Molecular and clinical epidemiology of carbapenem resistant *Acinetobacter baumannii* ST2 in Oceania: a multicountry cohort study

Sakiusa C. Baleivanualala,[a,b,c] Lupeoletalalelei Isaia,[a,c,d] Swastika V. Devi,[b] Benjamin Howden,[e,f] Claire L. Gorrie,[e,f] Silivia Matanitobua,[g] Sajnel Sharma,[h] Donald Wilson,[b] Silpa Kumar,[h] Komal Maharaj,[h] Scott Beatson,[i] Lusiana V. Boseiwaqa,[h] Kristin Dyet,[j] John A. Crump,[k] Philip C. Hill,[c,k] and James E. Ussher[a,c,l,*]

[a]Department of Microbiology and Immunology, School of Biomedical Sciences, University of Otago, Dunedin 9054, New Zealand
[b]College of Medicine, Nursing and Health Science, Fiji National University, Suva, Fiji
[c]Maurice Wilkins Centre for Molecular Biodiscovery, University of Auckland, Auckland 92019, New Zealand
[d]Tupua Tamasese Mea'ole Hospital, Apia, Samoa
[e]Microbiological Diagnostic Unit, Peter Doherty Institute for Infection & Immunity, University of Melbourne, Melbourne, Victoria 3000, Australia
[f]Department of Microbiology & Immunology, Peter Doherty Institute for Infection & Immunity, University of Melbourne, Melbourne, Victoria 3000, Australia
[g]Fiji Centre for Disease Control, Tamavua, Suva, Fiji
[h]Colonial War Memorial Hospital, Suva, Fiji
[i]Australian Infectious Diseases Research Centre, University of Queensland, Brisbane, Queensland 4072, Australia
[j]Institute of Environmental Science and Research Ltd., Porirua 5022, New Zealand
[k]Otago Global Health Institute, University of Otago, Dunedin 9054, New Zealand
[l]Southern Community Laboratories, Dunedin Hospital, Dunedin 9016, New Zealand

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Summary

Background Carbapenem resistant *Acinetobacter baumannii* (CR*Ab*) is categorised by the World Health Organization (WHO) as a pathogen of critical concern. However, little is known about CR*Ab* transmission within the Oceania region. This study addresses this knowledge gap by using molecular epidemiology to characterise the phylogenetic relationships of CR*Ab* isolated in hospitals in Fiji, Samoa, and other countries within the Oceania region including Australia and New Zealand, and India from South Asia.

Methods In this multicountry cohort study, we analysed clinical isolates of CR*Ab* collected from the Colonial War Memorial Hospital (CWMH) in Fiji from January through December 2019 (n = 64) and Tupua Tamasese Mea'ole Hospital (TTMH) in Samoa from November 2017 through June 2021 (n = 32). All isolates were characterised using mass spectrometry, antimicrobial susceptibility testing, and whole-genome sequencing. For CWMH, data were collected on clinical and demographic characteristics of patients with CR*Ab*, duration of hospital stay, mortality and assessing the appropriateness of meropenem use from the treated patients who had CR*Ab* infections. To provide a broader geographical context, CR*Ab* strains from Fiji and Samoa were compared with CR*Ab* sequences from Australia collected in 2016–2018 (n = 22), New Zealand in 2018–2021 (n = 13), and India in 2019 (n = 58), a country which has close medical links with Fiji. Phylogenetic relationships of all these CR*Ab* isolates were determined using differences in core genome SNPs.

Findings Of CR*Ab* isolates, 49 (77%) of 64 from Fiji and all 32 (100%) from Samoa belonged to CR*Ab* sequence type 2 (ST2). All ST2 isolates from both countries harboured bla_{OXA-23}, bla_{OXA-66} and *ampC*-$_2$ genes, mediating resistance to β-lactam antimicrobials, including cephalosporins and carbapenems. The bla_{OXA-23} gene was associated with two copies of IS*Aba1* insertion element, forming the composite transposon Tn*2006*, on the chromosome. Two distinct clusters (group 1 and group 2) of CR*Ab* ST2 were detected in Fiji. The first group shared common ancestral linkage to all CR*Ab* ST2 collected from Fiji's historic outbreak in 2016/2017, Samoa, Australia and 54% of total New Zealand isolates; they formed a single cluster with a median (range) SNP difference of 13 (0–102). The second group shared common ancestral linkage to 3% of the total CR*Ab* ST2 isolated from India. Fifty eight of the 64 patients with CR*Ab* infections at the CWMH had their first positive CR*Ab* sample collected 72 h or more following admission. Meropenem use was deemed inappropriate in 15 (48%) of the 31 patients that received treatment with meropenem in Fiji. Other strains of CR*Ab* ST1, ST25, ST107, and ST1112 were also detected in Fiji.

*Corresponding author. Department of Microbiology and Immunology, University of Otago, New Zealand.
E-mail address: james.ussher@otago.ac.nz (J.E. Ussher).

Interpretation We identified unrecognised outbreaks of CR*Ab* ST2 in Fiji and Samoa that linked to strains in other parts of Oceania and South Asia. The existence of Tn*2006*, containing the bla_{OXA-23} and IS*Aba1* insertion element, within CR*Ab* ST2 from Fiji and Samoa indicates the potential for high mobility and dissemination. This raises concerns about unmitigated prolonged outbreaks of CR*Ab* ST2 in the two major hospitals in Fiji and Samoa. Given the magnitude of this problem, there is a need to re-evaluate the current strategies used for infection prevention and control, antimicrobial stewardship, and public health measures locally and internationally. Moreover, a collaborative approach to AMR surveillance within the Oceania region with technical, management and budgetary support systems is required to prevent introduction and control transmission of these highly problematic strains within the island nation health systems.

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Keywords: Acinetobacter baumannii; Carbapenem resistance; bla_{OXA-23}; Sequence type 2; Oceania

Research in context

Evidence before this study

We systematically searched Google Scholar, Pubmed, and Web of Science using the term "carbapenem resistant", "*Acinetobacter baumannii*", "carbapenemase", "antimicrobial resistance", "molecular epidemiology" and "Oceania". We identified reports on carbapenem resistant *A. baumannii* in Fiji, New Caledonia, French Polynesia, New Zealand, and Australia. We also found a study that describes molecular epidemiology of CR*Ab* isolates from Oceania and Asia. However, only one country from the Oceania region (Australia) was included in the study. We also found numerous studies on CR*Ab* in Australia. Moreover, Australian data was mostly used in various comparison studies of AMR as a representative of Oceania due to scarcity or non-submission of data from other Oceania countries. A recent published study on molecular epidemiology of CR*Ab* in New Zealand, utilising CR*Ab* isolates from patients admitted to New Zealand hospitals was also found; despite identifiable epidemiological linkages to other Oceania countries, including Fiji and Samoa, no isolates were collected from outside of New Zealand. To the best of our knowledge, there have been no comprehensive molecular epidemiological studies published utilising CR*Ab* isolates from low middle-income countries, upper middle-income countries, and high-income countries within the Oceania region. Moreover, no similar study including CR*Ab* isolates from multiple countries within the Oceania with South Asia including India has been done. There are no previous reports of CR*Ab* in Samoa and there are no recent reports of the prevalence of CR*Ab* from any Pacific Island countries.

Added value of this study

To our knowledge, this study is the first molecular epidemiological study that includes a cohort of clinical CR*Ab* isolates from multiple countries of different income levels as per World Bank categorisation in the Oceania region. Moreover, this is also the first comparison of CR*Ab* strains isolated from multiple countries in Oceania and India. Using whole genome sequencing and clinical epidemiological data, we identified undetected outbreaks of CR*Ab* ST2 in two major hospitals in Fiji and Samoa, with clonal links to isolates detected in Australia and New Zealand. One of the unrelated CR*Ab* ST2 outbreaks in Fiji was linked to India. We also identified multiple other strains of CR*Ab* (CR*Ab* ST1, ST25, ST107, ST1112) in Fiji. Inappropriate use of meropenem in Fiji was common and mortality associated with CR*Ab* infections was high. CR*Ab* ST2 carrying bla_{OXA-23} mediating resistance to carbapenems was the common clone circulating in Oceania.

Implications of all the available evidence

Our findings address a knowledge gap in the emergence and the mechanisms of resistance in CR*Ab* ST2 from Fiji, Samoa, and other Oceania countries. Our findings will assist in shaping sound polices on ways to prevent and control the emergence and spread of AMR pathogens within Oceania and to other parts of the world. It underscores the urgent need for comprehensive, effective, and sustainable AMR surveillance, as well as additional infection prevention and control precautions and sound antimicrobial stewardship. Moreover, a collaborative AMR surveillance activity within the Oceania region with technical, management, and budgetary support systems is urgently needed.

Introduction

Antimicrobial resistance (AMR) is a rapidly evolving global emergency that threatens to undo many of the achievements of modern medicine.[1] The threat is enormous, causing an estimated deaths of almost five million people in 2019 across the globe.[1] Among the six

leading bacterial pathogens causing these AMR associated deaths, carbapenem resistant *A. baumannii* (CR*Ab*) features prominently.[1]

A. baumannii is a gram-negative opportunistic pathogen, commonly associated with life threatening nosocomial infections and outbreaks, particularly in critical care settings.[2,3] It can colonise hospital environments, including invasive devices, dry surfaces, and human skin for extended periods.[4] It also has the ability to develop or acquire resistance to multiple classes of antimicrobials, including carbapenems, and has intrinsic resistance to desiccation and disinfectants.[5] As a result, infections are associated with increased healthcare costs, high morbidity and mortality.[6]

Carbapenem resistance in *A. baumannii* is usually mediated by carbapenem-hydrolysing class D β-lactamases (OXA-type carbapenemases).[7] Previous reports have shown that spread and acquisition of these carbapenemases is often linked to plasmids and other mobile genetic elements (MGEs) including transposons and insertion elements.[8,9] It has previously been shown that there are three epidemic international clonal (IC) lineages of *A. baumannii*, IC I, II, and III. The most common clone causing nosocomial outbreaks associated with carbapenem resistance belongs to IC II, which corresponds to sequence type (ST) 2 utilising the Pasteur multi locus sequence type (MLST) scheme.[10]

Oceania comprises 22 Pacific Island countries (PIC), Australia, and New Zealand.[11] Most of the PIC are geographically isolated with poor economic drivers leading to poor health infrastructure, high disease burden, lack of resources, and poor infection control practices, making them vulnerable to AMR-associated infections.[12] Fiji, an upper middle-income country (UMIC), is considered the economic and technological hub in the South Pacific and facilitates development, including medical assistance, throughout the Pacific.[13] Samoa, a low middle country (LMIC), has very close ties to New Zealand; the population of Samoans living in New Zealand is more than two thirds of the total population of Samoans living in Samoa.[14,15] Because of geographic proximity, New Zealand and Australia are frequent destinations for medical referrals from PIC, including Fiji and Samoa. Many Fijians also seek medical care in India.[16,17]

CR*Ab* has previously been reported in Fiji, French Polynesia, New Caledonia, Australia, and New Zealand.[2,3,18–21] However, unlike other regions, a comprehensive, multicountry molecular epidemiology study of CR*Ab* has not been conducted in the Oceania region.[22–25] In this study, we investigated the molecular epidemiology and phylogenetic relationships of CR*Ab* strains isolated from two major hospitals in Fiji and Samoa and determined whether there was evidence of transmission of CR*Ab*. Moreover, we investigated links to CR*Ab* from other countries within the Oceania region and to India, with which Fiji has frequent healthcare links.[16,17]

Methods

Study design and setting

We undertook cohort studies in Fiji and Samoa of patients with CR*Ab* infections, characterised isolates by whole genome sequencing, and compared these with sequences from Australian, New Zealand, and Indian CR*Ab* isolates.

From the Colonial War Memorial Hospital (CWMH), Fiji, 82 CR*Ab* isolates stored at the CWMH Microbiology Laboratory, isolated from 64 patients from the 1st of January 2019 through 31st December 2019, were received for analysis. One isolate was selected per patient; when CR*Ab* was isolated from the same patient on more than one occasion, the earliest isolate was included. From the Tupua Tamasese Mea'ole Hospital (TTMH), Samoa, 31 CR*Ab* isolates were collected from patients during two periods: from 15th November 2017 to 20th November 2018 and 23rd March to 8th June 2021. One isolate was selected per patient; when CR*Ab* was isolated from the same patient on more than one occasion, the earliest isolate was included. In addition, one isolates was recovered from 63 hospital environmental swabs taken from medical devices, doors, sinks, bed rails, and workstations (Appendix Table 1) collected over a two-week period from ICU, surgical, and medical wards from 20th April to 20th June 2021 at the TTMH.

CWMH is the largest public healthcare facility in Fiji.[26] It is a 523-bed hospital and manages 25,000 admissions annually. CWMH also serves as a teaching and national referral hospital for Fiji and other South Pacific Island countries. It is also the only public healthcare facility providing microbiology services within the central division of Fiji. TTMH is the main hospital in Samoa, with an estimated 250-bed capacity. It houses the national clinical laboratory, which receives and processes all clinical samples from all district hospitals and private clinics around Samoa.

Isolate identification and antimicrobial susceptibility testing

Identification of all isolates was confirmed by matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Biotyper; Bruker Daltonics, Billerica, MA, USA). Antimicrobial susceptibility testing (AST) was performed using the disc diffusion method in accordance with European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.[27] Antimicrobial discs (Mast) tested were amikacin (30 μg), gentamicin (10 μg), meropenem (10 μg), ciprofloxacin (5 μg), and sulfamethoxazole-trimethoprim (23.75–1.25 μg). In addition, the minimum inhibitory concentration (MIC) of meropenem was determined for all Fijian isolates by E-test (bioMérieux). The MIC of colistin (Liofilchem) was determined using the broth microdilution method according to EUCAST recommendations.[28] Carbapenem resistance was defined as *A. baumannii* having a zone diameter of <15 mm or an

MIC value of >8 mg/L to meropenem. All carbapenem resistant isolates were phenotypically screened for carbapenemase production using the adjusted modified carbapenemase inactivation method (AmCIM).[29] All isolates that produced a carbapenemase based on a positive AmCIM test underwent whole genome sequencing (WGS).

Whole genome sequencing and genomic data analysis

Genomic DNA was extracted from overnight cultures using the NucleoSpin® Tissue kit (MACHEREY-NAGEL, Düren, Germany) following the manufacturer's instructions. DNA samples were sent to the BGI Technical Solutions in Hong Kong for WGS and were sequenced with a BGISEQ-500 sequencer (MGI, China) generating 150 base pair paired end reads for analysis.[30] The quality of the reads, species identification, multi locus sequence type (MLST) Pasteur scheme (*cpn60, fusA, gltA, pyrG, recA, rplB, rpoB*), and phylogenetic relationship of the isolates were determined using the Nullarbor bioinformatics pipeline version 2.0.[31] AMR gene content was further checked using ResFinder (v4.1) at the Centre for Genomic Epidemiology and RGI (v5.2.0) and the Comprehensive Antibiotic Resistance Database.[32,33]

Representative isolates from each ST and cluster (FJ03, FJ06, FJ10, F16, FJ20, FJ96, WS006) from Fiji and Samoa were additionally sequenced using the MinION sequencer (Oxford Nanopore Technologies, ONT). These ONT reads were then aligned with their corresponding BGI short reads by Unicycler hybrid assembly pipeline v0.4.9b, generating complete reference genomes.[34] The presence of plasmids and other mobile genetic elements (MGEs), including transposons and insertion elements, were determined in all representative complete genomes using the PlasmidFinder and Mobile Element Finder tools available at the Centre for Genomic Epidemiology.[35] In addition, all AMR genes, transposons, and insertion elements were annotated using the BacAnt database (v3.3.3)[36] and visualised with SnapGene (v6.2.1)[37] and BLAST Ring Image Generator (BRIG).[38]

To determine phylogenetic relationships between isolates based on the core genome, sequences were aligned to a complete reference genome and the core genome and variants were determined using Snippy (v.4.6.0).[39] Recombinant regions were then removed from all aligned core genome sequences using Gubbins (v.2.3.4),[40] and the core genome single nucleotide polymorphisms (SNPs) extracted using SNP-sites.[41] Genetic clustering of isolates was determined using fastbaps in the R package.[42] A maximum-likelihood (ML) phylogeny was inferred from the non-recombinant core genome SNPs with FastTree (v2.1.10, double precision [No SSE3])[43]; the resulting trees were visualised using the online Interactive Tree of Life (iTOL) version 6.0.[44] Minimum spanning trees were generated and visualised using GrapeTree.[45] The pangenome of all CR*Ab* isolates that clustered together with CR*Ab* ST2 group 1 were analysed using Roary (v3.13.0).[46] Genes that were found to be exclusive to individual countries through pangenome analysis were subjected to annotation or characterisation using protein data obtained from NCBI and UniProt.[47,48] The gene presence and absence matrix was obtained from the Roary output. Moreover, the topology differences of the phylogenetic trees inferred from the core genome SNPs and the pangenome were visualised by Phylo.io.[49]

To put our findings in a broader geographical context, phylogenetic relationships were explored by comparing all CR*Ab* ST2 isolated from Fiji and Samoa with the CR*Ab* ST2 sequence data collected from Fiji's CR*Ab* ST2 historic outbreak in 2016/2017 (n = 14),[2] the Royal Brisbane and Women's Hospital in Australia in 2016–2018 (n = 22),[3] the Institute of Environmental Science and Research (ESR), New Zealand in 2018–2021 (n = 13), and from a collection of CR*Ab* ST2 across India in 2019 (n = 58) downloaded from European Nucleotide Archive (Appendix Tables 2–7).

For detailed methods used in the study, see Appendix p1–2.

Clinical data and analysis

All Fijian genomic results were integrated with clinical data including patients' demographics, length of hospital stay, admission diagnosis, specimen type, date of first positive culture, meropenem and colistin exposure, and patient outcome. Data were obtained from the laboratory information management system (LabIMS) and patient information system (PATIS) at the CWMH in Fiji. For Samoa, only patient demographics and location of admission extracted from Microbiology Laboratory registers were available for analysis. New Zealand patients' demographics and their travel history details were provided by ESR. No patient demographic data or travel history were associated with Australian or Indian sequences.

The prevalence of CR*Ab* was determined by analysing antimicrobial susceptibility testing results extracted from the LabIMS and Microbiology Laboratory register from CWMH and TTMH, respectively. Meropenem susceptibility testing in Fiji and Samoa is only performed if all antimicrobials tested show resistance or if specifically requested by the clinician.

The appropriateness of monotherapy with meropenem and combination therapy with colistin and meropenem was evaluated among 64 patients with CR*Ab* infections at the CWMH in 2019 infections using the date of initiation of therapy in relation to the date of first positive culture for CR*Ab*. The appropriateness of therapy was defined based on culture and antimicrobial susceptibility testing results: appropriate therapy was defined as meropenem monotherapy for treatment of

meropenem-susceptible *A. baumannii*, or colistin and meropenem combination therapy for treatment of CR*Ab*; inappropriate therapy was defined as meropenem monotherapy after first isolation of CR*Ab*, or colistin and meropenem and combination therapy after first isolation of colistin resistant *A. baumannii*. Data on meropenem exposure were not available from TTMH.

Nosocomial CR*Ab* infections were defined as patients who had their first positive CR*Ab* sample collected 72 h or more following admission. The in-hospital mortality was determined at 30 days following the date of first isolation of CR*Ab*. No 30 days post discharge mortality was considered due to inavailability of data. Data on mortality was not available from TTMH.

Research ethics

Ethics approvals for the study were obtained from the College Health Research Ethics Committee, Fiji National University (reference number 183.20), the Samoan Ministry of Health Research Committee, and the Human Ethics Committee (Health) at the University of Otago (reference numbers H19/115, H20/174, H21/001).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In 2019, a total of 1094 *A. baumannii* complex were isolated from 778 patients at Fiji's CWMH. Of the 778 patients, isolates from 444 (57%) were tested for susceptibility to carbapenems and 247 (56%) were resistant. Of 444 patients with *A. baumannii* isolates tested, 166 (37%) were from ICU and 130 (78%) of these were found to be resistant to meropenem. In Samoa's TTMH, 147 *A. baumannii* complex were isolated in 2019, of which 99 (67%) were tested for susceptibility to carbapenems and 59 (60%) were resistant.

Isolates were available from 64 (26%) of 247 of patients admitted to CWMH in 2019 from whom CR*Ab* had been isolated; the remaining CR*Ab* isolates had not been stored. There was no discernible pattern as to which isolates had been stored. CWMH cases had a median (range) age of 47 (<1–89) years and 37 (58%) were male (Table 1). Thirty-seven (58%) of the CWMH cases were i-Taukei (Indigenous Fijians), 25 (39%) were Fijian of Indian descent, and two (3%) were from other ethnic groups. Of those with CR*Ab*, 41 (64%) of 64 were from ICU and the rest from other areas of CWMH.

From Samoa's TTMH, 26 CR*Ab* isolates were available from November 2017 to November 2018 and 6 from March to June 2021; the latter time period included one environmental isolate and five isolates from patients. All CR*Ab* from TTMH were among Samoans with a median (range) age of 58 (<1–83) years and 16 (52%) were males.

Variables	Number (%) (n = 64)
Sex	
Male	37 (63)
Female	27 (37)
Ethnicity	
i-Taukei (Indigenous Fijians)	37 (58)
Fijian of Indian descendants	25 (39)
Others	2 (3)
Age	
Median (range), years	47 (<1–89)
Total number of CR*Ab* for WGS	
Invasive specimens[a]	29 (45)
Non-invasive specimens[b]	35 (55)
Time to first positive CR*Ab* after hospital admission	
Median (range), days	9·5 (0–56)
Length of hospital stay	n = 64
Median, day (range)	27·5 (3–84)
Length of ICU stay	n = 41
Median, days (range)	28 (3–84)
1–7 days	2 (5)
8–14 days	4 (10)
15–21 days	9 (22)
22–31 days	6 (15)
>31 days	20 (49)
Outcome	n = 38
Deceased	21 (55)
30-days mortality after date of first positive CR*Ab*	11 (52)

CR*Ab*, carbapenem resistant *Acinetobacter baumannii*; WGS, whole genome sequencing. [a]Invasive specimens, include blood culture, indwelling tips. [b]Non-invasive specimens, include sputum, wound swab, and urine.

Table 1: **Demographic and clinical characteristics of patients with positive CR*Ab*, CWMH, Fiji, 2019.**

All 96 CR*Ab* isolates received from Fiji's CWMH and Samoa's TTMH for analysis were confirmed as *A. baumannii* and were resistant to gentamicin, amikacin, trimethoprim/sulfamethoxazole, ciprofloxacin, and meropenem; the Fijian isolates all had meropenem MIC values > 32 mg/L. All isolates tested positive by AmCIM test, indicating the presence of a carbapenemase. However, all isolates from both hospitals were found to be susceptible to colistin.

Phylogenetic analysis of CR*Ab* from Fiji

Phylogenetic analysis of the available isolates from Fiji's CWMH showed five distinct clusters corresponding to five known sequence types (Fig. 1a). Of *A. baumannii*, 49 (77%) of 64 belonged to the high-risk international clone IC-2 (ST2), 8 (13%) belonged to IC-1 (ST1), 3 (5%) to ST25, 2 (3%) to ST107, and 2 (3%) to ST1112.

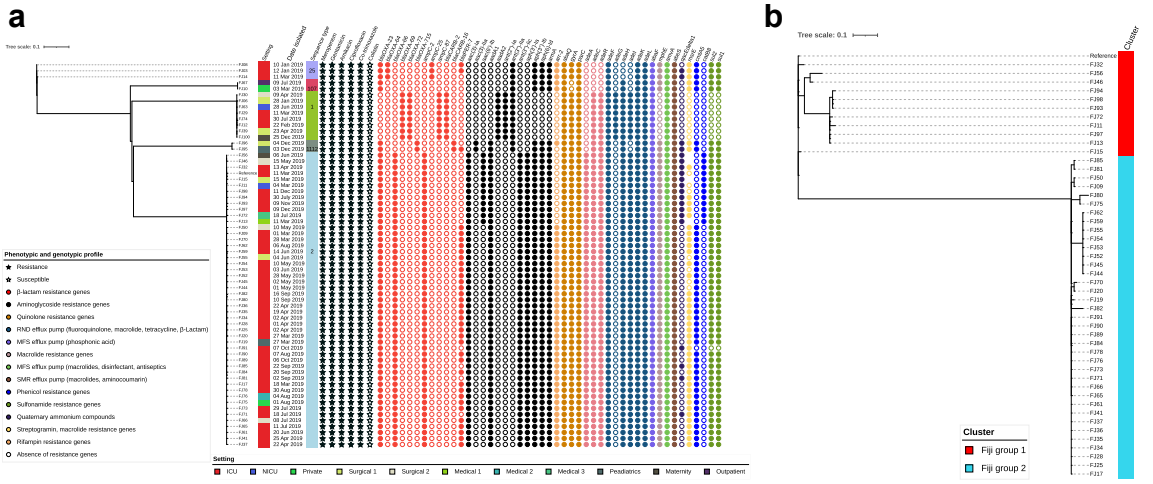

Fig. 1: **Core genome SNP based phylogeny of CRA*b* isolated in CWMH, Fiji, 2019. a)** Core genome SNP based phylogeny of CRA*b* isolated in Fiji's CWMH, 2019. Phylogenetic tree inferred from core genome SNPs of 64 *A. baumannii* isolates. The core genome was generated from at least 93% of the available sequence for all isolates. The core SNP density was 49,983 SNPs across 4,062,284 bp in the reference genome. The reference genome used was FJ16. The tree was rooted on the Fiji's earliest isolate (FJ08). The tree is annotated with collection date, locations where patients were admitted, and AMR phenotypic and genotypic profile. The scale bar signifies the frequency of mutations per site. **b)** Core SNP based phylogeny of Fiji CRA*b* ST2, 2019. Reference used was FJ16 (earliest isolate within group 1). The core genome was generated from at least 93% of the available sequence for all isolates. The core SNP density was 90 SNPs across 4,062,284 base pairs (bp) of the reference. Two clusters (group 1 and group2) were detected by fastBAPS and differed by 159 SNPs. The tree was rooted on the Fiji's earliest isolate from Fiji group 1. AMR abbreviation: *Aph*, aminoglycoside phosphotransferase; *Arm*, aminoglycoside resistance methylase; *ANT*, aminoglycoside nucleotidyltransferase; *AadA*, aminoglycoside adenylyltransferase; *Aac*, aminoglycoside acetyltransferase; *AbaF*, *A. baumannii* fosfomycin efflux; *abaQ*, *A. baumannii* quinolone resistance transporter; *Ade*, adenine deaminase; *Arr*, rifampin ADP-ribosyltransferase; *ABC*, ATP-binding cassette; *CAT*, chloramphenicol acetyltransferase; *cmlA*, chloramphenicol resistance gene; *MPH*, macrolide phosphotransferase; *MFS*, major facilitator superfamily; *RND*, Resistance-Nodulation-Division; *SuI*, sulfonamide resistance gene; *SMR*, small multidrug resistance.

When CR*Ab* ST2 were independently analysed, two distinct clusters (Fiji groups 1 and 2) were observed among the ST2 isolates (Fig. 1b). Group 1 comprised 12 (18%) isolates that, when re-analysed alone using the earliest group 1 isolate as the reference genome, had a median (range) SNP difference of 7 (0–17) between isolates (Appendix Fig. 1a). Group 2 comprised 37 (58%) isolates which, when re-analysed alone using one of the group 2 isolates as the reference genome, had a median (range) SNP difference of 1 (0–11) between isolates (Appendix Fig. 1b). Of CR*Ab* ST2, 37 (76%) of 49 were collected from the ICU, including one isolate from the neonatal ICU (NICU). CR*Ab* ST2 isolates were also collected from various other locations within CWMH, including the medical, surgical, paediatric, and private wards.

All CR*Ab* ST25 isolates were collected from the ICU. When the three ST25 isolates were independently analysed using the earliest isolate as a reference genome, one isolate was found to be closely related to the reference genome with 12 SNP difference; both these closely related isolates (FJ03 and FJ08) differed from the third isolate by 250 and 238 SNPs, respectively suggesting the presence of two clones of CR*Ab* ST25 (Appendix Fig. 1c). Both the ST107 isolates, collected from outpatients and the private ward, were separated by 3 SNPs when using the earliest isolate (FJ10) as the reference genome. The two ST1112 isolates, collected from the paediatric and surgical one wards, were closely related with a SNP difference of one when using the second ST1112 isolate as a reference genome. All the eight CR*Ab* ST1 isolates, collected from various locations within CWMH, formed a single cluster with median (range) SNP difference of 1 (0–5) using the earliest ST1 isolate as a reference genome (Appendix Fig. 1d). The eight CR*Ab* ST1 isolates were collected from ICU (n = 2), surgical 1 (n = 2), surgical 2 (n = 1), NICU (n = 1), medical 1 (n = 1), and maternity wards (n = 1).

Phylogenetic analysis of CRA*b* from Samoa

All Samoa's TTMH CR*Ab* isolates belonged to ST2 (Fig. 2). Of 32 ST2 isolates, 26 (81%) were isolated between November 2017 and November 2018, while the remaining 6 (19%) were isolated from March to June 2021. Twenty (77%) of 26 were collected from inpatients, with 18 of these isolated from three wards: surgical (n = 9), internal medicine (n = 7), and ICU (n = 2). The six (19%) isolates in the later collection period comprised isolates from five patients and one isolate (WS-333) from a ventilator used by patients in

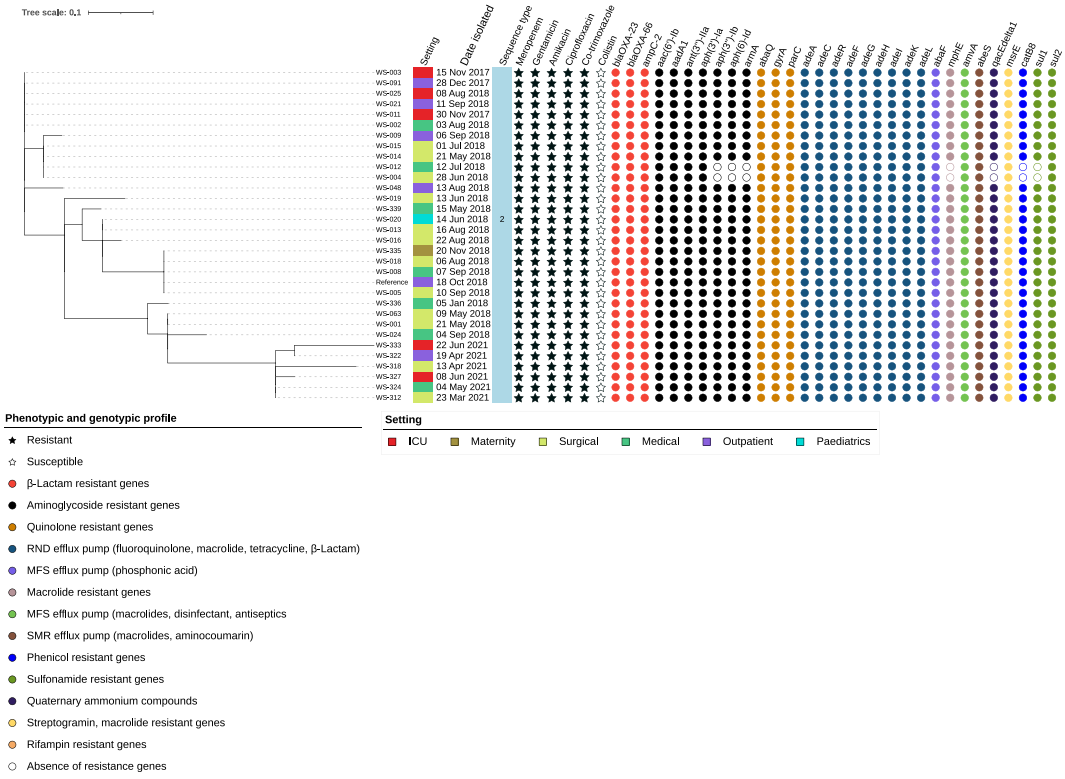

***Fig. 2:* Core genome SNP based phylogeny of CRA*b* isolated in TTMH, Samoa, 2017–2018, 2021.** Core genome SNP based phylogeny of CRA*b* ST2 isolated in Samoa's TTMH, 2017–2018, 2021. Phylogenetic tree inferred from core genome SNPs of 32 *A. baumannii* isolates. The core genome was generated from at least 96% of the available sequence for all isolates. The core SNP density was 36 SNPs across 4,051,297 bp in the reference genome. The reference genome used was WS006 isolated from October 2018. The tree was rooted on the Samoan earliest isolate (WS003). The tree was annotated with collection date, locations where patients were admitted, AMR phenotypic and genotypic profile. The scale bar signifies the frequency of mutations per site. AMR abbreviation: *Aph*, aminoglycoside phosphotransferase; *Arm*, aminoglycoside resistance methylase; *ANT*, aminoglycoside nucleotidyltransferase; *AadA*, aminoglycoside adenylyltransferase; *Aac*, aminoglycoside acetyltransferase; *AbaF*, *A. baumannii* fosfomycin efflux; *abaQ*, *A. baumannii* quinolone resistance transporter; *Ade*, adenine deaminase; *Arr*, rifampin ADP-ribosyltransferase; *ABC*, ATP-binding cassette; *CAT*, chloramphenicol acetyltransferase; *cmlA*, chloramphenicol resistance gene; *MPH*, macrolide phosphotransferase; *MFS*, major facilitator superfamily; *RND*, Resistance-Nodulation-Division; *Sul*, sulfonamide resistance gene; *SMR*, small multidrug resistance.

the ICU. When all isolates were analysed using WS006 as the reference, we found that they were closely related and clustered together with median (range) SNP difference of 7 (0–19). Moreover, the isolate from the ventilator differed by 4–5 SNPs from two CRA*b* isolated one and three months earlier from patients admitted to the internal medicine and surgical units, respectively.

AMR genotype of CRA*b* from the Fiji and Samoa

All ST2 isolates from Fiji and Samoa harboured $bla_{\text{OXA-23}}$, $bla_{\text{OXA-66}}$, and *ampC*-2 genes, which depending upon the genetic context, can mediate resistance to β-lactam antimicrobials, including cephalosporins and carbapenems. Of CWMH group 2 ST2 isolates, 33 (89%) of 37 harboured $bla_{\text{PER-7}}$, which encodes an extended-spectrum beta-lactamase (ESBL). No Samoan isolates harboured $bla_{\text{PER-7}}$. All CRA*b* ST2 isolates from both Fiji and Samoa harboured aminoglycoside resistance genes *aph(3′)-Ia*, *aph(3′)-Ib*, *aph(6′)-Id*, *aadA1*, *ant(3′′)-Iic* and *armA*, conferring high level resistance to clinically available aminoglycosides, such as amikacin and gentamicin. Some aminoglycoside resistance encoding genes were only detected in one group of Fijian and Samoan isolates: *aac* (*6′*)*-Ib* was only detected in Fiji group 1 and 30 (94%) of 32 Samoan isolates, and *aac* (*3*)*-Ia* was only detected in Fiji ST2 isolates. All Fijian isolates of various STs and all Samoan isolates were found to harbour mutations at loci S81L in *gyrA*, and S84L, V104I, and D105E in *parC* conferring high-level fluoroquinolone resistance.

The presence of various efflux pump genes such as *adeABC*, *adeIJK* (both resistance-nodulation-cell division (RND)), *abaQ* (major facilitator superfamily (MFS)), and *abeS* (small multidrug resistance (SMR)) in all isolates from Fiji and Samoa likely contributed resistance to disinfectants, antiseptics, and fluoroquinolone, tetracycline,

macrolide, and β-lactam antimicrobials. Genes encoding resistance to macrolides (*mph(E)*), sulfonamides (*sul1* and *sul2*) and chloramphenicol (*catB8, cmlA5*) were also detected in all ST2 isolates from both CWMH and TTMH. All Fiji group 1 ST2 isolates and 30 (94%) of 32 of Samoan isolates harboured *qacEdelta1*, a quaternary ammonium compound resistance gene mediating resistance to benzalkonium, benzethonium, and chlorhexidine, commonly used hospital disinfectants. In addition to intrinsic $bla_{\text{OXA-51-like}}$ β-lactamase genes, that can cause carbapenem resistance in the correct genetic context, all CR*Ab* belonging to ST25, ST107, and ST1112 harboured $bla_{\text{OXA-23}}$, while all ST1 isolates carried the $bla_{\text{OXA-72}}$ gene. The CR*Ab* ST1 isolates also encoded a novel cephalosporin resistance-associated *ampC-87* gene.

Mobile genetic elements (MGEs)

With the exception of ST1, all other STs (ST2, ST25, ST107 and ST112) contained composite transposon Tn*2006* (4805 bp), which has two copies of the IS*Aba1* (1180 bp) insertion element flanking $bla_{\text{OXA-23}}$, on the chromosome, explaining resistance to carbapenems (Fig. 3).[9] Of note, the Fiji group 1 CR*Ab* ST2 isolate contained two copies of Tn*2006* (a and e) in its genome while the Fiji group 2 and Samoa CR*Ab* ST2 isolates only contained one (a and g respectively). No insertion sequences were found upstream of $bla_{\text{OXA-51-like}}$ genes in any ST or of $bla_{\text{OXA-72}}$ in the CR*Ab* ST1.[50] The Fiji group 1 and Samoa CR*Ab* ST2 isolates, but not the Fiji group 2 isolate contained an IS*26*-composite transposon Tn*6279* (20,960 bp), which carried multiple resistance genes including *mph(E)*, *msr(E)*, *armA*, *sul1*, *catB8*, and *aph(3)-Ia* (c).[51] Furthermore, IS*26* (820 bp) and Tn*6292* (822 bp) were found in close proximity or adjacent to each other within the genomes of the Fiji (both group 1 and 2) and Samoa CR*Ab* ST2 isolates (c, f and g).[52] The CR*Ab* ST2 isolates from Fiji (both group 1 and group 2) and Samoa all contained IS*Aba1* upstream of the chromosomal *ampC-2* (b), and *A. baumannii* resistance genome islands 1 (AbGR1), which encompassed a partial region of Tn*6172* (11,720 bp) containing the aminoglycoside resistance genes *aph(6)* and *aph(3)-Ib* (d and h).[8] Distribution of all MGEs in Fiji CR*Ab* ST1, ST25, ST107 and ST1112 are shown in Appendix Fig. 2.

Phylogenetic relationship of CR*Ab* ST2 in Fiji and Samoa

Next, the phylogenetic relationships between the CR*Ab* ST2 isolates from Fiji, Samoa, and Fiji's historic 2016/2017 CR*Ab* ST2 outbreak were assessed. Of the two Fiji 2019 ST2 groups (Fig. 1b), group 1 was closely related to the 2016/2017 Fiji outbreak clone and to the isolates from TTMH (Fig. 4a). When the analysis was repeated with only the Fiji 2019 group 1 and 2016/2017 Fiji isolates, they were found to be closely related, with a median (range) SNP difference of 9 (0–17) (Appendix Fig. 3). Moreover, when all Samoan isolates were included, they were also closely related to the Fiji 2019 group 1 and the 2016/2017 Fiji outbreak clone with a median (range) SNP difference of 13 (0–30) (Fig. 4b).

Phylogenetic relationship of CR*Ab* ST2 in Oceania and India

We next assessed the phylogenetic relationships of the CR*Ab* ST2 isolates from Fiji and Samoa with CR*Ab* ST2 isolates from New Zealand, Australia, and India. Of New Zealand CR*Ab* ST2 isolates, 7 (54%) of 13 and all isolates from Australia shared common ancestry to Fiji's 2019 group 1 outbreak and all isolates from Samoa (Fig. 5a). When re-analysed with only those isolates clustering with Fiji 2019 group 1 and Samoa, they were found to be closely related and clustered together with a median (range) of 12 (0–28) SNP difference in the core genome (Fig. 5b). Within this cluster, 2 (29%) of 7 of the New Zealand isolates were collected from Samoans living in New Zealand (NZ-225 and NZ-197); these isolates were closely linked to isolates from Samoa, differing from the earliest Samoan isolate (WS-003) by 2 and 5 SNPs, respectively (Fig. 5b). We also found that 2 (15%) of 13 of the New Zealand CR*Ab* ST2 isolates likely shared common ancestry to 4 (7%) of 58 of the Indian CR*Ab* ST2 isolates analysed, with a median (range) of 3 (0–14) SNPs (Fig. 5c); all of these related isolates contained $bla_{\text{NDM-1}}$, $bla_{\text{OXA-23}}$, and $bla_{\text{OXA-66}}$. Interestingly, these New Zealand isolates were isolated from patients who had been hospitalised in Fiji in 2020 and 2021. Furthermore, our phylogenetic analysis showed that all Fiji 2019 group 2 outbreak isolates also clustered with 2 (3%) CR*Ab* ST2 isolates from India (Fig. 5a). When re-analysed, they were found to be separated from the two Indian isolates by 21–25 SNPs (Fig. 5d). Moreover, both the Fiji 2019 group 2 outbreak isolates and these Indian isolates contained the ESBL gene $bla_{\text{PER-7}}$.

Similar visualisations of transmission of CR*Ab* ST2 within the Oceania region are available at: https://microreact.org/project/rDbNkT7KGdDm5FpMEnGRN5-oceania-crab-st2.

Pan-genome analysis

The pangenome comprised 4124 genes, of which 2858 (69%) were core genes (genes present in 99%–100% of the isolates), 496 (12%) were soft-core genes (present in 95% to less than 99% of the isolates), 406 (10%) were shell genes (genes present in 15% to less than 95% of the isolates), and 364 (9%) were cloud genes (genes present in 0% to less than 15% of the isolates). Genes encoding hypothetical proteins accounted for 54% (n = 2214) of the pangenome and 43% (n = 1221) of core genes.

Both the core genome SNP and pan-genome phylogeny trees demonstrated similar topologies (Appendix Fig. 4). By comparing the gene content, we found that some genes were shared by many isolates, while others were unique to only a few isolates (Appendix Fig. 5 and

Table 8). Together, this indicates the existence of divergent gene content patterns among these isolates which are consistent with the phylogenetic relationships determined by core genome SNP analysis, and which align, in part, with geographic origins, potentially reflecting local adaptation (Appendix Fig. 5).

Clinical epidemiological analysis (Fiji)

From the 64 patients with CR*Ab* infections (cases) at the Fiji's CWMH, 58 (91%) had been admitted for 72 h or longer at the time the first CR*Ab* positive sample was collected. Among the 58 cases, 45 (78%) had CR*Ab* ST2, six (10%) had ST1, three (5%) had ST25, two (3%) had ST1112, and two (3%) had ST107. Of these, 28 (48%) CR*Ab* were isolated from invasive samples, including indwelling tips and blood cultures, and 30 (52%) were from non-invasive samples, including urine, sputum, and wound swabs. The median (range) hospital stay of these 58 cases was 28 (3–84) days. The median (range) duration from ward admission to first positive CR*Ab* was 9·5 (3–38) days. Among the 58 cases, 41 (71%) were admitted to the ICU, of which 36 had CR*Ab* ST2, three had ST25, and two had CR*Ab* ST1 (Fig. 6).

Among the 64 cases, 18 were not treated with meropenem or colistin and 15 did not have any treatment records available. Of the 31 cases treated with meropenem or colistin, 21 (68%) received meropenem monotherapy and 10 (32%) received combination therapy with meropenem and colistin. No cases were treated with colistin monotherapy. Among the 31 treated cases, six (19%) were appropriately treated with meropenem as meropenem monotherapy was given prior to CR*Ab* isolation. Of the six, four continued with meropenem for two days after first isolation of CR*Ab* by culture; median (range) time to initiation of meropenem monotherapy in these six patients prior to first positive CR*Ab* was 7 (3–14) days. Meropenem use was deemed inappropriate in 15 (48%) cases as monotherapy was initiated and continued after CR*Ab* had been identified by culture. The median (range) time to initiation of meropenem monotherapy after first positive CR*Ab* was 8 (1–32) days. All meropenem and colistin combination therapy was administered after CR*Ab* was identified by culture. Combination therapy took a median (range) duration of 7·5 (5–16) days to be initiated after the first isolation of CR*Ab*. The median duration of meropenem monotherapy and meropenem and colistin combination therapy were 6 (1–19) days and 6 (4–21) days, respectively.

Of the 64 cases, 38 (59%) cases had records on whether they were still alive or deceased. Among the 38 cases, 21 (55%) died, of which 17 were from ICU, three from surgical 1 ward, and one from maternity ward. All of those who died had acquired CR*Ab* during their hospital stay, with the median (range) time to first positive CR*Ab* after hospital admission of 9 (3–56) days. Seven of the 21 deceased cases received monotherapy with meropenem, three combination therapy, and seven

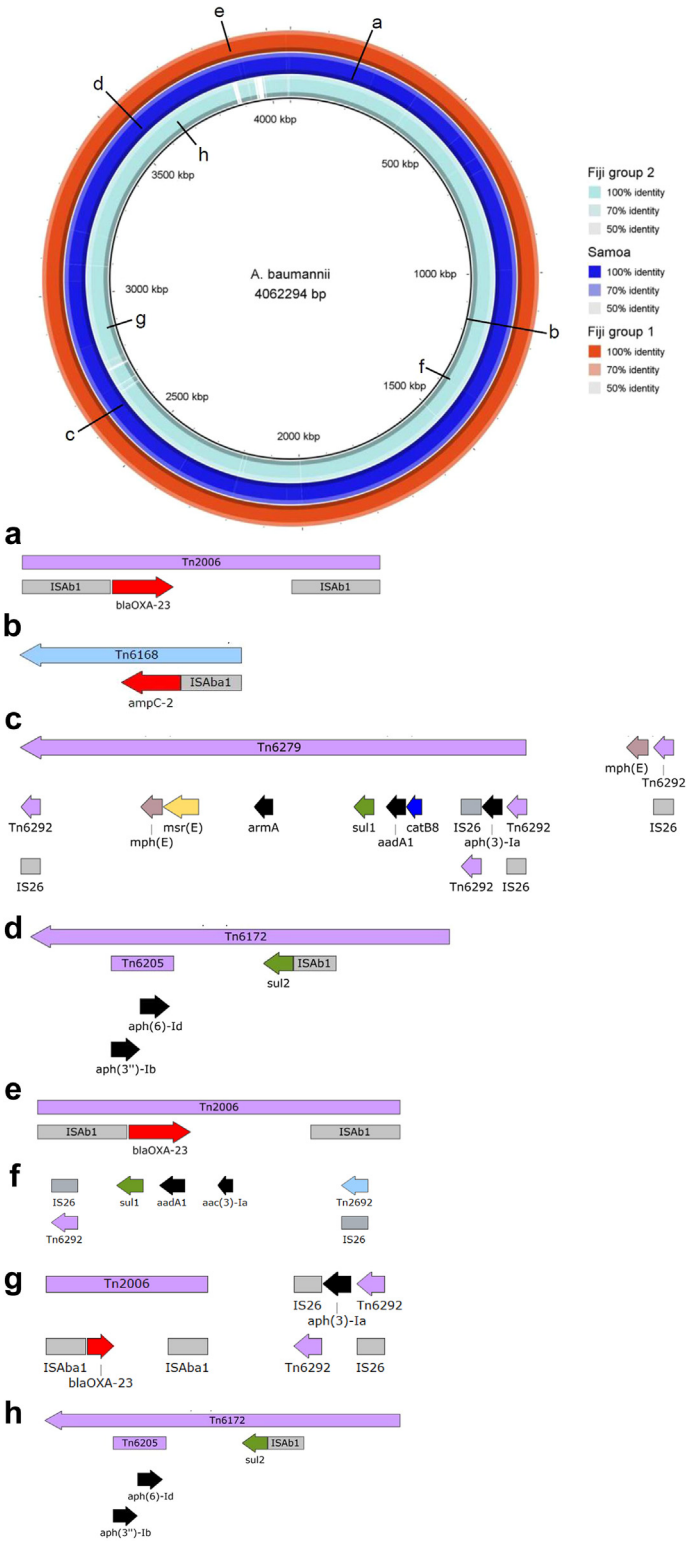

***Fig. 3:* Comparative distribution of mobile genetic elements and AMR genes in CR*Ab* ST2 isolates from Fiji (2019), and Samoa (2017–2018, 2021).** A circular representation of the completed genomes of Fiji (FJ16 [group 1] and FJ20 [group 2]) and Samoa (WS006) ST2

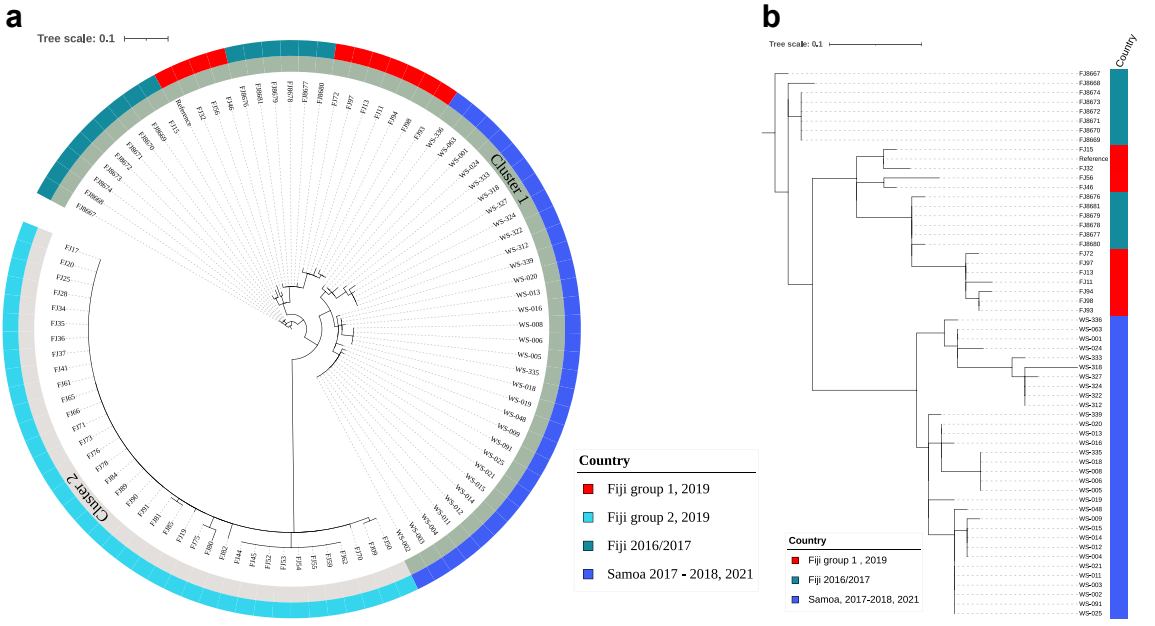

Fig. 4: **Core genome SNP phylogeny of CR*Ab* ST2 isolates from Fiji (2016/2017), Fiji (2019), and Samoa (2017–2018, 2021). a)** Phylogenetic analysis inferred from core genome SNPs of 94 CR*Ab* ST2 isolates; 48 from Fiji's CWMH in 2019, 14 from 2016/2017 Fiji outbreak, and 32 from Samoa's TTMH from 2017 to 2018 and 2021. The reference genome used was the earliest CWMH group 1 2019 isolate (FJ16). The core genome was generated from at least 94% of the available sequence for all isolates. The core SNP density was 121 SNPs across 4,062,284 base pairs of the reference. Two distinct clusters of CR*Ab* ST2 isolates were detected. The first cluster comprised all the CR*Ab* ST2 from Fiji's 2019 group 1 outbreak (Appendix Fig. 1b), Fiji's 2016/2017 outbreak, and all isolates from Samoa. The second cluster comprised all the CR*Ab* ST2 from Fiji's 2019 group 2 outbreak (Appendix Fig. 1b). The two clusters were separated by 46 bp. **b)** Phylogenetic analysis inferred from core genome SNPs of Fiji group 1 2019 isolates, Fiji's 2016/2017 NICU isolates, and the Samoan isolates from 2017 to 2018 and 2021. The earliest Fiji group 1 2019 isolate (FJ16) was used as the reference. The core genome was generated from at least 94% of the available sequence for all isolates. The core SNP density was 75 SNPs across 4,062,284 base pairs of the reference. The tree was rooted on the earliest isolate (FJ8667) from Fiji outbreak in 2016/2017. The median core SNP (range) difference of all the 57 isolates was 13 (range: 0–30).

received neither meropenem nor colistin. Among the seven who received meropenem monotherapy, five were inappropriately treated and two were among the four cases that were initially treated with meropenem prior to first CR*Ab* isolation and continued for more than two days after CR*Ab* was reported. Moreover, 18 (86%) of the 21 decedents had CR*Ab* ST2 infections and remaining three were ST1, ST25, and ST111. Of those who died, 11 (52%) of 21 died within 30 days after first positive CR*Ab* isolation of which three (27%) received monotherapy with meropenem, five (45%) did not receive either meropenem or colistin, and three (27%) did not have any treatment record available.

Details of patients' demographics are shown in Table 1 and Appendix Tables 2–7. A timeline of CR*Ab* in the ICU is shown in Fig. 6.

isolates and the distribution of MGEs carrying AMR genes visualised by BRIG. The inner circle represents Fiji group 2 (FJ20), the middle circle represents Samoa (WS006), and the outer circle represents Fiji group 1 (FJ16). Where a line crosses a circle it indicates that MGE is present in that position in the genome. MGEs are shown in the boxes below **(a–h)**.

Discussion

Our study has found an alarmingly high prevalence of CR*Ab* in Fiji and Samoa. In Fiji, there were seven distinct clusters of closely related CR*Ab* corresponding to five sequence types (ST1, ST2, ST25, ST107, and ST1112), with CR*Ab* IC II/ST2 the most common. There were two distinct outbreak strains of CR*Ab* ST2. One outbreak strain, Fiji 2019 group 1, had been circulating in Fiji since at least 2016/2017, and accounted for all CR*Ab* at Samoa's TTMH; it was also detected among Samoans admitted to hospital in New Zealand, and in Australia, suggesting the existence of an Oceania outbreak strain. The second outbreak strain in Fiji (Fiji 2019 group 2), was closely related to isolates from India, suggesting trans-national spread of this clone between South Asia and Fiji. Given the lack of effective antimicrobial agents available for treatment and the poor outcomes following infection, urgent actions such as sound infection and prevention control measures, strong antimicrobial stewardship, and public health and AMR surveillance strategies are required to control the transmission of CR*Ab* within Fiji, Samoa, and beyond.

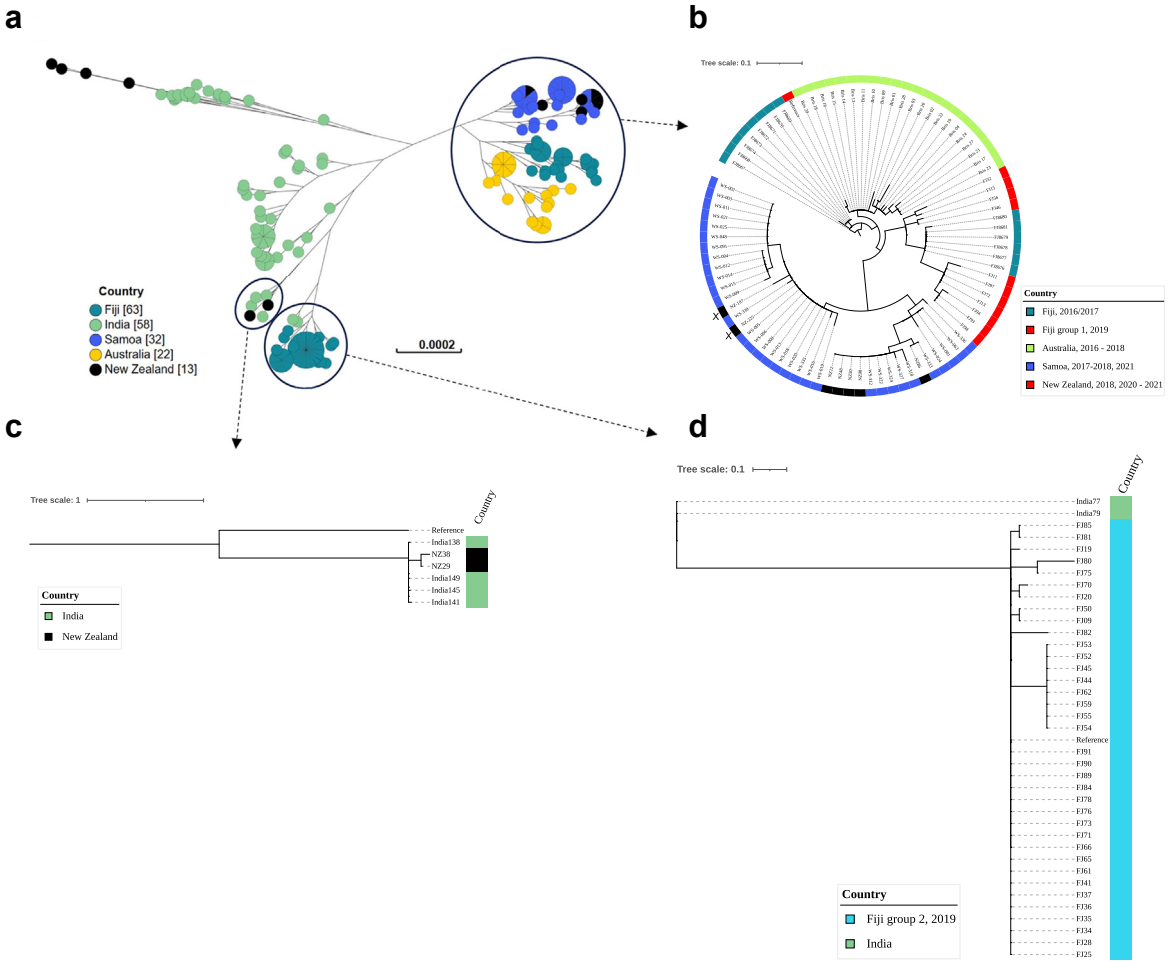

Fig. 5: **Core SNP based phylogeny of CRA*b* ST2 isolates from Fiji (2016–2017), Fiji (2019), Samoa (2017–2018, 2021), New Zealand (2018, 2020–2021), Australia (2016–2018), and India (2019). a)** Minimum spanning tree inferred from core genome SNPs of CRA*b* ST2 isolates from the Oceania region (Fiji, Samoa, Australia, New Zealand), and India. The reference genome used was the earliest 2019 Fiji isolate (FJ16). The core genome was generated from at least 91% of the available sequence for all isolates. All branches are in logscale and visualised in Grape Tree. **b)** Phylogenetic analysis inferred from core genome SNPs of Fiji 2019 group 1 and CRA*b* ST2 isolates clustering with group 1 (CWMH's NICU isolates from 2016/2017, isolates from Samoa, isolates from Australia, and selected isolates from New Zealand). The reference genome used was the earliest Fiji group 1 2019 isolate (FJ16). The core genome was generated from at least 91% of the available sequence for all isolates (n = 87). The core SNP density was 81 SNPs across 4,062,284 base pairs of the reference. 'X' denotes CRA*b* ST2 isolated from Samoans living in New Zealand. **c)** Phylogenetic analysis inferred from core genome SNPs of 2 of the 13 (15%) isolates from New Zealand and four of the 58 (7%) isolates from India shown to cluster in A. The reference genome used was the earliest Fiji group 1 isolate (FJ16). The core genome was generated from at least 94% of the available sequence for all isolates. The core SNP density was 74 SNPs across 4,062,284 bp of the reference.The tree was rooted to the reference. **d)** Phylogenetic analysis inferred from core genome SNPs of two isolates from India and all Fijian isolates from Fiji group 2. The reference used is the earliest isolate in group 2 (FJ17). The core genome was generated from at least 96% of the available sequence for all isolates. The core SNP density was 42 SNPs across 4,068,504 bp of the reference. The tree was rooted to the Indian isolate (India 77) collected in 2019.

The large number of clinical isolates of *A. baumannii* and the high prevalence of carbapenem resistance, when tested, suggests a heavy burden of CR*Ab* associated infections at Fiji's CWMH, particularly among patients admitted to the ICU, and at Samoa's TTMH. Notably, the prevalence of carbapenem resistance among *A. baumannii* in Fiji and Samoa was higher than that reported from elsewhere in Oceania countries, including the main hospital from French Polynesia (41·7%, n = 24),[18] a tertiary hospital in New Caledonia (24·8%, n = 202),[19] Australian public hospitals (3.4%, n = 901),[53] and New Zealand hospitals (4·4%, n = 405).[21] However, the prevalence was lower than that reported in other hospitals in UMIC such as Malaysia (79%,

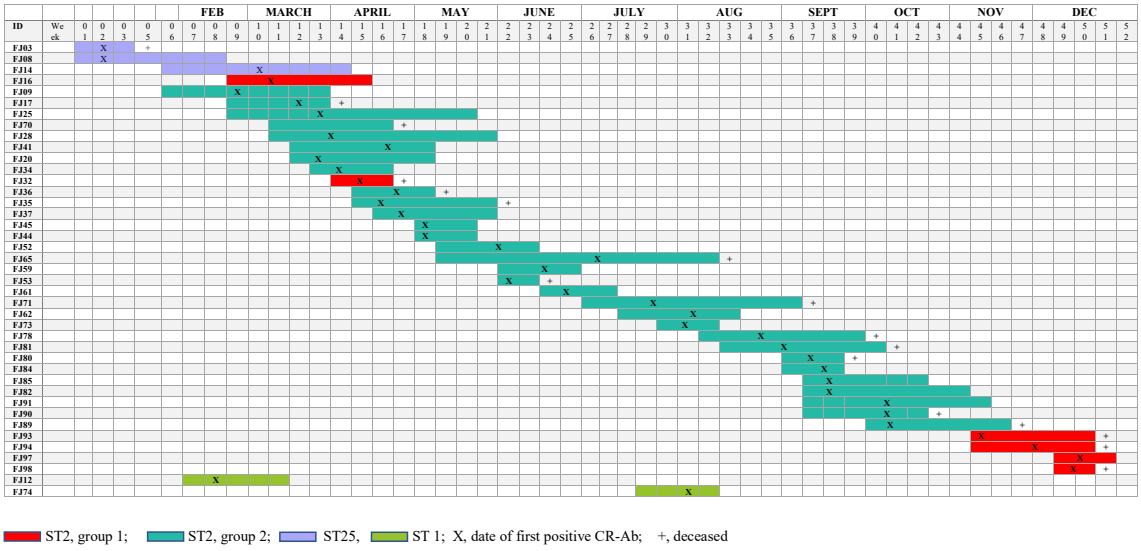

Fig. 6: **Admission timeline of ICU patients with CR*Ab* by week, CWMH, Fiji, 2019.**

n = 162),[54] Thailand (69·7%, n = 47,962),[55] and China (75·1%, n = 24,622),[56] and LMIC such as India (84.8%, n = 7204).[57]

All CR*Ab* isolates from Fiji and Samoa were resistant to all antimicrobials tested except colistin. This phenotype was consistent with the multiple resistance genes and efflux pumps they encoded. With the exception of the CR*Ab* ST1 isolates, all CR*Ab* isolates contained Tn*2006*, which carries the acquired carbapenem-hydrolysing class D β-lactamase $bla_{\text{OXA-23}}$ flanked upstream and downstream by IS*Aba1*. In contrast, the CR*Ab* ST1 isolates carried the acquired $bla_{\text{OXA40-like}}$ β-latamase gene $bla_{\text{OXA-72}}$ with no adjacent insertion sequences, which has been reported to be associated with carbapenem resistance.[58] While almost all of the isolates also encoded an intrinsic $bla_{\text{OXA-51-like}}$ β-lactamase ($bla_{\text{OXA-69}}$ in ST1, $bla_{\text{OXA-66}}$ in ST2, $bla_{\text{OXA-64}}$ in ST25, and $bla_{\text{OXA-715}}$ in ST1112), this was unlikely to be contributing to resistance as no upstream insertion sequences were found.[59] Dissemination of $bla_{\text{OXA-23}}$ has also been reported elsewhere in the Asia–Pacific region, such as French Polynesia, New Caledonia, Australia, New Zealand, China, and India.[3,18,19,60–63] The $bla_{\text{OXA-72}}$ gene is less common but has been previously reported in the Asia–Pacific region in Thailand, Taiwan, and China.[50,58,64,65]

Almost all CR*Ab* ST2 identified from Fiji were from cases who had been hospitalised for 72 h or longer at the time the first CR*Ab* positive sample was collected. These findings indicate that patients were likely not colonised with CR*Ab* ST2 upon admission, but rather acquired infections during their stay. The same pattern was also observed with CR*Ab* ST1, ST25, and ST107. The risk of colonisation and infection may be attributed to prolonged exposure to organisms present in the hospital environment, particularly in the ICU, due to lapses in infection prevention control practices, prolonged hospital stays, and exposure to broad-spectrum antimicrobials. While we cannot identify a specific point source for the two CR*Ab* ST2 outbreaks in Fiji, the close genetic similarity of CR*Ab* ST2 isolates within group 1 and group 2 suggests separate introduction of these two outbreak clones into Fiji.

Phylogenetic relationships of CR*Ab* have been previously reported separately from Australia and New Zealand.[3,63] To the best of our knowledge, ours is the first molecular epidemiological study of CR*Ab* that includes isolates from multiple countries within the Oceania region. There is no definitive core genome SNP cut off value to distinguish outbreak from non-outbreak for CR*Ab*. Using core SNP analysis, genetic clustering, AMR determinants, and epidemiological linkages, we identified that all isolates within each respective cluster at each hospital in Fiji and Samoa during each collection period differed by ≤19 SNPs. Therefore, 19 SNPs or less is a possible threshold to discriminate outbreaks or clusters within the same hospital.

Ours is the first report of CR*Ab* ST2 from Samoa. We identified a prolonged clonal outbreak from at least November 2017 through November 2018 across seven different hospital wards. Moreover, the same clonal outbreak clone was detected during the subsequent sampling period from March through June 2021 indicating the ongoing transmission of CR*Ab* ST2 in Samoa. Interestingly, the detection of this outbreak clone from hospital equipment suggests the significant threat posed by this

clone in Samoa. While this clone is part of the Oceania CR*Ab* ST2 strain, differences in gene content were also noted in the pangenome analysis. Genes involved in amino acid metabolism and transport (*aspT*, *yddG*, and *ygeA*) and lipid transport (*pqiB*) were lost in the later Samoan isolates, while these genes were present in the earlier Samoan and Fiji group 1 isolates.[66] In contrast, the pangenome showed little difference between the Fiji 2016/2017 and Fiji 2019 group 1 isolates. Furthermore, while the Samoan isolates were closely related to the Fiji 2016/2017 and Fiji 2019 group 1 CR*Ab* isolates based on the core genome SNP analysis (median 13, range: 0–30), the representative complete genome of the Fiji 2019 group 1 isolate contained two copies of *Tn2006* while the Samoan isolate contained only one; it was not possible to determine this for the Fiji 2016/2017 isolates as a complete genome was not available. Altogether, this may represent adaptation of the Oceania clone with time and by location through gene loss and movement of MGEs.

The second Fiji CR*Ab* ST2 outbreak clone (Fiji 2019 group 2) shared common ancestry to two isolates in India, a country with which Fiji has strong medical linkages. All isolates of this outbreak clone, from both Fiji and India, carried both the ESBL ($bla_{\text{PER-7}}$) and class D carbapenemase ($bla_{\text{OXA-23}}$) genes. This is the first time $bla_{\text{PER-7}}$ carrying *A. baumannii* has been reported in Fiji and the Oceania region. We also demonstrated that two clinical CR*Ab* ST2 that were isolated in New Zealand from patients who had recently been hospitalised in Fiji, were unrelated to either the Oceania outbreak clone or the second outbreak clone in Fiji. They co-produced $bla_{\text{OXA-23}}$, and $bla_{\text{NDM-1}}$, mediating high level carbapenem resistance. This suggests that there may be additional outbreak clones of CR*Ab* ST2 circulating in Fiji, although acquisition in New Zealand cannot be excluded. Given that only 26% of CR*Ab* from Fiji in 2019 were available for WGS, it would not be surprising if there were additional CR*Ab* ST2 clones circulating. Moreover, detection of multiple strains of CR*Ab* (ST1, ST25, ST107 and ST1112) in Fiji suggests that there were likely to have been multiple previous introductions into Fiji, although acquisition of carbapenem resistance in Fiji cannot be excluded. While we cannot definitively identify the source country due to limited availability of epidemiological data, the close phylogenetic relationship of isolates from Fiji, Samoa, New Zealand and Australia suggests that these isolates all share a common ancestor, and that international travel may have contributed to the spread and acquisition of CR*Ab* ST2 in the Oceania region.

Our study also highlights the role of MGEs, such as transposons and insertion sequences, in the dissemination of AMR genes in *A. baumannii*'s genome. Of particular concern is the composite transposon Tn*2006*, carrying $bla_{\text{OXA-23}}$ flanked by IS*Aba1* elements, which has been shown to increase the mobility of the carbapenemase gene in *A. baumannii* strains worldwide.[9,67] The presence of Tn*6168* with IS*Aba1* upstream of the chromosomal *ampC* gene, further enhances resistance to penicillins and extended spectrum cephalosporins. The presence of these and other MGEs (Tn*6292*, Tn*6172*, IS*Aba24*, IS*Aba125*, and IS*26*) increases the risk of transmission of AMR determinants through horizontal gene transmission in Fiji, Samoa, and the wider Oceania region.

The inappropriate use of broad-spectrum antimicrobials, including carbapenems, has been one of the major drivers for carbapenem resistance.[68] Although policies and guidelines are in place in Fiji to combat AMR, high levels of inappropriate use of meropenem were still observed. This is relatively higher than some hospitals in other UMIC such as Thailand (19·4%, n = 36),[69] LMIC such as Iran (13%, n = 100),[70] and high income countries such as Oman (39%, n = 18).[71] Moreover, delays in initiation of appropriate therapy to treat CR*Ab* infection were also observed in Fiji. This highlights the need for a focus on antimicrobial stewardship and improved communication between the laboratory, the infection prevention and control service, clinicians, and the pharmacy.

Implementation of, and adherence to, contact precautions and controlling environmental contamination through routine hand hygiene, use of effective disinfectants, and thorough hospital environmental cleaning of both medical equipment and surfaces with routine monitoring are important interventions to control nosocomial outbreaks.[72] Of note, we found that all isolates in Fiji 2019 group 1, some isolates within Fiji 2019 group 2, and the majority of Samoan isolates harboured the quaternary ammonium compound resistance gene *qacEdelta1*, which has been reported to confer high level resistance to disinfectants such as benzalkonium, benzethonium, and chlorhexidine that are commonly used in hospitals.[73] One isolate from Samoa's SG2 was isolated from a ventilator used in the ICU, which was closely related to two patient isolates from two different wards. While we did not investigate the directionality of transmission, these results highlight the importance of infection prevention and control precautions and the possibility of this ventilator as a source of infection.

Infections with CR*Ab* have consistently shown a high mortality due to limited availability of antimicrobials to which they are susceptible.[2,74] The 30-day mortality (52%) among patients within the ICU at the Fiji's CWMH after first isolation of CR*Ab* is alarming. Despite the threat posed by these CR*Ab* ST2 and previous infection prevention and control reports and recommendations, Fiji and Samoa continue to face challenges in infection prevention and control and suboptimal practices that have contributed to previous nosocomial outbreaks.[2]

Our study has several limitations. First, isolates were only available from 26% of the patients with CR*Ab* infections over the study period at Fiji's CWMH. This

might underestimate the population diversity of CR*Ab* strains in Fiji. Second, there were no clinical or epidemiological data available from Samoa's TTMH, limiting our ability to determine the drivers and outcomes of CR*Ab* infections in Samoa. Third, although we identified that international travel played a significant role in the spread of CR*Ab*, we cannot determine with certainty the specific source countries due the lack of sequence data from other countries and the unavailability of data on overseas travel and hospitalisation for patients from Fiji, Samoa, Australia, and India. Fourth, of the 24 countries in Oceania, only four were included in this study (representing LMIC, UMIC and high-income countries), therefore our study may not represent the incidence or strains of CR*Ab* circulating in other countries in Oceania.

Our study identified the emergence of two prolonged, parallel, undetected nosocomial outbreaks of CR*Ab* ST2 in two major hospitals in Fiji and Samoa and the existence of an Oceania CR*Ab* ST2 outbreak clone. We also hypothesised that India could be the source for the second outbreak in Fiji and potentially other CR*Ab* ST2 outbreak clones circulating in Fiji. Previous introduction of CR*Ab* ST1, ST25, ST107, and ST1112 into Fiji were also identified. The study underscores the need for a collaborative, comprehensive, effective, and sustainable AMR surveillance system in Oceania. This may include the combination of passive surveillance, utilising existing available data, and targeted surveillance that focuses on collecting data and isolates specifically for AMR surveillance from all hospitals across Oceania. This will require collaborative work between a variety of services within hospitals, including pharmacies, microbiology laboratories, infection prevention and control, clinicians and epidemiologists. We have also shown the need for improvements in antimicrobial stewardship and additional infection prevention and control precautions in Fiji and Samoa. Moreover, this study demonstrates the power of WGS to detect outbreaks and the detail in which the threats are understood, ultimately informing timely and effective interventions.

Contributors

Conceptualisation, S.C.B, L.I, P.C.H, J.A.C, J.E.U; writing—original draft preparation, S.C.B; writing—review and editing, S.C.B, L.I, S.V.D, B.H, C.L.G, S.M, S.S, D.W, S.K, K.M, S.B, L.V.B, K.D, J.A.C, P.C.H, J.E.U; collection of samples from Fiji; S.V.D, S.M; collection of data from Fiji, S.V.D, S.S, S.K, K.M, L.V.B; interpretation of data from Fiji, S.C.B, D.W, J.E.U; provision of sequence data, interpretation of data from Fiji, B.H, C.L.G; collection of samples and data from Samoa, L.I; interpretation of data form Samoa, L.I, P.C.H, S.B, J.E.U; provision of sequence data and data collection from ESR, New Zealand, interpretation of New Zealand data, K.D; funding acquisition, S.C.B, L.I, P.C.H, J.A.C, J.E.U.

Data sharing statement

Raw sequence data from this study have been deposited at the NCBI SRA database under BioProject accession number PRJNA1001798. Raw sequence data from Fiji's CR*Ab* ST2 historic outbreak in 2016/2017 have been deposited under BioProject accession number PRJNA1007430. Raw sequence data from New Zealand from 2018 to 2021 have been deposited under BioProject accession number PRJNA1005029.

Declaration of interests

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100896.

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