

Background

- Healthcare associated infection (HAI) outbreaks are a significant patient safety risk, as well as being costly and time consuming to investigate.
- Determining whether transmission has occurred is a major challenge for infection prevention and control teams (IPCTs) as typing results do not always have sufficient granularity or robustness to unequivocally define strains and epidemiological data is not always available to establish links between patients and the environment. Whole genome sequencing (WGS) has emerged as a typing tool but it has not yet been routinely applied in NHS HAI outbreaks.
- We report the first five years findings of a WGS service established to confirm or refute outbreaks in NHS Tayside and NHS Grampian.**

Purpose

- To assess the clinical benefits of translating genomics into clinical practice for the investigation of community and HAI outbreaks.

Materials and Methods

- Since 2013 bacterial isolates have been sent to the Infection Group, School of Medicine, University of St Andrews for WGS (Illumina Inc, San Diego, CA, USA).
- Clinical specimens were first collected as part of routine care and initially processed for bacterial identification and antibiotic susceptibility testing at the Departments of Medical Microbiology in NHS Tayside and NHS Grampian (ISO 15189:2012 accredited).

Results

- Over 400 community and hospital isolates were sequenced including *optrA* gene positive enterococci, Meticillin-resistant *Staphylococcus aureus* (MRSA), Carbapenemase producing *Enterobacteriaceae* (CPE), Vancomycin-resistant *Enterococcus faecium* (VREfm) and extended-spectrum beta-lactamase (ESBL) positive Gram-negative bacteria.
- Community outbreaks included:** MRSA, *E. coli* hospital outbreaks, Group A *Streptococcus* and *E. coli* in care homes, *optrA* gene positive linezolid resistant *E. faecalis* in the community and secondary care.
- Secondary care outbreaks included:** *Listeria monocytogenes*, *Pseudomonas aeruginosa* and *Klebsiella spp.* in Neonatal Intensive Care Units (NICU) and Adult ICU, maternity ward Group A *Streptococcus*, Orthopaedic VREfm, respiratory clinic *P. aeruginosa* and Renal ward CPE.
- WGS results for a NICU *P. aeruginosa* outbreak and ESBL *E. coli* community hospital outbreak were available before routine reference laboratory results.
- Some of the key clinical benefits identified when using WGS are outlined in table 1.

Table 1. Examples showing Clinical Value of WGS

Clinical Value of WGS	Examples
 <p>WGS provided results with greater granularity than routine typing methods</p>	<ul style="list-style-type: none"> In the case of <i>Listeria spp.</i> WGS confirmed two patient's isolates were indistinguishable prompting repeated hospital kitchen inspections which identified the handling of salads and meat did not meet national recommendations. Catering facilities were temporary closed until remedial action was undertaken.
 <p>Genomic analysis enhanced the detection of 'alert organisms'</p>	<ul style="list-style-type: none"> WGS identified a patient to be colonised with two different strains of VREfm highlighting that IPCTs should consider asking for a variety of patient samples (including repeats and sequential). It also identified that vancomycin-sensitive <i>Enterococcus faecium</i> (VSEfm) isolates from two separate patients were related to a VREfm cluster, uncovering a hidden transmission event. It may therefore be more appropriate for IPCTs to consider enterococci clone transmission in healthcare facilities and communities.
 <p>WGS can replace the need for multiple tests</p>	<ul style="list-style-type: none"> WGS can be used to improving turn-around times of results and subsequently improving outbreak investigations. Variable number tandem repeat (VNTR) typing and pulsed-field gel electrophoresis (PFGE) were both required for confirming transmission in a <i>P. aeruginosa</i> ICU outbreak. WGS can streamline testing during CPE outbreak investigations.
 <p>Genomic analysis can be used to rule out outbreaks</p>	<ul style="list-style-type: none"> Outbreak group meetings can be halted and targeted measures discontinued freeing hospital services from closure and disruption. Of value in outbreaks with high consequences e.g. maternity ward Group A <i>Streptococcus</i> and outbreaks in ICU/NICU. Also beneficial when conventional typing is unable to unequivocally show whether isolates are linked or not.
 <p>WGS can be utilised to investigate new resistance mechanisms</p>	<ul style="list-style-type: none"> WGS can determine movement of different resistance elements. WGS identified the new plasmid-mediated <i>optrA</i> gene highlighting the risk that linezolid resistance could transfer therefore patients required isolation to prevent onwards transmission. WGS findings can be used to inform the development of polymerase chain reaction (PCR) based screening which is particularly useful when phenotypic methods or antibiotic susceptibility testing is not accurate.

Conclusion

- When married to epidemiological data WGS can provide the ultimate discrimination enabling IPCTs to carry out outbreak investigations efficiently and effectively.
- It can assist in the formulation of case definitions and support or refute hypotheses in relation to lines of transmission.
- WGS is particularly useful in outbreaks involving rare organisms or when conventional typing is unable to unequivocally show whether isolates are linked or not.
- WGS can be utilised to test the effectiveness of IPC measures as well as to rule out outbreaks, minimising disruption to healthcare services.
- Real-time sequencing could be used to streamline clinical microbiology services by reducing unnecessary testing.
- With the global threat of antimicrobial resistance (AMR) dissemination WGS is a valuable tool with the potential to generate greater understanding of the development of new resistance mechanisms and dissemination of resistance elements.
- Implementing WGS as a standard of care in real-time would be a major advance in day-to-day IPC practice.**