Successful management of a multi-species outbreak of carbapenem-resistant organisms in Fiji: a prospective genomics-enhanced investigation and response

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Summary

Background Fiji is a Pacific Island nation grappling with the increasing threat of antimicrobial resistance (AMR). While genomic technologies are increasingly utilised to understand the emergence and spread of AMR globally, its application to inform outbreak responses in low- and middle-income settings has not been reported.

Methods Through an established capacity building program, suspected carbapenem-resistant organisms (CRO) identified at Colonial War Memorial Hospital in Fiji (Jan 2022–Oct 2023) underwent whole genome sequencing and analysis. Following a rapid increase in CROs, a joint outbreak investigation including detailed genomic epidemiology was undertaken. A multi-modal response was co-designed and implemented by hospital staff, and circulating strains monitored to assess impact.

Findings Six large genomic clusters accounted for 73% (n = 223/304) of all sequenced CRO isolates. Four genomic clusters (*Acinetobacter baumannii* NDM-1, *A. baumannii* OXA-23/OXA-58, *Escherichia coli* NDM-7, *Pseudomonas aeruginosa* NDM-1) were investigated in detail, with affected wards differing between species. Following outbreak interventions, *E. coli* and *P. aeruginosa* clusters decreased rapidly, however *A. baumannii* transmission persisted. Repeated international importation of CROs into Fiji were suspected.

Interpretation Carbapenem-resistant pathogens pose a major threat to the health system in Fiji. Genomics technologies are useful for understanding AMR and guiding successful response, in these settings. Strategies to ensure access to, and judicious use of the technology are justified.

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Research in context

Evidence before this study

Antimicrobial resistance (AMR) is one of the greatest threats to human health globally, with carbapenem-resistant organisms recently identified by the WHO as the critical risk group. Pathogen genomics technologies have emerged as an essential tool to understand AMR pathogen spread and detect outbreaks, however the application or added-value of technology in low-resource settings has not been clearly demonstrated. We searched PubMed, medRxiv, and bioRxiv for primary research studies published from database inception until June 2024 with no language filters, using combinations of "genomics", "antimicrobial resistance", "outbreaks", and "infection control" and then filtered for low-resource settings. We identified 16 papers that described the molecular epidemiology of drug-resistant infectious diseases in these settings (bacterial infections and *Mycobacterium tuberculosis*), and only one study that used genomics to investigate the impact of new infection control interventions against an outbreak of a single bacterial drug-resistant species (*Pseudomonas aeruginosa*) but did not use genomics to understand the outbreak and design the intervention.

Added value of this study

This study has two major findings. Firstly, using genomics and detailed epidemiological investigation we identify and highlight the threat of extreme drug-resistant bacterial pathogens in the Pacific, a region that has limited data available to describe the AMR threat. Providing compelling evidence for the presence and ongoing spread of these highest risk AMR pathogens in this setting has major implications for the threat of this problem throughout the whole Pacific Island region. Secondly, we demonstrate that genomics technologies can be effectively and efficiently applied to understanding and responding to complex outbreaks of AMR pathogens in low-resource settings. We show that this is achievable through established collaborations between in-country partners and reference laboratories that are able to sequence, analyse and effectively communicate genomic data results in a meaningful timeframe. Combining capacity building programs complemented with translational research activities such as described here highlight the opportunity to generate evidence on the value of new technologies in these settings while also supporting effective responses to the identified risk.

Implications of all the available evidence

This study highlights the urgent threat of critical risk group AMR pathogens in the Pacific Islands and highlights the need to ensure access to appropriately utilised technologies such as pathogen genomics to understand and target interventions against this threat, even in resource limited settings.

Introduction

Antimicrobial resistance (AMR) is a rapidly growing global health threat, with significant clinical, societal and economic impact.[1] Globally, AMR is associated with ten million lives lost and >US$1 trillion in direct and indirect costs per year,[1] with a disproportionate burden of infectious diseases and AMR in low-to middle-income countries (LMICs).[2] In the Western Pacific Region it is estimated AMR will lead to 5.2 million excess deaths and USD$148 billion excess costs between 2020 and 2030.[3] AMR can emerge and spread in many microbial species, however one of the most critical threats are carbapenem-resistant organisms (CROs).[4] CROs are increasing in prevalence globally and associated with substantial outbreaks in health care settings.[5–7] Infections caused by CROs can have very limited remaining treatment choices, significantly impacting patient outcomes.[8]

There is evidence of an increasing threat from critical multidrug resistant organisms (MDROs) within and across Pacific Island Countries,[9–13] however there remains significant uncertainty about the burden and transmission dynamics of CROs. In 2016, a high-profile outbreak of multidrug resistant *Acinetobacter baumannii* was identified in Fiji's largest tertiary hospital, the Colonial War Memorial Hospital (CWMH), and subsequent investigation uncovered substantial mortality, including in neonates.[14] CWMH is the principal teaching and referral hospital for the Central and Eastern Divisions of Fiji, with a 531-bed capacity, including an eight-bed adult intensive care unit (ICU) and a 28-bed neonatal intensive care unit (NICU). Importantly, Fiji is the education, tourism and business hub for Pacific Island Countries, and MDRO outbreaks in Fiji are likely to spread beyond its borders, resulting in significant regional impact.

Recognising this, the Fiji Ministry of Health and Medical Services has taken a coordinated, proactive approach to addressing AMR, through the development of a National AMR Action Plan, governed by a National AMR Committee, and with implementation supported by internationally funded programs.

The Combating Antimicrobial Resistance in Pacific Island Countries (COMBAT-AMR) program, funded by the Australian Government Department of Foreign Affairs and Trade's Centre for Health Security, has provided capacity building and training to strengthen prevention, surveillance and response to AMR across the Pacific Region since 2020. These activities have been leveraged to enhance understanding and response to MDROs in Fiji through a translational research program (funded by the Australian Government Medical Research Future Fund), which has facilitated implementation of routine screening and enhanced IPC measures in response to the emerging CRO threat at CWMH, and will assess their impact.

A comprehensive response to MDROs in healthcare settings requires a multi-dimensional approach including improving laboratory, infection prevention and control (IPC), and water, sanitation and hygiene (WASH) capacity, good clinical governance, and alignment with public health efforts and policy direction.[15] Understanding and controlling hospital MDRO outbreaks is often hindered by patients with unrecognised asymptomatic colonisation, long-term carriage, and frequent healthcare exposure.[16] Detailed investigation of affected patients and organisms is often needed to unpick time and location of exposure and risk, to effectively direct IPC interventions. Laboratory characterisation of isolates via methods such as phenotypic antimicrobial susceptibility testing (AST) and whole genome sequencing (WGS) can identify mechanisms of multidrug resistance and guide clinical treatment, and when combined with detailed epidemiological data, can enable mapping of transmission pathways and guide IPC interventions.[16]

On February 9, 2023, an outbreak was declared by the CWMH IPC team, following reports from clinical staff that they were observing an increase in CRO bloodstream infections in the adult ICU. An investigation was initiated to determine the extent, setting, and potential source(s) of the outbreak. The Infection Prevention Control Committee's recommendation was to seek assistance, and at the request of CWMH Medical Superintendent the COMBAT-AMR team supported the CRO outbreak investigation and response as an extension of their ongoing capacity building initiatives. Here we report on the findings and impacts of this investigation, including the use of WGS and extended AST to characterize CROs at CWMH and, combined with epidemiological data, examine suspected transmission or acquisition of CROs within the facility.

Methods

Patient and sample identification

The CWMH microbiology laboratory prospectively identified all patients with a carbapenem-resistant Gram-negative bacteria isolated from any sample collected between 10 January 2022 and 16 October 2023, using previously reported standard laboratory methods.[10] One suspected CRO isolate per species, per patient, was referred to the WHO Collaborating Centre for AMR (WHOCC-AMR), Doherty Institute, Melbourne, Australia, for confirmation and characterisation, as outlined below. Samples were initially referred as part of a research project from August 2022, and continued prospectively following outbreak declaration.

Bacterial identification and antimicrobial susceptibility testing at WHOCC-AMR laboratory

Bacterial species was confirmed using matrix-assisted laser desorption ionization–time of flight (MALDI-ToF), and samples excluded from analysis if a viable isolate could not be obtained. Routine AST was performed on isolates received prior to June 2023, and a subset from any time in the study period were chosen for extended AST, ensuring the predominant clusters were represented (Supplementary methods Table S1). All AST results were interpreted using Clinical Laboratory Standards Institute (CLSI) guidelines, except where indicated (Supplementary methods Table S1). Extensively drug-resistant (XDR) organisms were defined using standardised criteria.[17] Phenotypic results were excluded if the bacterial identification did not match the genus reported by the referring laboratory.

Whole genome sequencing and bioinformatic analyses

Isolates were sequenced on Illumina NextSeq 2000 with 150 bp paired end reads as previously described.[18] Sequence quality control and genome assembly was conducted through the Bohra pipeline (https://github.com/kristyhoran/bohra) (Supplementary methods). Sequences were excluded from analysis if average read depth was below 20, <80% of bases had Phred quality score of ≥30, or *in silico* speciation did not match the expected genus. Multi-locus sequence typing (ST) was performed using mlst (v. 2.19.0) (https://github.com/tseemann/mlst). *In silico* detection of AMR determinants was performed using abritAMR.[18]

Phylogenetic analyses

Phylogenetic analyses were used to characterise the relationships between isolates. Analysis was conducted for any group of ≥2 sequences with the same species and/or ST. To enable focused investigation of species or STs with diverse clades, where required, separate subset analyses were conducted, where the maximum distance between any two sequences was limited to 1200 SNPs and ≥80% of bases were aligned. Single linkage

clustering was performed on the resulting core genome alignment with a threshold of ≤23 SNPs, as previously described (Supplementary methods),[19] and further refined as described below. Phylogenetic trees were inferred using IQtree.[20] To assess their relationship to previous outbreaks and international strains study sequences were uploaded to NCBI (BioProject PRJNA1114318) and integrated into the pathogen detection portal, and a secondary phylogenetic analysis including historical sequences of the same species and ST combination previously sequenced at the WHOCC-AMR laboratory was performed.

Epidemiological investigation and outbreak response

A team of COMBAT-AMR epidemiologists, infectious disease physicians and IPC consultants visited CWMH to conduct epidemiological data collection and a review of outbreak response. Epidemiological data were collected by the CWMH IPC and COMBAT-AMR teams via retrospective review of patient medical records. Data on patient admission, hospitalisation history and medical devices were collected, where available. Integrated genomic and epidemiological analyses were conducted for dominant clonal groups identified through phylogenetic analysis, and clustering was refined below the ≤23 SNP threshold by visual inspection of phylogenetic relationships and overlaid with available patient ward, bed movement and prior hospitalisation data.[16] Investigation results were used to identify wards and other exposures linked to suspected CRO transmissions. Interviews with hospital staff and inspection of affected wards were conducted to review existing IPC activities, identify potential hospital and environmental risk factors, and generate recommendations to guide further response.

Ethics

Approval was obtained from the Fiji National Health Research and Ethics Review Committee (FNHRERC Number 45/2023). Consenting participants for screening of high-risk groups were counselled, patient information was provided, and consent form signed.

Role of the funding source

The study sponsor had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

Demographic and clinical data

Suspected CROs were identified from 337 patients at the CWMH laboratory and referred to the WHOCC-AMR, Melbourne. Where demographic data were available, patients were more likely to be male (n = 162/291, 58%) with a median age of 47 years (range 0–77 years) (Table 1).

Regular CRO screening was introduced at the time of outbreak declaration on 9 Feb 2023 (Supplementary methods). Half of all patients with sample collection after this date were identified through rectal swab screening (50%, n = 63/125), compared to only one patient in the period prior (0.5%, n = 1/212), demonstrating a likely substantial number of unidentified colonised patients. The remaining 81% (n = 273/337) of patients were identified through a clinical sample, most commonly urine or other non-invasive site (Table 1). However, for almost a third of patients (n = 95/337, 28.2%), a CRO was identified from a blood culture, sterile site or invasive medical device (excluding urinary catheters) (Table 1).

Bacterial identification and antimicrobial susceptibility testing

WHOCC-AMR obtained viable isolates for 92.3% (n = 311/337) of patients with a suspected CRO referred from CWMH. Four dominant bacterial species were identified, *A. baumannii* complex (n = 137/311, 44.1%), *Escherichia coli* (n = 89/311, 28.6%), *Pseudomonas aeruginosa* (n = 45/311, 14.5%) and *Klebsiella pneumoniae* (n = 34/311, 10.6%). Routine AST results were included for 205 isolates, of which 192 were resistant to meropenem, yielding a 93.7% concordance with the CWMH Microbiology Laboratory (Table 2). Almost all meropenem resistant isolates were XDR organisms (95.8%, n = 184/192) defined using recognised approaches,[17] with high levels of resistance to fluoroquinolones, aminoglycosides and cephalosporins observed, alongside carbapenems (Table 2). Most concerningly, 75% (n = 49/65) of *Escherichia* and 88% (n = 14/16) *Klebsiella* isolates were resistant to all routinely tested antimicrobial classes.

Extended AST was performed on a subset of carbapenem-resistant *Escherichia*, *Acinetobacter* and *Pseudomonas* isolates to determine the potential utility of 'last-line' antimicrobials in Fiji. Susceptibility remained high to colistin for all bacterial species, while all tested *Escherichia* remained susceptible to amikacin, and all *Acinetobacter* to tigecycline (Table 3).

Whole genome sequencing

Sequence types and AMR resistance genes

WGS was performed on all 311 viable isolates and *in silico* speciation, MLST and AMR gene detection performed on the 304 (97.7%) sequences which met quality control metrics (Supplementary methods Table S2). Carbapenemase genes were identified in 275/304 (90%) of sequences, however, this differed by genus, including only 68% of both *Pseudomonas* (n = 34/50) and *Klebsiella* (n = 23/34) isolates, compared to 99% of *Acinetobacter* (n = 133/134) and *Escherichia* (n = 85/86) (Fig. 1, panel B). All seven

Patient characteristics	Date of initial sample collection		Total
	Pre-outbreak declaration	Post-outbreak declaration	
Age (years, median, range)[a]			47 (0–77)
Male (n, % of time period)	98/166 (59.0%)	71/125 (56.8%)	162/291 (58.1%)
Sample type (n, % of time period)			
Screening (rectal swab)	1 (0.5%)	63 (50.4%)	64 (19.0%)
Other	211 (99.5%)	62 (49.6%)	273 (81.0%)
Urine	77 (36.6%)	22 (17.6%)	99 (29.4%)
Blood	43 (20.3%)	17 (13.6%)	60 (17.8%)
Other sterile site	4 (1.9%)	7 (5.6%)	11 (3.3%)
Device-related[b]	22 (10.4%)	2 (1.6%)	24 (7.1%)
Other	65 (30.7%)	14 (11.2%)	79 (23.4%)
Total	212	125	337

[a]Age available for 103 patients. Insufficient data for stratification by time period. [b]Includes central and peripheral lines, endotracheal tubes and wound drains, does not include catheter urines.

Table 1: **Demographic and clinical characteristics of patients with suspected CRO isolates collected between January 2022–October 2023, identified at CWMH and submitted to WHOCC-AMR for further characterisation.**

P. aeruginosa ST664 isolates, and 3/7 *P. aeruginosa* ST235 did not harbour any known resistance genes (Fig. 1, panel B).

Overall, diversity of sequence types was low, especially for *Escherichia* and *Acinetobacter*, which each contained a single ST accounting for 95% (n = 82/86) and 84% (n = 112/135) of sequences respectively (Fig. 1). Diversity of carbapenemase genes within a single ST was similarly low and three dominant combinations of species, ST and carbapenemase genes emerged, namely NDM-1 &/or OXA-23 producing *A. baumannii* ST2, NDM-7 producing *E. coli* ST 410, and NDM-1 producing *P. aeruginosa* ST 773 (Fig. 1, panel B).

Phylogenetic analysis of species and sequence type combinations

Twenty phylogenetic analyses were performed including 91% of sequenced isolates (n = 282/304) (Supplementary methods Table S2). This represented all groups of ≥2 sequences with the same species and ST, and a maximum pairwise distance of 1200 SNPs. Eighteen clusters of highly-related isolates were identified with a

Antimicrobial		*Acinetobacter*	*Escherichia*	*Klebsiella*	*Pseudomonas*	Total
Total isolates		75	65	19	46	205
Meropenem	Susceptible	5 (7%)		2 (11%)	2 (4%)	9 (4%)
	Intermediate			1 (5%)	3 (6%)	4 (2%)
	Resistant	70 (93%)	65 (100%)	16 (84%)	41 (85%)	192 (94%)
Susceptibility profiles of meropenem resistant isolates, N resistant (%)						
Amikacin			7 (11%)	2 (13%)	33 (80%)	
Amoxicillin-clavulanic acid			65 (100%)	16 (100%)		
Ampicillin			65 (100%)	16 (100%)		
Cefazolin			65 (100%)	16 (100%)		
Cefepime			65 (100%)	16 (100%)	31 (76%)	
Cefoxitin			65 (100%)	16 (100%)		
Ceftazidime		64 (91%)	65 (100%)	16 (100%)	33 (80%)	
Ceftriaxone		64 (91%)	65 (100%)	16 (100%)		
Ciprofloxacin		57 (81%)	65 (100%)	15 (94%)	33 (80%)	
Gentamicin		69 (99%)	65 (100%)	16 (100%)	38 (93%) [a]	
Nitrofurantoin			64 (98%)	12 (75%)		
Norfloxacin			65 (100%)	15 (94%)		
Piperacillin-tazobactam		70 (100%)	65 (100%)	16 (100%)	40 (98%)	
Ticarcillin-clavulanic acid		70 (100%)	65 (100%)	16 (100%)	41 (100%)	
Tobramycin		67 (96%)	65 (100%)	16 (100%)	40 (98%)	
Trimethoprim			64 (98%)	16 (100%)		
Trimethoprim-Sulfamethoxazole		69 (99%)	64 (98%)	10 (63%)		

% isolates resistant
- <10%
- 10-30%
- >30%
- Undetermined or not tested

[a] where no interpretive criteria and MIC ≥16.

Table 2: **Antimicrobial susceptibility by bacterial genus, suspected CRO isolates collected between January 2022–June 2023, identified at CWMH Testing performed using VITEK and interpreted using CLSI criteria (see Supplementary methods for further information).**

Genus	Antimicrobial n (% of tested)												
Carbapenemase gene(s)	Amikacin[a]		Cefiderocol[c]			Ciprofloxacin[a]		Colistin[b,d]		Mecillinam[b] (oral)			Tigecycline[a,e]	
Interpretation	S	R	S	I	-[f]	S	R	S	R	S	I	R	≤1 mg/L	>1 mg/L
Escherichia														
NDM-7	12 (100%)		12 (100%)				12 (100%)	12 (100%)		3/9 (33%)	2/9 (22%)	4/9 (44%)		
Acinetobacter														
NDM-1, OXA-23		10 (100%)	10 (100%)				10 (100%)	10 (100%)					10 (100%)	
OXA-23		7 (100%)	1 (14%)		6 (86%)	2 (29%)	5 (71%)	6 (86%)	1 (14%)				6 (86%)	1 (14%)
OXA-23, OXA-58	2 (100%)		2 (100%)			2 (100%)		2 (100%)					2 (100%)	
Pseudomonas														
NDM-1		3 (100%)	2 (100%)				3 (100%)	3 (100%)						2/2 (100%)
None		2 (100%)	1/1 (100%)				2 (100%)	2 (100%)						1/1 (100%)

% isolates resistant <10% 10-30% >30% Undetermined or not tested

Testing performed via [a]broth microdilution (Sensititre™ GN6F plate) (amikacin, ciprofloxacin, tigecycline), [b]VITEK® (extended AST-XN25 card) (colistin, mecillinam), or [c]disc diffusion (cefiderocol). Results interpreted using CLSI criteria, except where indicated as follows: [d] interpreted using EUCAST breakpoints, [e] no interpretive criteria available, minimum inhibitory concentration provided, [f] zone diameter <15 mm (no interpretative category provided).

Table 3: **Extended antimicrobial susceptibility, among a subset of carbapenem-resistant isolates collected between January 2022–October 2023, identified at CWMH.**

median of 4.5 isolates (range 2–82) per cluster (Supplementary Table S3). Of note, the six largest clusters together accounted for 73% (n = 223/304) of all sequenced isolates. These large clusters included 112 *A. baumannii* ST2 (Clusters 1–4); 82 *E. coli* ST410 (Cluster 5) and 29 *P. aeruginosa* ST773 (Cluster 6).

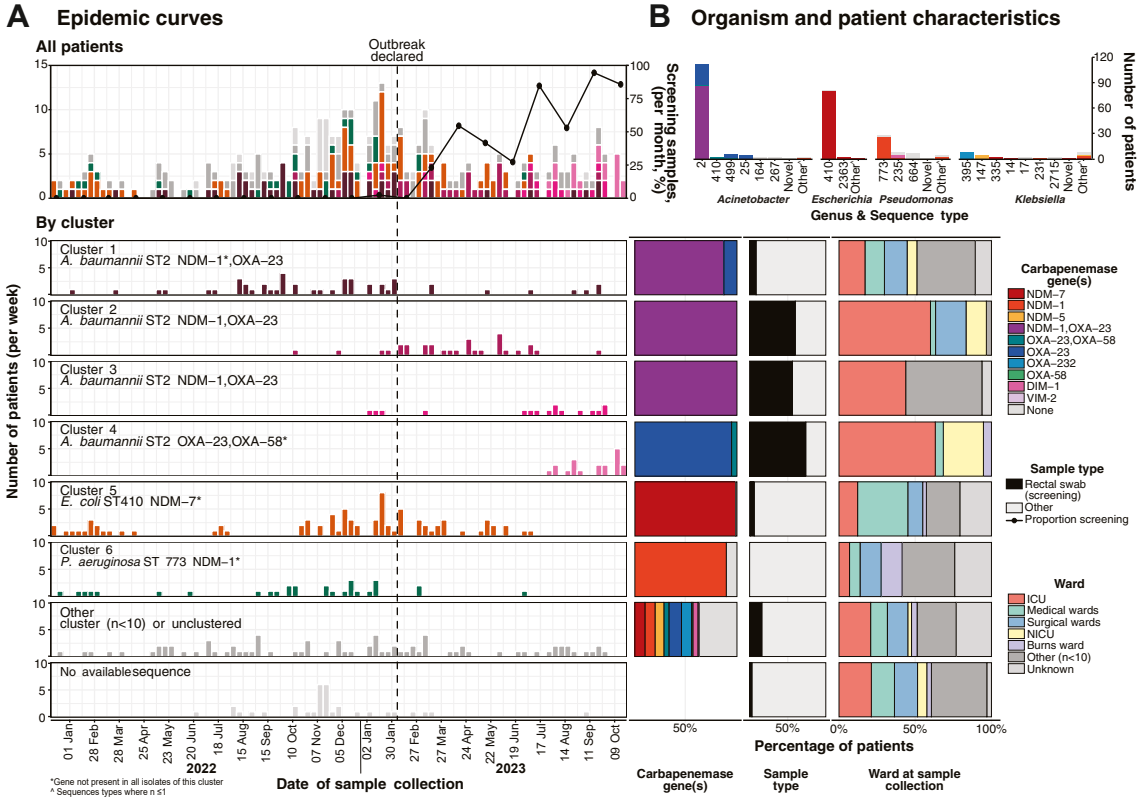

Fig. 1: **Results of genomic epidemiological investigation into CRO outbreak at CMWH, Fiji. A)** Epidemic curve and characteristics of genomic clusters among sequenced suspected CRO isolates collected between January 2022–October 2023, identified at CWMH. **B)** MLST and carbapenemase genes, by bacterial genus, for sequenced suspected CRO isolates collected between January 2022–October 2023, identified at CWMH.

Clusters 1, 5 and 6 persisted throughout the entire study period, each including isolates collected >12 months apart (Fig. 1, panel A).

Integrated investigation of dominant clusters

Integration of patient movement data with phylogenetic analysis suggested several genomic clusters were linked to specific CWMH wards (Fig. 1). Patients in Clusters 1–4 (*A. baumannii* ST2) were commonly linked to ICU and/or Acute Surgical Ward (ASW); those in Cluster 5 (*E. coli* ST410) to the Acute Medical Ward (AMW); and Cluster 6 (*P. aeruginosa* ST773) to the highly interconnected Burns, ICU and Acute Medical/Surgical wards.

A. baumannii *ST2*. *A. baumannii* ST2 has been associated with at least two previous outbreaks at CWMH, including those in the NICU in 2017,[14] and the ICU in 2019.[9] On phylogenetic analysis, four clusters of *A baumannii* ST2 were identified (Fig. 1), each genomically distinct from one another, and from the previously reported outbreaks.

'Cluster 1' contained 47 highly related isolates of NDM-1 and OXA-23 (n = 41) or only OXA-23 (n = 6) producing *A. baumannii* ST2, collected between February 2022 and March 2023 (median 3 SNPs, IQR 2–5). Patients with movement data were frequently admitted to three geographically close wards on the east wing, which all utilised shared staff and equipment, ICU (n = 8/42), ASW (n = 5/42), and AMW (n = 4/42), or had samples collected whilst in areas with high patient movement to and from these wards (e.g., operating theatre, or the New Surgical Ward) (n = 4/42).

Clusters 2 & 3 comprised 30 and 16 isolates respectively, all harbouring both NDM-1 and OXA-23 genes (Fig. 1) (Cluster 2–median 3 SNPs, IQR 1–4; Cluster 3—median 7, IQR 3–10). These clusters may have emerged later than Cluster 1, with samples first collected in October 2022 and January 2023 (Fig. 1). As with Cluster 1, patients in these clusters were most frequently admitted to the ICU (54%, n = 25/46), and ASW (n = 6/46, all Cluster 2).

Cluster 4 (19 isolates) was the most recent *A. baumannii* ST2 cluster to emerge, with earliest samples collected in July 2023 (Fig. 1, Panel A) (median 2 SNPs, IQR 1–3.5). NDM-1 is absent from this cluster, with OXA-23 alone (n = 18) or OXA-23 and OXA-58 genes detected. Affected patients were most frequently admitted to the ICU (63%, n = 12/19) and NICU (21%, n = 4/19) wards.

E. coli *ST410*. Phylogenetic analysis revealed all 82 *E. coli* ST410 sequences formed a highly-related cluster (median 11 SNPs, IQR 6–15), harbouring NDM-7 (n = 81/82, Cluster 5) (Fig. 1). Patient ward data were available for 66/82 patients in Cluster 5, who were more frequently admitted to the AMW (36%, n = 24/66) at time of sample collection. However, geographical proximity and movement of staff, equipment and patients between AMW, ICU and ASW is frequent, and an additional 18 patients (27%) were identified in these linked wards. Whilst *E. coli* ST410 is commonly reported globally, NDM-7 producing *E. coli* ST410 has not been reported in the published literature.

P. aeruginosa *ST773*. All ST773 isolates were found to harbour NDM-1 (Fig. 1), and on phylogenetic analysis were highly related to each other forming Cluster 6 (median 7 SNPs, IQR 5–12) (Fig. 1). Patients with sequences in this cluster were more dispersed than the previously described groups at the time of sample collection, with 12 different wards identified, and more than two patients admitted only to Burns (n = 4) and New Surgical Ward (n = 4) (Fig. 1, panel A).

Comparison to international sequences

Comparison with publicly available data indicated *A. baumannii* strains included in this study were distinct from sequences collected during the 2017–2019 CWMH outbreak (NCBI SNP cluster PDS000076292.63).[9] Instead, Clusters 1 & 4 (PDS000075983.161 and PDS000132235.30, respectively) both separately shared a most recent common ancestor with international sequences, particularly from South Asia. While direction of spread cannot be determined, Fijian patients commonly travel to South Asia for medical care, a recognised risk-factor for CRO colonisation, and international samples pre-date local identification, which may suggest repeated parallel importation.[16] Conversely, Clusters 2 & 3 together (PDS000183783.1), and *E. coli* ST410 Cluster 5 (PDS000183722.1) formed unique groups, suggestive of potential local emergence. Importantly, surveillance sequences collected from two patients in Victoria, Australia sat within identified *E. coli* and *A. baumannii* genomic clusters. Further investigation revealed both patients reported prior hospitalisation in Fiji, and while no onwards transmission was detected, this finding demonstrates the ongoing risk for exportation and regional spread.

Outbreak response

Immediately following the declaration of a CRO outbreak in February 2023, the CWMH ICU was closed for thorough environmental cleaning. Screening of patients on affected wards commenced, informed by the genomic and epidemiological evidence of CRO transmission in ICU and other high-risk locations. Programs to increase access to WASH facilities and hand hygiene were introduced hospital wide. In March 2023, a multi-disciplinary COMBAT-AMR team attended CWMH to support outbreak management efforts. Interviews with staff and observation on

affected wards informed subsequent recommendations to improve IPC, antimicrobial stewardship and laboratory diagnostic capacity (Table 4). Based on advice of COMBAT-AMR, CWMH initiated an Outbreak Management Team in May 2023, providing oversight of outbreak response and with responsibility for progressing implementation of the remaining recommendations. Training in Responding to Outbreaks of Antimicrobial-resistant Pathogens in Health-care Facilities,[21] developed by the WHO Western Pacific Regional Office, was also provided for CWMH and other Fijian hospital staff, to strengthen preparedness, early detection and response to CRO outbreaks. Based on results from expanded AST testing and genomic resistance gene profiles the Fiji MOH rapidly imported new "last-line" therapeutics for invasive CRO infections (Table 4).

Impact of genomics-informed response

Following outbreak declaration and implementation of control strategies, genomic analyses indicated a change in circulating strains (Fig. 1). A decline in Clusters 5 (*E. coli* ST410) and 6 (*P. aeruginosa* ST 773) was evident, with no sequences of either identified subsequent to July 2023. The comparative increase in patients with carbapenemase-producing *Acinetobacter* may be explained by the concurrent implementation of a targeted screening program in the ICU, where these strains have predominated (Fig. 1). Importantly, the detection of CRO in clinical samples, which are less affected by changes in testing practices, decreased dramatically over time.

Discussion

The threat posed by increasing AMR to global health security and the disproportionate impact in low-and-middle income settings is clear.[2] The value of genomics in the LMIC has not been previously investigated. In this study we utilized genomics to identify multiple concurrent outbreaks of the highest threat CRO pathogens that were resulting in large numbers of clinical infections in CWMH. In hospital transmission dynamics differed between species, informing targeted interventions, and with genomics continuing post-intervention to demonstrate cluster specific impacts. Comparisons with international genome data highlighted suspected repeated importation driving CRO outbreaks in Fiji and possible local evolution of the NDM-7 *E. coli* ST410 outbreak. Exportations of CROs from Fiji to Australia highlight the regional threat posed by these outbreaks.

Infections with CROs from multiple different bacterial species persisted over the study period (Table 2). This contrasts with previous reports from Fiji which documented CRO outbreaks caused by a dominant clone of *A. baumannii*.[9,14] The genomic epidemiological investigation informed a multi-modal intervention, including temporary closure of the ICU, and initiated rapid importation of new antimicrobials into the country

Infection prevention and control	
Outbreak response	• Convene an Outbreak Management Team • Implement additional screening of patients on affected wards to identify patients colonised with CRO • Cohort CRO colonised patients in an isolated area of the ward separated from non-colonised patients and manage using contact precautions • Utilise electronic patient management system to record patient bed movement information • Reinforce communication requirements of CRO status when transferring patients between wards in CWMH and to other health services
Hand hygiene	• Promote hand hygiene compliance hospital-wide to staff, visitors and carers • Provide education, training and a program of hand hygiene auditing
Environmental cleaning and repairs	• Review current environmental cleaning products and procedures hospital-wide (SOP for environmental cleaning was endorsed June 2023) • Institute enhanced cleaning activities on affected wards and high transmission areas (Acute Medical and Surgical Wards) • Review cleaning and sterilisation processes in theatre and reprocessing practices of endoscopes and other reusable medical devices • Institute an equipment replacement and repair program (difficulty in achieving this recommendation due to limited resource and budget) • Undertake building renovations and repairs to improve toilet-to-patient ratios wherever possible and to improve the ability to isolate patients
Antimicrobial stewardship	

Access to effective treatment options	• Seek access to additional antibiotics to improve treatment options available to patients with CRO infections
	• Obtain newer antibiotics not on the Fiji Essential Drug list through the National Medicines & Therapeutic Committee (NMTC) of Fij, particularlyi:
	  • *E. coli*—ceftazidime-avibactam plus aztreonam
	  • *P. aeruginosa*—ceftazidime-avibactam
	  • *A. baumannii*—colistin and tigecycline
	• Consider approval/auditing system for highly restricted drugs in healthcare facilities.

Laboratory recommendations	
Improved CRO identification and testing	• Build capacity to enable laboratories to accurately test and detect CROs in a timely manner in clinical and screening samples • Ensure laboratories can accurately perform AST for "last-line" antimicrobials

Table 4: **Recommendations for the control and prevention of outbreaks of carbapenem-producing organisms at CWMH, March 2023.**

based on the genomic analyses and enhanced phenotypic testing (Table 4). A change in bacterial population structure was documented following outbreak response. This suggests that the interventions had some impact, with the apparent elimination of some previously abundant outbreak strains. However, the persistence of the *Acinetobacter* ST2 clones despite increased IPC efforts, and the recurrent outbreaks of this species since 2017, may indicate environmental sources not effectively eradicated by current interventions, with repeated importations also potentially impacting control efforts. Further work to investigate risk factors and environmental sources of carbapenem-resistant *Acinetobacter* at CWM is ongoing.

Internationally there is increasing interest in the use of genomics for enhancing infection control surveillance and response at facility,[22,23] and multi-facility,[24,25] level. There are several issues to address to make this useful, including; i) timeliness of results, ii) reproducibility of methodology, iii) collection of relevant epidemiological data, and iv) the effective communication of integrated results to laboratory staff, IPC staff, clinicians and public health stakeholders.[24] We have previously addressed these systematically through the establishment of a statewide CRO surveillance program in Victoria, Australia,[16] and a recent genomics "superbugs" program across multiple health facilities.[24] These systematic approaches to the collection, analysis and reporting of data from the WHOCC-AMR in Australia to partners in Fiji facilitated the inclusion of genomic data in the outbreak investigation and response. The results of this study highlight that carefully considered, genomics-enhanced investigation of CRO cases in Fiji should be continued.

Interestingly, one of the dominant CRO outbreak clones, *E. coli* ST410, is emerging globally as a high-risk hypervirulent clone demonstrating increased AMR.[26,27] This clone has not been previously associated with the NDM-7 gene, which may indicate local emergence within Fiji. While many *E. coli* ST410 hospital outbreaks have been reported, it has also been associated with acquisition outside of hospital settings and has been isolated from community environmental and animal samples.[26] This should be considered in future investigations in Fiji to determine if this emerging global clone is restricted to healthcare settings in Fiji or is more widespread.

This study is an observational report and it is therefore not possible to draw definitive conclusions regarding the true impact of this investigation on the burden of CROs at CWMH in Fiji. Several factors may have reduced effectiveness of the response, including that timely detection was hampered by insufficient meropenem disc supply, high staff turnover, and requirement to refer isolates to Australia for sequencing. At time of outbreak detection, in-country sequencing capabilities had been established at Fiji Centre for Disease Control (Fiji CDC), but did not yet have sufficient throughput. We are now working with Fiji CDC, through a DFAT funded project, to build local sequencing capacity and establish a national genomics hub at Fiji CDC, while continuing work to strengthen diagnostic capacity and timely detection of CROs at CWM and other Fijian Hospitals. Nonetheless, we believe that the capacity to deeply understand the molecular epidemiology of the multiple concurrent outbreaks was a critical step in affirming the intervention approach. Genomics suggested a larger hospital-wide outbreak, providing valuable evidence of the need for action in a stretched health-care system with multiple competing priorities for medical staff and hospital administrators. The ability to use genomics to understand the apparent impact of interventions on the concurrent outbreaks was also highly valuable.

Ultimately, a sustainable approach to enhanced surveillance and response to high-risk AMR pathogens is being developed in Fiji, with applicability to other LMIC settings. While ensuring the basics of good laboratory diagnostics, robust IPC strategies and effective antimicrobial stewardship are available, a pragmatic, value-based approach to enhanced surveillance, including using genomics, is also required. Given the size of the country and movement of patients between health facilities, it is unlikely this problem is restricted to a single hospital. A national approach to enhanced surveillance through integrating laboratory data, collecting key hospital level epidemiological data and the considered use of genomics, which is now available at the Fiji Centre for Disease Control, will improve ongoing responses to outbreaks of this highly concerning pathogens.

Contributors

TYS, CRL, RJ, MW and BPH conceived the study and designed the study protocol. TYS, RJ, MW, AGS, DC, KB, SK, AD, AL, SG, TD, IN, AG, EB, AK, SP, AV, AK, SA, PP, FH, RN, CL undertook the outbreak investigation and designed the interventions. RN, TYS, AGS, DC, KB, AJ, BPH provided clinical microbiology and infection prevention and control perspectives and expertise to study design and analysis. SA, PP, KH, RJ managed sample testing and reporting. CRL, TYS, JL, KH, MW, NS, BPH analysed and interpreted the data. TYS, CRL, MW, JL and BPH had access to and verified all raw data. TYS, CRL, RJ, MW and BPH prepared the manuscript. All authors read and approved the final manuscript and approved the submission for publication.

Data sharing statement

Genome sequences are deposited in GenBank under BioProject PRJNA1114318. Accession numbers and sample data are available in Supplementary methods Table S2.

Declaration of interests

All authors declare no competing interests and confirm that authors or their institutions have not received any payments or services in the past 36 months from a third party that could be perceived to influence, or give the appearance of potentially influencing, the submitted work.

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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.2024.101234.

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