Following recent improvements in sequencing technologies, whole genome sequencing (WGS) is set to become a crucial tool in the control of antimicrobial resistance. WGS has already shown considerable promise for the surveillance of infection, the development of new diagnostic tests and the identification of resistance.

Infectious diseases are often transmitted globally. So rapid detection and identification of outbreaks, and the exchange of information between different authorities and research facilities, are essential to identify trends and control spread. WGS could have a major part to play in this process.

**Impact on patient care**
Professor Sharon Peacock at the University of Cambridge specialises in the role of sequencing technologies in diagnostic microbiology and public health. In 2013 she provided the first evidence that bacterial WGS could be used in clinical practice to impact on patient care. The infection control team at the study hospital had identified several infants in a special care baby unit (SCBU) infected with superbug methicillin-resistant Staphylococcus aureus (MRSA) over a six-month period. Although a link was suspected, a persistent outbreak could not be confirmed with conventional methods. The use of WGS confirmed the outbreak, and also identified a larger population of 26 related cases. Analysis showed that transmission had occurred within the SCBU, between mothers on a post-natal ward, and in the community. WGS data were used to propose and confirm that infection by a staff member had enabled the infection to persist during periods without known infection on the SCBU and after a deep clean. This individual was successfully treated, after which the outbreak ceased. This demonstrated that healthcare and community-associated infection should no longer be regarded as separate entities.

Professor Peacock says, "This study demonstrates that sequencing of microbial pathogens can influence the quality of infection control and patient care."

**Better antimicrobial stewardship**
MRC-funded researchers at the University of Oxford have also used WGS to assess the transmission of fellow superbug Clostridium difficile (C. difficile). Dr David Eyre and Professor Sarah Walker demonstrated that far fewer cases of C. difficile infection were transmitted from symptomatic patients than expected, with other cases mostly likely coming from asymptomatic individuals or an environmental source such as water or animals, and food. They analysed whole genome sequences of samples obtained from all patients with C. difficile infection in Oxfordshire over 3.6 years and found that 45 per cent were sufficiently genetically diverse to suggest transmission from sources other than symptomatic patients. However, the whole genome sequences were also used to show that the incidence of cases transmitted from other symptomatic patients and cases from other sources both declined similarly over the study. These results demonstrate the importance of interventions to reduce susceptibility to disease in
Antimicrobial resistance

exposed patients, such as better antimicrobial stewardship, rather than just reducing transmission from symptomatic patients. They also illustrate the value in combining information from whole genome sequencing with traditional epidemiology. The use of rapid benchtop sequencing5 again allowed the identification of genetically related cases in almost real time so that cases clearly linked by a hospital or community contact can be targeted to prevent further spread.

100,000 genomes project

Other MRC-funded researchers in Oxford have also demonstrated the value of using whole genome sequencing to investigate clusters of cases of Mycobacterium tuberculosis6,7. Professors Derrick Crook and Tim Peto found that whole genome sequencing could identify previously unrecognised links between cases, more than doubling the number of tuberculosis transmissions previously identified through standard methods. It was also able to refute the possibility of transmission between other cases, saving hours of work trying to work out how transmission could have happened. The technique could also identify super-spreaders and predict the existence of undiagnosed cases, potentially leading to early treatment of infectious patients and their contacts. This work has led to whole genome sequencing being adopted by Public Health England, initially in a pilot study within the “100,000 genomes” project, working towards widespread implementation in English tuberculosis reference laboratories from 2016.

Professor Peacock has also successfully used WGS to investigate a case of multi drug-resistant (XDR) Mycobacterium tuberculosis8. This proved more accurate than standard methods, with WGS detecting mixed infection by two distinct strains of M.tuberculosis, which was not identified by standard genotyping. This has important implications for distinguishing relapse from reinfection and for identifying secondary cases of infection. The study also highlighted the potential of WGS to predict the antimicrobial resistance of M.tuberculosis, which could reduce the time taken to implement effective antimicrobial therapy for XDR M.tuberculosis. This would benefit individual patient care and could help to contain the spread of infection.

References

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