The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Whole-Genome Sequencing: Opportunities and Challenges for Public Health, Food-borne Outbreak Investigations, and the Global Food Supply

John R. Dunn

Communicable and Environmental Diseases and Emergency Preparedness, Tennessee Department of Health, Nashville

(See the major article by Hoffmann et al on pages 502–8.)

Keywords. *Salmonella*; whole-genome sequencing; public health; PFGE; global food supply; outbreak investigation.

Food-borne disease is burdensome, affecting 1 in 6 persons or an estimated 48 million ill, 128 000 hospitalized, and 3000 deaths in the United States annually [1]. In addition, societal costs from lost lives, lost labor, lost wages, and even lost revenue in the food industry are substantial. Globally the burden is even higher, and multinational outbreaks due to the global movement of contaminated foods are being described increasingly. The global food supply links nations and economies, emphasizing the need to view food safety with an integrated farm-to-fork lens. As predicted, advances in molecular techniques and information management have been transformative for food-borne disease investigation [2].

Almost 2 decades have passed since the Centers for Disease Control and Prevention (CDC) launched a national molecular subtyping system known as PulseNet, and since that time it has become an indispensable laboratory surveillance system for detection of multijurisdictional food-borne outbreaks. With PulseNet, public health authorities developed a unique system able to link bacterial isolates that could identify food-borne outbreaks dispersed far and wide geographically with only a few cases. Notable examples of PulseNet's impact include elucidation of the association of *Escherichia coli* O157 and ground beef [3], as well as numerous produce-associated outbreaks [4, 5]. Not only food-borne disease investigations have been enhanced; investigations related to direct animal contact have improved as well [6, 7]. Indeed, PulseNet has facilitated more cluster evaluations, faster outbreak investigations, and timelier regulatory interventions and has undoubtedly prevented many illnesses and deaths [8].

A national success story, PulseNet won the prestigious Innovations in American Government Award because of its substantial contribution to public health [9]. Its standardized methods of enzymatically restricting bacterial DNA into large fragments and then subjecting them to pulsed-field gel electrophoresis (PFGE) creates a unique molecular "fingerprint" suitable for real-time data transmission, computer analysis, and epidemiological investigation. With this history of success, it is with not without some nostalgic reluctance that the public health community is moving away from PulseNet as we currently know it. However, technological opportunities compel moving forward to build on the success of the past 2 decades. Advances in and increased availability of whole-genome sequencing (WGS) have arrived, as well as innovative ways to analyze the standard epidemiological data of person, place, and time.

In this issue of *The Journal of Infectious Diseases*, Hoffmann et al [10] describe a retrospective analysis of a multistate US *Salmonella* Bareilly outbreak associated with tuna imported from India. They demonstrate the promise of combining WGS and analytical tools to trace food-borne pathogens through complex international distribution networks, leading to the source of the contaminated food. The context for the retrospective analysis is a 2012 food-borne outbreak with >400 reported cases in 28 states [11]. Hoffmann et al illustrate the power of WGS by analyzing a cross-section of environmental, regulatory, and human historical and outbreak-related *Salmonella* Bareilly isolates to differentiate clonal PFGE clusters into distinct genetic lineages associated with the contaminated tuna source. The phylogenetic analysis pointed to a common origin at a facility in India, while excluding *Salmonella* Bareilly lineages not associated with the outbreak.

Geographic mapping and use of transmission networks are core epidemiological tools that also proved valuable in understanding the global supply chain and source of infection. Hoffmann et al [10] used not only the advances in WGS analysis but also other innovative technologies to visualize and analyze the epidemiological data, resulting in pinpointing the source of the contaminated

Received 11 May 2015; accepted 18 May 2015; published online 20 May 2015.

Correspondence: J. R. Dunn, Communicable and Environmental Diseases and Emergency Preparedness, Tennessee Department of Health, 710 James Robertson Pkwy, Nashville, TN 37243 (john.dunn@tn.gov).

The Journal of Infectious Diseases® 2016;213:499–501
 DOI: 10.1093/infdis/jiv298

tuna. Especially intriguing was the use of the ubiquitous Google Earth to visualize the overall transmission network of *Salmonella* Bareilly isolates. In a proof of concept of sorts, the authors demonstrate that WGS is a precise forensic tool that, when coupled with epidemiological analysis, enables new opportunities to investigate outbreaks and get closer to their root causes in our elaborate food global supply chain.

The evidence presented in this retrospective analysis is promising. However, there are some unavoidable realities to consider in the rapidly evolving evaluation of and transition to WGS. Notably, the existing paradigm of clinical microbiology is changing. For more than 100 years, dating back to Robert Koch, physicians and public health officials have relied on isolation and characterization of bacteria to understand disease and develop both patient-specific treatment plans and public health interventions. The success of both PulseNet and WGS depend, at least for the moment, on the availability of clinical isolates. However, clinical microbiology laboratories are increasingly moving away from primary isolation of pathogens to culture-independent diagnostic testing (CIDT). These tests are of great benefit, providing multipathogen diagnostic panels with remarkably brief turn-around times. Clinical laboratories are increasingly using CIDT methods and are less likely to conduct primary isolation, forecasting a clinical isolate drought for public health laboratories [12].

Because the national surveillance network starts at the nexus of clinical medicine and public health, we must address this issue to assure that isolates are available to public health laboratories. Already, the CDC has published guidelines pleading for clinical laboratories to conduct cultures alongside CIDT for Shiga toxin–producing *E. coli* [13]. Obviously, this additional culturing adds cost without tangible individual patient benefits for some pathogens. Downstream effects of CIDT are stretching the already poorly funded public health infrastructure as more and more clinical laboratories forward CIDT-positive specimens and broths to public health laboratories for primary pathogen isolation. Public health laboratories need additional resources to conduct primary isolation of CIDT-positive specimens and to incorporate WGS into the existing work flow. The CDC is responding by providing state public health laboratories with equipment and training for WGS, but more will be needed to facilitate the transition while maintaining current capacity. Infectious disease physicians and other medical providers have always been key public health partners and can be influential advocates to support these needs.

Another critical component of the "new" PulseNet-WGS model will be to continue the process of evaluating and prioritizing cluster investigations, using data from all relevant disciplines: laboratory medicine, environmental health, and epidemiology. For nearly 2 decades, PulseNet has served as a cluster detection tool by which outbreaks are investigated using a multidisciplinary approach. We should anticipate that the increased precision of WGS will create more clusters for evaluation, further emphasizing the need to collect high-quality exposure or risk factor data. Timely interviewing of case patients, descriptive analyses, implementation of case-control studies, and trace-back methods will continue to be important in interpreting and acting on molecular clusters identified by PFGE, WGS, or the next next-generation subtyping method.

Massive amounts of data with WGS present analytical challenges, and the quest to make WGS a near real-time cluster detection tool for all food-borne pathogens is daunting. The availability of WGS data on human, environmental, and food isolates through massive genetic libraries, in combination with epidemiological data or limited metadata, will contribute not only to ruling in a suspected food but also, and perhaps as importantly, to ruling out a suspected food. As the tools are developed to conduct analyses as part of our routine public health activities, there will be a need to maintain a multidisciplinary approach, including industry partners, to aid in interpretation of food safety risks and sources of contamination.

Industry partners can add much as this transition occurs. The global supply chain plays a critical role in multinational economies and allows the US population to have a diverse international diet year round. Government and industry partnerships must be strengthened in response to real-time hypotheses about transmission networks and origins of food-borne outbreaks. The process of testing these hypotheses will benefit from government and industry collaboration because industry food safety professionals typically have the most market knowledge about global supply chains and can rapidly assess plausibility for a given product, commodity, or ingredient.

As Hoffmann et al [10] describe a retrospective analysis of *Salmonella* and explore intriguing opportunities for data analysis, federal public agencies are pushing forward with updating the PulseNet system. Despite growing pains, the early results are promising. In late 2013, the US Food and Drug Administration and CDC partnered with public health jurisdictions across the country to begin real-time WGS of all *Listeria monocytogenes* isolates collected from ill persons in the United States. In the 18-plus months since then, WGS has been shown to be a powerful analytical tool in several multistate *Listeria* outbreaks linked to sprouts, cheese, and, most recently, ice cream. Plans are underway at the CDC to transition to routine WGS for Shiga toxin–producing *E. coli*, *Salmonella*, and *Campylobacter*. Improving food-borne outbreak investigations while enhancing the safety of our global food supply is challenging, but the future appears bright with the dawn of WGS as a routine public health tool.

Notes

Financial support. The Tennessee Department of Health receives funding through cooperative agreements with the Centers for Disease Control and Prevention.

Potential conflict of interest. Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States—major pathogens. Emerg Infect Dis **2011**; 17:7–15.
2. Tauxe RV. Molecular subtyping and the transformation of public health. Foodborne Pathog Dis **2006**; 3:4–8.
3. Rangel JM, Sparling PH, Crowe C, Griffin PM, Swerdlow DL. Epidemiology of *Escherichia coli* O157:H7 outbreaks, United States, 1982–2002. Emerg Infect Dis **2005**; 11:603–9.
4. Marder EP, Garman KN, Ingram LA, Dunn JR. Multistate outbreak of *Escherichia coli* O157:H7 associated with bagged salad. Foodborne Pathog Dis **2014**; 11:593–5.
5. Angelo KM, Chu A, Anand M, et al. Outbreak of *Salmonella* Newport infections linked to cucumbers—United States, 2014. MMWR Morb Mortal Wkly Rep **2015**; 64:144–7.
6. Nakao JH, Pringle J, Jones RW, et al. 'One Health' investigation: outbreak of human *Salmonella* Braenderup infections traced to a mail-order hatchery—United States, 2012–2013. Epidemiol Infect **2015**; doi:10.1017/S0950268815000151.
7. Goode B, O'Reilly C, Dunn J, et al. Outbreak of *Escherichia coli* O157: H7 infections after petting zoo visits, North Carolina State Fair, October-November 2004. Arch Pediatr Adolesc Med **2009**; 163:42–8.
8. McCollum JT, Cronquist AB, Silk BJ, et al. Multistate outbreak of listeriosis associated with cantaloupe. N Engl J Med **2013**; 369:944–53.
9. Harvard Kennedy School for Democratic Government and Innovation. PulseNet. http://www.innovations.harvard.edu/pulsenet. Accessed 1 May 2015.
10. Hoffmann M, Luo Y, Monday SR, et al. Tracing origins of the *Salmonella* Bareilly strain causing a food-borne outbreak in the United States. J Infect Dis **2016**; 213:502–8.
11. Centers for Disease Control and Prevention. Multistate outbreak of *Salmonella* Bareilly and *Salmonella* Nchanga infections associated with a raw scraped ground tuna product (final update). http://www.cdc.gov/salmonella/bareilly-04-12/index.html. Accessed 1 May 2015.
12. Iwamoto M, Huang JY, Cronquist AB, et al. Bacterial enteric infections detected by culture-independent diagnostic tests—FoodNet, United States, 2012–2014. MMWR Morb Mortal Wkly Rep **2015**; 64:252–7.
13. Centers for Disease Control and Prevention. Recommendations for diagnosis of Shiga toxin–producing *Escherichia coli* infections by clinical laboratories. MMWR Morb Mortal Wkly **2009**; 58(RR-12):1–20.