty raising sufficient funds to advance our commercialization of ZEMDRI in the way we intended and our revenues from sales of ZEMDRI to date have been very limited," the report read. Achaogen did not respond to a request for comment. But despite the efficacy of its drug, the company presents a cautionary tale.

People will buy innovative products in almost any other part of the economy, but doctors will still keep even the most innovative antibiotic behind the glass and use it only in the most dire circumstances.

"Antibiotic stewardship is a good thing, but devastating for the company developing it," Outterson said.

The irony is that despite the drug's sales failing to keep up with Achaogen's operating costs, the company actually spent comparatively little to develop it: Part of the funding came from a $124.4 million contract with the Biomedical Advanced Research and Development Authority, or BARDA, part of the Department of Health and Human Services. In fact, BARDA, the National Institutes of Health, the nonprofit CARB-X and others provide a large share of the funding for the development of new antibiotics.

That is not unusual.

"You can go from discovery to Phase III trials without paying a dime of capital," Spellberg said in a phone interview.

Yet, despite yielding more than 40 new antibiotics in the pipeline, the current system of subsidies and incentives is part of the problem, according to Spellberg. The issue is that the antibiotics in development are not very strategically aimed at difficult pathogens.

"The majority do not target unmet need," he said. "They are not hitting the problem pathogens we have, and the few that do are redundant."

Pathogens considered major or even urgent threats by the Centers for Disease Control and Prevention include CRE, methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococci (VRE), extended-spectrum B-lactamases (ESBL) and Clostridium difficile (Cdif). Yet, annual incidence of drug-resistant bacterial infections in the US can vary widely – from 500,000 for Cdif to only 9,000 for CRE, according to the CDC – further complicating generation of profit from treatments for them.

For example, Spellberg pointed out that the FDA has approved multiple competing drugs to treat CRE in the past few years. Given the rare incidence of CRE – which causes 600 deaths annually from the 9,000 infected – have not tended to generate strong sales figures. The Medicines Company's Vabomere (meropenem/vaborbactam), which received FDA approval in August 2017 for complicated urinary tract infections caused by CRE, had much better sales in 2018 than Zemdri. But at $7.4 million – according to the 2018 annual report of Melinta Therapeutics, which completed a deal to to acquire The Medicines Company in January 2018 – the drug can hardly be called a blockbuster.

A long-term solution, Spellberg said, is a nonprofit model, whereby a nonprofit organization would perform the risky drug discovery and early-stage development work, while for-profit companies would come in and perform later-stage development and commercialization. CARB-X and the Wellcome Trust are examples of nonprofits helping to fund antibiotic development.

As such, the release of new antibiotics needs to be a slow, steady drip rather than a flood, Spellberg said.

However, another expert disagreed with Spellberg on the notion of nonprofits.

There is nothing inherent in a nonprofit that makes it different, said Ramanan Laxminarayan, director of the Washington-based Center for Disease Dynamics, Economics & Policy, in a phone interview. Rather, the important question is whether an organization – nonprofit or for-profit – has access to cheap capital and can make good bets.

The larger problem for antibiotics is not development costs, but reimbursement, and there needs to be a more rational reimbursement model with a willingness to pay more in cases when a patient is going to die without an antibiotic, Laxminarayan said. Drugs in other areas, like cancers, have an advantage because there's a willingness to pay tens of thousands of dollars to extend a patient's life by a few months, but nobody is willing to pay that for an antibiotic.

Another potential remedy would be to have a drug company act like a utility – a for-profit firm that would treat antibiotics like infrastructure, Outterson said. An even more radical proposal came from Jim O'Neill, a British former banker and ex-chairman of the Review on Antimicrobial Resistance, who in March recommended such "utility" drug companies as state-run entities. Still, Outterson said the for-profit utility model should be tried first. "But if that doesn't work, then try nationalization," he said.

Some believe that push incentives — where research and development risk is lowered by reducing the cost to do so — are not enough. Achaogen failed despite plenty of push funding, said Frank.

What is also needed, he said, are pull incentives, pull incentives that reward successful results that create a viable market. Here's pull incentives explained by a group of European and American researchers in a 2017 paper.

Recent headlines show the issue of antimicrobial resistance isn't limited to bacteria. The CDC recently sounded the alarm about a drug-resistant strain of the fungus Candida auris cropping up in US hospitals. To be sure, the situation for antifungals isn't quite as apocalyptic as it is for antibiotics. For one C. auris remains for the most part highly susceptible to existing drugs, Spellberg said.

Fungi become drug-resistant just as bacteria do, and drugs to treat fungal infections are, like antibiotics, unlikely to become blockbusters. However, fungi become resistant at a much slower rate, and antifungal resistance is mainly seen in extremely intensive healthcare settings like transplant hospitals.

"Some of the antifungal resistance problems people are talking about are somewhat overblown," he said.

However, Laxminarayan said the antifungal space is in even bigger trouble than antibiotics. While the economic issues are similar, there are fewer antifungal drugs and companies, Frank said the scientific challenges to developing new antifungals can be higher than for antibiotics, given the particular need to avoid toxicities.

Jersey City, New Jersey-based Scynexis is one company developing a treatment for drug-resistant fungal infections, ibrexafungerp, currently in several clinical trials, including one for C. auris. The company plans to file its first approval application with the FDA for ibrexafungerp next year. The drug is expected cost $450-600 per day, in line with the pricing of other antifungals, said company CEO Marco Taglietti, in a phone interview.

Drug-resistant fungal infections can be even deadlier than their bacterial counterparts, Taglietti said. He added push incentives to develop drugs against them don't exist, but that is starting to change.

Earlier this month, Sen. Charles Schumer, D-New York, called on the CDC to provide more funding for research against C. auris, and Taglietti hopes that will get some traction.

"This is the challenge we had as a company – we're not able to get support for research," he said.

The race against drug-resistant infectious is ultimately a scientific one. It's not about finding better treatments, but newer ones in an endless war that requires always staying one step ahead of ever-evolving germs, Taglietti said. On the one hand, it's important to practice good stewardship in order to delay resistance.

“But that creates a big challenge from an economic point of view – from the moment you launch your product after spending several hundreds of millions to develop it, it doesn’t sell,” he said.

The problem appears to be a vicious cycle of science and economics: Even existing push incentives, however generous, don’t make up for antibiotics’ lack of the large and chronic patient populations of cardiovascular disease drugs or the high prices of cancer drugs.

Achaogen’s fate might have been sealed from the start.