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SUPPLEMENT ARTICLE

NGSocomial Infections: High-Resolution Views of Hospital-Acquired Infections Through Genomic Epidemiology

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Hospital outbreak investigations are high-stakes epidemiology. Contacts between staff and patients are numerous; environmental and community exposures are plentiful; and patients are highly vulnerable. Having the best data is paramount to understanding an outbreak in order to stop ongoing transmission and prevent future outbreaks. In the past 5 years, the high-resolution view of transmission offered by analyzing pathogen whole-genome sequencing (WGS) is increasingly part of hospital outbreak investigations. Concerns over speed and actionability, assay validation, liability, cost, and payment models lead to further opportunities for work in this area. Now accelerated by funding for COVID-19, the use of genomics in hospital outbreak investigations has firmly moved from the academic literature to more quotidian operations, with associated concerns involving regulatory affairs, data integration, and clinical interpretation. This review details past uses of WGS data in hospital-acquired infection outbreaks as well as future opportunities to increase its utility and growth in hospital infection prevention.

Key words. hospital acquired infection; hospital epidemiology; hospital outbreak; nosocomial infection; pathogen sequencing; whole genome sequencing.

INTRODUCTION

Whole-genome sequencing (WGS) data are increasingly available to help guide hospital outbreak investigations [1]. In general, recovering whole genomes is only possible with next-generation sequencing (NGS), either by shotgun sequencing isolates when dealing with bacteria or fungi or primary clinical specimens in the case of viruses [2–4]. Investigating phylogenetic relationships among organisms is also a natural extension of the data offered by diagnostic metagenomic NGS approaches, described in other reviews in this supplement [5]. The value of WGS data increasingly is leading to interest in prospective rather than reactive sequencing of isolates [6, 7]. Pending batch size and throughput, costs have continued to drop to $100-200/isolate range, rivaling that of fully reimbursed polymerase chain reaction (PCR) tests. In this review, we showcase many of the past uses of WGS data in investigating hospital-acquired infection clusters across bacteria, viruses, and fungi, and highlight trends and issues in the continuing growth of WGS data in hospital epidemiology.

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BACTERIAL SEQUENCING IN HOSPITAL OUTBREAKS

By far the main driver of sequencing of pathogen genomes is the interest in understanding epidemiological relationships and antimicrobial resistance in bacteria. Antimicrobial resistance patterns serve as an early indicator of potential clonality of strains; however, much richer information can be obtained from sequencing [8]. Sequencing DNA extracted from bacterial isolates is simple, fast, and relatively inexpensive compared with many other sequencing approaches. The list of bacteria profiled by WGS in hospital outbreaks is too long to detail in its entirety in this review; however, it is worth noting the outsized impact of antimicrobial-resistant *Klebsiella pneumoniae*, *Acinetobacter baumannii,* and *Enterococcus faecium* in driving early adoption of genomics in hospital outbreaks [9–12]. Sequencing whole genomes in these organisms offer a scientific and epidemiological two-fer, revealing the varied mechanisms of antimicrobial resistance in these organisms while also allowing the investigation of transmission relationships among isolates. While these organisms continue to be a major focus of deep sequencing for hospital epidemiology [13–29], WGS has also become standard for *Enterobacter hormaechei, Staphylococcus aureus*, and *Clostridium difficile* hospital outbreaks and has even spread to more esoteric organisms such as *Burkholderia stabilis*, *Mycobacterium chimaera*, *Mycobacterium porcinum*, and *Helicobacter cinaedi* [30–41].

The sources confirmed by investigations using WGS cover the entire hospital or medical system—healthcare staff, a positioning

pillow, dental chair water units, and an ice machine [25, 42, 43]. When it comes to infection prevention, genomics demonstrates that every service and surface should be considered. Such studies have found that 9% of intensive care unit bloodstream isolates may be from clonal lineages [6], that endoscopes are commonly identified as potential vectors of transmission events in patients undergoing endoscopy [44, 45], and that lapses in contrast preparation and injection can be the cause of vancomycin-resistant enterococci and *Agrobacterium* spp. outbreaks in patients undergoing radiological studies or interventions [46, 47]. Donor-derived bacterial infections have been traced to solid organ transplants in the case of *Mycobacterium hominis* and a variety of antibiotic-resistant organisms [48–50]. *Mycobacterium chimaera* infections have been genomically and epidemiologically traced to water heater-cooler units use in cardiac surgery cases around the world [40, 51–55]. After description of a decade-long *Sphingomonas koreensis* outbreak associated with hospital plumbing at the NIH Clinical Center [56], there have been a growing number of stories of hospital-acquired infections from water systems and adaptations of bacteria to plumbing [57–64]. WGS has also been used to exculpate the hospital as a source of infection by identifying a lack of clonality and more likely community sources. Most notably, sequencing has been instrumental in helping to recognize the impressive burden of community-acquired *C. difficile* infection and/or colonization, along with importation into the hospital of extended-spectrum beta-lactamase *K. pneumoniae* and carbapenem-resistant Enterobacteriaceae from the community [32, 33, 65–67]. In pediatrics, WGS has significantly extended transmission tracking for *S. aureus* in the neonatal intensive care unit to determine exact sources, subtransmissions, and multiple clusters [68] well beyond the resolution afforded by typical *spa* locus or pulsed field gel electrophoresis typing [69, 70]. Transmission of specific group B streptococcus clones within the hospital via breast milk has also been clarified using bacterial genome sequencing [71].

By leaping first into WGS-informed epidemiology, bacteria are also the furthest along in regulatory considerations associated with the use of WGS data in clinical epidemiology. Whereas much of the sequencing in the first half of the past decade was entirely research-driven, clinically reportable bacterial WGS data for strain typing and epidemiological purposes has become increasingly available for outbreak investigations, starting first in the United States from the California Department of Public Health Laboratories [72]. The CDC soon followed with Clinical Laboratory Improvement Act-approved sequencing operations, helping to bring on additional state public health laboratories in the fold. Public health testing is generally used for the most common foodborne bacterial infections and turnaround times may be too slow for a hospital looking to investigate on ongoing cluster. Epidemiological sequencing for hospital-acquired infections is now making its way into the offerings of hospital and reference laboratories, including Mayo Medical Labs, ARUP, and University of Washington Medical Center [73, 74].

VIRAL SEQUENCING IN HOSPITAL OUTBREAKS

WGS for outbreaks of viruses in hospitals is still somewhat limited compared with bacterial WGS, mostly due to the difficulty of recovering viral genomes directly from clinical specimens. In contrast, the quantity of genetic material is much greater when studying bacteria, allowing for the use of shotgun sequencing. For recently emerged viruses with limited genetic diversity such as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Zika virus, amplicon tiling approaches simplify viral genome recovery [75–77]. The speed of transmission of many viral infections and limited therapeutic implications of viral sequencing also have limited its use in nosocomial outbreaks. Nonetheless, with emphasis on SARS-CoV-2 genomic surveillance and corresponding investment in viral genomic epidemiology, these hindrances can be overcome. In addition, the use of rapid multiplex panels increasingly helps infection preventionists identify potential outbreaks early in the same manner as antimicrobial resistance patterns may help recognize potentially related bacterial clones [78].

An early demonstration of the potential for real-time viral WGS to assist in a hospital outbreak investigation occurred in 2016 in the context of a human parainfluenza virus 3 (HPIV3) outbreak in pediatric patients [79]. Metagenomic NGS (mNGS) was used to recover the viral genomes, which was generally achievable for most specimens in the context of the high viral loads seen in pediatric respiratory virus infections [80]. This study also demonstrated the fast potential turnaround times of mNGS, with a total hands-on time of 6 hours, on-sequencer time of 18 hours, and time to result of 24 hours. Results confirmed the high genetic relatedness of the isolates in question and distinguished them from community-derived isolates from the same time period.

Interestingly, less than 5 months after the HPIV3 outbreak had been profiled, a very similar putative single-source hospital outbreak of rhinovirus was profiled from the same hospital with dramatically different results. Where the HPIV3 isolates were 100% identical to each other, the rhinoviruses in question were hundreds of years apart, despite some patients under investigation sharing the same room and all infections occurring on the same pod of one clinical unit [81]. These results highlight the incredible diversity of rhinoviruses as well as their exceptional widespread transmission such that multiple serotypes could appear to be a single outbreak.

With more than one hundred million cases and two million genomes sequenced to date, genomic epidemiology has no doubt informed hospital outbreaks of SARS-CoV-2. Investigators in South Korea, France, Ireland, Norway, South Africa, and the United States have reported nosocomial outbreaks of SARS-CoV-2 tracked with WGS data. In Lyon, researchers used a unique ORF6 accessory gene deletion to track transmission of a specific SARS-CoV-2 variant throughout the hospital, while also testing its impact on host gene expression [82]. In Seoul, investigators demonstrated the linkage of cases between 2 hospitals, reminiscent of the nosocomial transmission that drove

the Middle East Respiratory Syndrome Coronavirus outbreak in 2015 [83]. In Dublin, WGS demonstrated transmission from symptomatic and asymptomatic health care worker to patients who suffered a 33% mortality rate, while in San Francisco, testing throughout a nursing facility identified 3 separate introductions [84, 85]. Nanopore sequencing of SARS-CoV-2 cases in Norway illustrated the complex nature of suspected hospital outbreaks and ultimately confirmed 2 suspected outbreaks, revealed a third previously undetected outbreak, and refuted a separate suspected outbreak [86].

Two recent large studies of real-time sequencing to inform hospital infection prevention for viral outbreaks illustrate the many uses of WGS data. The first study molecularly profiled more than one hundred influenza A virus cases from hospital staff and inpatients from a New York City hospital over a 2-week period [87]. The investigation confirmed the high genetic relatedness of the main cluster, comprising 66 isolates, while also identifying 11 separate clusters that would not have been appreciated without sequencing. Combining these data with electronic health record data helped reconstruct the early transmissions that led to the widespread outbreak and also demonstrated that the viral outbreak strain had not significantly diverged from the vaccine strain administered to the healthcare workers less than 5 months earlier. A similar prospective study of norovirus transmission in a hospital-acquired outbreak partitioned 13 separate hospital-acquired cases into 3 separate clusters [88]. The outbreak illustrated the critical importance of infection prevention and the profound impact of viral infections in immunocompromised individuals, as exemplified by one individual infected during the outbreak who was persistently positive over the subsequent 258 days. Molecular profiling of these longitudinal specimens demonstrated an elevated rate of norovirus genome evolution, indicating the unique evolutionary forces associated with persistent viral infection in an immunocompromised host.

Genome or multiple-locus sequencing has also been used to investigate multiple hospital outbreaks associated with adenoviruses [89–91]. Culture helped to enrich the adenoviruses in question and limited genotyping helped to indicate the need for WGS for 11 cases of epidemic keratoconjunctivitis [89]. Viral WGS can also be applied to healthcare settings for animals, as demonstrated by a case of transmission of severe fever with thrombocytopenia syndrome virus from a sick cat to 2 veterinary personnel with identical genomes across all profiled isolates [92]. Viral donor-derived infections in organ transplant recipients have also been detailed with WGS including an account of arenavirus emergence and discovery [93].

FUNGAL SEQUENCING IN HOSPITAL OUTBREAKS

Fungal WGS is the least well-developed in infectious disease genomic epidemiology, as fungal genome sizes dwarf those of bacteria and viruses, driving up the cost of sequencing and informatics. Though fungi are notoriously under-sequenced, since many fungi are derived from soil, the evolutionary distance between hospital outbreak and unrelated isolates can be considerable, somewhat simplifying analyses [94]. Fungal WGS has been especially helpful for discovering contaminated medicines as a cause of widespread hospital-acquired infections, as in the case of *Exserohilum rostratum* fungal meningitis traced to preparation of methylprednisolone injections at a compounding pharmacy [95]. WGS analysis demonstrated nearly identical genomes among isolates from affected patients and pharmacy vials, which were separated from control isolates by >136 000 single nucleotide polymorphisms (SNPs) [96]. A similar multinational South American outbreak of *Sarocladium kiliense* was traced back to anti-nausea medication using WGS data in the absence of a reference genome, which was helped by the fact that related isolates were <5 single nucleotide variants (SNVs) apart and unrelated isolates differed at >20,000 SNVs [97]. Sequencing of a cluster of donor-derived *Coccidioides immitis* infections in 2011 resulted in genomically indistinguishable isolates [98].

Increasingly WGS has been applied to hospital outbreaks of *Candida auris*, an organism specifically targeted by the CDC for WGS work. The diversity of *C. auris* is matched by the high potential for hospital transmission in the context of strong antifungal selection pressures, and sequencing has identified multiple clonal lineages spreading within the same hospital [99–101]. Organ transplant donor-derived transmission of *C. auris* has also been documented [102, 103]. As is typical of fungal pathogens, WGS of *C. auris* shows strong regional phylogeographical hallmarks that help to pinpoint origins [104, 105]. Though the current resolution is low, as more fungal isolates are sequenced outside of the hospital, we expect to learn more about the specific geographical locations that human infections are derived from, allowing us to further discriminate those arising from inside the hospital.

FUTURE OF HAI OUTBREAK SEQUENCING

Past successes have demonstrated the clear role that WGS will continue to play in hospital epidemiology. However, integration of WGS data into hospital outbreak investigations is still the exception to the rule today. There are still a number of open areas for progress to realize its routine use (Table 1). For instance, sequencing is not routinely performed in a prospective manner, so we do not know what we are missing, nor in a timely manner, that enhances actionability (Figure 1). WGS data are not automatically integrated with the hyperlocal geospatial organization of the hospital building. Stable funding streams to bridge the gap between public health, hospital infection prevention, and the clinical laboratory are needed to allow for decentralized

Table 1. A Wishlist for Better Hospital-Acquired Outbreak Investigation With WGS Data

Wish	Actualized
Prospective sequencing	Roach et al. [6]; Casto et al. [88]
Smaller batch size, fast turnaround time	Quick et al. [106]
Routine clinical metadata integration	Berbel Caban et al. [107]
Clinical Laboratory Improvement Act-approved sequencing	Salipante et al. [73]; Kozyreva et al. [72]
Hospital building plan integration	T.B.D.
Metagenomic sequencing integration with phylogenetic analysis of all species detected	T.B.D.
Hospital lab sequencing, billed to public health	T.B.D.
Significantly increasing number of fungal genomes for geospatial and temporal resolution	T.B.D.

Abbreviations: T.B.D., to be determined.

sequencing and epidemiological investigation at scale. Here, we discuss what we hope the next 5-10 years will bring.

Improving Analytical and Total Turnaround Times

One of the main limitations of infectious diseases sequencing is that it is not sufficiently rapid given the critical need for a fast turnaround [108]. Most laboratories make use of Illumina short-read sequencers, which are highly accurate and have high capacities that work well for human genomic sequencing, the general provenance of genetics divisions. Compared with the many rapid infectious disease diagnostic platforms located in STAT labs that provide results in under an hour or two, NGS often takes at least a day on the instrument and most assays are run only once a week. Here, nanopore sequencers can offer much faster analytical turnaround times, finishing viral and bacterial genomes in hours [106, 109]. While nanopore sequencing is increasingly used in the context of outbreak sequencing abroad and in research, to date it has failed to make inroads into the clinical US sequencing market, where Illumina dominates [77, 110, 111].

Total turnaround time for sequencing is further exacerbated by the highly batched nature of Illumina sequencing. A common experience of outbreak sequencing is as follows. An outbreak is recognized and all the isolates of concern or all known positives for a given organism are rounded up and subjected to this highly batched sequencing process. The high genetic relatedness of the isolates is confirmed and the result is communicated to infection control. The lab is thanked and then promptly informed that there are 1-5 more isolates that are now of concern. Unfortunately, 1-5 isolates cannot really be sequenced in a validated or cost-effective manner with standard Illumina sequencers, especially when controls are included. A waiting game may ensue as more cases slowly accrue in a way that will align with laboratory workflow for testing that is, by nature, not reimbursed. Nanopore sequencing also has something to offer beyond its rapid pace, since the analytical capacity of the Oxford Nanopore Flongle or Minion takes

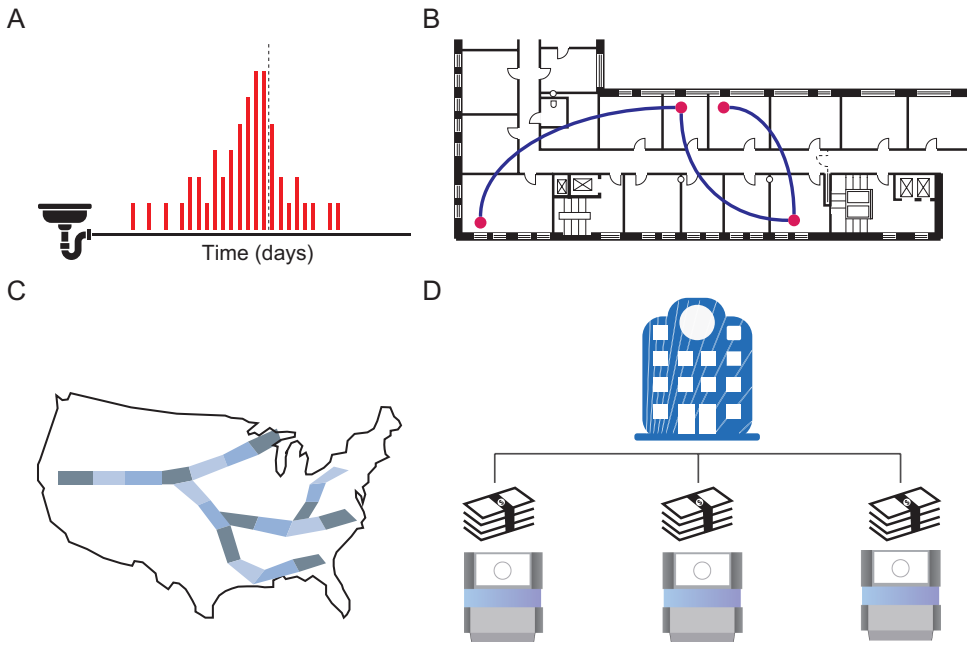

Figure 1. Next frontiers for whole genome sequencing to inform hospital-acquired infection investigations. (A) Real-time prospective sequencing of isolates with environmental sampling. The dotted line indicates infection prevention intervention. (B) Automated geospatial analysis of whole genome data that is informed by hospital building plans on a hospital-by-hospital basis. (C) Nationwide fungal whole genome sequencing to increase resolution and demonstrate environmental sources of fungal infections both inside and outside of the hospital environment. (D) Sustainable funding from public health for decentralized sequencing of pathogens in hospital clinical laboratories.

advantage of smaller batch sizes that work well with the need for rapid decision-making in the course of an ongoing hospital outbreak [112, 113]. Certainly, more work is required to determine the cost-effectiveness of pathogen sequencing in different settings, and it is likely that hospital outbreak sequencing is one of the most cost-effective use cases for microbial WGS.

The way infectious disease sequencing is organized has not helped drive sequencing growth. Isolate sequencing is not a reimbursable benefit for individual medical care and so it has been difficult to translate what can be done with what can be done sustainably. Since 2013, public health has dominated isolate sequencing, which has helped prime sequencing databases and analytical tools. However, public health financing can be fickle and public health laboratories are rarely staffed sufficiently or have the pre-analytics to provide rapid turnaround times required in clinical testing or outbreak sequencing. Furthermore, with public health entities offering sequencing for free and the potential need to connect sequencing with public health investigation, the market for reference clinical laboratory work in epidemiological sequencing has been inherently limited. The limited demand begets a vicious cycle of low volume in the lab, leading to prolonged turnaround times (listed as 30 days and 7-21 days from the reference labs detailed above), further limiting routine use.

Getting Paid for Sequencing, Getting Paid for Ordering Sequencing

All of the above trends could be helped by new payment models for sequencing. The now millions of sequenced SARS-CoV-2 isolates have demonstrated the remarkable sequencing capacity that exists and potential for more routine infectious disease sequencing. What has largely limited bringing this capacity online in the United States for all but the most concerning of threats is the lack of reimbursement associated with isolate sequencing [114]. Commercial insurance and Medicare payment models of reimbursing care for individual beneficiaries do not adequately capture the benefits accrued by epidemiological sequencing, where the benefit is distributed across a population. Instead, the costs of investigating a healthcare outbreak are borne by the hospital or related institution. It seems unlikely that isolate sequencing will become a reimbursable benefit for individual medical care anytime soon.

Instead, we must look to public health authorities to deputize and fund clinical laboratories to sequence isolates, since the capacity of public health cannot be routinely relied upon.

National SARS-CoV-2 sequencing efforts demonstrate a new way forward with CDC contracting directly with national and regional reference laboratories for isolate sequencing. These contracts couple the detection of SARS-CoV-2-positive specimens with the genome recovery, while setting standards for data upload. In effect, they recognize that the nation's clinical laboratories are part and parcel of the nation's public health system [115]. In addition to recognizing reality, this practice enhances turnaround time since there is no need to spend time finding isolates to ship to an additional laboratory for intake before sequencing. One hopes that the funding streams for this work will be maintained post-SARS-CoV-2 as the sequencing infrastructure can be used for all infectious diseases, as described above.

Democratization and Standardization of Analysis

Isolate sequencing has been further helped by increasing the standardization of informatics analysis protocols, algorithms, and platforms. Less than 5 years ago, analysis was entirely do-it-yourself and every outbreak performed analyses almost de novo, using a panoply of wet-lab protocols, sequencing platforms, read mappers, cutoffs, and visualizers, with limited quality control. Certainly, a great degree of diversity in outbreak sequencing still exists today; however, platforms such as NCBI Pathogen Detection for bacterial outbreaks and Nextstrain for viral WGS data have helped unite the field in visualization and analysis strategies [116, 117]. Here, NCBI Pathogen Detection deserves special mention as it can take raw data directly submitted to the NCBI Short Read Archive and integrate overnight into its growing phylogenetic trees, separated by SNP clusters, and detect antimicrobial resistance markers [118, 119]. While these global analyses have progressed considerably in recent years, in the world of hospital outbreak epidemiology, more work is needed on the microscale for integrating sequencing, building design, and clinical data [107].

There is much to be accomplished, however, as the scale of sequencing increases, shining a light on the scale of the problem. The need for new tools and to democratize outbreak sequencing outside of state public health is readily highlighted by the tens of thousands of different clusters for each well-sequenced bacterial species seen in NCBI Pathogen Detection. Not every hospital or even state can afford a genomic informatician to sort through and analyze the data from sequencers. Actionable insights for infection preventionists, medical laboratory scientists, nurses, and physicians should be able to be derived directly from the sequencer with minimal intervention. At least the number of isolates involved in a given hospital-acquired infection outbreak is generally small and achievable without significant infrastructure, which makes deputizing the laboratory work and epidemiological investigation all the more possible. Nonetheless, the analysis techniques and interpretations are still sufficiently niche that at least another 5-10 years of provider education and/or sincere attention to product design will be required before the results of outbreak sequencing analysis can be consumed in a routine manner.

Out of the Literature, Into the Lab

Over a decade of literature has now demonstrated the promise of pathogen WGS for outbreak epidemiology. The realization of this potential has been slowed by payment models that favor individual beneficiaries and also by waiting for providers to understand the value and potential of WGS and for clinical laboratories to be able to perform WGS. Intriguingly, the SARS-CoV-2 pandemic may have catalyzed overcoming these barriers by vastly increasing the supply of automated PCR diagnostics, leading laboratories to look

to new opportunities for growth, as well as new payment models with an emboldened public health system that is increasingly focused on molecular epidemiology with a willingness to contract directly with the private sector to increase sequence generation and execute on its results. While it is unlikely that pathogen WGS will reflect the availability of rapid PCR anytime soon, these trends portend a growing realization that sequence information is useful and important for clinical care and public health, along with an expectation that isolates *should be* sequenced. Whereas even 5 years ago, genomic epidemiology for hospital outbreaks constituted major publications, now the challenge is in getting out of the journals and into routine laboratory operations.

Notes

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