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Bacterial genome sequencing and analysis: paving the way for a Switzerland-wide molecular epidemiological surveillance platform

Marschall Jonas

Department of Infectious Diseases, Bern University Hospital and University of Bern, Switzerland

Clinical infectious diseases and, more specifically, infection prevention and control rely on support from microbiological laboratories. This support has evolved over time and now includes high-throughput whole genome sequencing (WGS), which can assist with typing in an outbreak setting or in infectious disease surveillance, deliver information on the microbial phylogeny and microevolution, and elucidate virulence and resistance characteristics. The scientific literature has exploded in recent years, with the combination of search terms "bacteria" and "whole genome sequencing" yielding 16 hits in 2000, 99 in 2010, and 1184 in the year 2017 (PubMed search, 6 October 2018). What Egli and colleagues – while educating the medical audience on the intricacies of WGS – propose in the article now published in *Swiss Medical Weekly* [1] is the next big step: establishing a national platform where bacterial isolates from all corners of Switzerland can be assembled and compared against each other in a standardised, reproducible way. Not only is this article timely in that it responds to urgent needs, as seen in a recent outbreak investigation of vancomycin-resistant enterococci that has come to national attention [2] or in the work-up of a *Burkholderia stabilis* outbreak that originated from contaminated wipes, presumably at the production site [3]. It can also be read as a manifesto for extracting a maximum of microbiological information and delivering it in a timely fashion to the infectious diseases clinician, hospital epidemiologist and public health expert. For this, the authors and their respective laboratories will use *Staphylococcus aureus* as a proof-of-concept pathogen and intend to establish common ground by creating an interlaboratory agreement on standard protocols, quality markers and the sharing of large amounts of interoperable data.

Returning to the topic of isolate typing for outbreak investigation, we have depended for decades on typing methods with limited resolution that were often characterised by tedious laboratory procedures. WGS offers nucleotide level resolution and with it, genotyping unlike any other in history. During an outbreak, WGS can readily assign newly detected bacterial isolates to the outbreak strain (or rule out clonality), and thereby provide continuous information while measures to contain the outbreak are implemented and evaluated. Accordingly, the first overview articles have been published that instruct the infection prevention community on how to use and interpret WGS data in the context of their daily work [4–7]. Both the uptake and the impact of WGS in the clinical setting are likely to be greater if three needs are met: (1) short turn-around time so that the dynamics of an outbreak and transmission pathways can be better understood in near real-time, (2) user-friendly feedback of results with tailored interpretative help, and (3) an open communication channel to the laboratory in order to resolve any questions that might arise.

Reviewing the literature on comparisons of WGS with older techniques, I would like to highlight a few examples that focused on outbreak investigations. Roetzer et al. compared WGS with traditional genotyping during a long-standing tuberculosis outbreak; they found that traditional typing falsely identified isolates as belonging to the cluster and saw that WGS findings matched the epidemiological links better than other forms of typing [8]. Dominguez et al. compared WGS with repetitive element palindromic PCR (repPCR) and pulse-field gel electrophoresis (PFGE) for a *Clostridium difficile* outbreak; the former had better discriminatory power and the authors highlighted that WGS was also able to detect toxin genes; on the other hand, WGS took longer than the two comparator approaches and was costlier [9]. Azarian et al. compared WGS with three other typing methods (PFGE, antibiograms and *spa* typing) in methicillin resistant *S. aureus* (MRSA) from outbreaks in neonatal intensive care units and noted that WGS identified certain cases as unrelated to the outbreak cluster. The authors assume that decision-making with regard to infection control measures would have differed, had WGS results been available in real-time [10]. Lytsy et al. compared WGS with PFGE and multi-locus sequence typing (MLST) in three vancomycin-resistant enterococcus outbreaks in Sweden; strain assignment was more accurate with WGS and MLST than with PFGE, and WGS had the highest discriminatory power, showed better epidemiological concordance, and appeared to be more user-friendly than the other methods [11]. Finally, Kozyreva et al. compared WGS with PFGE for a *Salmonella* outbreak in which WGS could link all strains to one clone, whereas PFGE identified three different patterns; the authors could

Correspondence:
Jonas Marschall, MD, Department of Infectious Diseases, Bern University Hospital and University of Bern, CH – 3010 Bern, jonas.marschall[at]insel.ch

replicate their WGS findings in a second laboratory, which speaks to the reproducibility of the method [12]. The list of studies comparing WGS with traditional typing methods is continuously growing [13] and is no longer limited to bacteria [14]. In summary, for a host of pathogens it is being demonstrated that WGS with its outstanding resolution is about to become the gold standard for the microbiological aspect of outbreak investigations.

Although there is – to my knowledge – no published evidence available yet to demonstrate that WGS has an impact on actual patient outcomes, there are many advantages to this technique (and certain limitations that the user of WGS data should be aware of, for example, that it is no substitute for clinical epidemiology). Given that WGS is becoming more widely available and affordable, we are at the onset of an exciting era in genomic infectious disease epidemiology. Once the proposed WGS platform for Switzerland has come to life, it should be accompanied by the joint creation of an agenda that connects with existing public health strategies, such as NOSO (on healthcare epidemiology and infection prevention) and StAR (on describing, combatting and preventing antimicrobial resistance). The stakeholders should include –- but are not limited to – the Swiss Society for Infectious Diseases, the Swiss Society for Hospital Hygiene, the National Centre for Infection Control (i.e., Swissnoso), the National Centre for Antibiotic Resistance (i.e., Anresis), the National Reference Laboratory for the Early Detection of Emerging Antibiotic Resistance (i.e., NARA), the Swiss Tropical and Public Health Institute, and players from veterinary medicine to allow for a One Health approach to bacterial ecology. For their part, the stakeholders need to ensure that the clinical annotations become equally standardized because only in this way will we harvest the maximum environmental, host and pathogen information. Clarifying the ownership of WGS data and regulating the data exchange are imperative and the close collaboration between microbiologists, laboratory technicians and bioinformatics specialists on one hand, and clinicians and infection prevention experts on the other hand a *conditio sine qua non*. In my opinion, an overarching agenda should contain the following elements: an operational agenda to ensure the functionality of a national WGS platform, a research agenda to identify projects on the spectrum from basic science to translational and clinical research, and a public health agenda to connect with and serve the above-mentioned stakeholders. I commend the authors of this article for taking the first steps in an endeavour that will greatly enhance our ability to identify, understand and manage outbreaks.

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