Can whole genome sequencing identify vancomycin resistant enterococci transmission events in haematology inpatients?

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Introduction

Healthcare associated infections caused by multi-drug resistant enterococci cause significant morbidity and mortality. Over the past 5 years, an increased rate of colonization and infections by vancomycin-resistant enterococci (VRE) has been observed at Sheffield Teaching Hospitals Foundation Trust (STHFT) particularly in haematology patients, despite the implementation of stringent infection control practices. Current typing methods for monitoring and investigation of potential outbreak strains include multi-locus sequence typing (MLST) and pulsed-field gel electrophoresis (PFGE), both of which are time consuming and laboratory intensive, limiting clinical utility during potential outbreak situations. With the rapidly reducing cost of whole genome sequencing (WGS) and therefore improved accessibility for laboratories, WGS could play an increasingly important role in infection control, producing a faster and more detailed return of results.

Outline

•PFGE and WGS were compared in 14 retrospective isolates (SLC1-14) in order to assess the discriminatory ability of novel methods against existing methodology (PFGE).

•26 prospective isolates (SLC15-40) collected from a cohort of haematology inpatients at STHFT between June and November 2017 were then analysed by WGS in order to assess the benefits of WGS for identifying cross-transmission events.

•Further analysis was carried out through pairing of WGS and patient movement data.

Methodology

- Collection of retrospective and prospective study isolates for WGS by MicrobesNG.
- Quality assessment of WGS reads was carried out using basic bioinformatics.
- Identification of vanA and vanB containing isolates.
- Creation of core genomes using Prokka version 1.13 (Seemann, 2014) and Roary version 3.10.2 (Page et al., 2015)
- Phylogenetic analysis based on core genomes. Data was loaded in to RxAML version 1.0.2 (Stamatakis, 2014) and best scoring maximum likelihood trees visualised in MEGA X (Kumar et al., 2018).
- Collection and analysis of patient movement data.

Results

A total of 40 isolates from 40 patients collected over a four-year period were included in analysis. 9 isolates were obtained from routine clinical specimens (including blood cultures, wound swabs, biopsies and urine) and the remaining isolates were cultured from VRE screens through collection of faecal and urine samples.

Comparison of current and novel methodology

Overall, the results for part 1 of this project show that WGS is comparable to existing PFGE methodology. Isolates SLC1-14 are shown to fall within the same clusters for both WGS and PFGE typing. No additional groupings were identified through the use of WGS methodology.

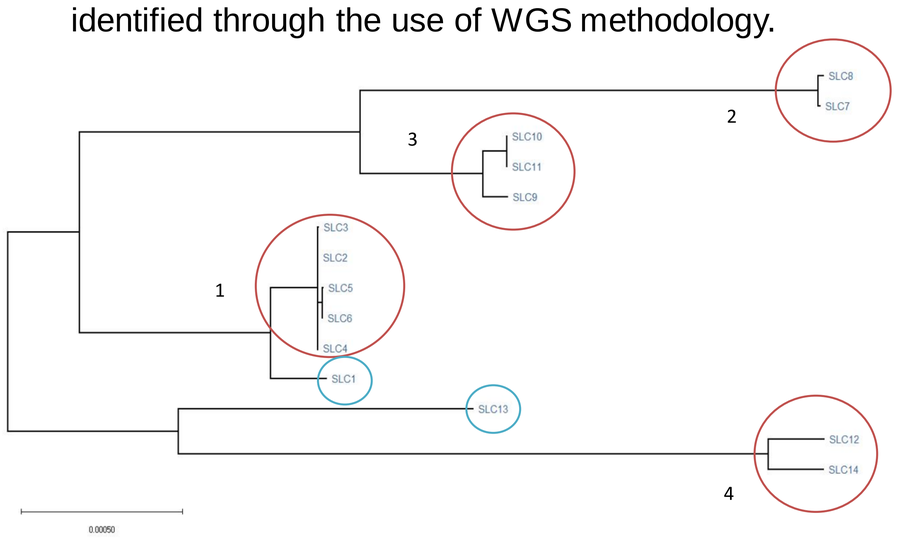

Figure 1: Newick tree based on the comparison of core genomes in isolates SLC1-14. Best scoring maximum likelihood tree was created using RxAML version 1.0.2 (Stamatakis, 2014) and visualised in MEGA X (Kumar et al., 2018). Clusters of isolates are numbered 1-4 and highlighted in red circles. Unique isolates are shown in blue.

WGS for identification of cross-transmission events

Comparison of core genomes for SLC15-40 suggests the presence of 5 distinct clusters and 8 potentially unique isolates. This suggests the potential involvement of up to 18 patients in transmission events within this study period. Encouragingly, even in the absence of epidemiological data, clustering of isolates shown through analysis of WGS in this study, suggests the possible transmission of isolates between patients.

Patient movement data

Interrogation of patient movement data for patients from which isolates SLC15-40 were isolated suggest 2 potential transmission events between 2 patients on 2 wards. The first suspected transmission is shown between P15 and P19 on ward O1R at STHFT (shown in Figure 2).

Screening identified the acquisition of a VRE in P19, 13 days after admission on to the same ward as P15. Coupled with analysis of WGS data suggesting that both isolates SLC15 and SLC19 belong to the same cluster, this suggests potential transfer of this strain between patients. A second event involving this same strain, shows potential transmission between P23 and P26 on ward P2 (shown in Figure 2). In this instance, both patients were positive shortly after admission on to this ward.

Discussion

WGS, particularly when paired with patient movement data is shown to be a highly powerful tool for the assessment of transmission events and in the surveillance of high risk wards. Furthermore, the wealth of information created from WGS enables in-depth analysis of data for further confirmation of results in order to clinically inform with confidence. Information such as SNP numbers is highly valuable in confirming strain relatedness alongside phylogenetic trees. These results suggest that, with further validation, WGS could be clinically utilised in STHFT.

Conclusion

This is the first time genetic and epidemiological data has been paired for the assessment of transmission networks at STHFT. Overall, results show that WGS is a powerful and reliable method for identifying strain relatedness of VRE isolates. When paired with patient movement, WGS is shown to be a highly effective tool for identifying cross-transmission events. Interrogation of both WGS data and patient movement data in isolates SLC15-40 identified the presence of multiple clusters of isolates in haematology in-patients and identified 2 possible transmission events of a single strain on 2 separate wards.

Patient movement

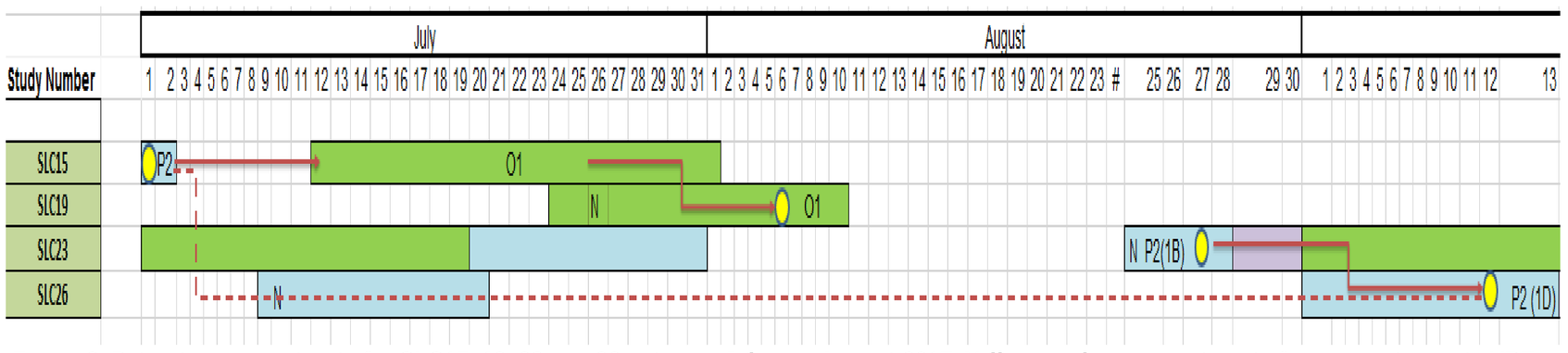

Figure 2. Patient movement data for SLC15, 19, 23 and 26 between July and August 2017. Yellow circle represents date found positive with VRE. Ward and length of stay represented by coloured blocks (green, blue and purple). Solid red line show potential routes of transmission and the dashed line shows an alternative route of transmission between patients.

Key reference
Raven, K., Gouliouris, T., Brodrick, et al. (2017). Complex Routes of Nosocomial Vancomycin-Resistant Enterococcus faecium Transmission Revealed by Genome Sequencing. *Clinical Infectious Diseases*, 64(7), pp.886-893.