'Game changer' antibiotic and others in works for superbug

Last summer, researchers reported that the *Clostridium difficile* superbug had overtaken methicillin-resistant *Staphylococcus aureus* as the most common hospital-acquired infection in the US, where around half a million people fall ill from the diarrhea-inducing bacterium each year. For most people, the decades-old antibiotics metronidazole and vancomycin can clear the infection. But in around a quarter of all cases, the symptoms come roaring back, often with life-threatening consequences.

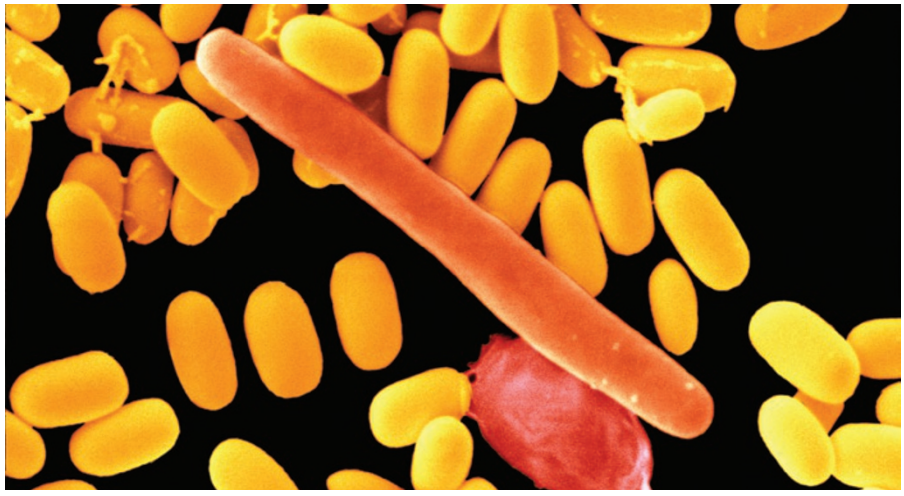
Given the potential for relapse to occur, researchers have been desperately seeking new, more effective drug options. The leading candidate to reach the market within the year is fidaxomicin, an antibiotic pill that inhibits the enzyme RNA polymerase in bacteria. In October, the drug's manufacturer, San Diego–based Optimer Pharmaceuticals, reported data at the Infectious Diseases Society of America annual meeting in Vancouver, British Columbia from two phase 3 trials showing that two daily doses of fidaxomicin were as effective at clearing *C. difficile* infections as four pills per day of vancomycin. What really stuck out, though, was that fidaxomicin cut the recurrence rate in half. A month later, Optimer announced that it had filed a new drug application with the US Food and Drug Administration (FDA) and asked the drug regulator for a faster-than-usual review.

"This is, in my mind, a game changer," says Kevin Garey, an infectious disease researcher at the University of Houston College of Pharmacy who is not affiliated with Optimer. "We've never been able to reduce the recurrence rates."

The Optimer phase 3 trials also showed that fidaxomicin was more sparing of 'good' intestinal bacteria than other drugs targeting *C. difficile*. "Fidaxomicin does much less damage to the microbiome and the colon flora," notes John Bartlett, chief of the Johns Hopkins University School of Medicine's division of infectious diseases in Baltimore. Doctors hypothesize that the presence of these good gut microbes prevents new drug-resistant bacteria from taking root in the gut.

If fidaxomicin is approved, Sherwood Gorbach, Optimer's chief medical officer, expects many doctors to prescribe the medication as a first-line defense against *C. difficile* infections. "We think right out of the gate that we have a substantial number of physicians who see the benefit of preventing recurrences," says Gorbach, who also studies infectious diseases at Tufts University School of Medicine in Boston.

But fidaxomicin has some competition. In terms of antimicrobial agents, Florida-based Nanotherapeutics plans to take its experimental drug ramoplanin into phase 3 trials later this year (the antibiotic pill blocks cell wall synthesis in bacteria, thereby preventing *C. difficile* replication); Massachusetts-based Cubist Pharmaceuticals has an ongoing phase 2 trial for its drug CB-183315, which disrupts the bacterial cell membrane; and some researchers are repurposing existing antibiotics currently approved to treat other bacterial infections.



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Clobbering Clostridium: New drugs take aim at *C. difficile* infections.

Toxic assets

The arsenal against *C. difficile* could soon include options beyond antibiotics. For example, in November the French vaccine maker Sanofi-Pasteur announced that it had started a phase 2 trial involving an estimated 650 people across 30 US health centers to test a preventative vaccine containing weakened versions of the two major toxins expressed by *C. difficile*. A phase 2 trial assessing the vaccine's ability to prevent relapse is also ongoing in the UK.

In April 2009, the pharma giant Merck also licensed a monoclonal antibody combination that targets and neutralizes the same two toxins. Last year, the developers of the therapy reported the results of a 200-person phase 2 trial showing that the antibody therapy reduced the rate of relapse in patients also taking metronidazole or vancomycin by more than 70% (*N. Engl. J. Med.* **362**, 197–205, 2010).

"The value is to do what metronidazole and vancomycin don't do, which is to prevent recurrence," says study author Donna Ambrosino, executive director of the University of Massachusetts Medical School's MassBiologics laboratory in Boston. However, according to Merck spokesman Ian McConnell, the New Jersey–based company has decided to hold off on taking the therapy into phase 3 trials. "It's quite a crowded marketplace, and a lot of people have seen the opportunity" for drugs targeting *C. difficile*, McConnell says.

This isn't the first time that clinical development of an antitoxin drug has been halted. In 2008, the Massachusetts-based biotech company Genzyme canceled its research program for an oral toxin-binding agent called tolevamer—a polymer also directed against *C. difficile*'s main virulence factors—after the drug proved less effective than vancomycin in two phase 3 trials.

Looking ahead, Dale Gerding, an infectious disease physician who studies *C. difficile* infections at the Edward Hines Jr. Veterans Affairs Hospital near Chicago, expects all the various approaches to serve complementary therapeutic purposes. "You're coming at this from many different directions, and all of them are going to have places where they're going to fit best," he says. "Some people are going to end up being vaccinated, some will get monoclonal antibodies, and it will depend on the needs of the patients."

But the price of these newer therapies—each of which analysts estimate will probably cost more than $1,000 for a full course of treatment if approved—could hinder their wide adoption. Danielle Drayton, an infectious disease market researcher with the Massachusetts-based pharmaceutical consulting firm Decision Resources, notes that oral vancomycin, sometimes costing upward of $500, is already off patent, and generic versions costing around half as much could soon be approved by the FDA. "This changes a little bit of the market dynamics," she says.

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