Staying Ahead of the Next Outbreak: How NGS is Adding Muscle to Public Health Efforts

A whole-genome view helps epidemiologists overcome traditional challenges of tracking disease origins and stopping outbreaks.

Public health scientists are on a constant hunt for new clues about how diseases spread from person to person. Driven by the goal to prevent and control outbreaks in the community, we seek to better understand transmission dynamics and track the origins of diseases such as tuberculosis and influenza. In a nutshell, that's what science of epidemiology is all about. And, as a longtime public health researcher and epidemiologist specializing in infectious disease, I can say that we still have much to learn about how pathogens make their way through our communities.

While we do know a lot of basic information about disease transmission —for example, we know that influenza is a droplet-based disease that's often spread through sneezing— we don't know much about how those diseases behave and evolve during an outbreak. Is there a "super-spreader" infecting lots of people? Do all outbreaks of a given pathogen progress in the same manner? What factor do social networks play in the spread of disease?
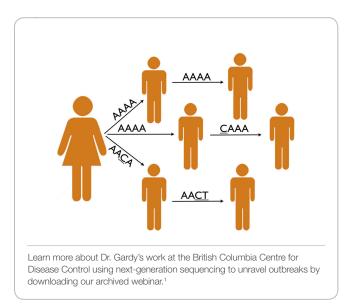
These are critical questions to consider as we seek to get ahead of dangerous outbreaks. Traditionally, public health researchers have sought answers using two main approaches:

Field epidemiology boils down to interviewing patients to find relationships between people, places, objects and behaviors. For example, by interviewing parents of children who were sickened by *E. coli,* my colleagues at the British Columbia Centre for Disease Control and the BC Public Health Microbiology and Reference Laboratory determined all of the kids had something in common: they attended a petting farm at a local fair.

Molecular epidemiology is a newer approach that involves "interviewing" pathogens themselves. Using genetic fingerprinting techniques, scientists look for phenotypic or genetic relationships between disease samples from patients. In addition to basic lab techniques such as serotyping, researchers do Sanger sequencing of short gene fragments; Multilocus Sequence Typing (MLST) and Mulitlocus VNTR Analysis (MLVA) are known as the gold-standard techniques in this space.

While these approaches are quite useful in theory, they present some significant challenges in reality. With field epidemiology, it's mostly an issue of resources. Public health departments don't have the time, money and personnel to investigate every outbreak to the extent they'd like.

On the molecular side there are a few issues, starting with resolution — or lack thereof. Genomic fingerprinting methods vary in terms of the clarity they provide. And even in best-case scenarios, they don't provide much insight beyond telling us which isolates are identical. For example, we don't know which disease samples are more closely

Learn more about Dr. Gardy's work at the British Columbia Centre for Disease Control using next-generation sequencing to unravel outbreaks by downloading our archived webinar.[1]

related than others, and we aren't able to tell the order of transmission (who coughed on whom?).

But the biggest downfall of molecular epidemiology is that there's a whole lot of useful genomic information that we're just not able to access. Of 2 million to 5 million base pairs on average in a bacterial genome, only a tiny percentage —an estimated 0.1 percent— is used in the best genotyping experiments.

NGS Makes 'Ultimate Genotyping' Possible

Enter the magical little box. That's what I call the benchtop sequencers that are allowing public health researchers like me to finally take a look at the whole genome, opening interesting new avenues of investigation.

Over the last few years, next-generation sequencing (NGS) technology has become accessible to public health labs, spawning the exciting field of genomic epidemiology. We can now sequence hundreds or even thousands of bacterial isolates quickly and affordably; Rather than look at just a tiny piece of the genome, we can now see the big picture.

By collecting pathogen samples from patients and comparing genome sequences, we're able to identify mutational markers that link cases to each other and overlay that information onto a map of social relationships between patients. This allows us to actually reconstruct the path by which an infectious agent worked its way through a population.

This is just we did in 2010 when we traced a large outbreak of tuberculosis to a super-spreader patient in the community.[2] Other pioneering public health research teams throughout the world have used NGS to help pinpoint the source of dangerous bacterial strains that were spreading quickly throughout hospitals.

A Smarter Use of Resources

Understanding how a pathogen enters and spreads through a population is central to managing an outbreak and avoiding future cases. NGS gives us a tool that can help us gain this understanding faster and more efficiently.

While whole-genome sequencing alone doesn't solve outbreaks, at least not yet. It represents a huge leap in our capabilities. This kind of detailed, high-resolution information is absolutely essential to develop evidence-based prevention and control strategies.

In addition, NGS can help direct our fairly limited field epidemiology resources. When we are able to obtain patient samples and sequence the first few cases, we can make inferences about how the disease is spreading and ask the right questions to find transmission chains and super-spreaders in the community. And combined with good field data, NGS can help us solve even the most confounding of cases.

Dr. Jennifer Gardy is a senior scientist focusing on genomics and molecular epidemiology at the British Columbia Centre for Disease Control. Her team's NGS-driven research to uncover the source of tuberculosis in British Columbia has been published in the New England Journal of Medicine.

References

1. http://www.illumina.com/events/webinars.ilmn
2. Gardy JL, Johnston JC, Ho Sui SJ, Cook VJ, Shah L, et al. (2011) Whole-genome sequencing and social network analysis of a tuberculosis outbreak. *N Engl J Med* 364:730-739.

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