Co-infections with different variants of SARS-CoV-2 are a key precursor to recombination events that are likely to drive SARS-CoV-2 evolution. Rapid identification of such co-infections is required to determine their frequency in the community, particularly in populations at-risk of severe COVID-19, which have already been identified as incubators for punctuated evolutionary events. However, limited data and tools are currently available to detect and characterise the SARS-CoV-2 co-infections associated with recognised variants of concern. Here we describe co-infection with the SARS-CoV-2 variants of concern Omicron and Delta in two epidemiologically unrelated adult patients with chronic kidney disease requiring maintenance haemodialysis. Both variants were co-circulating in the community at the time of detection. Genomic surveillance based on amplicon- and probe-based sequencing using short- and long-read technologies identified and quantified subpopulations of Delta and Omicron viruses in respiratory samples. These findings highlight the importance of integrated genomic surveillance in vulnerable populations and provide diagnostic pathways to recognise SARS-CoV-2 co-infection using genomic data.
Since the declaration of the COVID-19 pandemic by the World Health Organization on March 11th 2020, SARS-CoV-2 has gradually evolved into phylogenetically distinct lineages, some of which have been designated variants of concern (VOCs)\(^1,2\). These variants differ in terms of transmissibility, capacity to cause severe disease and the ability to evade post-vaccination derived immunity. The prevalence of individual VOCs in different global regions has been affected by the timing and location of their emergence and the corresponding measures for COVID-19 control\(^3\). Development and implementation of viral genomic surveillance and rapid sharing of genomic data has provided a critical capacity to distinguish and monitor SARS-CoV-2 variants and conduct risk assessments of their significance.

Co-infection with different SARS-CoV-2 lineages was rarely provided a critical capacity to distinguish and monitor SARS-CoV-2 variants and conduct risk assessments of their significance. Co-infection with different SARS-CoV-2 lineages was rarely reported during the first COVID-19 wave in 2020 prior to the introduction of vaccination programmes\(^4-6\), but it has been suggested that such co-infections could lead to greater severity and disease duration\(^7\). However, co-infections involving either VOC Delta or VOC Omicron have not yet been reported, nor have they been documented in immunosuppressed hosts, which may drive saltational evolution characterised by high numbers of new mutations\(^8\). As reports of SARS-CoV-2 recombinants emerge, understanding the frequency and drivers of recombination events that occur during SARS-CoV-2 co-infection becomes essential\(^8\). In this study we report cases of co-infection with Delta and Omicron in two immunocompromised individuals at risk of severe COVID-19 disease identified during local co-circulation of both SARS-CoV-2 lineages.

**Results**

**Clinical and epidemiological context.** Case A was a patient who returned a positive SARS-CoV-2-specific polymerase chain reaction (PCR) result from a nasopharyngeal swab after presenting to the Emergency Department of a Sydney hospital with mild respiratory symptoms. Case B was a patient diagnosed by SARS-CoV-2 PCR after presenting to the same hospital with fever. Further analysis of health records revealed that both patients had chronic kidney disease due to type 2 diabetes, obesity and ischaemic heart disease. In addition, both were receiving haemodialysis treatment for 4–5 h thrice weekly at the same community dialysis centre and were therefore potentially exposed to multiple and infectious COVID-19 cases during treatment sessions. Given the high community incidence of COVID-19, infection control measures implemented at the dialysis centre to prevent nosocomial transmission included physical distancing and masking of patients at all times, decontamination of treatment stations and dialysis equipment after each session, four-point personal protective equipment use by all clinical staff and regular testing of patients by SARS-CoV-2 PCR at the time of each treatment. Despite the similarities in patient demographics, they were unknown to each other, had not received haemodialysis at the same time nor used the same equipment or treatment station.

**SARS-CoV-2 viral load and testing for other respiratory viruses.** Two respiratory swabs collected from Case A on days 2 and 3, as well as two respiratory swabs from Case B collected on days 3 and 11, were subjected to nucleic acid extraction, quantitative SARS-CoV-2 PCR. Viral yield in samples was variable but still significant and suggesting the presence of viable virus (Table 1). PCR did not detect human influenza viruses A or B, respiratory syncytial virus, parainfluenza viruses 1, 2, and 3, human metapneumovirus or rhinovirus in samples from either case.

| Table 1 SARS-CoV-2 yield in Cases A and B. |
|--------------------------------------------|
| **Samples** | SARS-CoV-2 PCR Ct value | SARS-CoV-2 viral load | PANGO Lineage |
| Day 0 | 28.18 | 5713 | 3.8 Omicron BA.1; Delta AY.39.1 |
| Day 2 | 17.33 | 98,130,334 | 8.0 Omicron BA.1; Delta AY.39.1 |
| Day 3 | 23.44 | 404,527 | 5.6 Omicron BA.1; Delta AY.39.1 |
| Day 3 culture | 15.37 | 571,255,772 | 8.8 Delta AY.39.1 |
| Day 0 | 31.68 | 246 | 2.4 Omicron BA.1 |
| Day 3 | 19.26 | 17,317,514 | 7.2 Omicron BA.1; Delta AY.39.1 |
| Day 11 | 24.05 | 233,804 | 5.4 Omicron B.1.1.529; Delta AY.39.1 |

*Specimens only sequenced using Illumina methodology due to low viral load.

**COVID-19 serology and vaccination history.** Neither patient had prior evidence of COVID-19 infection. A previously described immunofluorescence assay (IFA)\(^9\) performed on sera collected from Case A on day 3 and Case B 5 months prior to the diagnosis did not detect SARS-CoV-2 antibodies (i.e. IgG, IgA and IgM IFA titres all <10, trimeric spike IgG negative, nucleoprotein IgG negative). Case B had received two doses of the COMIRNATY® (Pfizer) vaccine with the second dose 10 weeks prior to diagnosis. Case A remained unvaccinated by choice.

**SARS-CoV-2 viral culture.** Viral culture of the Case A, day 3 sample yielded Delta 4 days post-infection, the consensus genome recovered from this culture matched the genome reconstructed from the mixed sample. It is likely that Delta had overgrown Omicron as TMPRSS2 enhanced VeroE6 cells are less permissible to Omicron, but highly adapted to Delta infection\(^10\). Viral culture was retrospectively and unsuccessfully attempted for the specimen collected from Case A, day 2.

**SARS-CoV-2 genomic analysis.** Samples from both cases (Case A—day 2 after onset, Case B—day 3) underwent whole genome sequencing as part of the prospective genomic surveillance programme in New South Wales, Australia\(^11\). A sample from an epidemiologically linked household contact of Case A, Case C, who was diagnosed several days after Case A was also sequenced. In our public health surveillance system only genomes confidently assigned to SARS-CoV-2 lineages (see Fig. 1 for quality framework) are reported to the health authorities and shared globally via GISAID (https://www.gisaid.org). In contrast to the majority of community samples sequenced, a small proportion had unexpectedly high numbers of “heterozygous” (i.e., mixed nucleotides at a single site) calls (Supplementary Fig. 1) and could not be unambiguously assigned to a SARS-CoV-2 lineage by the PangoLin software. This observation triggered a case review in January 2022 to identify cases for which these results could be confirmed by testing of additional samples. Two cases (i.e. Cases A and B) with additional respiratory samples available for genome sequencing were selected.

Due to the low viral load in the day 0 samples from both cases, they were only able to be sequenced using Midwest primers and Illumina sequencing, while two longitudinal samples from each case with increased viral loads were subjected to further analyses.
In conclusion, these findings demonstrated the capacity of clinically and epidemiologically informed genomic surveillance to diagnose co-infections with significant SARS-CoV-2 variants and highlight the need for deeper analysis of genomic surveillance data in clinical and public health contexts. Identifying dual infections may guide the use of monoclonal antibodies that have reduced activity to the VOC Omicron. SARS-CoV-2 co-infections, particularly when they occur in vulnerable hosts, may underpin saltational evolution, thus emphasising the important role COVID-19 genomic surveillance will play in diagnostic virology, in the era of mass vaccination.
A commercially available synthetic RNA control (Wuhan-Hu-1) was employed to estimate the viral load of clinical specimens from the RNeasy RNA per specimen (cpy/µL). A standard curve and quantify the viral load per microlitre of extracted reference sequence, TWIST Biosciences NCBI GenBank accession MN908947.3) was used in ten-fold dilutions starting at 20,000 copies/µL to 2 copies/µL to generate a standard curve and quantify the viral load per microlitre of extracted RNA per specimen (cpy/µL). Additional RT-PCRs were used to investigate the presence of common viral respiratory viruses: human influenza viruses A and B, parainfluenza viruses 1, 2, and 3, respiratory syncytial virus, adenovirus, and rhinovirus.

**SARS-CoV-2 culture**. Respiratory specimens were cultured in VeroE6 cells expressing transmembrane serine protease 2 (VeroE6/TMPRSS2; JCRB1819) as previously outlined. Briefly, cell cultures were seeded at 1–3 × 10⁴ cells/cm² in Dulbecco’s minimal essential medium (Lonza, Basel, Switzerland) supplemented with 9% foetal bovine serum (FBS, HyClone). Media was replaced within 12 h with inoculation media containing 1% FBS with the addition of penicillin (10,000 U/mL), streptomycin (10,000 µg/L) and amphotericin B deoxycholate (25 µg/mL) (Lonza) to prevent microbial overgrowth and then inoculated with 100 µL of SARS-CoV-2 RT-PCR positive respiratory sample. The inoculated cultures were incubated at 37 °C in 5% CO₂ for 4 days and observed daily for cytopathic effect (CPE). Routine mycoplasma testing using RT-PCR was performed to exclude cell line mycoplasma contamination and culture work was undertaken under physical containment laboratory level 3 (PC3) biosafety conditions. The presence of CPE and increasing viral load as measured by the before mentioned SARS-CoV-2 RT-PCR was indicative of positive SARS-CoV-2 culture. RNA extracts were also subjected to the SARS-CoV-2 genome work as described below.

**Frequency of SARS-CoV-2 variant heterozygosity**. The frequency of “heterozygosity” (i.e., mixed nucleotides at a single site) during SARS-CoV-2 variant calling is monitored as part of our in-house bioinformatic quality control system, as is the inability to determine a SARS-CoV-2 Pango lineage designation on an otherwise complete and high coverage genome (Supplementary Fig. 1). These two markers signal that a specimen requires repeat extraction, SARS-CoV-2 amplification, library preparation and sequencing.

**SARS-CoV-2 whole genome amplification**. Tiling PCR was used to amplify the entire SARS-CoV-2 genome from RNA extracts of clinical specimens using primers outlined in the Midnight sequencing protocol. Each PCR included 12.5 µL Q5 High Fidelity 2x Master Mix (New England Biolabs), 1.1 µL of either pool 1 or pool 2 10×amp master mix, 2.5 µL of template RNA and molecular grade water was added to generate a total volume of 25 µL. Cycling conditions were: initial denaturation at 95 °C for 2 min, then 35 cycles of: 95 °C for 30 s, 55 °C for 30 s, 72 °C for 1 min 45 s, and a final extension step of 75 °C for 10 min. Pool 1 and pool 2 amplicons were combined and purified with a 1:1 ratio of AMPureXP beads (Beckman Coulter) and eluted in 30 µL of RNase free water. Purified products were quantified using Qubit™ 1x dsDNA HS Assay Kit (Thermo Fisher Scientific) and diluted to the desired input concentration for library preparation.

**Amplicon short-read library preparation**. Purified amplicon pools were used to generate sequencing libraries using Nextera XT (Illumina) according to the manufacturer’s instructions and pooled with the aim of producing 1 × 10⁸ reads per library. Sequencing libraries were then sequenced with paired-end 76-bp chemistry on the iSeq, Miniseq or Nextseq (Illumina) instruments.

**Amplicon ONT library preparation**. In parallel, the purified amplicon pools were also utilised to generate libraries using SQK-RBBK04 (ONT) according to the manufacturer’s instructions, loaded onto a R9.4.1 flow cell. Sequencing was performed on the GridION platform running MinKNOW version 2.1.0.25 with live base-calling on high accuracy mode with demultiplexing enabled (Guppy version 5.0.16). Sequencing run status was monitored on board MinKNOW and run was terminated after more than 20 MB of passed base-called data was obtained per sample.

**Respiratory viral enrichment using hybridisation capture probes**. The cDNA generated prior to whole genome amplification was used as input into the RNA Prep with Enrichment kit (Illumina). Second-strand cDNA synthesis, cDNA tagmentation, library construction, clean-up, and normalisation were performed according to manufacturer’s instructions. Individual libraries were then combined in 3-plex reactions for probe hybridisation. The RVOP v2 (Illumina) was used for probe hybridisation with the final hybridisation step held at 58 °C overnight. Hybridised probes were then captured and washed according to manufacturer’s instructions and amplified as follows: initial denaturation 98 °C for 30 s, 14 cycles of: 98 °C for 10 s, 60 °C for 30 s, 72 °C for 30 s, and a final 72 °C for 5 min. Library quantities and fragment size were determined using a Qubit 1x dsDNA HS assay and Agilent HS Tapestation and sequenced using 2 × 76-bp runs on the iSeq (Illumina).
Bioinformatic analysis of Illumina data. Raw sequence data files were processed using an in-house quality control procedure prior to further analysis (Fig. 1) as described previously11,12. De-multiplexed reads were quality trimmed using Trimmomatic v0.36 (sliding window of 4, minimum read quality score of 20, leading/trailing quality of 5 and minimum length of 36 after trimming)19. Briefly, reads were mapped to the reference SARS-CoV-2 genome (NCBI GenBank accession MN908947.3) using Burrows-Wheeler Aligner-mem version 0.7.1720, with unmapped reads discarded. Average genome coverage was estimated by determining the number of missing bases (Ns) in each sequenced genome. For amplicon generated reads variant calling and the generation of consensus sequences was conducted using iVar21, with soft clipping over primer regions (version 1.2.1, min. read depth >10x, quality >20, min frequency threshold of 0.1). Single nucleotide polymorphisms (SNP) were defined based on an alternative frequency >0.75 whereas minority allele frequency variants (MFV) were defined by an alternative frequency between 0.1 and 0.75. Variants falling in the 5’ and 3’ UTR regions were excluded. Polymorphic sites that have previously been highlighted as problematic were monitored22. To ensure the accuracy of variant calls only genomes with >90% genome coverage and a mean depth of >100x were included. The MFV calls were excluded in the base pair either side of the 5’ or 3’-end of indels due to potential mis-mapping. SARS-CoV-2 lineages were inferred using Phylogenetic

Fig. 3 Population and phylogenetic analysis of two cases of SARS-CoV-2 co-infection with Delta and Omicron VOCs. A Population analysis of key lineage-defining mutations in the SARS-CoV-2 spike gene for each specimen. Nucleotide frequency and relative coverage of genomic regions specific for either Omicron or Delta. The X-axis represents genomic positions and Y-axis indicates their relative frequencies derived from RVOP data. B Unrooted maximum likelihood phylogeny representing the sequences obtained from Cases A, B and C in the context of global diversity of SARS-CoV-2. Genomes generated as part of this study are labelled individually. The predominant Delta lineage in Australia, AY.39.1, is highlighted. The Delta strains from cases A and B are from separate clades of AY.39.1 circulating in Australia, whereas the two Omicron strains are both in the same sub-lineage of Omicron (BA.1) which dominated in Australia in December 2021–January 2022. Note that the Omicron samples from patients A and C are identical and hence overlap. Branch lengths are scaled according to the number of nucleotide substitutions per site.
Assignment of Named Global Lineages v1.2.86 (PANGO and PEARN)\textsuperscript{12,15}.

Bioinformatic analysis of ONT data. Quality control and consensus sequences were generated post run using the wf-artic workflow version 0.3.9 (https://github.com/epi2me-labs/wf-artic). To determine and quantify positional heterozygosity, mapping files generated by the wf-artic workflow were visualised on the Integrative Genomics Viewer\textsuperscript{23} version 2.8.6 and parsed using bam-readcount version 1.0.1 (https://github.com/ genome/bam-readcount).

Investigation of amplification bias in co-infection cases. Consensus and MFV were collated over constellations of mutations that define the SARS-CoV-2 lineages B.1.617.2 (Delta) and B.1.1.529, sub-lineage BA.1 (Omicron) for each genome investigated (https://github.com/cov-lineages/constellations/blob/main/constellations). This included ten unique genomic locations that define Delta (B.1.617.2) (ST19R, SI45R, SP681R, ORF3a:S26L, M382T, ORF7a:T120L, ND365G, NR203M, ND377Y) and Omicron (SD412G, ST478K, SD9592N). In addition to 17 polymorphisms that define the dominant Omicron sub-lineage BA.1 (orf1ab:K856R, de65133, nuc:TS386G, orf1ab:A271T, orf1ab:G1758V, nuc:C15240T, SA667V, de21765:6, de21987:9, de21987:9, orf2:2205 + GAGGCGACAA, SS371L, SG466S, SG460S, ST547K, SN856K, SL981F, M3D1G) mutations that co-exist in B.1.617.2 where not included (S:G142D, S:T478K, S:D950N). In addition to 17 polymorphisms that define Delta- and Omicron strains documented as circulating in Sydney at the time of the study. For Case B, the consensus genomes for the day 0 (Omicron only, Illimina Midnight) and day 3 (Delta dominant, Illimina RVOP to avoid Midnight amplification bias) samples were used. The Delta sequence for Case A, for which all three samples were of mixed lineage, was obtained from the day 3 sample viral culture. To obtain the Omicron sequence for Case A, the RVOP Illimina data from the day 3 sample that the culture was derived from was hand-reviewed to generate a consensus containing only the Omicron-specific SNPs, minus the Delta-specific SNPs seen in the culture sequence. The resulting reconstructed Case B Omicron genome was then compared to the Omicron sequence from Case C, who was assumed to have caught their infection from Case B; these two sequences matched. These four sequences, as well as the downloaded sequences from GISAID, were genome was then compared to the Omicron sequence from Case C, who was deposited in the National Center for Biotechnology Information (NCBI) GenBank (BioProject PRJNA633948). File accession details for each specimen are available in Supplementary Table 1. A complete list of SARS-CoV-2 genomes sourced from GISAID (www.gisaid.org) is available in Supplementary Data 1. Source data are provided with this paper.

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Author contributions
Study concept and design by V.S., R.J.R., J.D., M.G., E.M.S., A.A., and D.E.D. Sample processing and testing by R.J.R., C.L., C.N., M.R., J.E.A., J.J.-M., W.F., A.N.G., and Q.W. Sequencing and analysis by R.J.R., E.M.S., C.L., M.G., J.D., E.M., A.P.D., V.S., and E.C.H. SARS-CoV-2 viral culture by M.F., D.K., and R.J.R. SARS-CoV-2 serology by L.H. and M.N.O. Study coordination by V.S., L.K., S.C.-A.C., D.E.D., and J.K. V.S., R.J.R., and A.A. wrote the first manuscript draft with editing from E.C.H., E.M.S., L.K., S.C.-A.C., and D.E.D. The final manuscript was approved by all authors.

Competing interests
The authors declare no competing interests.

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