



STOPPING "SUPERBUGS" WITH GENOMICS

Technology-charged genomic sequencing could be the weapon we need to combat drug-resistant superbugs.

Hospitals can be dangerous breeding grounds for infectious bugs. Concentrated numbers of sick people, many with weakened immune systems, and healthcare workers moving quickly from person to person—all combine to create a perfect storm for quickly spreading germs.

BACTERIAL INFECTIONS ACCOUNT FOR MORE THAN 13 PERCENT OF DEATHS WORLDWIDE.

—National Center
for Biotechnology
Information, 2015

Most are easily killed with common antibiotics and pose no real threat. But decades of antibiotic overuse, constantly evolving microbes, and huge increases in worldwide travel are accelerating the growth of drug-resistant pathogens, leading experts to sound a global health alarm.

Quickly identifying specific strains is critical in fighting these persistent human enemies. But today's routine diagnostic methods aren't fast or accurate enough to effectively contain outbreaks, and they often lead to the incorrect or unnecessary use of antibiotics—thus contributing to the very problem that they're meant to solve.

To combat these "superbugs," researchers are now using the latest genomics technologies—in particular next-generation sequencing and whole-genome sequencing—to identify an infection's source and contain it before it causes real harm.

Left alone, the problem threatens to become one of the great public health crises of the 21st century. Bacterial infections account for more than 13 percent of deaths worldwide¹, and cases of multidrug-resistant bacteria in healthcare settings are exploding, even as the development of new antimicrobial drugs slows.

Researchers say we risk a recurrence of the pre-antibiotic era, when a sore throat could kill and minor surgery carried the imminent threat of death.

"We are approaching a cliff," said Michael Bell, MD, deputy director of CDC's Division of Healthcare Quality Promotion, in a CDC statement. "If we don't take steps to slow or stop drug resistance, we will fall back to a time when simple infections killed people."

To prevent this, researchers are also using genomic sequencing to pinpoint pathogens' source of resistance and potentially develop new drugs to stop them. With new outbreaks of Ebola, Zika, and other infections occurring all the time,

¹ National Center for Biotechnology Information, 2015

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these new genomic weapons are becoming more important than ever.

The power of genomics

Before sequencing, diagnosing an infection was painstakingly slow. Healthcare workers would take a sample—for example, swabbing the back of someone's throat for a potential case of strep—and let it grow in a lab. For slow-growing bacteria and viruses, that can take weeks.

And not all pathogens can be successfully cultured, meaning diagnoses can be faulty or even impossible, which can lead to tragic outcomes. Several other diagnostic techniques exist, but all have severe limitations; faster methods aren't as accurate, and more precise techniques take too long to be useful.

Sequencing, which has only recently become cost-effective and quick enough to help battle infectious diseases, sidesteps all these problems. Samples can be obtained directly from human tissue, thus eliminating the need for time-consuming culturing.

Definitive identification takes a few days at most, saving critical time that could mean controlling a would-be outbreak or giving someone the right treatment early enough to save their life.

Sequencing all 2,600 genes of *S. aureus*—the cause of staph infections and a troublesome drug-resistant strain called MRSA (methicillin-resistant *S. aureus*)—can be done in hours². Compare that to one of the common pre-sequencing methods, which analyzed only eight genes.

Once researchers have a pathogen's sequence, they compare it to known pathogens in a database, which tells them which drugs are most likely to be effective. They can also construct a “family tree” to see where exactly that particular bug came from, how it spread, and if it's a new strain that needs further study.

In one landmark incident profiled by the Wellcome Genome Campus in the UK, several babies at a Cambridge hospital's special care unit tested positive for MRSA. The cases appeared in clusters over several weeks with gaps in between, and hospital officials initially believed the clusters were unrelated.

After sequencing all positive MRSA cases and 100 hospital workers, they found that all the cases were related and pinpointed the transmission source to a single healthcare worker. Using this knowledge, they took steps to kill the infection, avoided further spreading, and ensured that no one became seriously ill.

“The expansion of whole-genome sequencing into public health surveillance activities represents a paradigm shift that has already saved lives by identifying and solving more outbreaks, faster,” said Beth Bell, MD, director of the National Center for Emerging and Zoonotic Infectious Diseases, in recent testimony before Congress.

² yourgenome.org by Wellcome Genome Campus; www.yourgenome.org/stories/tracking-superbugs

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—Jennifer Esposito
Worldwide General Manager,
Health and Life Sciences, Intel

Whole-genome precision

Infectious disease tracking illustrates the power of whole-genome sequencing, compared to more targeted methods. In cancer and other fields, for example, researchers typically sequence only a few genes of known importance.

By analyzing all of a pathogen's genes with incredible precision, researchers can see exactly what mutations arose when, and which of those could be responsible for drug resistance.

This research is central to the development of next-generation antibiotics. Typically, researchers discover new antibiotics by culturing soil bacteria and identifying the antimicrobial compounds some of them produce to avoid falling prey to other bacteria.

The process is time consuming and leads to many dead ends, given that most soil bacteria don't grow well in vitro. Genomics offers an entirely new approach, allowing researchers to identify both bacterial vulnerabilities and potential curative compounds in less time.

Take tuberculosis. Extensive genomic sequencing of *Mycobacterium tuberculosis* is allowing researchers to rapidly identify resistance mechanisms in TB bacteria, aiding in the development of new drugs to combat the quickly evolving microbes that cause this dreaded disease.

Sequencing also enables researchers to identify pathogens that can't be cultured through known techniques—pathogens that would otherwise remain unknown, to the profound detriment of public health.

Technology to match the threat

Practical technology is following the research. Software already exists to identify bacterial strains and their resistance profiles using a laptop, providing comprehensive reports in minutes.

"We don't want untreatable infections to become common," said Arjun Srinivasan, MD, CDC's associate director for Healthcare Associated Infection Prevention Programs, in a CDC release. CDC's "plans to combat this include obtaining real-time data about antibiotic use and trends to better understand prescribing practices in doctor's offices and ... hospitals." Getting this real-time data is critical, as is the ability to analyze it quickly and get actionable insights.

Sequencing has now been used for real-time tracking of the Ebola virus in West Africa and the Zika virus in Brazil. For Ebola, researchers flew a new portable sequencer in their luggage and were able to quickly map transmission patterns after identifying strains within 24 hours. Previous methods involved shipping blood samples to labs overseas, which took weeks³.

³ www.nature.com/nature/journal/v530/n7589/full/nature16996.html
<http://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0356-2>

Following these examples, health agencies around the world are calling to expand the practice to help stay ahead of any future outbreaks.

“Detection and surveillance are a really big part of containing these outbreaks,” said Jennifer Esposito, Intel’s worldwide general manager, health and life sciences. “Anything we can do to detect these infectious agents more quickly, as they’re happening, or to bring that information together and allow more real-time response to it, could help save lives.”

