

WORLD

DRUGS

In 1940, a British police officer named Albert Alexander was admitted to an Oxford infirmary with a *Staphylococcus aureus* infection. The disease began as a small sore on his lip a few weeks before, but had spread to his face, eyes, scalp and neck, leaving tracts of dead tissue. All treatments failed, including repeated surgeries to drain abscesses, so Alexander's doctors administered an experimental course of penicillin—the first-ever use of this now-iconic antibiotic—in a final attempt to save him. Remarkably, Alexander stabilized and began to recover—until five days later, when his doctors ran out of the miracle cure despite repurifying remains of the compound from his urine.

A few weeks later, as Dr. Brad Spellberg describes in his 2009 book, *Rising Plague: the Global Threat From Deadly Bacteria and Our Dwindling Arsenal To Fight Them*, Alexander died—a common outcome at the time for patients with infectious disease. An autopsy showed the bacteria had spread to almost every part of his body.

Fortunately, as penicillin supplies increased over the next decade, physicians saw unqualified success with previously untreatable infections, including the *S. aureus* that consumed Alexander. Spellman, a physician at Harbor-UCLA Medical Center, notes in his book an ecstatic quality in medical reports from the time:

“These doctors knew they had harnessed a power heretofore unseen in the millennia-long annals of medicine, as if drawing forth and bottling manna from the heavens.”¹

That euphoria did not last long. About one year after the first clinical use of penicillin, doctors reported a case of penicillin-resistant *S. aureus*, and within 10 years similar cases appeared throughout the world. Although the next three decades were a golden age for antibiotics, owing largely to the discovery by pharmaceutical companies of penicillin derivatives, by the 1990s bugs resistant to all combinations of antibiotics had emerged and were spreading through hospitals and the broader community.

Today, antibiotic resistance continues to grow—particularly in hospitals. The U.S. Centers for Disease Control and Prevention reported that in 2002 hospital-acquired infections afflicted 1.7 million Americans; stunningly, 99,000 of them died from those infections, most of which were antibiotic-resistant. Rates of infection in Canada are lower, but antibiotic-resistant strains of *S. aureus*, *Clostridium difficile*, vancomycin-resistant enterococcus and other serious infections are increasingly present in Canadian health care facilities, and previously healthy patients are dying from them. The World Health Organization recently listed

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antibiotic resistance as one of the top three threats to human health, and in Ontario, government-mandated public reports of hospital infection rates frequently produce alarming—and sometimes alarmist—media coverage.

Into this jittery milieu, the *Canadian Medical Association Journal* in 2009 published a review paper by Dr. Andrew Simor, director of clinical integrative biology at Sunnybrook Research Institute (SRI) and head of microbiology at Sunnybrook Health Sciences Centre.

Simor's paper, "Antimicrobial Resistance in Hospitals: How Concerned Should We Be?" surveyed biological mechanisms of resistance in bacteria and examined the growing impact of antibiotic resistance on patients and hospitals. It also added a Canadian-specific, globally relevant plan of action to the increasingly urgent call from infectious disease experts on what must be done to limit the impending calamity of 21st-century superbugs.

In this article, Simor, who is also a professor in medicine, and laboratory medicine and pathobiology at the University of Toronto, details three approaches that could curtail antibiotic resistance quickly. The first is surveillance—accurately tracking antibiotic resistance rates to compile region- and patient-specific data on risk. "We need baseline and ongoing measurements to see how infection rates are changing over time, and to gauge the impact of our interventions," says Simor. "Canada does not, at the moment, have an adequate, national surveillance system for antibiotic resistance." While we have some rudimentary measures in place, he says, some countries in Europe know their resistance rates for several major organisms, and therefore have a much stronger grip on the problem.

Second, Simor recommends better methods of infection prevention and control. This involves improved cleaning of contaminated environments and more effective isolation of infected patients,

among other methods. Unfortunately, not all of these measures are evidence-based, so progress is challenging. More research in this area is necessary, says Simor, to determine which infection control practices and interventions are likely to be most effective.

Third, Simor calls for more judicious use of antibiotics. "There is no question that one of the major drivers promoting the emergence and spread of antibiotic-resistant organisms in the community and health care settings is antibiotic use," says Simor. "Study after study, globally and in Canada, has documented a substantial amount of inappropriate use."

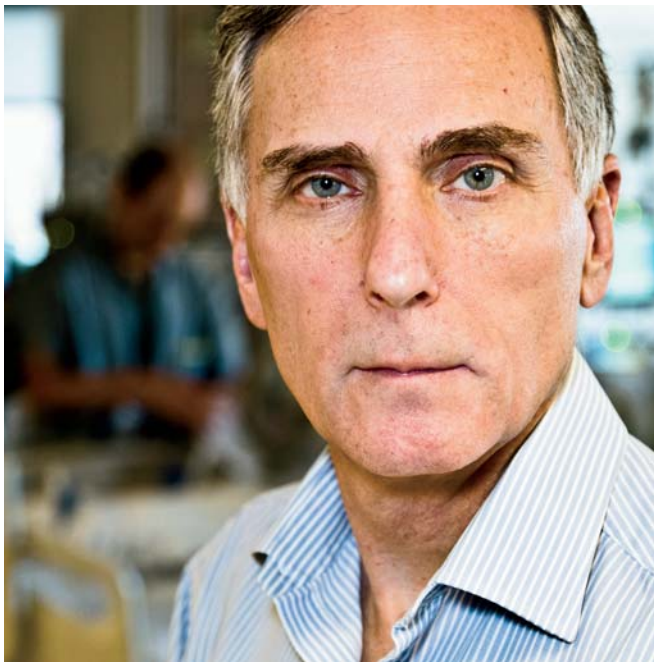
Scientists refer to this problem as "selective antibiotic pressure." To illustrate, Simor points to the role of genetic mutation, one of two main avenues by which bacteria become resistant. Most of the microbes in a particular infection may be susceptible to a particular antibiotic, with perhaps only 1% of them resistant. A physician may treat the infection with that antibiotic and kill 99% of the bacteria, but the remaining resistant microbes no longer have any susceptible competitors, so they become the dominant organism.

More worryingly, superbugs can also develop by acquiring mobile genetic elements from other types of bacteria. Use of one antibiotic can then drive resistance in other classes of organisms—and to other antibiotics that target those other classes. "It's a huge problem, and it underscores why it's so important that we use our antibiotics appropriately," says Simor.

The problem of antibiotic resistance has become so acute in large part because far fewer new antibiotics are coming onto the market precisely when resistance is rising, as Simor notes in his paper. Over the last two decades, pharmaceutical companies have put more resources into developing drugs for increasingly manageable chronic conditions like diabetes, hypertension and heart disease than they have for antibiotics, because the return on investment is far greater: a patient with a chronic condition may require a particular medication every day for decades, for example, while a typical course of antibiotics runs only days to weeks.

Compounding this profit-driven shift are tighter safety regulations and testing requirements for new agents. Greater awareness among consumers and physicians of drug toxicities, potential adverse effects and drug-drug interactions, spurred in part by more robust studies of large patient-record databases, has added tens of millions of dollars to the cost of bringing a new drug to market. Drug development expenses now range from hundreds of millions to billions of dollars per medication, so identification of a problem at a late testing stage can inflict significant financial damage.

Shrinking numbers of approvals for new antibiotics tell the story.



TOP TO BOTTOM: DR. NICK DANEMAN; DR. ANDREW SIMOR

The U.S., for example, approved 16 antibacterial drugs from 1983 to 1987, but only four from 2003 to 2007. Yearly decline between those two periods was consistent; moreover, there are few promising agents in the pipeline. The need for new drugs has become so critical that early in 2010, the Infectious Diseases Society of America, extending its “Bad Bugs Need Drugs” campaign, published a statement called the “10 x ’20 Initiative,” which set the goal of developing 10 new antibiotics by 2020 through cooperation among industry, government and academia.

While the issue of antibacterial drug development is gaining traction with policy makers in the U.S., Simor and Dr. Nick Daneman, a scientist in clinical epidemiology at SRI and doctor specializing in infectious diseases at Sunnybrook, are leading a pilot program based on the third tenet Simor outlined in his paper that could become a model for Canada. With critical care staff and pharmacists at Sunnybrook, they are monitoring antibiotic prescriptions in the hospital’s intensive care units to reduce antibiotic use.

The initiative is an active intervention that contrasts with passive approaches to overprescription like physician education, which research suggests is less effective. On the third day of any prescription for a broad-spectrum antibiotic (one able to fight a range of infection-causing bacteria), a team led by senior infectious disease pharmacist Dr. Sandra Walker and antibiotic stewardship

pharmacist Marion Elligsen reviews the patient’s charts, pharmacy information, and lab culture and susceptibility results. If the pharmacists believe the prescription may not be needed, then they discuss it with the infectious disease physicians on call, and feed a recommendation back to the critical care team. “It’s been very successful, very much because the critical care teams have been involved from inception to implementation,” says Daneman. “Our intervention has been tailored to their needs.”

Six months after starting the program, the research group had reviewed more than 400 prescriptions, and critical care staff had accepted nearly 90% of their recommendations; the immediate result was a 16% reduction in antibiotic use that saved \$140,000 in drug costs. The team will soon have data on the most important outcome — infection rates — which preliminary numbers suggest will be lower.

Over the next year, contingent on funding, the group has two goals: to extend the program to the whole hospital, and to compare long-term data on infection rates before and after the rollout in various Sunnybrook units, thereby adding scientific rigour to a research field that Daneman and Simor say lacks it.

That research on such interventions is insufficient is yet more evidence that the greatest challenge in containing infectious diseases is the remarkable shiftiness of microbes—which while pathogenic are also essential for life. Biological study has shown the genetic pathways on which antibiotics are based, and their corresponding resistance mechanisms, are more than two billion years old. Entering the stage a mere seven decades ago, medicine must indeed step quickly in this evolutionary tango. “We can no longer treat without thinking, in the belief that antibiotics have no potential for harm,” says Simor. “Those days are long gone.”

The Ontario Ministry of Health and Long-Term Care funded Sunnybrook’s antibiotic stewardship initiative through its program, Alternate Funding Plans for Academic Health Science Centres.

1. Brad Spellberg, *Rising Plague: the Global Threat From Deadly Bacteria and Our Dwindling Arsenal To Fight Them* (New York: Prometheus Books, 2009) 50.