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Sotrovimab shown to cause COVID-19 treatment-resistance mutations

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Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which causes Coronavirus disease 2019 (COVID-19) has spread rapidly worldwide causing over 480 million infections and >6 million deaths[1], prompting the development of vaccines and antiviral agents at an unprecedented pace[2]. Several SARS-CoV-2-neutralizing monoclonal antibodies (mAbs) have been developed and received emergency use authorisation by regulatory agencies with additional mAbs currently advancing through phase 3 clinical trials. These therapeutics have been registered for treatment of mild to moderate COVID-19 disease in those at risk of progressing to severe disease. These agents target the SARS-CoV-2 spike (S) glycoprotein and predominately act by blocking entry of the virus into the host cell.

Inside this issue

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The emergence of SARS-CoV-2 variants of concern (VOC) carrying mutations and deletions in the spike protein have vastly reduced the activity of these mAb. Several mAbs cocktails (e.g., bamlanivimab/etesevimab) appear to be have reduced activity against viruses with the spike protein mutations E484K and K417N/T found in the Beta and Gamma SARS-CoV-2 variants of concern (VOCs).[3,4] The emergence of Omicron VOC in November 2021, which contains over 30 mutations in the spike gene has resulted in a vast reduction in the activity of the mAb treatments available in Australia, including; Evusheld (Tixagevimab and Cilgavimab), Regen-Cov (Casirivimab and Imdevimab) and the cocktail Bamlanivirmab and Etesevimab.[5,6] However, Sotrovimab (VIR-7831, GlaxoSmithKline, Australia Pty Ltd), targets conserved viral epitopes in the spike protein and has retained activity against the Omicron sub-lineage BA.1[6], but recent reports suggest it has a reduced activity to BA.2[7].

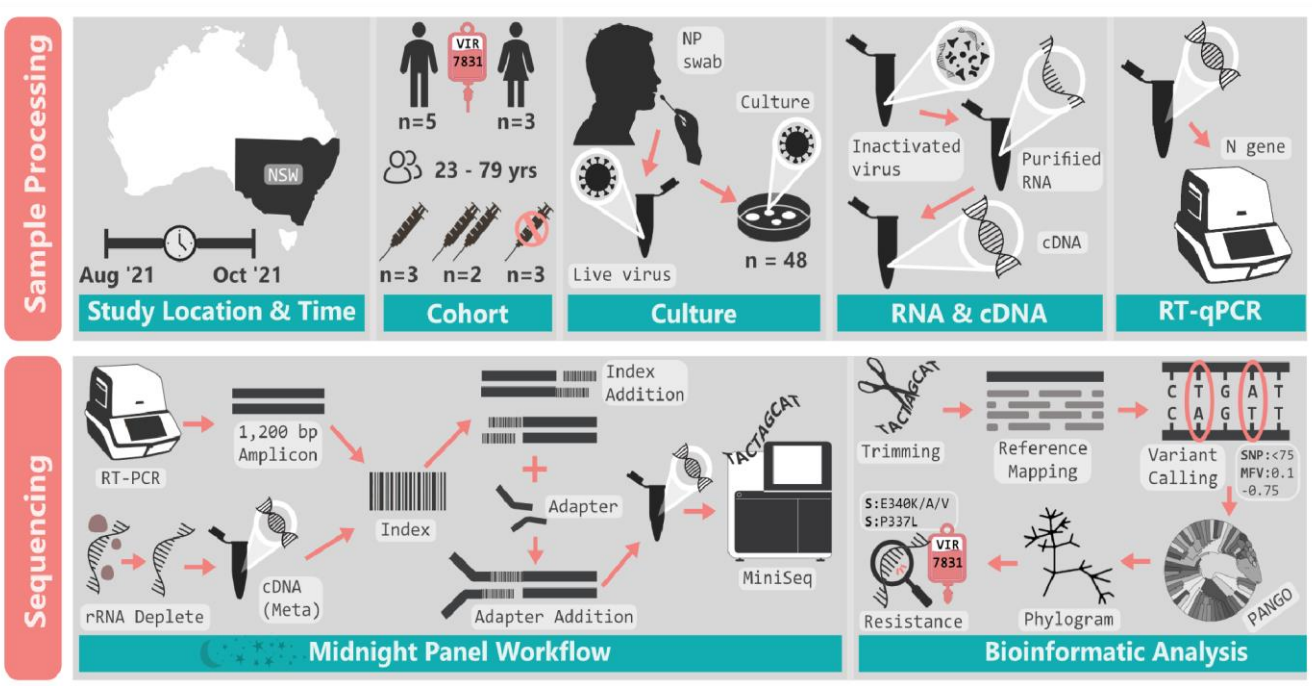
Sotrovimab is a human engineered monoclonal antibody that neutralizes SARS-CoV-2 and other sarbecoviruses, including SARS-CoV-1.[8] Sotrovimab acts by binding to a conserved epitope within the RBD, resulting in virus neutralization. The conservation of the epitope targeted by sotrovimab is supported by preservation of its activity *in vitro* against SARS-CoV2 VOC Alpha, Beta, Delta and Omicron VOC (Lineage BA.1).[9] Sotrovimab's safety and efficacy was evaluated in the phase 3, multicenter, randomised, double-blind, placebo-controlled COMET-ICE (COVID-19 Monoclonal Antibody Efficacy Trial–Intent to Care Early) trial. Trial recruitment targeted high-risk adults with symptomatic COVID-19 and interim results demonstrated a reduction in the risk of hospitalization (for >24 hours) or death from 7% in the placebo group to 1% in the sotrovimab group (85% relative risk reduction). Whilst evidence of sotrovimab effectiveness to prevent severe COVID-19 led to its approval for emergency use in the US, Singapore, Europe and Canada, Australia was one of the first countries to issue formal regulatory approval. However, the use of SARS-CoV-2-specific monoclonal antibodies targeting a single viral epitope warrants caution as *in vitro* [10,11] and clinical case studies have demonstrated rapid development of mutations conferring resistance after exposure to various SARS-CoV-2 mAbs.[3,12,13] Indeed, the acquisition of mutations in the sotrovimab target epitope at S protein amino acid positions 335-361 was reported during COMET-ICE [14]. Phenotypic characterization of these mutations demonstrated that high-level sotrovimab resistance (100 to 297-fold reduction in neutralization) was conferred by E340K/A/V, while a 10 to 304-fold reduction was also noted with the appearance of mutation P337L/T.[9] The acquisition of consensus mutations at S:E340K was also documented for 4 of 45 participants within the COMET-ICE trial. Observations of induced *in vitro* and clinical resistance has prompted the development of mAbs cocktails that simultaneously target multiple SARS-CoV-2 epitopes.[15] Here we report the rapid development of mutations *in vivo* that have been shown to confer high level resistance to sotrovimab *in vitro* and present a template for genomics guided use of mAbs.

We reviewed the first 100 patients to receive sotrovimab between August and November 2021 at a single center in Australia and identified eight persistently SARS-CoV-2 RT-PCR positive patients for whom respiratory tract specimens pre- and post-sotrovimab were available (R001-R008). Characterisation of the SARS-CoV-2 viral load, viability and genomic sequence of each specimen was performed (Figure 1). All cases had immune compromising conditions and were in hospital at the time of SARS-CoV-2 diagnosis. Two cases had 2 doses of Pfizer/BioNTech (R001 and R008), three cases had a single dose of Pfizer/BioNTech (R002, R003 and R007) and three cases were unvaccinated (R004, R005 and R006).

Genomic analysis uncovered that four (R001, R002, R003 and R004) of the eight patients acquired previously defined RBD mutations within 6-13 days after sotrovimab treatment (Figure 2). All four cases developed mutations at S:E340* in concordance with reports from the COMET-ICE trial and remained culture-positive for 23, 24, 12 and 15 days after sotrovimab treatment, respectively. Read frequencies of S:E340K/A/V mutations increased over the course of infection, in three cases the proportion of the viral population carrying these mutations exceeded 75% at days 7, 13 and 36 respectively (Figure 2). In addition, R002 developed a minority variant at P337L after fixation of the S:E340K mutation. A retrospective review of 11841 SARS-CoV-2 genomes reported by our centre in New South Wales (1st June – 11th November 2021) identified four additional cases with S:E340 mutations. For two of them, SARS-CoV-2 genomes were generated 5 and 11 days after sotrovimab treatment, respectively. The prevalence of mutations conferring resistance to sotrovimab internationally was low, with 130 (S:E340K), 101 (S:E340A), 24 (S:E340V) and 65 (S:P337L) genomes uncovered over the study period (6th January 2020 - 28th November 2021).

This is one of the first records of clinical and genomic outcomes following treatment of SARS-CoV-2 infection with sotrovimab and highlights the importance of genomic data to ensure the stewardship of mAbs administration. Prolonged infection with SARS-CoV-2, particularly in immunocompromised individuals, may allow rapid viral adaptations and intra-host variants to emerge. These individuals may receive a combination of new COVID-19 therapies to aid viral clearance and prevent severe disease [12,16].

Figure 1. Outline of molecular, phenotypic and next generation sequencing methodology



Key: NP swab – Nasopharyngeal swab; RT-PCR – reverse transcriptase real time polymerase chain reaction; N-gene – qRT-PCR amplifying the SARS-CoV-2 Nucelocapsid gene; rRNA deplete –rRNA Depletion (Human/Mouse/Rat), SNP – Single Nucleotide Polymorphism; MFV – Minority allele Frequency Variant; PANGO - Phylogenetic Assignment of Named Global Outbreak LINeages

Our findings demonstrated the acquisition of mutations in the RBD of the SARS-CoV-2 S protein 6-13 days after treatment with sotrovimab. The genomic position of these mutations has previously been suggested to decrease the ability of sotrovimab to neutralize SARS-CoV-2 by 10–297-fold. The most commonly detected mutation E340K (3 of 4 cases) was reported to confer the highest levels of resistance.

Previous *in vitro* studies have demonstrated that RBD mutations can lead to reductions in the effectiveness of mAbs and natural or vaccine-elicited neutralizing antibodies.[4,5,14,17] This study adds important clinical data to support the experimental evidence. The mutations described were within highly conserved epitopes of SARS-CoV-2 with <250 international genomes reporting S:E340K/A/V changes in the spike protein, and this mutation has not occurred in VOC Alpha, Beta, Gamma and Delta.

Our findings of persistence viral culture positivity in patients developing sotrovimab mutations also has implications for infection control and their release from isolation. Viral culture is used to determine the transmission risk of immunocompromised SARS-CoV-2 positive patients as part of Australian COVID-19 clinical management guidelines.[18] We document that SARS-CoV-2 was isolated from specimens collected from patients harboring resistant mutations up to 24 days post-sotrovimab treatment. This indicates that individuals may remain infectious after acquiring mutations and therefore can transmit resistant virus. This may result in reduced efficacy of sotrovimab and potentially of other immunotherapies, including vaccination, in sotrovimab-naïve individuals.

Australia has a relatively low incidence of COVID-19 infections and SARS-CoV-2 genomes are sequenced in a high percentage of diagnosed cases. We leveraged on this advantage and screened extensive SARS-CoV-2 genomic data to assess if transmission of these mutations has gone unrecognized. We identified only four genomes available on GISAID (of 11,841) containing the S:E340K mutation and a further six cases harboring the mutations in sub-consensus viral populations. Of these 10 cases, six had received sotrovimab, with no clinical information available for three cases. This indicates that the development of resistant mutations can be unrecognized, but extensive circulation of sotrovimab resistant virus is not evident at this early stage of sotrovimab use. However, most genomic surveillance strategies currently sample a single SARS-Cov-2 genome per diagnosed case, which may not provide sufficient resolution to detect mutations that develop following COVID-19 treatments and to explain the mechanism of breakthrough infections.

In conclusion, SARS-CoV-2 genome analysis and culture in patients treated with sotrovimab can assist in monitoring the progress of COVID-19 infection and managing infection control and duration of isolation periods. Post-marketing genomic surveillance of patients that receive monoclonal antibody therapy for SARS-CoV-2 is prudent to minimize the risk of treatment failure, and transmission of potentially more resistant SARS-CoV-2 variants in both healthcare settings and the community.

Figure 2. SARS-CoV-2 viral load dynamics and acquisition of resistant mutations following sotrovimab treatment.

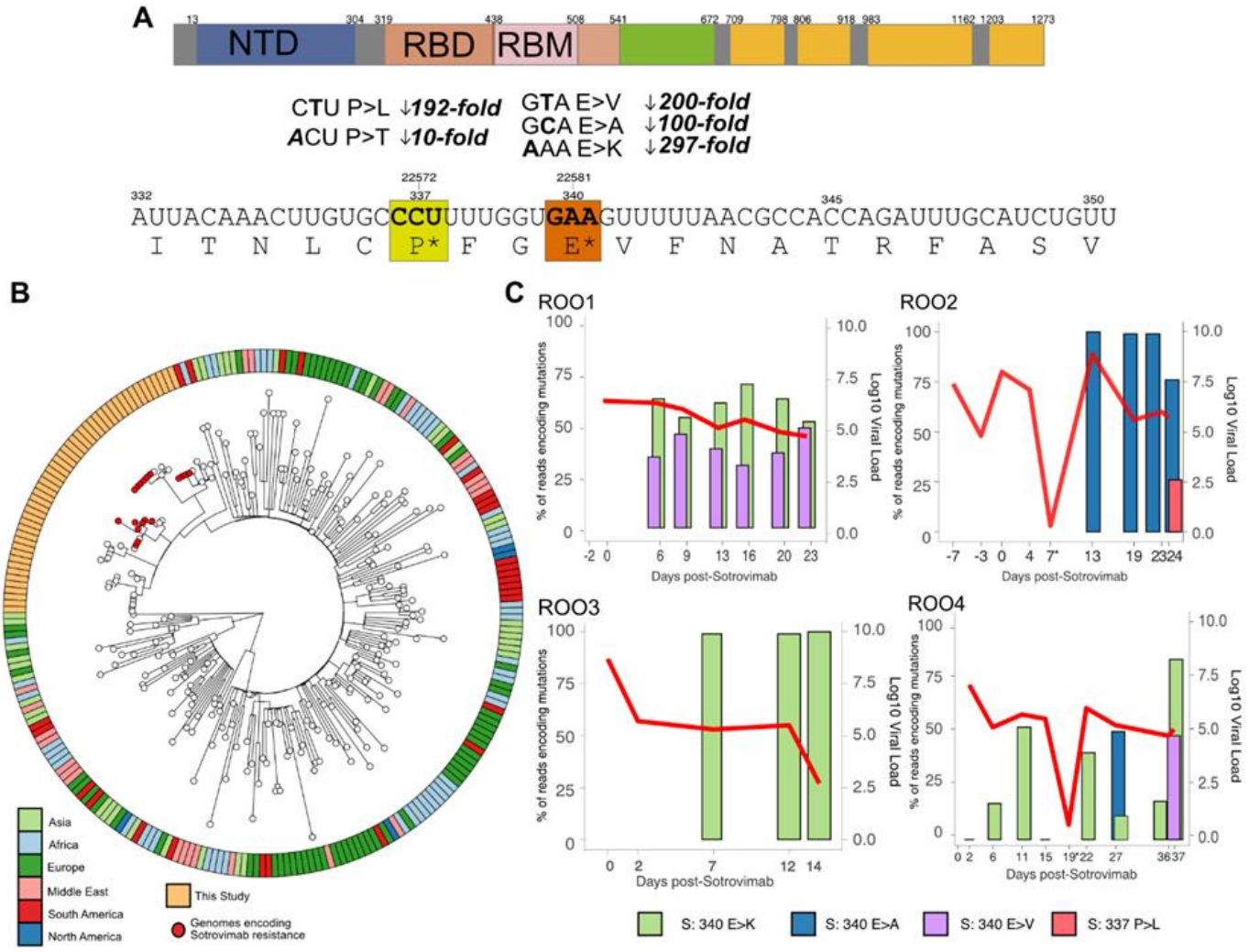
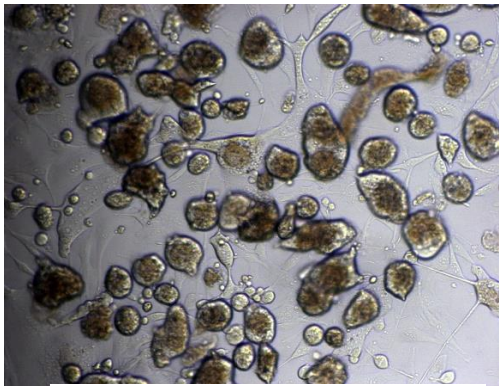
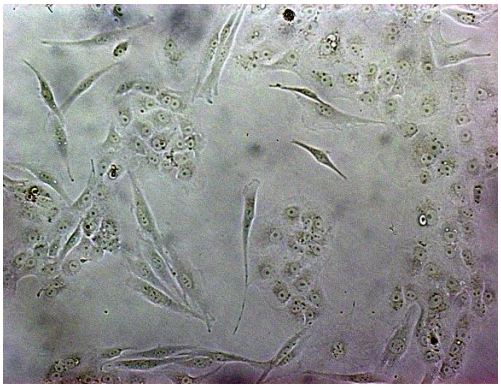


Figure 2. Acquisition of mutations conferring high level resistance to sotrovimab and dynamics of SARS-CoV-2 viral load. A) Depicts the co-ordinates of mutations that are acquired after sotrovimab treatment in the RBD of the spike protein. In this study we uncovered mutations (S:E340K/A/V and S:P337L/T) which have been reported to reduce the susceptibility to sotrovimab by 297, 100, 200, 192 to 10-fold, respectively. B) Subsampled global phylogeny of SARS-CoV-2 VOC Delta, the geographical region of each sequence is indicated in the outer metabar. SARS-CoV-2 genomes sequenced in this study are highlighted in orange in the outer metabar, red nodes indicate genomes that developed resistance-conferring mutations. C) The dynamics of four cases of SARS-CoV-2 infection treated with sotrovimab are outlined on separate graphs; the x-axis indicates the discrete collection of specimens pre- and post-sotrovimab infusion. The bar graph depicts the acquisition and read frequency (left y-axis) of mutations conferring high levels of resistance to sotrovimab (green S:340E>K, blue S:E340A, purple S:E340V and pink S:P337L) for each case. The overlayed red line graph shows the SARS-CoV-2 viral load at each sampling point (right-hand y-axis scale). The asterisks indicate two sampling timepoints in which a high-quality SARS-CoV-2 genome could not be recovered (R002, Day 7 and R004, Day 19). All cases that developed mutations conferring sotrovimab resistance (R001-R004) were hospitalized during sampling periods.



SARS-CoV-2 Delta Positive Culture



VeroE6 Cells SARS-CoV-2 Negative

Sotrovimab injection

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The added value of genomics for Shiga-toxin producing *Escherichia coli* Surveillance in New South Wales, Australia

Short Report

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Shiga-toxin producing *Escherichia coli* (STEC) are a group of pathogenic *E. coli* that collectively share the ability to produce Shiga toxin (Stx). Of the multiple serotypes associated with STEC, seven serotypes (namely O157, O26, O45, O103, O111, O121, and O145) are most commonly associated with human infection [1-3]. Infections by STEC can cause acute gastroenteritis and in some cases, progress to haemolytic uremic syndrome (HUS) [4]. STEC can produce two structurally similar but immunologically distinct toxins, namely, Stx1 and Stx2 which can be further subtyped into Stx1a, Stx1c, Stx1d, and Stx2a–2g [5]. Of all the subtypes, infections with STEC that produce either Stx2a, Stx2c or Stx2d are more likely to progress to HUS [6, 7]. This ability to produce Stx is conferred upon STEC by a bacteriophage (Stx (pro)phage) integrated into its chromosome [8]. Each Stx prophage carries one copy of the genes (*stxA* and *stxB*) needed to encode Stx and the presence of multiple *stx* subtypes in STEC, either the same or different subtypes, are indications of multiple integrated Stx prophages [8-10]. In addition, carriage of multiple isogenic *stx* (multiple copies of identical *stx* genes), especially clinically relevant subtypes, has been implicated with disease severity [10]. Apart from Stx, some STEC also harbour the Locus of Enterocyte Effacement (LEE) which encodes a Type III Secretion System and associated effectors responsible for intimate adhesion to intestinal epithelial cells and microvilli effacement [11].

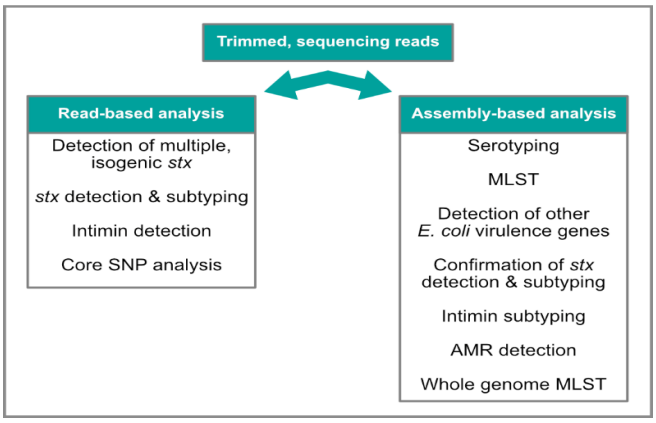

Figure 1. Analysis performed as part of the two-pronged approach for STEC genetic epidemiology. Detailed methodology and bioinformatic software is described within the publication.

In Australia, STEC is a notifiable infectious disease with two possible laboratory definitive evidence required for case definition. Laboratories can either confirm STEC by culture or by PCR, targeting the genes that encode Stx1 and Stx2 directly from clinical samples. While PCR is useful for the reduction of turnaround time to inform medical intervention, information useful for surveillance like serotype, stx subtype and presence of multiple isogenic stx, are not captured. This lack of information can be compounded by the fact that culturing of STEC from faeces is a non-trivial endeavour.

Prior to 2020, only serotype and/or Stx type are reported to public health databases. As whole genome sequencing (WGS) has been used to great effect for genetic epidemiology internationally, we endeavoured to set up a genomics workflow (Figure 1), designed around published bioinformatics software, to capture pertinent STEC information useful for public health surveillance. Key markers captured by this workflow include serotype, Multi locus sequence type (MLST) and Stx subtypes. To test this workflow, short-reads from 62 STEC derived from all isolates recovered from human cases of gastroenteritis and HUS in New South Wales between December 2017 and May 2020 were used.

Within our dataset, 19 different serotypes were detected with O157:H7 being the most common (n=22) serotype detected, consistent with previous reported epidemiology of STEC in Australia [12, 3]. To allow for a snapshot of pertinent STEC virulence factors, a 16-mer STEC virulence barcode was developed to be used in conjunction with *in-silico* serotyping. This barcode not only captured intimin (gene carried by the LEE) and Stx (up to 4 subtypes) subtypes but also allowed for the inference of multiple, isogenic *stx* genes from short read data. We envisioned that the STEC virulence barcode would be useful for surveillance and risk assessment of virulence although we cautioned that it is unlikely to be predictor of disease outcome.

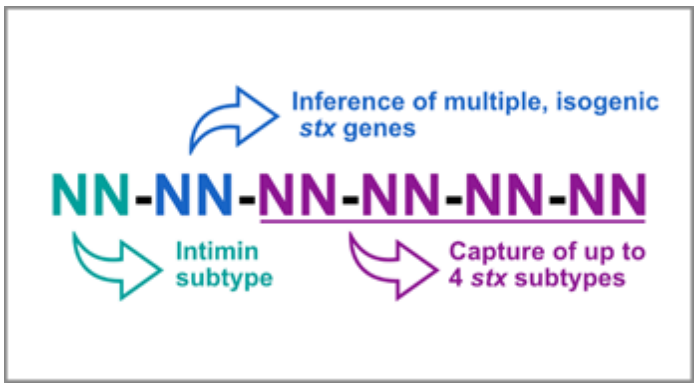

Figure 2. Format of the 16-mer STEC virulence barcode.

STEC are genetically diverse with the only uniting feature being the presence of the genes encoding Stx. This meant that genomic clustering solely by core single nucleotide polymorphism (SNPs) according to a single reference to represent all STEC is not the most appropriate way. To that end, a two-tiered clustering methodology was used to infer genetic relatedness between isolates. The first tier involved running the STEC assemblies through a general *E. coli* whole genome Multi Locus Sequence Typing (wgMLST) scheme to cluster the sequences and visualised as a minimum spanning tree. Our results showed that all genomes belonging to same serotype had clustered together (See Figure 3A in publication). In addition, the STEC virulence barcode can also be appended to the minimum spanning tree for quick interrogation of both genomic diversity and STEC virulence (See Figure 3B in publication). The second tier involved a core SNP analysis against an appropriate reference sequence, selected based on serotype and MLST sequence type, both of which are derived from the genomic workflow.

Apart from genomic clustering our paper also went on to investigate other virulence markers in STEC and we also postulated on a possible interplay between virulence and host factors that could repress the production of Stx1a, the most common Stx subtype detected in Australia (albeit with a O157:H7 bias) [12-15]. Indeed, we showed that with access to both isolates and WGS capabilities, a wealth of additional data useful for genomic epidemiology is made available. This genomic workflow is now utilised within the Microbial Reference Genomic Laboratory at CIDMLS for on-going surveillance of STEC in the state of New South Wales.

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Staff Profile

Dr Tanya Golubchik

Dr Tanya Golubchik is a computational microbiologist interested in applying modern genomics technologies to study how pathogens interact, evolve and affect their human hosts, and how we can use this knowledge to improve healthcare. After receiving her PhD in molecular biology from the University of Sydney, she moved to the University of Oxford to work on what was one of the earliest studies to combine epidemiological and genomic data: examining the role of recombination in the spread of pneumococcal vaccine escape variants. Using a custom genotyping chip, the project demonstrated that pneumococcal recombination involves the simultaneous uptake of multiple DNA fragments, creating unique 'mosaic' breakpoints that could be used to identify the new variants and track their spread. This project fuelled her interest in large-scale microbial genomics, and in 2010 she joined the newly formed UK Modernising Medical Microbiology consortium (MMM), a collaborative effort between researchers and clinicians to integrate pathogen genomics into clinical practice and public health policy. While with MMM, she developed research tools to make optimal use of the rapidly growing stream of pathogen genome data that was becoming available, enabling analyses at a scale of thousands of genomes. Her work on quantification of within-patient genetic diversity in *S. aureus* in asymptomatic carriage and during healthcare-associated outbreaks informed subsequent transmission studies, as well as exposing the involvement of mobile genetic elements in bacterial carriage and transmission. With clinical colleagues, she developed and validated methods for genotype-based prediction of antimicrobial resistance, and collaborated on the largest UK surveys of healthcare-associated *S. aureus* infection.

New sequencing technology developed in recent years has made it possible to deep-sequence pathogens directly from clinical samples, capturing genetic diversity of bacteria and particularly viruses at unprecedented resolution. In 2016, Tanya moved to the new Big Data Institute at the University of Oxford, where her research focussed on understanding within-host diversity in infection, including HIV, RSV and, most recently, SARS-CoV-2. She led the SARS-CoV-2 genome sequence analysis efforts at the Big Data Institute, quantifying minority viral populations to track variant emergence, and working together with the Oxford Vaccine Group on SARS-CoV-2 genetic diversity in vaccine trials. Tanya joined Sydney ID in March 2022 as Senior Lecturer in Computational Microbiology.

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UPCOMING EVENTS

Sydney ID Distinguished Lecture Series

Bats as reservoirs of viral disease and keystone species

Prof Linfa Wang

Professor of the Programme in Emerging Infectious Diseases at Duke-NUS Medical School, Executive Director PREPARE, Ministry of Health Singapore

18 May 2022

4:00pm – 5:00pm (AEST)

Registration:

Click here to register for this special event

Event Enquiries:

infectious.diseases@sydney.edu.au

CIDM-PH/Sydney ID Webinar

Japanese Encephalitis: One Health in Action

SAVE THE DATE…

PROGRAM & REGISTRATION COMING SOON

3 June 2022

1:00pm – 5:00pm (AEST)

Event Enquiries:

WSLHD-CIDM-PH@health.nsw.gov.au

CIDM centre for infectious diseases & microbiology Public Health

THE UNIVERSITY OF SYDNEY