Inner Workings: Taking evolution to the clinic

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Andrew Read is most at home around mice, mosquitoes, malaria, and math. An evolutionary biologist at Pennsylvania State University in State College, Read has built a career working with animal and theoretical models to study how pathogens develop drug resistance. Yet after 30 years in the laboratory, he decided to investigate a different biological system: doctors and patients.

Read sought a unique kind of research leave, but had to make the case to his dean. "If you want to be a rainforest ecologist, you've got to go hang out in a rainforest," he recalls saying when he made his pitch. "Likewise, if you want to be a hospital ecologist, you've got to hang out in a hospital."

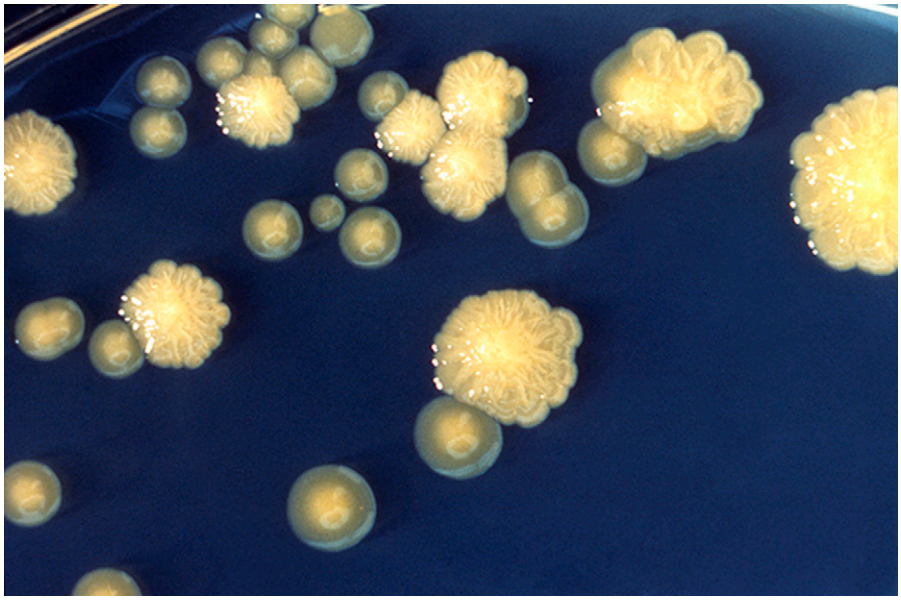
From March to August 2014, Read relocated to the University of Michigan Medical Center in Ann Arbor, where he tagged along with infectious-disease specialists making their rounds in the hospital ward. Every day, he watched the physicians struggle with difficult, sometimes life-threatening, cases of drug resistance, and their limited range of antibiotic options. He also attended weekly meetings dedicated to building coordinated, hospital-wide strategies for antibiotic use and stewardship.

The experience "was a complete eye-opener," Read says. "You get a look at what's in the drug toolkit that doctors are working with, and the bottom of the bucket is very visible."

Read's clinical secondment revealed what might be possible when basic researchers and physicians collaborate as part of an area sometimes called "evolutionary medicine." It also lay bare just how much more both professions need to learn about drug resistance.

Language Barriers

It wasn't easy moving from the language of evolutionary biology—Read's native tongue, scientifically speaking—to the language of clinical medicine. "If you listen hard you can make some sense of what's happening," Read says, "but it's very tricky if you're not drenched in the jargon."



An insidious superbug, *Enterobacter cloacae*, can leave patients in dire circumstances and clinicians perplexed. Image courtesy of the CDC.

Terms such as PICC line ("peripherally inserted central catheter"), angioedema, and LFTs ("liver function tests") don't mean much to a basic scientist, especially when said at the rapid-fire pace of most case presentations. However, after a month or two Read started to learn the lingo and understood enough of the clinical vernacular to chime in on issues of drug dosage and scheduling, aspects of the treatment regimen that have become standardized for many common infections. He asked questions about treatment regimens that are often taken for granted, quizzing doctors, for example, about whether these norms of therapy were helping or hindering efforts to avoid antibiotic resistance. "I got good enough at asking questions in my immediate area of interest," Read says.

Those questions offered a welcome fresh perspective for doctors like Robert Woods, a physician-scientist at the University of Michigan. "Having someone like Andrew there constantly asking you questions makes you double-check your decisions," Woods says. "He stimulated lots of interesting conversations that we probably wouldn't have had otherwise."

One of those conversations centered on a 56-year-old patient of Woods' who suffered from heart failure. Cardiac surgeons had implanted a mechanical pump attached to her heart to help deliver blood throughout her body. The device was a lifesaver, but the cable that extended from the pump out through the skin and connected to a battery often spurred infection.

At first, the problem was Methicillin-resistant *Staphylococcus aureus*, or MRSA, a bacterium known for defying many available treatment options. Woods prescribed a series of intravenous and oral antibiotics, but the bacteria kept evolving new defenses against the medicines. After nine months, the infection had gotten worse: an even more insidious superbug, called *Enterobacter cloacae*, had taken hold.

Woods brought the case to Read for an evolutionary perspective on how to avoid further drug resistance. Together, they considered the remaining antibiotic options and scoured the scientific literature for guidance. The two looked for data on how different strategies of drug administration might drive the evolution of more drug resistance or

In working together, evolutionary biologist Andrew Read (*Left*) and infectious disease clinician Robert Woods shared insights about antibiotic resistance. Image courtesy of Andrew Read.

usher in the invasion of an even more deadly pathogen for this particular type of infection, but they came up with few answers.

Fall to Pieces

The case made both men realize the striking disconnect between evolutionary theory and clinical practice. "We know evolution is the problem, and yet the sorts of information you'd want to help make these clinical decisions don't exist," says Woods. "All the pieces are there, we just couldn't put them together."

Without theory to guide him, Woods tried every class of antibiotic he had—fluoroquinolones, beta-lactams, carbapenems—but the *Enterobacter* kept growing increasingly impervious to the pharmaceutical onslaught. The woman was in and out of the hospital for months. Sadly, she eventually succumbed to the infection and died 18 months after Woods first started treating her.

Hoping to learn from tragedy and highlight the scope of the problem—what Read calls the "areas of ignorance"—Woods and Read collaborated on a case report describing what happened with this patient, published in the journal *Evolution, Medicine and Public Health* (1). "It's the first time I've ever done an *n* equals 1 study," Read says.

For researchers interested in translating evolutionary principles into clinical practice, Read highly recommends embedding oneself in a hospital setting. "Being kept honest and focused on the patient is really important," Read says. The holistic experience, he says, drove home the realities and contingencies of medicine that need to be considered when attempting to implement evolutionary ideas.

"It defined the research agenda for me," he adds. For example, in light of the way that patients actually encounter pathogens in clinical wards, Read is reevaluating the assumption that sequential monotherapies always bring about multidrug resistance faster than do drug mixtures.

Perhaps the closest thing to a formal program that approaches what Read did at Michigan happens each February during so-called "Evolutionary Medicine Month" at the University of California, Los Angeles. There, guest experts in evolutionary biology spend half a day visiting patient bedsides to offer their insights to medical trainees. They call it "Darwin on Rounds." Read's participation in 2013 inspired him to undertake the clinical immersion in Michigan.

"So many people have talked about the potential for evolutionary medicine," says Barbara Natterson-Horowitz, a cardiologist who codirects the evolutionary medicine program at the University of California, Los Angeles. "But until evolutionary biologists actually see what's going on in medicine, instead of trying to extrapolate it, and until physicians are hanging out with evolutionary biologists, the promise can't happen in the right way."

1 Woods R, Read A (2015) Clinical management of resistance evolution in a bacterial infection: A case study. *Evolution, Medicine, and Public Health*, 10.1093/emph/eov025.