Implementation of Genomic Surveillance for Antimicrobial Resistance: Typhoid Fever and *Klebsiella pneumoniae*

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AN ILLUMINATING session on the implementation of genomic surveillance for monitoring of antimicrobial resistance (AMR) patterns globally, and its role in public health, was held at the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Global Congress in Barcelona, Spain, from 27th–30th April 2024. Chaired by Sylvain Brisse, Institut Pasteur, Paris, France; and Maurizio Sanguinetti, Catholic University of the Sacred Heart, Milan, Italy, the session explored the various digital resources, and advancements in knowledge, underpinning the application of genomic surveillance for multidrug-resistant pathogens *Salmonella typhi* and *Klebsiella pneumoniae* (Kpn) as a promising measure against the threat of AMR to public health.

THE NEED FOR GENOMIC SURVEILLANCE

Kathryn Holt, London School of Hygiene & Tropical Medicine, UK, opened the session by highlighting the growing integration of genomic surveillance in public health, commenting: "The last 5 years has seen a real maturation of pathogen genomics, and its role in public health."

AMR, the so-called 'silent pandemic', is a significant and growing threat to public health. With the increasing prevalence of multidrug-resistant bacterial pathogens, the ability to track the genetic evolution of implicated strains with reference to key virulence factors, AMR determinants, and serotype, provides a clearcut avenue for infection prevention, and for monitoring the spread and impact of multidrug-resistant pathogens on a local, national, and global scale.

Despite the promising uses of genomic surveillance in tackling AMR, its implementation in clinical settings presents a host of challenges, as underscored by Holt: "The path from genomics data to actual knowledge we can act on is a very complex one." Indeed, even if sufficient sourcing and sequencing of data can be achieved, genomic surveillance cannot be accomplished without a sophisticated digital infrastructure, and data presentation that can be readily interpreted by epidemiologists, microbiologists, and healthcare professionals alike. During the session, Holt elaborated on her team's efforts to delineate the essential criteria for such an infrastructure, and the progress they have made in rendering genomic surveillance actionable.

Generating common lineage nomenclature for various resistant strains is one of the foremost requirements for making genomic surveillance a workable reality. When terminology differs by region, it invites the possibility for confusion and misunderstanding. Holt highlighted the need for universal nomenclature that can be recognised by all experts and healthcare professionals across the world.

TYPHOID FEVER

Typhoid fever (typhoid) is a systemic bacterial infection with *Salmonella enterica serovar typhimurium*. When treatment is delayed, it can result in serious complications, and ultimately prove fatal. At present, there are 11 million cases of typhoid globally, and 116,000 deaths per annum. Typhoid is most common in low-income countries where sanitation is poor, and clean water is not readily available. The infection is endemic in South Asia, most notably in Pakistan, India, and Bangladesh. Considering the importance of prompt, effective treatment, AMR represents a significant health risk for those infected.

In the absence of diagnosis, the majority of antibiotic treatment for typhoid fever is empirical therapy. Treatment guidelines are determined according to local resistance patterns, and increasingly the only option for complicated cases is admission of intravenous antibiotics, giving rise to more hospital admissions, increased economic burden, and morbidity.

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The *S. typhi* genome was first sequenced at the Wellcome Sanger Institute, Cambridgeshire, UK, in 2001.[1] Since then, our understanding of the population structure, resistance patterns, and strain diversity of *S. typhi* has significantly advanced, leading to the establishment of the Global Typhoid Genomics Consortium. This consortium aims to facilitate the sharing of typhoid genome data to enhance public health, enable the extraction and reporting of essential data, and promote the dissemination of genomic information for monitoring AMR and disease spread. These efforts intend to inform treatment guidelines and immunisation strategies, and ultimately reduce transmission.

Advancements in digital resources, in particular, have enabled the development of TyphiNET,[2] a multi-institutional global genomic surveillance network, supporting the visualisation of the *S. typhi* genotype and AMR data. Most notably, TyphiNET allows for the rapid integration of genomes into the global phylogeny without requiring extensive phylogenetic or comparative analysis.

A key goal of Holt and team is to generate common nomenclature, specifically that relating to *S. Typhi* strains. To achieve this, the team have produced an AMR dictionary that

highlights genetic determinants to look for, and how to interpret them with relevance to AMR. Sequenced genomes are uploaded following a defined metadata standard that specifies the purpose of sampling and the country of travel. These metadata help distinguish between routine sequencing and sequencing conducted in response to an outbreak or other specific events. Likewise, the inclusion of the country of travel provides global location data and information about the prevalence of specific strains and lineages per area, and local resistance patterns.

KLEBSIELLA PNEUMONIAE

Kpn was first described by Carl Friedlander in 1882,[3] after being isolated from the lungs of patients who had died of pneumonia, thus giving it its name. Kpn is an opportunistic pathogen, naturally found among the microbiota of the mouth, skin, and gastrointestinal tract, but proving highly virulent when it infects other parts of the body. Its extensive virulence is, concerningly, accompanied by extensive AMR, making it a desirable target for genomic surveillance.

Kpn is a leading cause of multidrug-resistant hospital-acquired infections and neonatal sepsis. It contributes significantly to disease burden and mortality, particularly in low- and middle-income countries. Its impact on neonatal sepsis has spurred considerable interest in maternal immunisation to protect neonates, the group most vulnerable to this disease. This interest led to the publication of the vaccine value profile for Kpn in March of this year, highlighting the potential to prevent approximately 400,000 cases of neonatal sepsis, and 80,000 deaths.[4] To support these efforts, Holt and his team have developed various modelling techniques to account for outbreak clusters in the data, and to generate regional and global estimates of antigen distributions. They have also created theoretical coverage estimates for different vaccine compositions to aid in the development of effective vaccines.

With the goal of monitoring the emergence and spread of AMR, and the appearance of hypervirulent lineages, alongside an investigation into nosocomial outbreaks and serotype distribution, Holt and colleagues contributed to the development of the *Klebsiella pneumoniae* Genomic Surveillance Platform (KlebNET-GSP),[5] which incorporates four key tools for genomic typing and analysis: Kleborate,[6] Kaptive,[7] Pathogenwatch,[8] and BIGSdb-Pasteur.[9] Kleborate and Kaptive were

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specifically developed by Holt and colleagues. The former provides accurate identification of species, lineage, resistance determinants, and virulence genotypes. The latter, conversely, enables bacterial surface polysaccharide locus typing and variant evaluation. BIGSdb-Pasteur[9] is a collection of databases of bacterial isolates, genomes, and genotypes based on multilocus sequence typing and whole genome-based typing. Pathogenwatch[8] specifically compares pathogen genome assemblies from different global regions, utilising data from BIGSdb-Pasteur[9] and Kaptive.[7]

Holt and team will host the first international symposium focused on Kpn from the 20th–22nd November 2024, at the Institut Pasteur in Paris, France. This symposium will feature workshops on the previously mentioned tools, as well as online drop-in sessions. Additionally, the conference will include lectures by leading experts from around the globe, covering various aspects of Kpn, including epidemiology, ecology, genomics, therapeutics, and surveillance.

CONCLUSION

Multidrug resistance represents a formidable public health challenge, evoking concerns about a regression to the pre-antibiotic era, where once easily treatable diseases give rise to excessive disease burden and high rates of mortality. Particularly vulnerable to these effects are populations in low- and middle-income countries, lacking sufficient access to healthcare, and facing heightened exposure to communicable disease risk factors. As the threat of AMR looms large, highly virulent superbugs like *S. typhi* and Kpn, still endemic in less developed regions, are sources of great concern. The digital infrastructure to which Holt and colleagues have contributed, and their evident potential in monitoring the spread of AMR and tailoring treatment guidelines according to the geographical prevalence of specific strains, presents a clear and promising pathway for mitigating the proliferation and impact of antimicrobial-resistant pathogens.

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