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In this issue:

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FROM THE EDITOR

Welcome to this edition of the ASA Breakpoints Newsletter where we highlight the ongoing programs of work to improve AMR surveillance in Australia.

We are pleased to present updates from the Australian Group on Antimicrobial Resistance (AGAR) program. The AGAR program is a core component of the Antimicrobial Use and Resistance (AURA) Surveillance System and facilitates collaboration of clinicians and scientists from key microbiology laboratories across Australia. We look forward to sharing the latest developments and achievements of the AGAR program with our readers, including the poster presentations ASA24, held in Sydney February this year.

We include an article from the CSIRO's HOTspots Surveillance and Response Program. HOTspots aims to strengthen cross-jurisdictional and cross-sector AMR surveillance, while simultaneously supporting antimicrobial stewardship (AMS) in regional and remote settings.

Travel award winners to attend ASA24 (**Abiodun David Ogunniyi**, University of Adelaide; **Nicholas Yee**, Murdoch University; **Adam Stewart**, Queensland University) provide their feedback from Annual Scientific Meeting, and **Sewunet Admasu Belachew**, who was awarded the Keryn Christiansen ASA Research Award, provides an outline of his research plan. We also include the posters from ASA24 that received the Best Poster Awards (Auriane Form, Murdoch University; **Nicola Woodfield**, Melbourne Pathology).

In our "In The Spotlight" section, where we shine the light on recent doctoral work, we congratulate **Rekha Pai Mangalore** on her PhD program titled "Implementing beta-lactam antibiotic therapeutic drug monitoring in the intensive care unit". We look forward to exploring her research and its future implications on practice in this issue. We have also brought back our regular photo quiz, thank you to **Sadid Khan** for this issue's content.

Please contact me if you have comments or suggestions for future issues of the Breakpoints Newsletter. Make sure you follow us on social media and check out the updated ASA website. Also, a special call out for any creative people who wants to contribute to the front cover image for future issues.

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Front Cover: https://agargroup.org.au

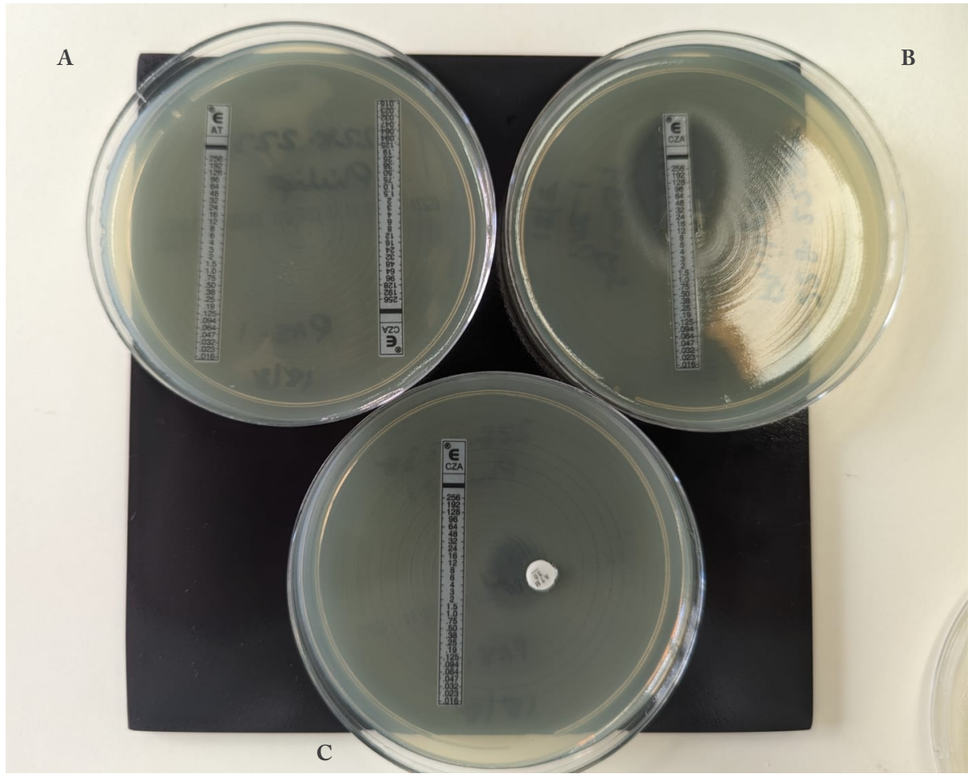
PHOTO QUIZ

A patient who suffered a motor vehicle accident overseas is repatriated from an overseas intensive care unit to your hospital. The patient develops a ventilator associated pneumonia, and culture of purulent endotracheal aspirate secretions yields heavy growth of *Pseudomonas aeruginosa.* Initial susceptibility testing reveals resistance to all first line agents tested. Additional susceptibility testing demonstrates resistance to ceftazidime/avibactam, ceftolozane/tazobactam, cefiderocol, imipenem/relibactam and meropenem/vaborbactam; the isolate demonstrated susceptibility to colistin by broth microdilution and wild type when assessed against systemic fosfomycin breakpoints. Testing for phenotypic carbapenemase production using the carbapenem inactivation method (CIM) was positive; a Xpert Carba-R PCR (Cepheid) detected the presence of a NDM metallo-beta-lactamase.
Given the presence of an Ambler Class B metallo-beta-lactamase in this isolate of *Pseudomonas aeruginosa*, synergy testing between ceftazidime/avibactam and aztreonam was performed [Figure 1]. Plate A demonstrates results for aztreonam (AT) and ceftazidime/avibactam (CZA) when tested separately using commercial gradient strip diffusion. Plate B demonstrates the strip overlay methodology (AT strip allowed to diffuse into media, and then replaced by a CZA overlaid in the same position). Plate C demonstrates a disc approximation method, where an aztreonam disc is plated 15-20mm from the midpoint of a CZA strip.

What interpretations can be made from these results?

What limitations of this testing are important to discuss?

What advice would you provide regarding use of ceftazidime/avibactam in combination with aztreonam?



PRESIDENT'S REPORT

The Australian Society for Antimicrobial returned to Sydney this year for highly successful 23rd Annual Scientific Meeting, "Antimicrobials 2024". Once again, the ASA Committee created a diverse, engaging and informative program, and I thank the committee for their considerable effort.

It was a pleasure to welcome two international plenary speakers for the first time in several years, **Professor Frederic Laurent** and **A/Prof. Yohei Doi**, and we thank **Professor Sharon Chen** immensely for stepping in at very short notice when our third international speaker was unable to attend.

The opening plenary was presented by A/Prof Doi from University of Pittsburgh and Japan, who provided a comprehensive review of Treatment Options for Carbapenem Resistant Non-Lactose Fermenters. On day two Frederic Laurent from the University of Lyon led us on a tour through the comprehensive French phage therapy program in Phage Therapy: A Reality at the Bedside. Professor Sharon Chen provided us with an exhaustive update on New Antifungals on day 3.

A key component of our program is the Howard Florey Oration. This award recognises a scientist who has made a significant contribution to the understanding of and appropriate use of antimicrobials, and our 2024 Oratory was **Professor Jon Iredell**. Jon's current roles include Centre Director, NHMRC Centre of Research Excellence in Critical Infection and conjoint Professor of Medicine and Microbiology, Sydney Medical School/ Westmead Institute and the Marie Bashir Institute, with his research focussing on infections in critical care, including the study of bacterial septic shock, and in bacterial genetics and ecology. Jon has been fundamental in developing phage therapies in Australia, and his presentation focussed on the phage therapy story. We congratulate Jon for his achievements and look forward to more success with Phage Australia.

Symposium covered a broad range of topics, including "Management and Prevention of Staphylococcus aureus infections", "The Hospital Microbiome", "An Update on Guidelines", "AMR Risk Groups in the Community" and "One Health". As always, the Year in Clinical Infectious Diseases and Year in Clinical Microbiology proved to be both educational and eye-opening at times, and I would like to thank **Katie Flanagan** and **Tony Korman** for all their work they put into

these presentations, as well as all invited speakers, without whom the conference would not have been such a success. The ASA meeting is an opportunity to judge and present our ASA research awards and grants.

The 2024 ASA Research Grant of $25,000 was awarded to **Sewunet Belachew** from the University of Queensland for "Investigating antimicrobial use in Aboriginal and Torres Strait Islander Queenslanders with cancer diagnosis: Insights for effective antimicrobial stewardship". This year the committee took the opportunity of renaming our Research award the "Keryn Christiansen ASA Research Award", in recognition of Keryn's role as a foundation member of ASA and her many years of service on the ASA Committee. I would like to take this opportunity to thank Keryn for her outstanding commitment to ASA, and hope that we continue to see her at "Antimicrobial" well into the future.

I would like to congratulate our three ASA Travel Award winners, awarded to members presenting abstracts at the meeting; **Abiodun David Ogunniyi** from The University of Adelaide, **Nicholas Wei Tek Yee**, Murdoch University and **Adam Stewart**, The University of Queensland.

The 2024 ASA Poster Travel Award for a poster presentation, consisting of a return airfare, conference registration and accommodation to attend ASA 2025, went to **Auriane Form**, of Murdoch University.

The 2024 ASA/bioMerieux Travel Award for proffered poster or oral presentation dealing with the issue of identification of antimicrobial resistance was won by **Nicola Woodfield** of Melbourne Pathology.

Many of the Antimicrobials 2024 presentations and posters are available in the members area of the Society's website due to the generosity of speakers who have agreed to make their presentations and posters available on the website.

Antimicrobials 2025 will be held in Melbourne, and I look forward to seeing everyone there in February.

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IN THE SPOTLIGHT

Implementing beta-lactam antibiotic therapeutic drug monitoring in the intensive care unit

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Introduction

Fixed-dose beta-lactam antibiotic (beta-lactam) therapy in critically ill septic patients results in unpredictable and variable plasma concentrations.[1] This is due to the impact of altered pathophysiology that occurs in critical illness such as changes to volume of distribution and clearance, hypoalbuminemia, fluid shifts, and the use of organ support (e.g., extracorporeal membrane oxygenation) on beta-lactam pharmacokinetics (PK).[1] Subtherapeutic beta-lactam concentrations can lead to treatment failure and emergence of resistance while supratherapeutic concentrations carry the risk of toxicity. Both scenarios lead to poor clinical outcomes. Therapeutic drug monitoring (TDM) as a dose optimisation tool has been recommended to improve exposure and individualise beta-lactam dosing.[2] Given the importance of early adequate antibiotic exposure in sepsis, the overall aim of my PhD is to address the implementation of beta-lactam TDM in the ICU. The specific aims are to outline 1. the rationale for beta-lactam TDM; 2. the impact of beta-lactam TDM on clinical outcomes; 3. stakeholder-perceived barriers and enablers to beta-lactam antibiotic TDM; and 4. piloting the implementation of beta-lactam TDM and demonstrating the feasibility of conducting a randomised controlled trial in the critical care setting. The specific beta-lactams included in these studies are meropenem, piperacillin (with tazobactam) and cefepime.

As a prelude to these aims, we conducted a literature review describing the beta-lactam PK/PD index (T>MIC) for optimal efficacy and outlined the PK/PD targets, the rationale and indications for beta-lactam TDM (Tables 1 and 2.).[3] We developed a clinical workflow that outlines key steps and decision points in the TDM process, delineating essential roles, and specifying necessary resources that facilitate the incorporation of beta-lactam TDM in routine practice (Fig. 1.).[3] Establishing the rationale and mapping out the workflow constitute the preliminary actions in developing an implementation strategy for beta-lactam TDM.

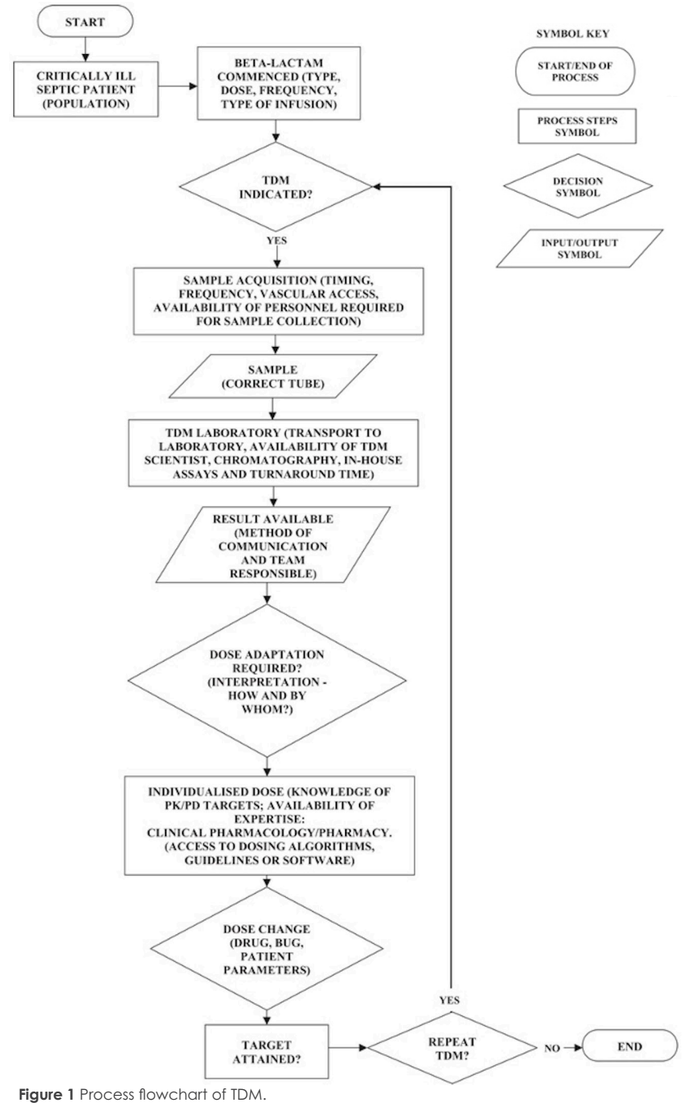
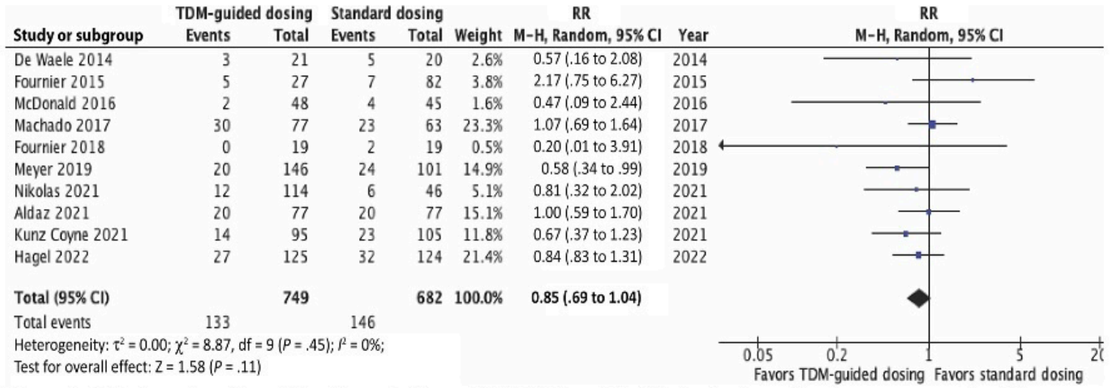
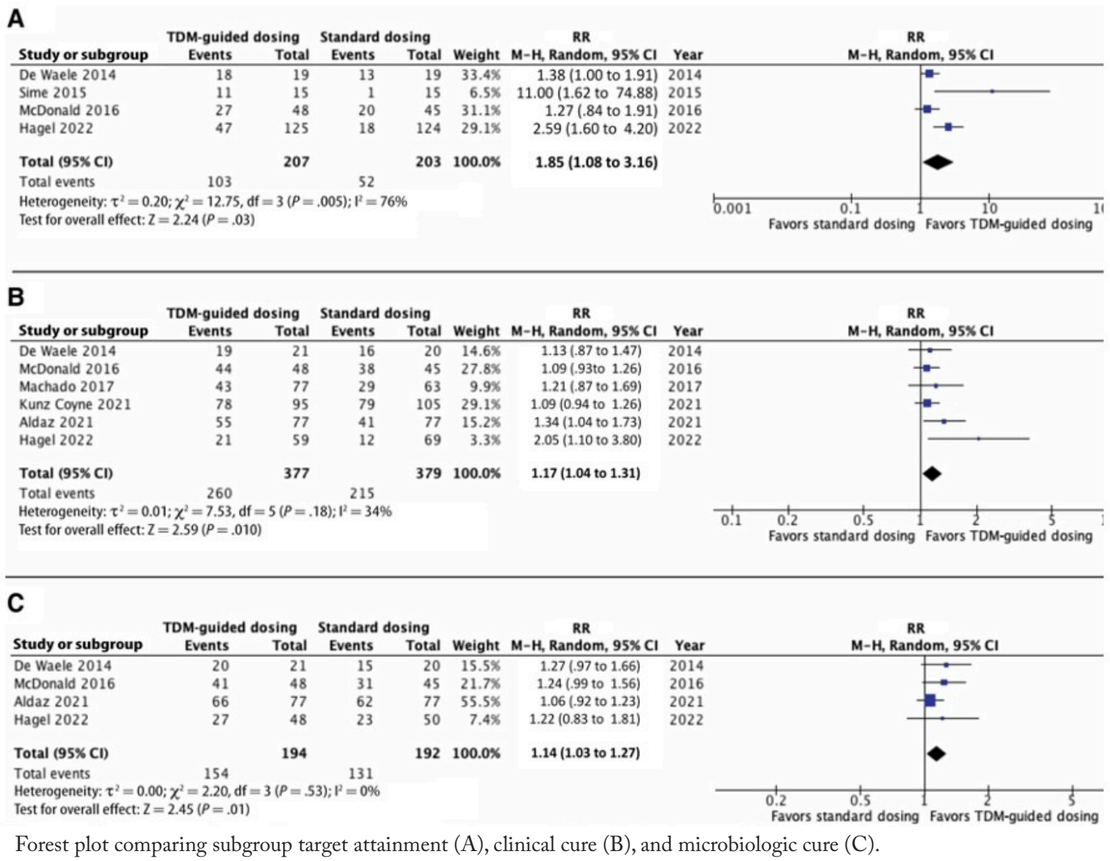


Figure 1 Process flowchart of TDM.



Forest plot showing the risk of mortality with TDM-guided beta-lactam dosing compared with standard dosing.



Forest plot comparing subgroup target attainment (A), clinical cure (B), and microbiologic cure (C).

Figure 2 Forest plots comparing outcomes. The blue squares represent the effect estimates from individual studies; the size of the square is proportional to the weight of the study. The horizontal lines represent the 95% CI of the study estimate. The black diamond represents the pooled effect size. Abbreviation: CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel Test; RR, risk ratio; TDM, therapeutic drug monitoring

Research studies

In the first study, we assessed beta-lactam antibiotic exposure from standard dosing by conducting a prospective observational study in the ICU. In this study, we included critically ill septic patients (n = 37), who were treated with either meropenem (n = 20), or piperacillin (n = 17).[4] We measured plasma concentrations at the mid-point and end of the dosing interval. A significant portion of the study population did not achieve the desired drug exposure targets; 27.8% of the patients had concentrations < 50%*f*T>MIC (subtherapeutic), and 50% of the patients had concentrations < 100% *f*T>MIC.[4] The study highlighted significant variability in plasma concentrations with standard dosing regimens. We found a variation of over 140-fold and over 200-fold in the trough concentrations of piperacillin and meropenem, respectively, underscoring the high degree of pharmacokinetic variability in septic patients and the need to re-evaluate our dosing regimens.[4]

Next, we evaluated the impact of beta-lactam TDM on patient outcomes through a systematic review and meta-analysis.[5] We included 11 studies assessing beta-lactam TDM-guided dosing vs standard dosing, n = 1,463 participants. TDM-guided dosing was associated with improved clinical and microbiological cure and treatment response as well as improved target attainment: clinical cure (RR, 1.17; 95% CI, 1.04 - 1.31), microbiological cure (RR, 1.14; 95% CI, 1.03 to 1.27), treatment failure (RR, 0.79; 95% CI, 0.66 to 0.94), and target attainment (RR, 1.85; 95% CI, 1.08 to 3.16). No statistically significant association was demonstrated with mortality or length of stay (Fig. 2.).[5] However, these studies were limited by their sample size, delays to TDM and subsequent dose adaptation, inclusion of critically ill patients without infection, and overall a high risk of bias.

> “The study highlighted significant variability in plasma concentrations with standard dosing regimens.”

Following this redearch, we conducted a qualitative study using the Theoretical Domains Framework and Capability, Opportunity and Motivation Behaviour Change model to inform stakeholder-perceived barriers and facilitators to beta-lactam TDM implementation.[6] We conducted semi-structured interviews with pharmacists, nurses, laboratory scientists and physicians (n = 40).[6] Interview data were analysed using thematic analysis. The overall themes were; necessity for clear guidelines and processes involving dose adaptation and provision of tailored, stakeholder-specific education and training, the importance of interdisciplinary trust and collaboration, the need for strong leadership, governance and diagnostic stewardship, the timely availability of assays and results, and infrastructure support Teamwork and collaboration were also recurring themes as were regular audit and feedback. An interesting finding was that stakeholders did not view mortality benefits as a critical measure for successful uptake. Instead, they highlighted the delivery of safe and effective antibiotic treatments as a key facilitator. Successful and sustained uptake of beta-lactam TDM necessitates engagement of stakeholders throughout the implementation process and beyond.[6]

We then conducted a pilot feasibility randomised controlled study (results to be published, protocol number ACTRN12623000032651). In preparation for this study, we collaborated closely with our clinical pathology laboratory to develop and validate in-house assays for the key beta-lactam antibiotics. The primary aims of this trial being to evaluate the feasibility of recruitment and early randomisation (within 24-48 hours of study antibiotic commencement), and the fidelity of TDM implementation. We hypothesised that early randomisation to beta-lactam TDM in the ICU is feasible, that TDM processes can be applied as intended, and that TDM-guided dose adaptation is acceptable to clinicians. Our secondary aims include providing preliminary data on the impact of TDM on target attainment, clinical and microbiological cure, and safety. The preliminary findings of this pilot are encouraging, suggesting

Table 1. Pharmacokinetic/pharmacodynamic targets for beta-lactam antibiotics for efficacy and toxicity

Beta lactam class	PK/PD target (efficacy)	PK/PD threshold for toxicity
Penicillin Cephalosporin Carbapenem Monobactam	≥ 50%*f*T>MIC 40 – 70% *f*T>MIC 40%*f*T>MIC[1] 50%*f*T>MIC	[1]Variable depending on organ involved and type of beta-lactam. *f*T > 6-10xMIC is considered toxic.
[2]Beta-lactam (all classes) threshold in critically ill	100%*f*T>MIC or 100%*f*T>4xMIC	Neurotoxicity PIP: C_{min} > 361.4 mg/L[8] MEM: C_{min} > 64.2 mg/L[8] FLX: C_{min} > 125.1 mg/L[8] FEP: C_{min} > 20 - 40 mg/L[9] FEP: C_{ss} > 60 mg/L[10] Nephrotoxicity PIP: C_{min} > 452.65 mg/L[8] MEM: C_{min} > 44.45 mg/L[8]

[1]No clear threshold has been identified, threshold values derived from retrospective data. [2]Targets for maximal efficacy based on animal studies, in vitro studies and some clinical studies; FLX, flucloxacillin

Table 2. Indications for beta-lactam TDM

Indications
Critically ill with suspected or proven sepsis
Augmented or reduced renal clearance
ECMO and CRRT
Special populations: Immunocompromised, severe burns, extremes in body size, i.e., very low BMI/cachexia or morbid obesity*
Deep-seated infections*, e.g., CNS, bone and joint, heart valve, pacemaker, vascular graft
Incomplete source control or high inoculum infections*
Infections with less susceptible organisms
Suspected toxicity, i.e., cefepime, imipenem and meropenem

*Limited data, authors' recommendations; ECMO, extra-corporeal membrane oxygenation; CRRT, continuous renal replacement therapy; CNS, central nervous system; BMI, body mass index.

that beta-lactam TDM can be executed with efficiency and has the potential to be adopted into standard sepsis management protocols in routine clinical practice.

Recommendations & conclusions

We know that changes in PK, patient pathophysiology, and pathogen characteristics are key considerations when optimising dosing and exposure. [7] Beyond these, our work identifies three additional considerations when implementing beta-lactam TDM: (healthcare) provider engagement, partnership between healthcare teams and organisational leadership, and provision of resources and infrastructure. The preliminary phase of implementation is underpinned by process planning, the establishment of a robust conceptual workflow framework, and the precise assignment of roles and responsibilities. Engaging stakeholders is paramount and their insights are invaluable, providing the necessary data to effectively trial the intervention. Securing sustained commitment is instrumental for long-term implementation success.

Key findings & recommendations

- Standardised dosing protocols result in variable and suboptimal drug exposures.
- TDM-guided dosing of beta-lactams significantly enhances the likelihood of achieving therapeutic targets.
- Current prospective studies have limitations that hinder definitive conclusions regarding clinical outcomes; hence, future research must tackle these issues to clarify the impact of TDM-guided dosing on patient-centred outcomes.
- Understanding the barriers and facilitators perceived by stakeholders is crucial to developing effective implementation strategies.
- Before deploying TDM practices, it is important to outline processes, clearly define provider roles and responsibilities, and conduct feasibility studies to evaluate the efficacy of the processes in place.

Closing remarks

In essence, my PhD offers a theoretical justification for beta-lactam TDM and a practical and actionable plan for its adoption, underpinned by insights from research. It highlights the role of beta-lactam TDM in driving a shift towards more individualised and effective care within a complex setting such as the ICU.

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19th International Symposium on Staphylococci and Staphylococcal Infections

18 - 21 August 2024
Perth, Western Australia

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ISSSI 2024

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Abstract Submission Deadline
Friday 31st May 2024

Early Bird Registration Deadline
Friday 12th July 2024

Accommodation Booking Deadline
Friday 12th July 2024

PLENARY SPEAKERS

MICHAEL OTTO

TIM STINEAR

SUSAN HUANG

JON IREDELL

ANTON PELEG

INTRODUCTION

Dear Colleagues,

It is a pleasure to invite you to participate in the 19th International Symposium on Staphylococci and Staphylococcal Infections, which will be held on 18 – 21 August 2024 in Perth, Australia - Perth Convention and Exhibition Centre.

ISSSI 2024 will cover many interdisciplinary subjects regarding staphylococci and staphylococcal infections. Sessions will be presented by the world's leading experts in each of the research fields. Oral and poster sessions will be an integral part of the program as well, and all delegates are invited to submit abstracts. To promote discussion and interaction between delegates and the invited speakers, the meeting's registration includes the welcome and farewell receptions, the conference dinner, lunches and morning and afternoon teas.

ISSSI 2024 will be held at the Perth Convention and Exhibition Centre located in the heart of the city. World class public transport, hotels and internationally acclaimed bars and restaurants are all within walking distance from the Centre. The Perth international and domestic airport terminals are only a short transit to the city and are serviced by numerous daily direct flights from Asia and Europe.

We are confident that you will find the symposium's programme both scientifically stimulating and informative and we look forward to meeting you in Perth.
Kind regards from the ISSSI 2024 Organising Committee:

Geoffrey Coombs // Murdoch University, Australia
Shakeel Mowlaboccus // Murdoch University, Australia
Dorte Frees // University of Copenhagen, Denmark
Anders Rhod Larsen // Statens Serum Institute, Denmark

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ISSSI 2024

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CALL FOR ABSTRACTS

The 19th International Symposium on Staphylococci and Staphylococcal Infections invites the submission of abstracts for consideration at the conference.
Abstract submission STRICTLY closes Friday 31 May 2024.
All submissions must be made via the online Abstract Submission Portal - www.isssi2024.org

ISSSI TRAVEL AWARD

A number of Young Investors Travel Awards will be provided to applicants under the age of 35, who will be presenting at the International Symposium on Staphylococci and Staphylococcal Infections (ISSSI). Up to five travel awards will be available.

Each successful awardee will be granted AUD1,000 towards the costs of their travel to Perth and their accommodation as well as a free symposium registration. They will also be presented with an award certificate during the symposium.

All young investigators who submit an abstract are encouraged to apply. The awards will be based on the abstract submitted by an applicant who should be the presenting author (poster or oral presentation).

If you wish to apply for an award, please submit your application to ASA at info@asainc.net.au by 31 May 2024.
The application should include a copy of the abstract and for the abstracts with more than one author, a letter stating the relative contribution of the application towards the research.

REGISTRATION

	Early Bird	Standard
Standard Registration	$1,250.00*	$1,500.00
Low and Middle Income Countries (LMICs)	$750.00**	$900.00**
Student Registration	$750.00*	$900.00
Day Registration	$550.00*	$650.00

All registration fees are in AUD.
*Early Bird Discount expires **Friday 12 JULY 2024**
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AMR SURVEILLANCE

HOTspots

AMR surveillance and response in northern Australia

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CSIRO's HOTspots Surveillance and Response Program (HOTspots) monitors the epidemiology of antimicrobial resistance (AMR) to inform regional, national and international actions.

Established in 2019, HOTspots is part of CSIRO's Australian e-Health Research Centre (AEHRC), the largest digital health research program in Australia. AEHRC's leading contribution to national informatics and interoperability initiatives ensures the HOTspots team is at the heart of the latest technological advancements in digital transformation and health service delivery for AMR.

The program aims to strengthen cross-jurisdictional and cross-sector AMR surveillance, while simultaneously supporting antimicrobial stewardship (AMS) in regional and remote settings that have historically fallen outside of surveillance reach.[1] HOTspots currently focuses on northern Australia, where the health and economic burden of AMR is exceedingly high and geographically diverse.[2]

HOTspots works with key stakeholders across northern Australia, including, but not limited to, the Northern Territory Primary Health Network (NT PHN), NT Government, and the Queensland Statewide Antimicrobial Stewardship Program.

Key objectives of the HOTspots program include:

- Capacity building of the regional and rural healthcare workforce through the National Aboriginal Community Controlled Health Organisation's (NAACHO) AMS Academy and NT PHN training programs.
- Strengthening stewardship programs in hospitals and community healthcare clinics
- Working with guideline developers (i.e., Central Australian Rural Practitioners Association (CARPA) Standard Treatment Manual and inclusion of HOTspots in NT PHNs HealthPathways**).**
- Developing digital solutions (i.e., surveillance website and customisable antibiograms) that facilitate AMR data use and sharing across sectors and jurisdictions.
- Informing the need for public health action in a region of high burden and low resourcing.

At the national level, HOTspots has contributed to nation-wide surveillance through submission of data to the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System, providing access to data not previously covered by existing surveillance systems.

HOTspots combines data from key pathology providers representing over 200 public, private and defence hospitals, community clinics, aged care, and prison facilities across Western Australia, Northern Territory, and Queensland where access to healthcare, and availability of health infrastructure, is limited.

HOTspots collects pathology data from 13 organisms. More complete data,for trends and geographical coverage, are available for ten organisms. See Figure 1 for HOTspots data collection and visualisation processes.

Data are currently updated every 6 months and are validated at the time of data receipt.

A flagship of the HOTspots program is the HOTspots digital surveillance platform (**https://amr-hotspots.net/**). It is currently the only implemented[2] and evaluated[3] digital AMR surveillance tool used by clinicians at the point of care and for local and national AMR priority settings. HOTspots displays region-specific antimicrobial susceptibility and demographics data on key bacterial isolates to support clinical decision making based on information that is relevant to their local patient population. The HOTspots digital platform is an open-access, interactive data visualisation tool featuring maps, plots, and antibiograms offering insight into AMR behaviour and trends over time (refer Figure 2).

Through a growing network of international collaborations, HOTspots continue to contribute to global[4-6] and Australian burden of disease studies[7-12].

The HOTspots team is continually innovating and expanding, bringing new collaborators on board with a plan to expand the program geographically. The goal is to create an Australia-wide AMR atlas.

HOTspots is also exploring program expansion beyond human antimicrobial resistance to include monitoring the spread of AMR in animal populations and investigating the movement of resistant pathogens in the environment.

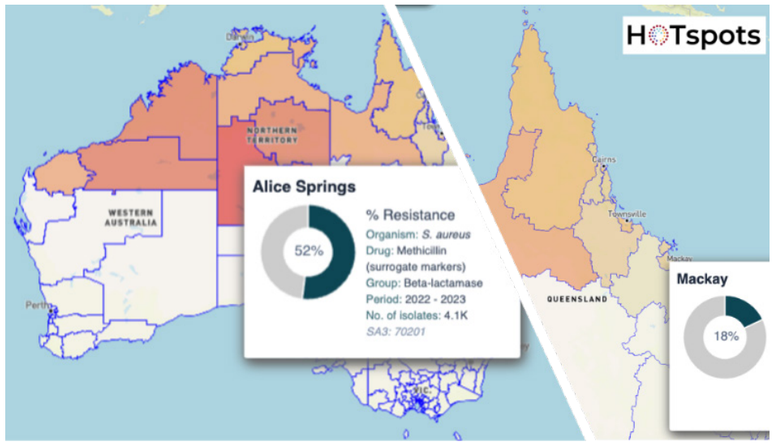

Figure 2. The HOTspots digital surveillance platform outputs https://amr-hotspots.net/

Data collection and visualisation

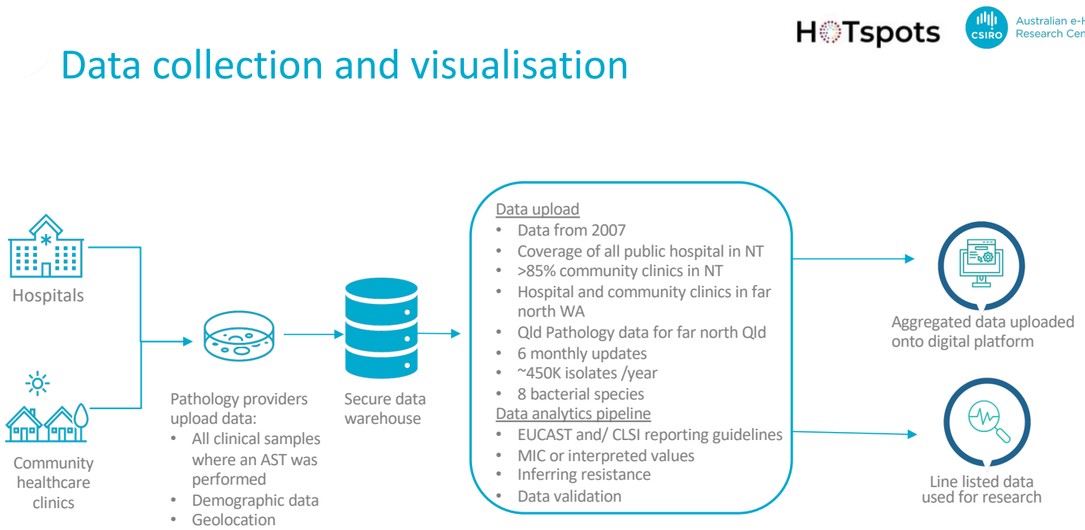

Figure 1. HOTspots data collection and visualisation.

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AMR SURVEILLANCE

ANTIBIOTIC RESISTANCE IN GRAM-NEGATIVE BACTERIA:

AGAR GnSOP genetic and genomic data (2019-2022)

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Background

The Australian Group on Antimicrobial Resistance (AGAR) performs annual surveillance to monitor changes in antibiotic resistance (AMR) in Gram-negative pathogens (Gram-negative Surveillance Outcome Program, GnSOP). The program now includes Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter* spp. from bacteraemia episodes [1].

Until recently, selected AMR determinants in GnSOP were detected by PCR only. Isolates from 2015-2016 with a carbapenemase gene underwent short-read whole genome sequencing (WGS) at the Microbiological Diagnostic Unit, Peter Doherty Institute and those from 2017-2018 were sequenced as part of the standard GnSOP programme, with WGS expanded to other isolates from 2019. To date, >4,000 isolates referred for further analysis have been sequenced: over 70% of those referred in 2019 and 2020, with a specific focus on *Escherichia coli* and *Klebsiella pneumoniae* with an extended-spectrum β-lactamase (ESBL) phenotype, and all referred isolates (more details in annual reports [1]) since 2021 (**Figure 1A**). WGS data (Microbial Genomics Reference Laboratory, Westmead Hospital) were assembled and analysed using a modified version of the Nullarbor bioinformatic pipeline [2] and a custom pipeline to accurately detect AMR genes. This pipeline also identifies mutations in chromosomal genes associated with AMR, including *gyrA* and *parC* (fluorquinolone resistance) and in porin genes and gene encoding penicillin binding proteins (PBPs), both of which can contribute to β-lactam resistance. Additional funding in 2020 enabled long-read (PacBio Hi Fi) sequencing of selected isolates (n=48), to generate full plasmid assemblies and better identify genetic contexts of selected AMR genes.

Here, we summarise recent data about the dominant Gram-negative clones circulating in Australia and their genetic determinants of AMR, as well as the genetic locations of important AMR genes, mainly focusing on *Escherichia coli* isolates 2019-2022 (presented as two proffered talks at ASA Antimicrobials 2024).

Escherichia coli is the predominant species and ST131 is the dominant sequence type.

Of n=36,281 Gram-negative isolates recovered from bacteraemia episodes in Australia since 2019, over half were *E. coli* (n=20,038) [1] (**Figure 1A**). The globally disseminated *E. coli* sequence type (ST) 131, [3-5], was also the dominant ST in Australia (1,041/2,479=42%) in all four years (**Figure 1B**). Other ST consistently identified over this time are ST1193, ST69, ST38 and ST73 (2-10% of *E. coli* with WGS every year. **Figure 1B**). In contrast, isolates of other prevalent species, *Klebsiella pneumoniae* complex and *Enterobacter cloacae* complex, belong to many different STs (data not shown).

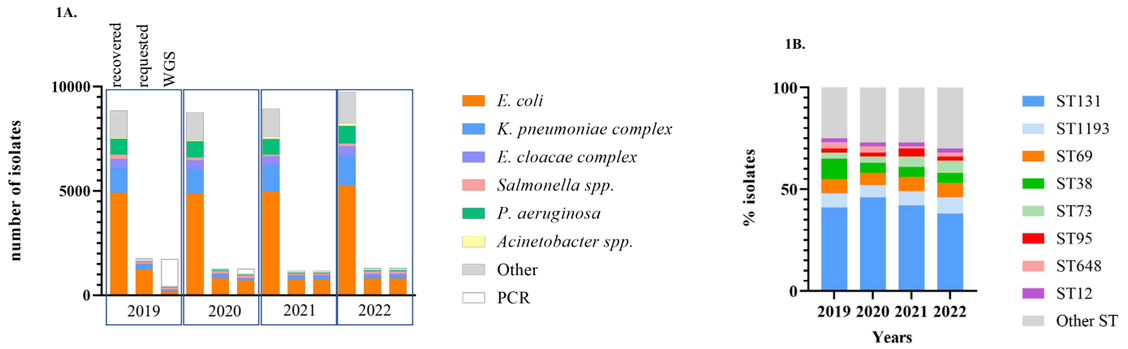

Figure 1 Species and sequence types of isolates from, GnSOP 2019-2022. **A.** recovered, total no. of Gram-negative isolates recovered from bacteraemia episodes; requested, isolates sent to The Westmead Institute for Medical Research for further analysis (PCR in 2019 and 2020 and/or WGS from 2019); WGS: requested isolates that underwent WGS. **B.** Major *E. coli* STs identified in GnSOP (2019-2020).

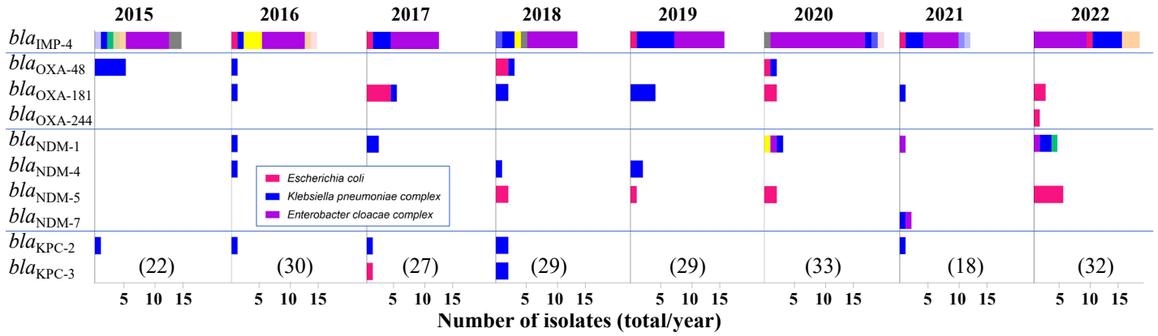

Figure 2. Carbapenemase genes identified in GnSOP isolates (n=220, 2015-2022). For simplicity, only the most common carbapenemase genes detected are listed on the left. The main bacterial species carrying carbapenemase genes are shown in the key. Remaining colours correspond to other *Klebsiella* spp. (pale purple). *Serratia marcescens* (pale pink), *Citrobacter* spp. (grey), *Acinetobacter* spp. (yellow) and *P. aeruginosa* (green). bla_{OXA-23} and $bla_{GES/VIM}$ were also detected, mostly associated with *Acinetobacter* spp. and *P. aeruginosa*, respectively. More information on carbapenemase genes is available in annual reports [1].

Few isolates carry a carbapenemase gene

The prevalence of carbapenemase genes is low in Australia (n=220 carbapenemase genes detected in 4,061 isolates sequenced since 2015) but these are clearly dominated by bla_{IMP-4} (n=117/220, **Figure 2**). *E. cloacae* complex and *K. pneumoniae* complex isolates have been driving the spread of bla_{IMP-4}, usually associated with M2 or HI2 plasmids (in at least 73 isolates, data not shown), as previously reported [6-8]. Smaller numbers of isolates with carbapenemase genes in the bla_{OXA-48}-like group or with bla_{NDM} or bla_{KPC} variants have also been consistently detected, mainly *E. coli* and *K. pneumoniae* complex, with relative proportions varying from year to year (**Figure 2**). bla_{OXA-23} and $bla_{GES/VIM}$ were almost exclusively associated with *Acinetobacter* spp. and *P. aeruginosa*, respectively, with a couple of exceptions [1]. Resistance to carbapenems could be generally explained by the presence of carbapenemase genes in Enterobacterales.

In *K. pneumoniae* complex isolates meropenem non-susceptibility was sometimes explained by ESBL or *ampC* genes in combination with porin mutants.

Resistance to ESBL and quinolones.

bla_{CTX-M} genes have remained the most prevalent AMR genes conferring resistance to widely used third-generation cephalosporins (ceftazidime and ceftriaxone) in bloodstream infection episodes in Australia 2019-2022 (shown for *E. coli* in **Figure 3A**). Some plasmid-borne *ampC* genes (mostly bla_{CMY-2}-like: n=166/376 or and bla_{DHA}: n=208/376 with *ampC*) were also detected, mostly in *E. coli* ST other than ST131. As with *E. coli* overall, ST131 is the predominant ST carrying bla_{CTX-M}, mainly *fimH*30 and *fimH*41 subtypes with $bla_{CTX-M-15}$ or $bla_{CTX-M-27}$, but ST1193, ST69, ST38, ST73, ST95, ST648 and ST12 also carry bla_{CTX-M} genes (mainly $bla_{CTX-M-15}$, $bla_{CTX-M-27}$ or $bla_{CTX-M-14}$; **Figure 3B**). *K. pneumoniae* complex isolates with an ESBL phenotype mainly carry $bla_{CTX-M-15}$ and/or bla_{DHA-1} (data not shown). Quinolone resistance is mainly associated with chromosomal mutations (*gyrA*, *parC*, *parE*) in specific *E. coli* STs (ST131, ST1193) but with plasmid-borne determinants (*aac(6')-Ib*-cr, *qnr*) in *K. pneumoniae* (data not shown).

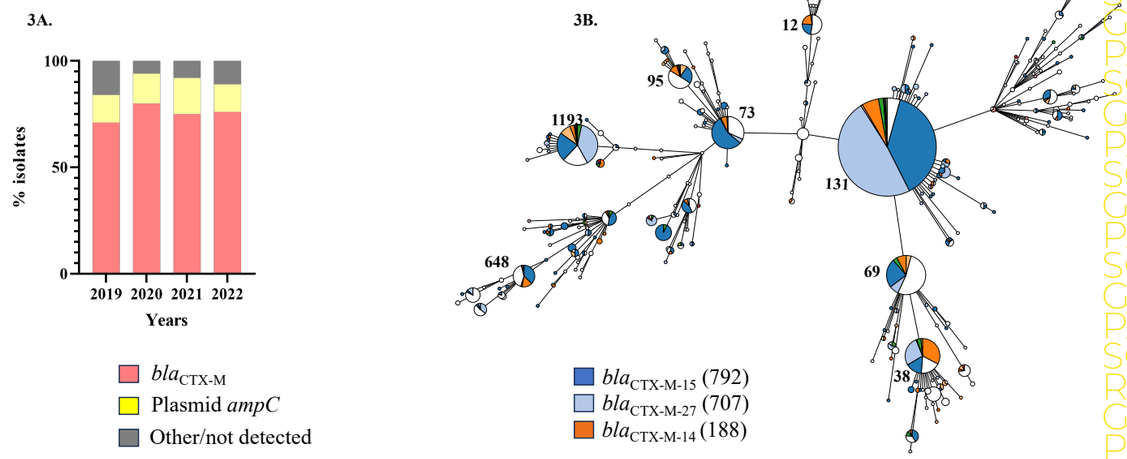

Figure 3. bla_{CTX-M} genes in *E. coli* with an ESBL 2019-2022. **A.** Main AMR genes likely to explain the ESBL phenotype. **B.** Minimum spanning tree of all sequenced *E. coli* isolates (n=2,479) based on their MLST profile (generated with GrapeTree [13]). Each circle corresponds to a distinct ST, with its size proportional to the number of isolates that it contains (for scale, 1,041 isolates are ST131). Within the circle for each ST, the proportion of strains harbouring each bla_{CTX-M} gene is shown as a coloured sector. The key shows the most common bla_{CTX-M} genes but $bla_{CTX-M-55}$ (light orange), $bla_{CTX-M-3}$ (red), $bla_{CTX-M-24}$ (light green) and other bla_{CTX-M} genes (dark green) were also found, and isolates without a bla_{CTX-M} gene are left white. A total of 1,833 *E. coli* isolates carry a bla_{CTX-M} gene.

Chromosomal integration of $bla_{\text{CTX-M}}$ genes in *E. coli*

Although it is assumed that AMR genes in Gram-negative organisms generally disseminate on plasmids, critical AMR genes are increasingly reported on bacterial chromosomes [9-12]. Analysis of short-read WGS data for the 1,833 *E. coli* isolates with a $bla_{\text{CTX-M}}$ gene sequenced since 2019 suggests that these genes are mainly found on the chromosome in some major pandemic lineages (ST131, ST38, ST1193, ST12) with insertion mediated by two insertion sequences (IS), IS*Ecp1* or IS*26*. In cases where the chromosomal contexts could be identified, these vary depending on the specific combination of bacterial lineage and $bla_{\text{CTX-M}}$ gene. Most isolates carry one $bla_{\text{CTX-M}}$ gene on the chromosome, but in some several copies of the same $bla_{\text{CTX-M}}$ gene have been inserted, while others also carry the same $bla_{\text{CTX-M}}$ gene on a plasmid. Long-read sequencing of selected isolates with multiple copies of $bla_{\text{CTX-M}}$ confirmed a chromosomal location in most cases. Some *K. pneumoniae* complex and *E. cloacae* complex isolates also carry $bla_{\text{CTX-M}}$ gene(s) on the chromosome.

Plasmids carrying $bla_{\text{CTX-M-27}}$ in *E. coli*.

Nine isolates from 2020 carrying $bla_{\text{CTX-M-27}}$, the most common $bla_{\text{CTX-M}}$ group 9 gene, underwent long-read sequencing to confirm the location of this gene (plasmid and/or chromosome) and provide references for analysis of short-read data. Complete plasmids were successfully assembled for 7/9 isolates from ST where $bla_{\text{CTX-M-27}}$ was most common (light blue in **Figure 2B**; n=4 ST131 *fimH*41, n=2 ST38 and n=1 ST1193). Different multi-replicon F-type plasmids were identified in the different ST. These plasmids have some backbone components in common and generally carry the same core set of AMR genes in addition to $bla_{\text{CTX-M-27}}$ [*dfrA17*, *aadA5*, *sul1*, *mph*(A), *strAB*, *sul2* and *tet*(A)] but in slightly different contexts. Searching short-read data for all *E. coli* of ST131 *fimH*41, ST38 and ST1193 with $bla_{\text{CTX-M-27}}$ 2020-2022 for key components and boundaries in these plasmids in suggest that particular ST mainly carry the same plasmid type.

Conclusions

In addition to identifying the most common AMR genes, previously detected by PCR, incorporation of WGS into national Gram-negative surveillance has allowed us to identify specific AMR gene variants, the most common ST carrying AMR genes, the location of important AMR genes (in plasmid(s) and/or on the chromosome) and the contribution of chromosomal mutations to AMR (e.g., in porins, PBPs, *gyrA*, *parC*). The use of long read sequencing is also helping to generate complete accurate assemblies of key reference plasmids carrying AMR genes in Gram-negative pathogens in Australia.

Acknowledgments
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KERYN CHRISTIANSEN ASA RESEARCH GRANT

Insights for effective antimicrobial stewardship

Investigating antimicrobial use in Aboriginal and Torres Strait Islander Queenslanders with cancer diagnosis

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BACKGROUND

Cancer continues to pose a significant public health challenge in Australia, especially among Aboriginal and Torres Strait Islander Peoples (hereafter, respectfully referred to 'Indigenous Australians'). Health disparities are notably pronounced among Indigenous Australians, with significantly higher cancer mortality rates and lower 5 year survival (1).

In Queensland over 30,000 individuals were diagnosed with cancer in 2020 (2). In addition to complex cornerstone cancer treatments, appropriate use of antimicrobials plays a crucial role in the care of cancer patients. As many cancer treatments, such as chemotherapy, radiation, and stem cell transplantation, can compromise the patient's immune system, they may become more susceptible to infections (3). Antimicrobials, which include antibiotics, antifungals, and antivirals, are employed to prevent, and treat these infections, ensuring that the patient remains healthy enough to continue with their cancer treatments (3).

Antimicrobial resistance (AMR), the phenomenon where germs (bacteria, viruses, or fungi) causing infections resist the effects of medicines used to treat them, has emerged as a global health threat (4, 5). This concerning phenomenon is currently unfolding in Australia (4). Antimicrobial misuse and overuse largely contribute to the emergence of resistance, rendering these life-saving medications ineffective. The current evidence indicates that Australians frequently use antibiotics. For instance, among 28 European nations, Australia ranks eighth in antibiotic usage (4), leading to a heightened risk of AMR. While there is not evidence specifically addressing antimicrobial use in Indigenous Australians diagnosed with cancer, existing research does suggest elevated antimicrobial use within this community (6-8). For cancer patients, whose immune systems are often compromised due to treatment modalities, the consequences of ineffective antimicrobial therapy can be dire (9). Individuals with cancer have a threefold increased risk of dying to severe infections compared to those without cancer (9). Infections contribute to nearly 50% of fatalities among patients with haematological disorders or solid organ cancers (10).

Awareness about rational antimicrobial use and the repercussions of AMR among cancer patients and caregivers, are crucial for ensuring the judicious use of antimicrobials. In addition, understanding antimicrobial use patterns is crucial as it informs decisions. However, limited research exists on the patterns/trends, understanding, and practices of antimicrobial use among Indigenous cancer patients, despite its importance in their care. Furthermore, antimicrobial stewardship – a systematic effort to ensure responsible antimicrobial use – can mitigate AMR risks in cancer patients (11, 12). Yet, its establishment within Indigenous Australian cancer patients potentially poses unique challenges and opportunities that are not yet explored.

HYPOTHESIS

Knowledge and attitudes towards antimicrobial use and AMR among Indigenous Australians diagnosed with cancer may be influenced by cultural beliefs, past experiences, trust, or mistrust in the healthcare system. As such, an understanding of the beliefs,

knowledge, and practices of Indigenous Australians diagnosed with cancer, concerning antimicrobial use, is crucial. Indigenous cancer patients in Australia may have unique antimicrobial use patterns compared to non-Indigenous patients due to differences in healthcare access, sociocultural factors, or infectious disease prevalence. Investigating this can guide targeted interventions involving Aboriginal and Torres Strait Islander Community Controlled Health Organisations (ACCHOs) and policy to improve antimicrobial stewardship and healthcare equity. Furthermore, there could also be specific barriers, possibly rooted in communication gaps, or cultural differences, along with the disease condition, that hinder judicious use of antimicrobials in Indigenous cancer patients. Identifying key stakeholders, including patients, physicians, nurses, and caregivers, and understanding their perspectives, can provide actionable insights to bridge the gap between current practices and effective antimicrobial stewardship tailored for Indigenous Australians with cancer diagnosis.

STUDY DESIGN

This project is designed in two large phases, ensuring comprehensive data collection and subsequent actionable insights, tailored for Indigenous Queenslanders with cancer diagnosis.

PHASE 1: EXISTING LANDSCAPE OF ANTIMICROBIAL USE AND THE KAP FRAMEWORK

PHASE 1A: ANTIMICROBIAL USE PATTERNS

The extent and type of antimicrobials utilised will be examined using linked Queensland CancerCost MOD data covering 2011 to 2018. We aim to analyse antimicrobial use patterns or trends among adult Indigenous Queenslanders with cancer, including the types of cancer, when antibiotics are administered, and comorbidity conditions. Data access is secured. This phase also expected to help tailor the upcoming survey tool for Indigenous populations and guide participant focus.

PHASE 1B: CROSS-SECTIONAL SURVEY

The aim of this phase is to develop or tailor and test a comprehensible, meaningful, and culturally appropriate tool for examining the knowledge, attitudes, and personal experiences related to antimicrobial use and AMR among adult Indigenous Queenslanders recently diagnosed with cancer. The survey will include questions and measures informed by the literature, the findings from phase 1A, team discussions, and expert input, with lead investigator expertise guiding the process. Participants will also have the opportunity to indicate if they would be willing to participate in Phase 2 of this study.

This is a standalone project, however, one of our strategic advantages lies in the commencement of a prospective First Nations cohort study (CanCo) in January 2024. CanCo will recruit adult Indigenous Queenslanders within the first 8 weeks of being diagnosed with cancer. CanCo provides a well-established research environment and a direct access to invite potential participants for our survey. We aim for around 190 sample.

Furthermore, the alliance between our project and the CanCo is fortified by shared investigators, encompassing experienced researchers in Indigenous health, increased feasibility for participant recruitment and effective project execution.

PHASE 2: QUALITATIVE INTERVIEWS

The next phase will include in depth interviews to gain a deeper understanding of the experiences and insights of participants on antimicrobial use and AMR.

Participants for this phase will include patients, caregivers of patients and health professionals.

Following analysis of the survey data and team consultation, we will develop a semi-structured interview guide focusing on several key areas:

- Personal experiences related to antimicrobial use and AMR.
- Patient and health professional information and resources.
- Identification of barriers and facilitators that influence the rational use of antimicrobials within this patient group.
- Potential solutions and strategies that could improve effective antimicrobial stewardship for these patients.

OUTCOME: TARGETED RESOURCES AND TAILORED TOOL

Our primary goal is to develop actionable strategies and resources based on the findings of phase 1 and 2. This includes creating targeted resources such as informative fact sheets for patients and their caregivers. These strategies and resources are envisioned as cornerstones for both patients and health professionals, providing essential information and practical guidance to raise awareness and demonstrate effective ways to utilise antimicrobials wisely within Indigenous Australians with cancer diagnosis. Additionally, this project produces a tailored tool for assessing the knowledge, attitudes, and practices of Indigenous Australians diagnosed with cancer regarding antimicrobial use and AMR.

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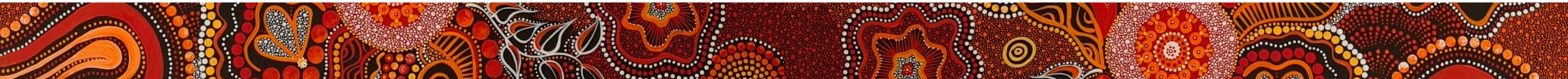

QUIZ ANSWER

There is no current endorsed method for synergy testing for ceftazidime-avibactam and aztreonam by either EUCAST or CLSI. Many different methodologies have been proposed as surrogate approximations for the checkerboard broth microdilution [1-2]. The figure demonstrates two of these methods in the published literature.

The majority of the literature regarding synergy testing relates to Enterobacterales (where the main mechanism of carbapenem resistance is mediated through carbapenemases). Methods of synergy testing have higher degrees of categorical error with testing *Pseudomonas aeruginosa*, where multiple mechanisms of resistance can occur and often co-exist. Unlike Enterobacterales, the most common mechanisms of carbapenem resistance in *Pseudomonas aeruginosa* are not carbapenemases, but instead upregulation of cell wall multi-drug efflux pumps (most commonly MexAB – affecting multiple different beta lactams including aztreonam) or downregulation of cell wall porins (most commonly OprD – specific to carbapenems). Carbapenemase producing *Pseudomonas aeruginosa* isolates however do occur and are typically related to exposures in higher risk geographical regions. There is no utility of synergy testing in *Pseudomonas aeruginosa* isolates that do not carry a Class B metallo-beta-lactamase.

The figure highlights some of the challenges of some of the surrogate methods for determination of synergy. Images B and C demonstrates an augmented zone of inhibition, but assessments can be quite subjective. This is important in *Pseudomonas*, as even if activity against the MBL is restored, other mechanisms of resistance that are likely present may still result in phenotypic resistance. The degree of synergy demonstrated in the figure is to a much lesser degree than what is typically seen with Enterobacterales. Aztreonam-avibactam susceptibility testing using gradient strip diffusion was performed on this isolate, which determined an MIC of 8 mg/L. The proposed breakpoints for aztreonam-avibactam AST are ≤ 4 mg/L for Enterobacterales and ≤ 8 mg/L for *Pseudomonas aeruginosa* (aligned with the aztreonam clinical breakpoints for both CLSI and EUCAST) [2]. This isolate falls within the susceptible range but is sitting close to the breakpoint. Mechanisms of aztreonam-avibactam resistance in *Pseudomonas* are primarily mediated through upregulation of the efflux pump MexAB (with risk of resistance on treatment), but less commonly may be due to mutations in the omega loop of Pseudomonal ampC, acquired KPC mutants, or PBP3 mutations [3].

Given the limitations of the synergy testing methodology for *Pseudomonas aeruginosa*, an aztreonam/avibactam MIC close to the proposed breakpoint, and risk of further resistance through alternative mechanisms of resistance, ceftazidime/avibactam and aztreonam should be used cautiously. Drug exposure and source control should be optimised where possible in the context of the type of infection being treated, the use of combination therapy with other antimicrobials should be considered, and the patient closely monitored for signs of treatment failure on therapy. If available and appropriate for the clinical context, adjunctive bacteriophage therapy could be considered.

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ASA24 CONFERENCE FEEDBACK

I was awarded a Travel Grant by the Australian Society for Antimicrobials to attend the Antimicrobials 2024 conference held at the Sydney International Convention Centre. At the conference, I gave an oral presentation entitled

BIOLUMINESCENT MOUSE MODELS OF BACTERIAL INFECTION TO TEST EFFICACY OF NEW DRUG CLASSES AGAINST MULTIDRUG-RESISTANT BACTERIAL PATHOGENS

In summary, I presented our findings demonstrating that the first-generation 2-aminopyrimidine compound NCL195 is a potential candidate for further preclinical development as a specific treatment for multidrug-resistant infections either as a stand-alone antibiotic for Gram-positive infections or in combination with sub-inhibitory concentrations of colistin for Gram-negative infections (Figure 1). The bioluminescent models, which enable a substantial decrease in test animals, are a refinement to conventional quantitative culture for bacterial pathogenesis and for preclinical efficacy testing of new drug classes for treating bacterial infections.
I received a lot of positive feedback from the talk, one of which has led to the commencement of a collaboration with Prof Sam Abraham (Murdoch University, Western Australia) to use our bioluminescent mouse infection models for efficacy assessment of new drug classes developed by Industry against multidrug-resistant pathogens.

The Howard Florey Oration by Prof Jon Iredell was exemplary, highlighting the critical importance of antimicrobials (and the need for new generations of antimicrobials) in infection control in many settings.
The talk by Prof Frederic Laurent on the increasing importance of phage therapy in clinical settings and the Pfizer Symposium by clinicians, researchers, medicinal chemists and the highlighted regulatory hurdles to deployment of new antimicrobials were quite informative.

A clear message throughout the conference is the inexorable problem of antimicrobial resistance and the urgent, unmet need for new drugs for bacterial, viral and fungal infections, exemplified by talks from Profs Yohei Doi, Catriona Bradshaw and Sharon Chen.

To summarise, I found Antimicrobials 2024 was a fantastic conference; I learnt quite a lot and was also able to establish new collaboration networks. Thanks very much for the Travel Award and the opportunity to give an oral presentation.

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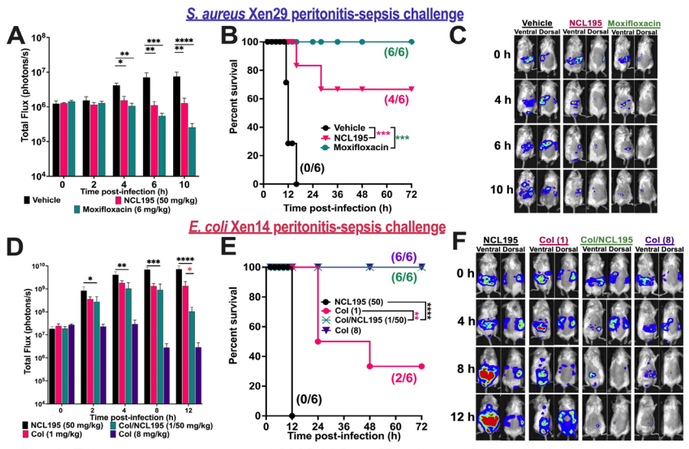

Fig. 1. Efficacy evaluation of oral NCL195 +/- IP colistin (Col) in bioluminescent bacterial peritonitis-sepsis challenge models. (**A–C**), CD1 male mice (n=6) infected IP with 3×10^7 CFU *S. aureus* Xen29 and treated orally with vehicle only, NCL195 (50 mg/kg) or moxifloxacin (6 mg/kg) [4 doses 4 h apart], or (**D–E**), infected IP with 1×10^8 CFU col-resistant *E. coli* Xen 14 and treated with 50 mg/kg NCL195, 1 mg/kg Col, 1+50 mg/kg Col+NCL195 [4 doses 4 h apart], or Col [8 mg/kg; 2 doses], from 0 h post-infection. Bioluminescence imaging performed on IVIS Lumina XRMS Series III system at the indicated times. **A,D),** Total photon counts; **B,E),** Survival times; **C,F),** Representative ventral and dorsal images of mice. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. **Statistics: (A,D),** Multiple t-tests, **(B,E)**, Log-rank (Mantel-Cox)

COMMENTARY FEEDBACK FOR ANTIMICROBIALS 2024

Held at the International Convention Centre Sydney along the beautiful Darling Harbour, Antimicrobials 2024 was an insightful conference. Attending my first conference as a first-year PhD candidate and presenting my poster abstract was an incredibly rewarding experience for me. Presenting my first poster abstract as a PhD candidate allowed me to share my knowledge and hone my skill sets, such as publicly speaking to a diverse audience and answering questions effectively when asked during the poster session.

Having brought together like-minded clinicians, researchers, and industrial leaders to present scientific developments and updated guidelines, this conference has allowed me to learn and expand my knowledge on interesting findings outside my field of expertise. There are a several talks that I enjoyed. Professor Jon Iredell spoked about bacterial adaptation during the Howard Florey Oration and Dinner, as he went through the bacterial fitness landscape model, bioremediation, and precision therapeutics. Professor Frédéric Laurent gave a fascinating talk regarding the reality of phage therapeutic research, phage training, and the bioproduction of phages. Professor John Turnidge gave a comprehensive talk during the EUCAST workshop. As a research candidate, I am familiar with EUCAST breakpoints. What interests me is the implementation and impact of the "susceptible-increased exposure" category, and guidance when there are no breakpoints.

Perhaps the most memorable talk was "The Year in Clinical Microbiology" by Professor Tony Korman. Professor Korman gave a humorous and remarkable summary regarding the discipline and brought up two fascinating papers: the use of artificial intelligence in managing bloodstream infections and an editorial review regarding the relevance of a microbiologist in 2030.

Overall, this conference was an eye-opening, positive experience for me. I benefitted from showcasing my poster abstract and attending different talks. Antimicrobials 2024 enabled me to see collaborative antimicrobial stewardship efforts from various sectors as a result of the Australian One Health approach. I look forward to attending Antimicrobials 2025.

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I attended the Australian Society of Antimicrobials (ASA), ANTIMICROBIALS 2024 conference held in Sydney where I gave an oral presentation titled

THIRD-GENERATION CEPHALOSPORIN-RESISTANT KLEBSIELLA PNEUMONIAE COMPLEX BLOODSTREAM INFECTION IN ADULT PATIENTS: CHANGING EPIDEMIOLOGY AND DETERMINANTS OF POOR OUTCOMES.

The presentation was co-authored by Professor Kevin Laupland, Professor David Paterson, Dr Patrick Harris, and Ms Felicity Edwards. In summary, I presented 20 years of data from Queensland, Australia describing *Klebsiella pneumoniae* bloodstream infection in the public hospital system (>7,000 patient-episodes). The main points of the presentation were that adjusted incidence rose 4.5% per year over the entire study period, with crude incidence of third-generation cephalosporin-resistant episodes rising approximately 10% per year. Risk factors for death were consistent with published data, although third-generation cephalosporin resistance was not identified as a risk factor. Although a rising proportion of individuals with significant comorbidities within the population may explain the rising incidence of *Klebsiella pneumoniae* bloodstream infection, increasing virulence among local bacterial isolates cannot be completely excluded. Further prospective surveillance and microbiological evaluation is required.

Associate Professor Yohei Doi presented on TREATMENT OPTIONS FOR CARBAPENEM RESISTANT NON-LACTOSE FERMENTERS. This was an exceptional presentation from an international expert. He highlighted the growing need for effective antimicrobials for problematic bacteria including metallo-beta-lactamase producers. He presented data on novel beta-lactams and beta-lactamase inhibitors in pre-clinical and clinical phases of development. This is an exciting area and I look forward to reading about the performance of many of these novel agents in future clinical trials. Professor Steven Tong presented on THE *S. AUREUS* NETWORK ADAPTIVE PLATFORM (SNAP) - UPDATE. It is always an absolute privilege listening to an international leader in clinical trials and staphylococcal infection. The SNAP trial continues to go from strength to strength and has now recruited well over 2,000 trial participants. This platform trial will simultaneously evaluate many of the important clinical questions we encounter in our daily clinical practice when managing *S. aureus* bloodstream infection. I look forward to seeing the preliminary data and changing my practice (or not) accordingly. The ASA ANTIMICROBIALS 2024 conference is an excellent meeting which brings together content experts from many different fields related to infectious diseases and microbiology. I look forward to attending many more in the years to come.

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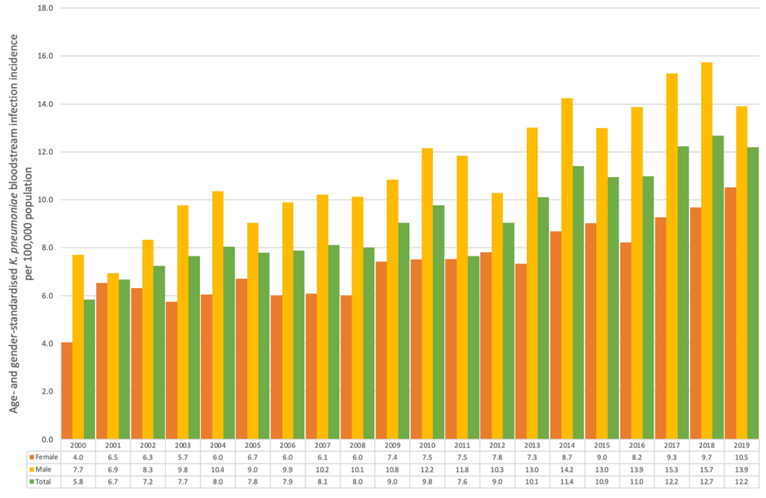
Figure 1. Standardised incidence per 100,000 population of *Klebsiella pneumoniae* bloodstream infection between 2000-2019



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Female	4.0	6.5	6.3	5.7	6.0	6.7	6.0	6.1	6.0	7.4	7.5	7.5	7.8	7.3	8.7	9.0	8.2	9.3	9.7	10.5
Male	7.7	6.9	8.3	9.8	10.4	9.0	9.9	10.2	10.1	10.8	12.2	11.8	10.3	13.0	14.2	13.0	13.9	15.3	15.7	13.9
Total	5.8	6.7	7.2	7.7	8.0	7.8	7.9	8.1	8.0	9.0	9.8	7.6	9.0	10.1	11.4	10.9	11.0	12.2	12.7	12.2

ASA23 POSTER TRAVEL AWARD A SHORT COMMENTARY

In the vibrant hub of Darling Harbour, the International Convention Centre hosted Antimicrobials 2024, featuring a comprehensive array of sessions showcasing the latest advancements in antimicrobial research. As a final year PhD candidate within the School of Veterinary Science at the University of Queensland, I was honoured to receive the Antimicrobials 2023 Poster Travel Award to attend Antimicrobials 2024 in Sydney and be part of such an insightful and valuable platform.

This conference brought together leading experts from around the globe and offered a range of plenary sessions. Professor Yohei Do (University of Pittsburgh) discussed treatment options for carbapenem-resistant non-lactose fermenters, Professor Frédéric Laurent (University of Lyon) covered the laboratory processes and compassionate use of phage therapy, and Professor Sharon Chen (Westmead Hospital) addressed the urgent need for new antifungals.

Antimicrobials 2024 also featured five symposium sessions covering *Staphylococcus aureus*, One Health, the hospital microbiome, updated guidelines, and AMR risk groups in the community, along with two breakfast symposiums. One particularly notable session was the One Health Symposium, which emphasised the interconnectedness of human, animal, and environmental sectors in the fight against AMR, highlighting the need for a holistic approach to address AMR challenges.

The conference also featured several proffered paper sessions which were particularly insightful. Dr Aminath Shausan (CSIRO) presented on the use of a spatial epidemiological approach to identify population-level factors influencing the risk of AMR using antimicrobial susceptibility results within the HOTspots surveillance program. Mr Andrey Verich (University of New South Wales) demonstrated the potential use of machine learning analysis in the rapid screening of gene variants contributing to AMR for *Neisseria gonorrhoeae*. These presentations underscored the importance of employing innovative methods to enhance antimicrobial stewardship efforts and the understanding of AMR.

It was wonderful to be part of the proffered paper session which housed numerous talks related to AMR in animals. I had the pleasure of presenting my research on the molecular epidemiology of *Staphylococcus* species from dogs with skin and ear infections, highlighting highly resistant and virulent methicillin-resistant *Staphylococcus pseudintermedius* sequence types (STs) that could complicate treatment success. This session also featured a great talk by Dr Soo Sum Lean (Murdoch University) on critically important antimicrobial (CIA) resistances in *Escherichia coli* from Australian silver seagulls, revealing human-associated clones and transmission risk among humans, seagulls and the environment. Professor Sam Abraham (Murdoch University) presented an insightful talk on CIA *E. coli* isolated from pig herds, emphasising the need for highly sensitive, high-volume AMR surveillance using high-throughput robotics as an infection control tool in humans and animals to mitigate the risk of CIA resistance.

The poster sessions also delivered a variety of research. Notably, Ms Brighid Carey (Australian Commission on Safety and Quality in Health Care) reported on the encouraging overall decrease in community antimicrobial prescribing from 2015 to 2022, expressing the crucial need to ensure that this downward trend continues. Also, Dr Christopher Mullally (Murdoch University) presented interesting research showing a lack of persistence of international lineages of *N. gonorrhoeae* in Western Australia following border closures due to COVID-19.

Overall, Antimicrobials 2024 was a resounding success, offering a dynamic and insightful platform for sharing research and ideas. It was a privilege to be part of such an enriching event.

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ASA24 AGAR POSTERS

The Australian Group on Antimicrobial Resistance (AGAR)
Australian *Enterococcus* Surveillance Outcome Program (AESOP) 2022

D. A. Daley[1,3], G. W. Coombs[1,2,3] P. Shoby[2] and S. Mowlaboccus[1,2,3] on behalf of the Australian Group on Antimicrobial Resistance

[1]The Australian Group on Antimicrobial Resistance, Fiona Stanley Hospital, WA, [2]Antimicrobial Resistance and Infectious Diseases Laboratory (AMRID), Murdoch University, WA, [3]Department of Microbiology, PathWest Laboratory Medicine, Fiona Stanley Hospital, WA.

INTRODUCTION

In 2022, 33 institutions servicing 55 hospitals across Australia participated in the AGAR Australian *Enterococcus* Surveillance Outcome Program (AESOP). The objective of AESOP 2022 was to determine the proportion of enterococcal bacteraemia isolates in Australia that exhibited antimicrobial resistance in particular to ampicillin and glycopeptides, and to characterize the molecular epidemiology of the *E. faecium* isolates.

METHODS

Isolates

From 1 January to 31 December 2022 participating laboratories collected all enterococci isolated from blood cultures (excluding duplicates within a 14-day period). Data were collected on age, sex, date of admission and discharge, clinical manifestation and mortality at 7 and 30 days post blood culture collection.

Susceptibility testing

Isolates were identified by the participating laboratories and antimicrobial susceptibility testing was performed using the Vitek® 2 (bioMérieux, France) or the BD Phoenix™ (Becton Dickinson, USA) automated microbiology systems. EUCAST breakpoints were utilised for interpretation.

Whole genome sequencing

Whole genome sequencing (WGS) was performed on *E. faecium* isolates by the AMRID laboratory at Murdoch University, WA.

RESULTS

- 1,535 episodes of enterococcal bacteraemia were identified with 92.8% of episodes caused by *E. faecalis* (812, 52.9%) or *E. faecium* (613, 39.9%).
- Other enterococcal species included *E. lactis* (*n* = 29), *E. casseliflavus* (21), *E. gallinarum* (17), *E. avium* (16), *E. raffinosus* (13), *E. hirae* (5), *E. durans* (4), *E. gilvus* (2) and one each of *E. dispar*, *E. cecorum* and *Enterococcus* spp. (unspeciated) (Figure 1).
- The mean patient age was 64 years, 67.4% of patients were male.
- 67.0% of *E. faecalis* and 25.6% of *E. faecium* were community-onset. The most common principal clinical manifestation was urinary tract infection in *E. faecalis* (22.5%) and febrile neutropenia in *E. faecium* (19.8%).
- All-cause mortality at 30 days was 21.2% (95% CI 19.0-23.5). There was a significant difference in mortality between *E. faecalis* and *E. faecium* episodes (17.2% vs 26.9%, p<0.01), and between vancomycin susceptible and vancomycin non-susceptible *E. faecium* episodes (19.7% vs 34.4%, *P* < 0.01) respectively.

E. faecalis

- In 2022, 13.0% of *E. faecalis* were high-level gentamicin resistant compared to 15.3% in 2021. No ampicillin, vancomycin, teicoplanin or linezolid resistance was seen in 2022.
- One daptomycin-resistant isolate from NSW was confirmed with an MIC of 8 mg/L. This isolate was ST16 and harboured the F478L GdpD mutation.

E. faecium

- In 2022, 95.4% of *E. faecium* were ampicillin resistant. Increases in resistance from 2021 to 2022 were seen in vancomycin (40.2% to 46.9%) and high-level gentamicin (32.3% to 44.2%). Teicoplanin resistance decreased from 14.0% in 2021 to 13.2% in 2022.

RESULTS (continued)

Figure 1. Enterococcal species, 2022

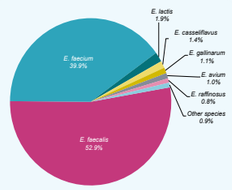


Figure 3. *Enterococcus faecium* sequence types

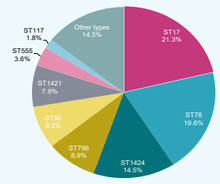


Figure 2. Vancomycin-resistant *Enterococcus faecium*, WHO European region and Australia, 2022

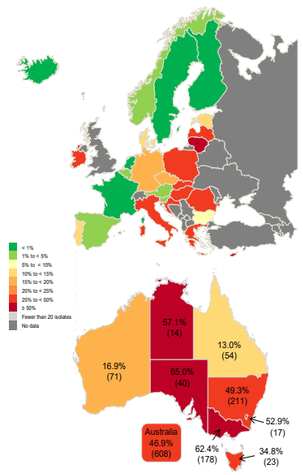
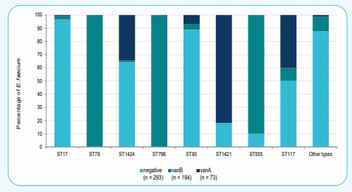


Figure 4. *Enterococcus faecium* sequence types, by state and territory, 2022

Figure 5. *van* genes in *Enteroccus faecium* sequence types, 2022



- Australia's rate of vancomycin resistance ranks in the top quarter when compared to the EARS-Net program and the WHO CAESAR network (Figure 2).
- Two linezolid-resistant *E. faecium* from Victoria were confirmed. Both harboured the G2576T 23S rRNA mutation. One isolate with a linezolid MIC of >256 mg/L was ST2217, vancomycin resistant and harboured the *vanB* gene. The second isolate with a linezolid MIC of 8 mg/L was ST1424 and vancomycin susceptible.
- One daptomycin resistant *E. faecium* from NSW with an MIC of 24 mg/L was ST78 and harboured the A20D Cls mutation. This isolate was also vancomycin-resistant and harboured the *vanB* gene.
- 560/613 (91.4%) of *E. faecium* were available for typing by WGS.
- 62 STs were identified with 85.5% characterised into eight major STs (≥10 isolates): ST17, ST78, ST1424, ST796, ST80, ST1421, ST555 and ST117 (Figures 3 and 4). There were 40 STs with a single isolate.
- 48.8% of *E. faecium* harboured *van* genes; 35.1% *vanB*, 13.7% *vanA*. Distribution of *van* genes by sequence type are seen in Figure 5.

CONCLUSIONS

- The AESOP 2022 study has shown although predominately caused by *E. faecalis*, enterococcal bacteraemia in Australia is frequently caused by ampicillin-resistant high-level gentamicin-resistant *E. faecium*.
- The *vanB* operon was historically the dominant genotype, although there was a steady increase in *vanA* from 2013 to 2018 when *vanA* predominated. In AESOP 2022 the *vanB* genotype was the most dominant.
- In addition to being a significant cause of healthcare-associated sepsis, the emergence of multiple multi-resistant hospital-adapted *E. faecium* strains has become a major infection control issue in Australian hospitals.
- Further studies of the enterococcal genome will contribute to our understanding of the rapid and ongoing evolution of enterococci in the hospital environment and assist in preventing their nosocomial transmission.

Acknowledgements

We wish to thank the staff of the AGAR laboratories for the collection of data and isolates.

The AGAR Surveillance Outcome Programs are funded by the Australian Government Department of Health and Aged Care.

AUSTRALIAN GROUP on ANTIMICROBIAL RESISTANCE

Murdoch University

The Australian Group on Antimicrobial Resistance (AGAR)
Australian *Enterococcus* Surveillance Outcome Program (AESOP) 2013–2022

D. A. Daley[1,3], G. W. Coombs[1,2,3] P. Shoby[2] and S. Mowlaboccus[1,2,3] on behalf of the Australian Group on Antimicrobial Resistance

[1]The Australian Group on Antimicrobial Resistance, Fiona Stanley Hospital, WA, [2]Antimicrobial Resistance and Infectious Diseases Laboratory (AMRID), Murdoch University, WA, [3]Department of Microbiology, PathWest Laboratory Medicine, Fiona Stanley Hospital, WA.

INTRODUCTION

AGAR began surveillance of antimicrobial resistance in *Enterococcus* spp. from blood cultures in 2013.

The objectives of the AESOP program was to determine the proportion of *E. faecalis* and *E. faecium* bacteraemia isolates demonstrating antimicrobial resistance with particular emphasis on assessing susceptibility to ampicillin, the glycopeptides and the associated resistance genes and monitoring the molecular epidemiology of *E. faecium*.

METHODS

Isolates

Participating laboratories collected all enterococci isolated from blood cultures (excluding duplicates within a 14-day period).

Susceptibility testing

Isolates were identified by the participating laboratories and antimicrobial susceptibility testing was performed using the Vitek® 2 (bioMérieux, France) or the BD Phoenix™ (Becton Dickinson, USA) automated microbiology systems. EUCAST breakpoints were utilised for interpretation.

Whole genome sequencing

Whole genome sequencing (WGS) was performed on *E. faecium* isolates by the AMRID laboratory at Murdoch University, WA.

RESULTS

- A total of 11,680 episodes of enterococcal bacteraemia were identified with 94.2% of episodes caused by either *E. faecalis* (6,318) or *E. faecium* (4,682). There has been no significant change in the proportion of *E. faecalis* and *E. faecium* isolates over the ten-year period 2013-2022.

E. faecalis

- Resistance rates for key antimicrobials from 2013-2022 are shown in Figure 1. Resistance to ampicillin, vancomycin, teicoplanin and linezolid remains rare.
- There has been a decreasing trend in high-level gentamicin resistance since 2014.

E. faecium

- Resistance rates for key antimicrobials from 2013-2022 are shown in Figure 2.
- Over the 10-year period, there was decreasing trends in vancomycin rates in Australia, notably in Queensland, New South Wales, and South Australia. Over the last 5-year period, South Australia had a significant increasing trend (*P* = 0.0019) (Figure 3).
- There was an increasing trend in teicoplanin rates in Victoria over the 10-year period. For the last 5-years, decreasing rates were seen in Victoria (*P* < 0.0091), the Australian Capital Territory (*P* = 0.0213) and Australia overall (*P* = 0.0003) (Figure 4).
- The 10-year trend for high-level gentamicin in Australia is decreasing overall despite an increase seen in 2022.
- The proportion of *vanB* positive *E. faecium* declined from 41.6% in 2013 to 21.3% in 2020 with an increase to 35.1% in 2022 (Figure 5). *vanA* positive *E. faecium* increased from 2.6% in 2013 to 26.1% in 2018 with a decline to 13.7% in 2022.
- The most frequently isolated STs from 2013-2022 are shown in Figure 6. There have been significant increases in ST78 and ST17. ST1421 and ST1424 which were first isolated in 2015 and 2016 respectively, peaked in 2019 but has decreased each year since. ST203 and ST555 showed a significant decline over the10-year period.

RESULTS (continued)

Figure 1. *Enterococcus faecalis*, antimicrobial resistance, 2013-2022

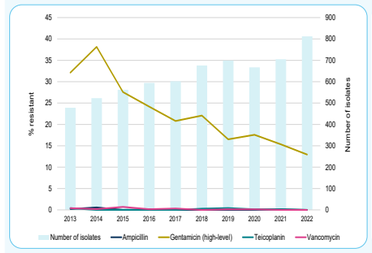


Figure 2. *Enterococcus faecium*, antimicrobial resistance, 2013-2022

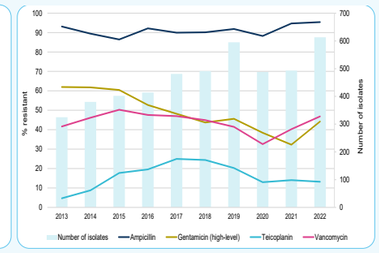


Figure 3. Vancomycin-resistant *Enterococcus faecium*, state and territory, 2013–2022

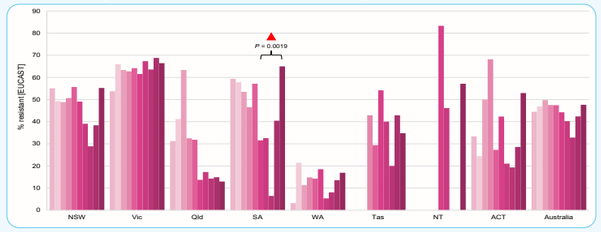
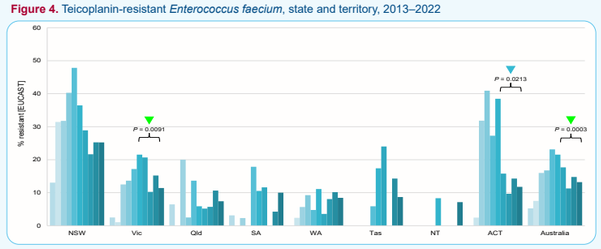


Figure 4. Teicoplanin-resistant *Enterococcus faecium*, state and territory, 2013–2022



Figures 3 and 4: Chi-square test for trend for past five years (2018-2022); significant increase ▲ *P* <0.01 or decrease ▼ *P* <0.01, ▼ 0.01 < *P* <0.05
Notes:
1. Percentage resistance determined using EUCAST 2023 breakpoints for all years.
2. Data only from hospitals consistently reporting for all five years were included.

Figure 5. *Enterococcus faecium* van genes, 2013–2022

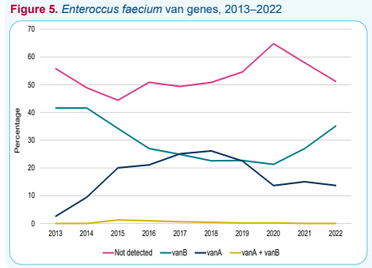
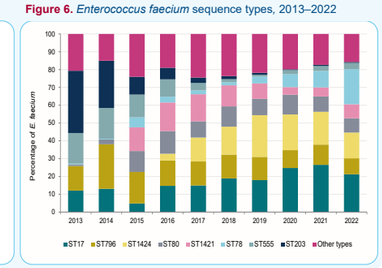


Figure 6. *Enterococcus faecium* sequence types, 2013–2022



CONCLUSIONS

- Although predominately caused by *E. faecalis*, enterococcal bacteraemia in Australia is frequently caused by ampicillin-resistant high-level gentamicin-resistant *E. faecium*.
- The *vanB* operon was historically the dominant genotype, although there was a steady increase in *vanA* from 2013 to 2018 when *vanA* predominated.
- Vancomycin resistance in *E. faecium* remains high at 46.9% in 2022. Teicoplanin resistance ranged from 4.7% in 2013 to 24.9% in 2017, 13.2% in 2022.

Acknowledgements

We wish to thank the staff of the AGAR laboratories for the collection of data and isolates.

The AGAR Surveillance Outcome Programs are funded by the Australian Government Department of Health and Aged Care.

AUSTRALIAN GROUP on ANTIMICROBIAL RESISTANCE

Murdoch University

The Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Surveillance Outcome Program (ASSOP) 2022

D. A. Daley[1,3], G. W. Coombs[1,2,3] P. Shoby[2] and S. Mowlaboccus[1,2,3] on behalf of the Australian Group on Antimicrobial Resistance

[1]The Australian Group on Antimicrobial Resistance, Fiona Stanley Hospital, WA, [2]Antimicrobial Resistance and Infectious Diseases Laboratory (AMRID), Murdoch University, WA, [3]Department of Microbiology, PathWest Laboratory Medicine, Fiona Stanley Hospital, WA.

INTRODUCTION

In 2022, 33 institutions across Australia servicing 55 hospitals participated in the AGAR Australian *Staphylococcus aureus* Surveillance Outcome Program (ASSOP). The primary objective of ASSOP 2022 was to determine the proportion of *S. aureus* bacteraemia (SAB) isolates in Australia that exhibited antimicrobial resistance, with particular emphasis on susceptibility to methicillin, and to characterize the molecular epidemiology of the methicillin-resistant *S. aureus* (MRSA).

METHODS

Isolates

From 1 January to 31 December 2022 the 33 participating laboratories collected all *S. aureus* isolated from blood cultures (excluding duplicates within a 14-day period). Data were collected on age, sex, date of admission and discharge and mortality at 7 and 30 days post blood culture collection.

Susceptibility testing

Isolates were identified by the participating laboratories and antimicrobial susceptibility testing was performed using the Vitek® 2 (bioMérieux, France) or the BD Phoenix™ (Becton Dickinson, USA) automated microbiology systems. European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were utilised for interpretation.

Whole genome sequencing testing

Whole genome sequencing (WGS) was performed on MRSA isolates at the AMRID laboratory, Murdoch University, WA.

RESULTS

- 3,214 unique episodes of SAB were identified.
- The mean patient age was 59 years. 66.6% of patients were male.
- 77.5% of episodes were community-onset.
- All-cause mortality at 30 days was 17.5% (95%CI 16.1-19.0). There were no significant difference in mortality between hospital-onset and community-onset SAB (19.5% and 17.0% respectively) (P = 0.16). There was however between MRSA and methicillin-susceptible *S. aureus* (MSSA) bacteraemia (21.4% and 16.8% respectively) (P = 0.02).
- Osteomyelitis/septic arthritis (20.8%) and skin/skin structure (19.7%) were the most common principal clinical manifestations.

MSSA

- With the exception of the β-lactams and erythromycin, antimicrobial resistance in MSSA was rare (Table 1). Resistance was not detected for daptomycin, vancomycin, linezolid or teicoplanin by CLSI criteria.

MRSA

- 15.0% (481) *S. aureus* were methicillin resistant. Comparison with EARS-Net and WHO CAESAR data is shown in Figure 1. One MRSA isolate with a daptomycin MIC of 1.5 mg/L harboured the A302V MprF and A23V Cls2 mutations. Resistance was not detected for vancomycin, linezolid or teicoplanin by CLSI criteria.
- 449 (93.3%) MRSA were available for typing by WGS. Overall 13.6% and 86.4% were classified as healthcare-associated (HA) and community-associated (CA) clones respectively (Figure 2). 52.5% and 78.4% of HA-MRSA and CA-MRSA respectively were community-onset.

RESULTS (continued)

Table 1. *Staphylococcus aureus* susceptibility data, 2022

	Methicillin-resistant					Methicillin-susceptible				
		CLSI		EUCAST			CLSI		EUCAST	
Antimicrobial	Number	% I	% R	% S-IE	% R	Number	% I	% R	% S-IE	% R
Benzylpenicillin*	480	–†	100.0	–†	100.0	2,719	–†	74.9	–†	74.9
Ciprofloxacin	479	1.3	29.4	69.3	30.7	2,724	0.7	2.2	97.0	3.0
Clindamycin§	479	0.0	23.0	0.0	24.2	2,722	0.0	10.8	0.0	11.5
Erythromycin	478	17.6	28.7	–†	29.7	2,669	28.2	13.2	–†	13.9
Gentamicin	479	3.3	5.8	–†	11.3	2,724	0.8	0.7	–†	3.5
Mupirocin (high-level)	346	–†	2.0	–†	2.0	2,096	–†	1.2	–†	1.2
Rifampicin	479	0.0	1.0	–#	1.5	2,721	0.1	0.3	–#	0.6
Tetracycline/doxycycline	479	0.0	10.9	–†	13.2	2,720	0.1	2.7	–†	3.5
Trimethoprim–sulfamethoxazole	478	0.4	1.7	0.4	1.7	2,723	0.2	0.3	0.1	0.4

I = intermediate; R = resistant; S-IE = susceptible, increased exposure

* = β-lactamase adjusted; † = no category defined; § = constitutive + inducible; # = rifampicin concentration range on some cards restricts category interpretation

Figure 1. Methicillin-resistant *Staphylococcus aureus*, international comparisons, WHO European region and Australia, 2022

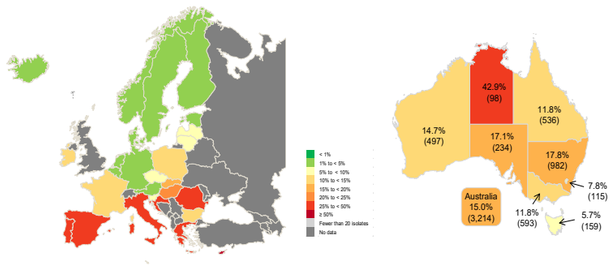


Figure 2. HA- and CA-associated MRSA clones, by state and territory, 2022

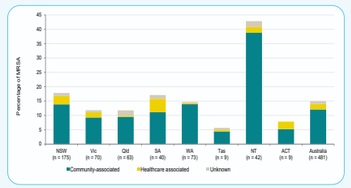


Figure 3. HA-associated MRSA, by state and territory, 2022

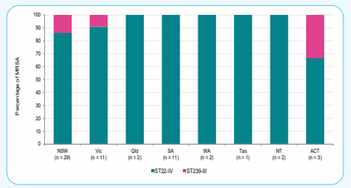
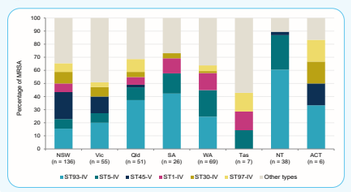


Figure 4. CA-associated MRSA, by state and territory, 2022



- Two HA-MRSA clones were identified, ST22-IV [2B] (EMRSA-15) and ST239-III [3A] (Aus-2/3 EMRSA) (Figure 3).
- Although polyclonal (64 clones), 71.9% of CA-MRSA clones were classified into eight major sequence types (ST): ST93-IV, ST5-IV, ST45-V, ST1-IV, ST30-IV, ST97-IV, ST953-V and ST8-IV (Figure 4).
- Overall 166 (37.0%) of MRSA were PVL positive, all of which were CA-MRSA.

CONCLUSIONS

- ASSOP 2022 has demonstrated antimicrobial resistance in SAB in Australia remains a significant problem and is associated with a high mortality. This may be due, in part, to the high prevalence of methicillin-resistant SAB in Australia.
- MRSA must remain a public health priority and continuous surveillance of SAB and its outcomes and the implementation of comprehensive MRSA strategies targeting hospitals and long-term care facilities are essential.

Acknowledgements

We wish to thank the staff of the AGAR laboratories for the collection of data and isolates.

The AGAR Surveillance Outcome Programs are funded by the Australian Government Department of Health and Aged Care.

AUSTRALIAN GROUP on ANTIMICROBIAL RESISTANCE

Murdoch University

The Australian Group on Antimicrobial Resistance (AGAR) Australian *Staphylococcus aureus* Surveillance Outcome Program (ASSOP) 2013–2022

D. A. Daley[1,3], G. W. Coombs[1,2,3] P. Shoby[2] and S. Mowlaboccus[1,2,3] on behalf of the Australian Group on Antimicrobial Resistance

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INTRODUCTION

In 2013, AGAR began the Australian *Staphylococcus aureus* Surveillance Outcome Program (ASSOP). The objectives were to determine the proportion of *S. aureus* bacteraemia isolates in Australia that exhibited antimicrobial resistance in particular to methicillin, and to characterize the molecular epidemiology of the methicillin resistant isolates.

METHODS

Isolates

Participating laboratories collected all *S. aureus* isolated from blood cultures (excluding duplicates within a 14-day period).

Susceptibility testing

Isolates were identified by the participating laboratories and antimicrobial susceptibility testing was performed using the Vitek® 2 (bioMérieux, France) or the BD Phoenix™ (Becton Dickinson, USA) automated microbiology systems. EUCAST breakpoints were utilised for interpretation.

Whole genome sequencing

Whole genome sequencing (WGS) was performed on methicillin-resistant *S. aureus* (MRSA) isolates by the AMRID laboratory at Murdoch University, WA.

RESULTS

- In the 10-year period 2013 to 2022, 26,484 *S. aureus* bacteraemia episodes were reported. Of these 17.7% (4,689) were methicillin resistant.

MSSA

- Resistance rates for key antimicrobials are shown in Figure 1. There has been significant decreasing 5-year trends in resistance rates to penicillin (χ^2 for trend P = 0.0033) and fusidic acid (χ^2 for trend P = 0.0491).
- Over the past 5-years, significant increasing trends have been observed in resistance rates to erythromycin (χ^2 for trend P = 0.0216), clindamycin (χ^2 for trend P = 0.0030), and gentamicin (χ^2 for trend P < 0.0001).

MRSA

- Since 2016, the proportion of *S. aureus* that was methicillin-resistant began to decline nationally, although there were notable variations at state and territory level (Figure 2). From 2018 to 2022, there was a significantly decreasing trend in MRSA in Australia χ^2 for trend P < 0.0242), notably in WA (χ^2 for trend P = 0.0074).
- Resistance rates for key antimicrobials are shown in Figure 3. Significant decreases have been observed in most key antimicrobials. This is largely due to the significant decrease in healthcare-associated MRSA clones in particular the multi-resistant ST239-III (Figures 4 and 5).
- Although numbers and diversity of CA-MRSA have increased, the most common sequence types have remained fairly stable with the exception of the increase seen in ST93-IV (Figure 6).

CONCLUSIONS

- AGAR surveillance remains core to Australia's response to the problem of increasing AMR. AGAR data contribute to understanding AMR in Australian human health settings, and to informing the national response to AMR.
- AGAR contributes internationally through annual contribution of data on *S. aureus* from blood to the World Health Organization (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS).

Figure 1. Methicillin-susceptible *Staphylococcus aureus*, resistance to key antimicrobials, 2013–2022

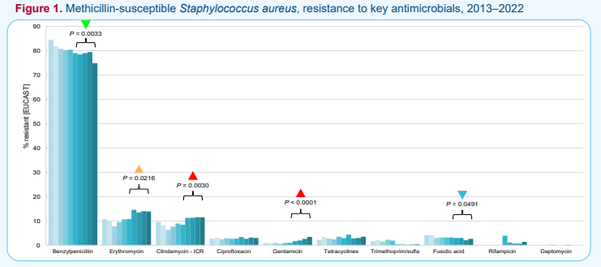


Figure 2. Proportion of methicillin-resistant *Staphylococcus aureus*, by state and territory, 2013–2022

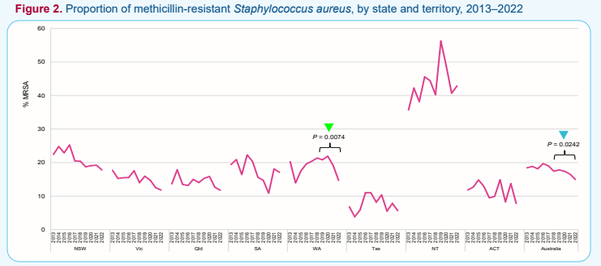


Figure 3. Methicillin-resistant *Staphylococcus aureus*, resistance to key antimicrobials, 2013–2022

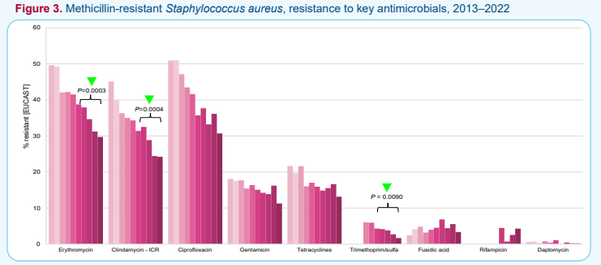


Figure 4. Healthcare- and community-associated MRSA, 2013–2022

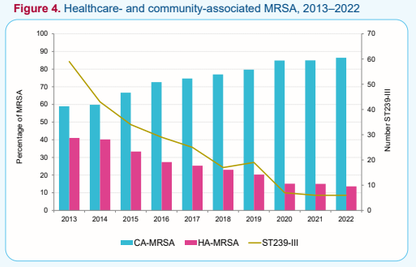


Figure 5. Healthcare-associated MRSA sequence types, 2013–2022

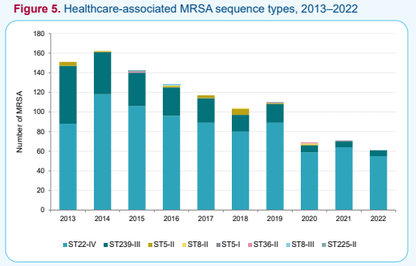
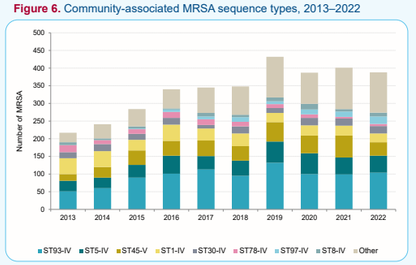


Figure 6. Community-associated MRSA sequence types, 2013–2022



Figures 1 to 3: χ^2 test for trend for past five years (2018-2022); significant increase ▲ P <0.01 0.01, ▲ < P <0.05 or decrease ▼ P <0.01, ▼ 0.01 < P <0.05

Notes: 1. Percentage resistance determined using EUCAST 2023 breakpoints for all years. 2. Data only from hospitals consistently reporting for all five years were included.

Acknowledgements

We wish to thank the staff of the AGAR laboratories for the collection of data and isolates.

The AGAR Surveillance Outcome Programs are funded by the Australian Government Department of Health and Aged Care.

AUSTRALIAN GROUP on ANTIMICROBIAL RESISTANCE

Murdoch University

The Australian Group on Antimicrobial Resistance Report from the Gram-negative Surveillance Outcome Program (GnSOP) 2022 – Susceptibility Data

J. M. Bell[1], T. Gottlieb[2,3], A. Fajardo Lubian[3,4], S. Partridge[3,4,5], and J. Iredell[3,4,5] for the Australian Group on Antimicrobial Resistance

[1]The Australian Group on Antimicrobial Resistance, [2]Concord Hospital, Sydney, [3]The University of Sydney, [4]Westmead Institute for Medical Research, [5]Westmead Hospital, Sydney

INTRODUCTION

The Australian Group on Antimicrobial Resistance (AGAR) Gram-negative Surveillance Outcome Programme (GnSOP) focuses on the collection of resistance and demographic data on *Enterobacterales*, *Pseudomonas aeruginosa* and *Acinetobacter* species isolated from patients with bacteraemia.

METHODS

Isolates

From 1 January to 31 December 2022, 33 laboratories servicing 55 participating hospitals across Australia collected either all or up to 200 isolates (*Enterobacterales*, *P. aeruginosa* or *Acinetobacter* spp.) from different patient episodes of bacteraemia. Isolates were identified using the routine method for each laboratory.

Susceptibility testing

MICs were determined using Vitek® 2 (BioMérieux) or Phoenix™ (BD). The results were analysed using CLSI and EUCAST breakpoints (January 2023). *E. coli*, *Klebsiella* spp., *Proteus* spp. and *Salmonella* spp. with ceftazidime or ceftriaxone MIC > 1 mg/L, or cefoxitin MIC > 8 mg/L, any other *Enterobacterales* with cefepime MIC > 1 mg/L, *Salmonella* spp. with ciprofloxacin MIC > 0.25 mg/L, all isolates with meropenem MIC > 0.125 mg/L, all isolates with amikacin MIC > 32 mg/L, and all isolates with colistin MIC > 4 mg/L were referred for whole genome sequencing (WGS).

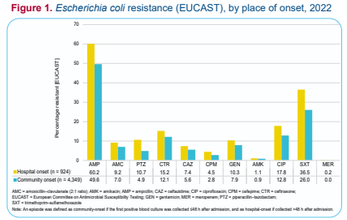
Whole genome sequencing

WGS was performed on all referred isolates using the Illumina NextSeq™ 500 platform. Data were analysed using a modified version of the Nullarbor bioinformatic pipeline.

RESULTS

- Most (86.7%) of the 9,739 gram-negative isolates analysed were *Escherichia* (54.2%), *Klebsiella* (18.8%), *Pseudomonas* (8.6%), or *Enterobacter* (5.1%).
- For *E. coli*, the percentage of isolates resistant to most antimicrobials tested in 2022 was similar to those for 2021, except for ciprofloxacin, where a 11.1% increase in resistance was seen (2021, 12.3%; 2022, 13.7%), notably in NSW and SA.
- Ciprofloxacin resistance rates in 2022 were 13.7% overall for *E. coli*, 17.8% for hospital-onset (HO) and 12.8% for community-onset (CO), and for *K. pneumoniae* complex 7.8% overall, 11.3% HO and 6.3% CO (Figure 1).

Figure 1. *Escherichia coli* resistance (EUCAST), by place of onset, 2022



- Among *E. coli* isolates, 14.4% had an extended-spectrum β-lactamase (ESBL) phenotype (HO, 17.2%; CO, 13.8%). Percentages for *K. pneumoniae* complex isolates were slightly lower at 7.5% overall (HO, 12.7%; CO, 5.3%). The proportion of ESBLs by state and territory and place of onset is shown in Figure 2.
- Of 683 *E. coli* with confirmed β-lactamase gene(s), 578 (84.6%) had $bla_{\text{CTX-M}}$ gene, either $bla_{\text{CTX-M}}$ group 1 (*n* = 295), $bla_{\text{CTX-M}}$ group 9 (*n* = 282), or a CTX-M group 1/9/1 hybrid (*n* = 1). $bla_{\text{CTX-M}}$ group 1 genes were dominant in Vic, SA, and the ACT. $bla_{\text{CTX-M}}$ group 9 genes were more prevalent in Qld, WA, and Tas.
- Among *K. pneumoniae* complex with confirmed β-lactamase gene(s), 73 of 91 (80.2%) contained a $bla_{\text{CTX-M}}$ gene: $bla_{\text{CTX-M}}$ group 1 (*n* = 65), $bla_{\text{CTX-M}}$ group 9 (*n* = 6), or $bla_{\text{CTX-M}}$ group 1 + $bla_{\text{CTX-M}}$ group 9 (*n* = 2).
- The β-lactamase genes detected in *Enterobacterales* with an ESBL phenotype are shown in Figure 3.
- A little over one-third (108/265, 40.8%) of *E. coli* and 15.6% (10/64) of *K. pneumoniae* complex with cefoxitin MIC > 8 mg/L contained one or more plasmid-borne *ampC* gene(s), mostly bla_{DHA}.
- Comparison of *E. coli* and *K. pneumoniae* resistance rates to key antimicrobial groups in Australia and the WHO European region countries are shown in Figure 4.
- Overall, 32 (0.3%) isolates from 31 patients harboured a carbapenemase gene (Table 1).

RESULTS (continued)

Figure 2. Proportion of *Escherichia coli* and *Klebsiella pneumoniae* with extended-spectrum β-lactamase phenotype, by state and territory, 2022

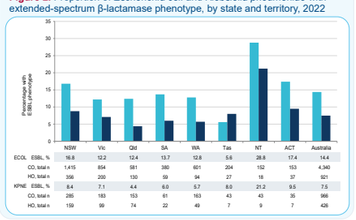


Figure 3. β-lactamase genes detected in *Enterobacterales* with extended-spectrum β-lactamase phenotype, 2022

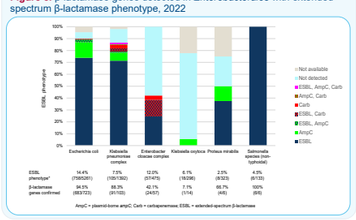
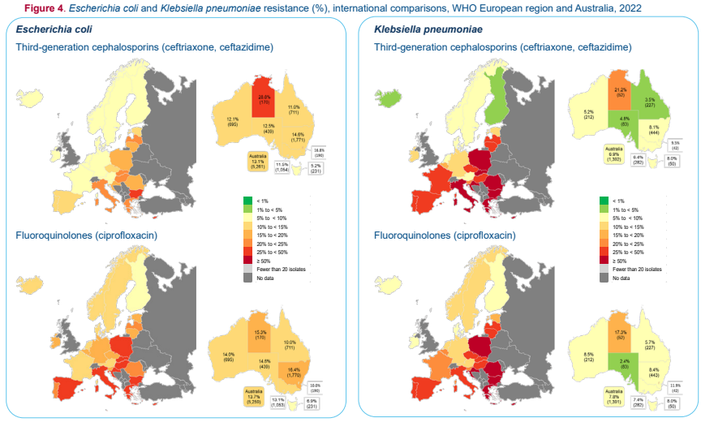


Figure 4. *Escherichia coli* and *Klebsiella pneumoniae* resistance (%), international comparisons, WHO European region and Australia, 2022



- The prevalence of carbapenemase genes among *Enterobacterales* was 0.3% (29/8,773), mostly carrying $bla_{\text{IMP-4}}$*. For HO bacteraemia caused by *E. cloacae* complex the rate increased to 3.5%. Only 1.6% (2/126) *Acinetobacter* and 0.1% (1/840) *P. aeruginosa* harboured carbapenemase gene(s).

Acknowledgements

We wish to thank the staff of the AGAR laboratories for the collection of data and isolates.

The AGAR Surveillance Outcome Programs are funded by the Australian Government Department of Health and Aged Care.

AUSTRALIAN GROUP on ANTIMICROBIAL RESISTANCE

CONCLUSIONS

- Compared with European countries, Australia ranks towards the middle in rates of resistance to third-generation cephalosporins in *E. coli*, but in the bottom quarter in rates of resistance to fluoroquinolones. In *K. pneumoniae* complex isolates, resistance to both fluoroquinolones and third-generation cephalosporins is low (<10.0%).
- Carbapenem resistance attributable to acquired carbapenemase genes is still uncommon in patients with bacteraemia in Australia.

Table 1. Number of carbapenemase and associated resistance genes, by species, and state and territory, 2022

Gene	S/T	Species	ST	MIC	ESBL type*	PMQR gene†	RMT	MCR
$bla_{\text{IMP-4}}$ (*n* = 18)	NSW	*E. hormaechei* (*n* = 2)	62	≥ 16	$bla_{\text{VEB-3}}$	*aac(6')-Ib-crA, qnrB2*	–§	–§
	NSW	*E. hormaechei*	134	> 8	–§	*qnrB2*	–§	*mcr-9*#
	NSW	*E. hormaechei*	110	≥ 16	$bla_{\text{SHV-12}}$	*aac(6')-Ib-crA, qnrB2*	–§	*mcr-9*#
	NSW	*E. hormaechei*	50	≥ 16	–§	–§	–§	–§
	NSW	*E. hormaechei*	105	≥ 16	$bla_{\text{CTX-M-15}}$	*aac(6')-Ib-crC, qnrB2*	–§	–§
	NSW	*K. pneumoniae*	3155	≥ 16	–§	–§	–§	–§
	NSW	*K. pneumoniae*	27	≥ 16	–§	*qnrB2*	–§	–§
	NSW	*S. marcescens*	–§	≥ 16	–§	–§	–§	–§
	Vic	*S. marcescens*	–§	8	–§	–§	–§	–§
	Vic	*S. marcescens*	–§	≥ 16	–§	–§	–§	–§
	Vic	*E. hormaechei*	114	≥ 16	$bla_{\text{SHV-12}}$	*aac(6')-Ib-crA, qnrA1*	–§	*mcr-9*#
	Vic	*K. pneumoniae*	1564	≥ 16	$bla_{\text{CTX-M-15}}$	*aac(6')-Ib-crC, qnrB (x2)*	–§	–§
	Qld	*E. cloacae*	–§	≥ 16	$bla_{\text{SHV-12}}$	*aac(6')-Ib-crA, qnrB2*	–§	*mcr-9*#
	NT	*K. pneumoniae*	307	≥ 16	$bla_{\text{CTX-M-15}}$	*aac(6')-Ib-crC, qnrB1*	–§	–§
	ACT	*K. pneumoniae*	517	≥ 16	–§	*qnrB2*	–§	–§
	ACT	*E. coli*	4088	≥ 16	–§	–§	–§	–§
$bla_{\text{NDM-5}}$ (*n* = 4)	NSW	*E. coli*	648	≥ 16	$bla_{\text{CTX-M-15}}$	*aac(6')-Ib-crC*	–§	–§
	NSW	*E. coli*	405	8	$bla_{\text{CTX-M-15}}$	*aac(6')-Ib-crC*	–§	–§
	Vic	*E. coli*	131	≥ 16	$bla_{\text{CTX-M-15}}$	–§	*rmtB1*	–§
	WA	*E. coli*	410	≥ 16	$bla_{\text{CTX-M-15}}$	–§	–§	–§
$bla_{\text{NDM-5, OXA-181}}$ (*n* = 1)	NSW	*E. coli*	205	4	–§	*qnrS1*	–§	–§
$bla_{\text{NDM-1}}$ (*n* = 3)	Vic	*K. pneumoniae*	313	≥ 16	$bla_{\text{SHV,}}$ $bla_{\text{CTX-M-15}}$	*aac(6')-Ib-crC, qnrB1, qnrB4*	–§	–§
	Qld	*K. variicola*	1563	≥ 16	–§	*aac(6')-Ib-crC, qnrB4*	–§	–§
	Qld	*E. hormaechei*	111	≥ 16	$bla_{\text{SHV-12,}}$ $bla_{\text{CTX-M-15}}$	*aac(6')-Ib-crC, qnrB1, qnrS1*	–§	–§
$bla_{\text{NDM-1, OXA-181}}$ (*n* = 1)	Vic	*K. pneumoniae*	11	2	$bla_{\text{CTX-M-15}}$	*aac(6')-Ib-crC, qnrS1*	*rmtC*	–§
$bla_{\text{OXA-181}}$ (*n* = 1)	NSW	*E. coli*	410	0.5	–§	*qnrS1*	–§	–§
$bla_{\text{OXA-244}}$ (*n* = 1)	NSW	*E. coli*	10	2	–§	–§	–§	–§
$bla_{\text{OXA-23}}$ (*n* = 2)	Vic	*A. baumannii complex*	2	≥ 16	–§	–§	*armA*	–§
	NT	*A. baumannii complex*	2	≥ 16	–§	–§	*armA*	–§
$bla_{\text{NDM-1}}$ (*n* = 1)	NSW	*P. aeruginosa* (*n* = 1)	654	≥ 16	–§	–§	*rmtB4*	–§

ESBL = extended-spectrum β-lactamase (TEM-, SHV-, CTX-M-types or pAmpC); MCR = mobile colistin resistance; MIC = meropenem (mg/L); ST = sequence type; S/T = state or territory
† Plasmid-mediated quinolone resistance: *aac(6')-Ib-cr, qnr*, efflux (*qepA, oqxAB* - not included if intrinsic to species)
§ Not detected
* *mcr-9* is not associated with a colistin resistant phenotype but is typically found on HI2 plasmids which may carry $bla_{\text{IMP-4}}$

The Australian Group on Antimicrobial Resistance Report from the Gram-negative Surveillance Outcome Program (GnSOP) 2022 – Clinical Outcomes

J.M. Bell[1], T. Gottlieb[2,3] and J. Iredell[3,4,5] for the Australian Group on Antimicrobial Resistance

[1]The Australian Group on Antimicrobial Resistance, [2]Concord Hospital, Sydney, [3]The University of Sydney, [4]Westmead Institute for Medical Research, [5]Westmead Hospital, Sydney

INTRODUCTION

The Australian Group on Antimicrobial Resistance (AGAR) Gram-negative Surveillance Outcome Programme (GnSOP) 2022 survey focused on resistance and demographic data on *Enterobacterales*, *Pseudomonas aeruginosa* and *Acinetobacter* species. Survey objectives were to monitor resistance (including co-resistance and multi-resistance), and to detect critical emerging resistance.

This report documents the available clinical features and bacteraemia outcomes.

METHODS

Thirty-three laboratories servicing 55 hospitals from all States and mainland Territories of Australia participated in the 2022 survey. Each hospital collected either all or up to 200 isolates from different patient bacteraemia episodes. In patients with more than one isolate, a new episode was defined if another positive blood culture was collected ≥ 2 weeks after the initial positive culture.

RESULTS

- A total of 9,739 gram-negative episodes were recorded. *Enterobacterales* accounted for 90.1%, followed by *P. aeruginosa* (8.6%) and *Acinetobacter* species (1.3%).
- Four genera made up 86.7% of all isolates (*Escherichia* 54.2%, *Klebsiella* 18.8%, *Pseudomonas* 8.6%, and *Enterobacter* 5.1%) (Figure 1).
- For gram-negative bacteraemia, the proportion from males was 53.7% (Figure 2), and 4.3% were from children (<18 y).

Figure 1. Top ten species causing bacteraemia, 2022

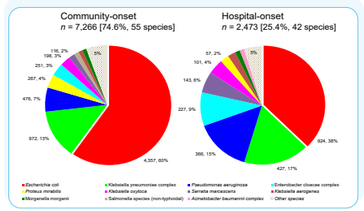
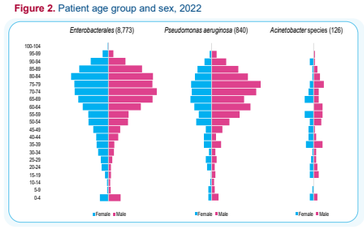


Figure 2. Patient age group and sex, 2022



- Overall, 74.6% of episodes were designated community-onset (CO), first positive blood culture collected ≤ 48 h after admission. Only 17.5% of *E. coli* bacteraemia was hospital-onset (HO); whereas 31.9% of *Klebsiella*, 43.6% of *P. aeruginosa*, and 46.3% *Enterobacter* bacteraemias were HO (Table 1).
- Urinary tract infection was the most frequent principal manifestation for CO episodes caused by *Enterobacterales* (51.2%) and *P. aeruginosa* (34.7%).
- For HO episodes, urinary tract infection (*Enterobacterales* 24.7%, *P. aeruginosa* 23.2%) and febrile neutropenia (*Enterobacterales* 22.5%, *P. aeruginosa* 24.1%) were the most common.
- For *Enterobacterales*, device-related urinary tract infections were more common for HO than CO episodes (23.6% versus 9.4%, *P* < 0.0001).
- The majority of patients with an *Enterobacterales* bacteraemia (44.7%) stayed in hospital stay for < 7 days post bacteraemia (CO, 52.1%; HO, 21.6%). Just over one-third (34.1%) of patients with HO bacteraemia caused by *Acinetobacter* species, and over one-quarter (28.4%) with bacteraemia caused by *P. aeruginosa* remained in hospital for more than 30 days.
- The 30–day all-cause mortality was 12.5% for *Enterobacterales*, 18.4% for *P. aeruginosa*, and 13.0% for *Acinetobacter* species) (Table 3).
- A significant difference in 30-day all-cause mortality was seen between CO and HO with *Enterobacterales* bacteraemia (11.9% vs 14.4%, *P* = 0.0118).
- There was a significant difference in 30-day all-cause mortality between children (3.7%, 11/295) and adults (12.9%, 778/6,023) for *Enterobacterales* (*P* < 0.0011).

RESULTS (continued)

- Nationally, 53.8% of all *E. coli* isolates were resistant to at least one of five key antimicrobial groups (aminopenicillins, fluoroquinolones, third-generation cephalosporins, aminoglycosides and carbapenems); 2.9% were resistant to four groups.
- For *K. pneumoniae* complex, 10.9% were resistant to at least one antimicrobial group (fluoroquinolones, third-generation cephalosporins, aminoglycosides and carbapenems).
- Just over 1 in 5 (21.1%) of *P. aeruginosa* were resistant to at least one antimicrobial group (piperacillin–tazobactam, fluoroquinolones, ceftazidime, aminoglycosides or carbapenems).

CONCLUSIONS

- Gram-negative sepsis is common in Australia and continues to be a significant cause of morbidity and mortality.
- There was little change in the demographic and clinical features of Gram-negative bacteraemia in Australia in the GnSOP 2022 survey.

Table 1. Species recovered, by place of onset, 2022

Organism	Community % (*n*)	Hospital % (*n*)	Total
*Gram-negative species**	*74.6 (7,266)*	*25.4 (2,473)*	*9,739*
Acinetobacter species	66.7 (84)	33.3 (42)	126
Enterobacterales	76.5 (6,708)	23.5 (2,065)	8,773
Escherichia coli	82.5 (4,349)	17.5 (924)	5,273
Klebsiella pneumoniae complex	69.4 (968)	30.6 (427)	1,395
Enterobacter cloacae complex	52.4 (250)	47.6 (227)	477
Proteus mirabilis	82.4 (267)	17.6 (57)	324
Klebsiella oxytoca	66.0 (196)	34.0 (101)	297
Serratia marcescens	44.4 (114)	55.6 (143)	257
Klebsiella aerogenes	60.8 (79)	39.2 (51)	130
Morganella morganii	70.9 (78)	29.1 (32)	110
Citrobacter freundii complex	74.2 (72)	25.8 (25)	97
Salmonella species (non-typhoidal)	91.8 (89)	8.2 (8)	97
Other *Enterobacterales* (*n* = 38)	77.8 (246)	22.2 (70)	316
Pseudomonas aeruginosa	56.4 (474)	43.6 (366)	840

* *Enterobacterales*, *Acinetobacter* and *Pseudomonas aeruginosa*

Table 2. Principal clinical manifestation, organism group, 2022

Principal clinical manifestation	Organism group, % (n)			Total
	Acinetobacter species	*Enterobacterales*	*Pseudomonas aeruginosa*	
Urinary tract infection	3.4 (4)	45.1 (3,462)	29.8 (225)	43.2 (3,691)
Biliary tract infection (including cholangitis)	3.4 (4)	15.0 (1,151)	4.8 (36)	13.9 (1,191)
Febrile neutropenia	7.8 (9)	9.3 (714)	18.4 (139)	10.1 (862)
Intra-abdominal infection other than biliary tract	4.3 (5)	10.2 (782)	7.4 (56)	9.9 (843)
No identifiable focus	20.7 (24)	7.4 (567)	9.3 (70)	7.7 (661)
Other clinical syndrome	17.2 (20)	6.0 (460)	11.8 (89)	6.7 (569)
Device-related infection without metastatic focus	23.3 (27)	3.2 (245)	9.7 (73)	4.0 (345)
Skin and skin structure infection	17.2 (20)	2.7 (204)	7.8 (59)	3.3 (283)
Osteomyelitis/septic arthritis	2.6 (3)	0.9 (67)	0.7 (5)	0.9 (75)
Device-related infection with metastatic focus	0.0 (0)	0.3 (23)	0.3 (2)	0.3 (25)
Total	116	7,675	754	8,545

Table 3. Place of onset setting and 30-day all-cause mortality, 2022

Organism	Community-onset		Hospital-onset		Total	
	Number	Deaths % (*n*)	Number	Deaths % (*n*)	Number	Deaths % (*n*)
*Gram-negative species**	*5,178*	*12.4 (642)*	*1,874*	*14.7 (276)*	*7,052*	*13.0 (918)*
Acinetobacter species	71	15.5 (11)	37	8.1 (3)	108	13.0 (14)
Enterobacterales	4,758	11.9 (565)	1,560	14.4 (224)	6,318	12.5 (789)
Escherichia coli	2,998	11.1 (334)	690	13.3 (92)	3,688	11.6 (426)
Klebsiella pneumoniae complex	707	12.2 (86)	319	13.8 (44)	1,026	12.7 (130)
Enterobacter cloacae complex	188	10.1 (19)	180	16.1 (29)	368	13.0 (48)
Proteus mirabilis	203	20.7 (42)	44	18.2 (8)	247	20.2 (50)
Klebsiella oxytoca	143	11.9 (17)	74	14.9 (11)	217	12.9 (28)
Serratia marcescens	83	16.9 (14)	106	12.3 (13)	189	14.3 (27)
Klebsiella aerogenes	66	16.7 (11)	36	13.9 (5)	102	15.7 (16)
Morganella morganii	58	20.7 (12)	25	24.0 (6)	83	21.7 (18)
Citrobacter freundii complex	57	15.8 (9)	22	13.6 (3)	79	15.2 (12)
Other *Enterobacterales* (*n* = 38)	255	8.2 (21)	64	20.3 (13)	319	10.7 (34)
Pseudomonas aeruginosa	349	18.9 (66)	277	17.7 (49)	626	18.4 (115)

* *Enterobacterales*, *Acinetobacter* and *Pseudomonas aeruginosa*

Acknowledgements

We wish to thank all of the contributing laboratories throughout Australia who provided isolates and or information for this study.

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AUSTRALIAN GROUP on ANTIMICROBIAL RESISTANCE

The Australian Group on Antimicrobial Resistance Report from the Gram-negative Surveillance Outcome Program (GnSOP) 2013–2022

Jan Bell[1], Thomas Gottlieb[2,3] and Jonathan Iredell[3,4,5] for the Australian Group on Antimicrobial Resistance

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INTRODUCTION

In 2013, AGAR began the ongoing *Enterobacterales* Sepsis Outcome Program. In 2015, *Pseudomonas aeruginosa* and *Acinetobacter* species were added, and the program evolved into the Gram-negative Surveillance Outcome Program (GnSOP).

The aim of GnSOP is to monitor resistance, and to detect critical emerging antimicrobial reistance (AMR) in Gram-negative isolates from patients with documented bacteraemia.

METHODS

- Participating laboratories servicing hospitals from all States and mainland Territories of Australia, collected either all or up to 200 isolates from different patient bacteraemia episodes. Species were identified using the routine method for each laboratory. MICs were determined using commercial systems Vitek® 2 (BioMérieux) or Phoenix™ (BD). The results were analysed using EUCAST breakpoints (January 2023).
- The number of institutions included increased from 24 in 2013 to 48 in 2017 and 55 in 2022. In addition, the relative distribution of sites has changed with the addition of three more paediatric and/or facilities providing specialist obstetric services, from 2017, and one additional site in 2019 and another in 2020 and the inclusion of hospitals from north-west regional Western Australia from 2015.

RESULTS

- A total of 71,444 *Enterobacterales* have been studied since 2013, with 5,947 *P. aeruginosa* and 851 *Acinetobacter* since 2015.
- Overall rates of resistance to key antimicrobial agents over the period 2013–2022 are shown in Figure 1 for *Escherichia coli* and the *Klebsiella pneumoniae* complex in Figure 2.
- The frequency of *E. coli* with an ESBL phenotype increased from 8.4% in 2013 to 14.5% in 2018 and has remained at steady at 14% since 2019 (Figure 3). For *K. pneumoniae* complex isolates, the frequency of ESBL phenotypes was lower than that observed among *E. coli*, increasing from 6.8% in 2013 to 10% in 2018 to 2020, decreasing to 7.9% in 2021 and 7.6% in 2022 (Figure 3).
- The frequency of multidrug resistant (MDR) *E. coli* increased from 8.3% in 2013 to a peak of 12.6% in 2019, and decreased to 10.7% in 2022 (Figure 4). Although the rate of MDR among community-onset isolates (collected ≤ 48-h after admission) increased in 2022 (10.3%) compared to 2021 (9.1%), the increase was not statistically significant. For the *K. pneumoniae* complex, the frequency of MDR peaked at 6.2% in 2018, and has fallen to 2.8% in 2022.
- Over the past five years (2018–2022), a significantly decreasing trend in fluoroquinolone (FQ) resistance in *E. coli* was observed in Victoria, Western Australia, and the Australian Capital Territory. Victoria was the only state with significantly decreasing trends in third-generation cephalosporin (3GC) and aminoglycoside (AG) resistance in *E. coli* (Figure 5A).
- Over the past five years, Victoria was the only state with significantly ($P < 0.01$) decreasing trends in FQ, 3GC, and AG resistance in *K. pneumoniae* complex (Figure 5B).

RESULTS (continued)

Figure 1. *Escherichia coli*, resistance to key antimicrobials, 2013–2022

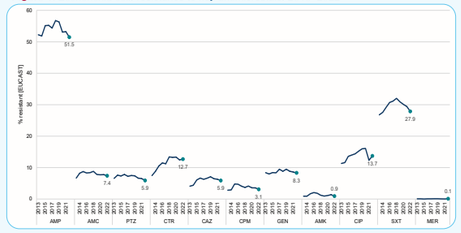
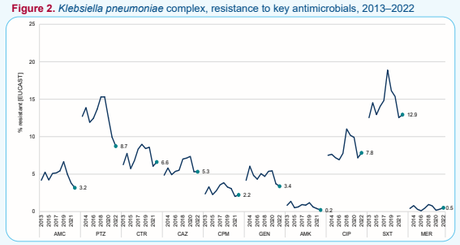


Figure 2. *Klebsiella pneumoniae* complex, resistance to key antimicrobials, 2013–2022



AMC = amoxicillin–clavulanate (2:1 ratio); AMK = amikacin; AMP = ampicillin; CAZ = ceftazidime; CIP = ciprofloxacin; CPM = cefepime; CTR = ceftriaxone; GEN = gentamicin; MER = meropenem; PTZ = piperacillin–tazobactam; SXT = trimethoprim-sulfamethoxazole

Figure 3. 10-year trend in *Escherichia coli* and *Klebsiella pneumoniae* complex isolates with an ESBLphenotype, 2013–2022

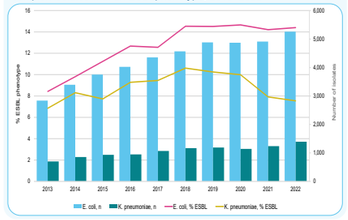
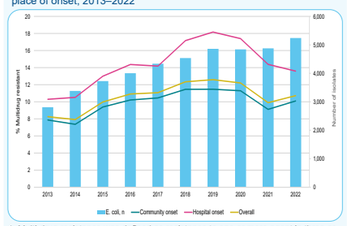


Figure 4. 10-year trend in mutlidrug-resistant *Escherichia coli*, by place of onset, 2013–2022

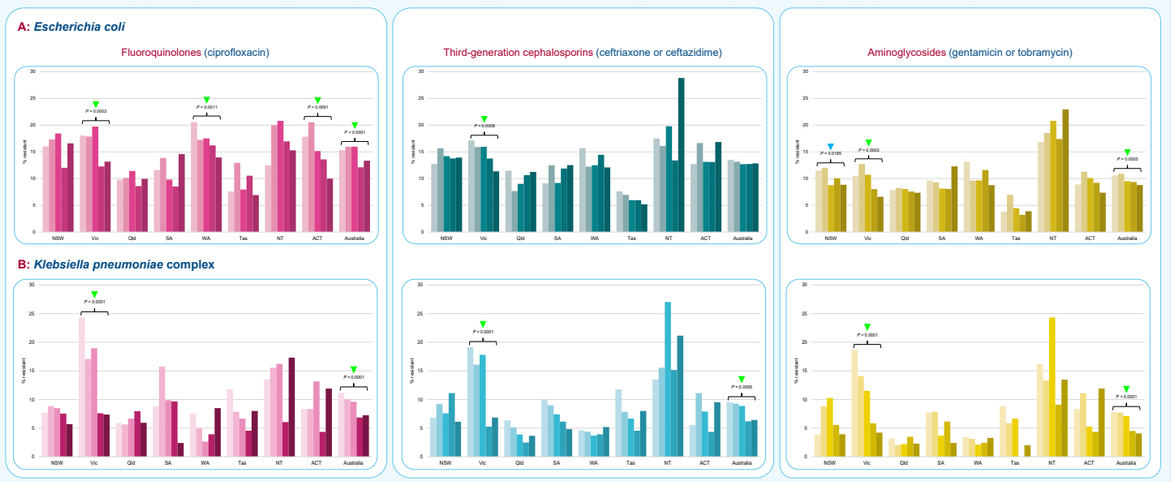


1. Multi-drug resistance was defined as resistance to one or more agent in three or more antimicrobial categories.
2. Antimicrobial categories (agents) were aminoglycosides (gentamicin or tobramycin), carbapenems (meropenem), extended-spectrum cephalosporins (ceftriaxone or ceftazidime), fluoroquinolones (ciprofloxacin), and penicillins (ampicillin).

CONCLUSIONS

- AGAR data show different longitudinal trends of *E. coli* resistance to key anti-gram-negative antimicrobial agents, such as ceftriaxone and ciprofloxacin, by state and territory.
- AGAR surveillance remains core to Australia's response to the problem of increasing AMR, and contributes to understanding AMR in Australian human health settings, and to informing the national response to AMR.

Figure 5. Resistance (%) to fluoroquinolones, third-generation cephalosporins and aminoglycosides, *Escherichia coli* (A) and *Klebsiella pneumoniae* complex (B), by state and territory, 2018–2022



Chi-square test for trend for past five years (2018-2022); significant decrease ▼ $P < 0.01$, ▼ $0.01 < P < 0.05$
Notes: 1. Percentage resistance determined using EUCAST 2023 breakpoints for all years. 2. Data only from hospitals consistently reporting for all five years were included.

Enterococcal Bacteraemia in Paediatric Patients From Across Australia, 2020-2021

***Anita Williams[1]**, Geoffrey Coombs[2,3,4], Denise Daley[3,4], Shakeel Mowlaboccus[2,3], Christopher Blyth[1,5,6,7], on behalf of the AGAR Kids Group*

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BACKGROUND

Enterococcal species can cause a variety of infections, including urinary tract and intra-abdominal infections, endocarditis, and meningitis. Globally, *Enterococci* spp. account for approximately 10% of all bacteraemia cases.

Since 1986, the Australian Group on Antimicrobial Resistance (AGAR) has captured clinical and microbiological data to monitor changes in antimicrobial resistance in *Enterococcus spp.* isolates.

METHOD

Demographic data, date of blood culture collection, genus and species of the bacteria isolated, and relevant antimicrobial susceptibility test results are collated from 30 participating laboratories servicing 49 healthcare institutions across Australia.

Principal clinical manifestation and outcomes are collected from related clinical datasets. Consecutive isolates from distinct bacteraemic episodes in patients <18 years were analysed. To account for changes over time, trends were assessed in three-year time periods. Minimum inhibitory concentration (MIC) interpretation was as per EUCAST 2022 rules using the AMR for R Package (v2).

RESULTS

Overall, 170 enterococci were reported to AGAR 95 isolates in 2020 and 75 isolates in 2021. Most isolates were identified as *E. faecalis* (n: 122, 71.8%); 24.1% were *E. faecium* (n:41). The largest proportion of episodes were from NSW (40%) and Victoria (34.1%).

Isolates were most frequently reported from patients <1 years old (43.0%) and were mostly neonates (22.3%). The most frequent clinical manifestation was device-related infection without metastatic focus (n: 40; 23.5%). Over half of the episodes were hospital onset (n: 98; 57.6%), and 37.1% of infections were polymicrobial.

Almost one-fifth of isolates were resistant to ampicillin (19.6% 95%CI: 13.9–26.5%); one isolate was *E. faecalis*, whilst the rest were *E. faecium* (n: 32). Over 70% of ampicillin resistant isolates were hospital-onset (72.7%, n: 24).

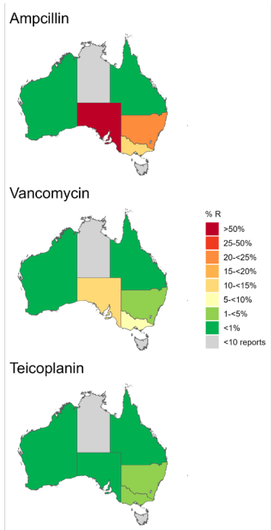
Eight isolates were resistant to vancomycin (4.7%), and three to teicoplanin (1.8%); all glycopeptide- resistant isolates were *E. faecium* and hospital-acquired, significantly lower than in adult populations (15.0% for 2020-2021, $p<0.001$).

Five *Enterococcus* spp. isolates were multi-drug resistant (MDR) – all *E. faecium.* Four of the five isolates were reported from Victoria.

Two *E. faecium* isolates harboured *vanA* (both from NSW) and six harboured *vanB* (two from SA, and four from Victoria). No isolates harboured both *vanA* and *vanB*.

The most frequent *E. faecium* sequence type was ST17 (n: 9, 20.5%), and ST1421 (n: 7, 15.9%)

	Tested	Resistant	%	95% CI	
Ampicillin	168	33	19.6	13.9	26.5
Vancomycin	170	8	4.7	2.1	9.1
Teicoplanin	170	3	1.8	0.4	5.1



CONCLUSION

Hospital-onset infections are an important origin of Enterococcal infections in paediatrics, with device-related infections a key source.

Resistance in Enterococci overall is lower in children than adults across Australia, particularly Vancomycin-resistant *E. faecium* infections. Nevertheless, ampicillin resistance is high, and monitoring should be ongoing.

AGAR Kids Group:
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Gram Negative Bacteraemia in Children From Across Australia, 2020-21

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BACKGROUND

Gram negative bacteraemia is associated with significant morbidity and mortality in children. Increasing rates of antimicrobial resistance (AMR) are reported globally, with bacteraemia surveillance providing a unique opportunity to assess AMR and outcomes.

Since 1986, the Australian Group on Antimicrobial Resistance (AGAR) has captured clinical and microbiological data to monitor changes in antimicrobial resistance in gram negative isolates, specifically Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter spp.*

METHOD

Demographic data, date of blood culture collection, genus and species of the bacteria isolated, and relevant antimicrobial susceptibility test results are collated from 30 participating laboratories servicing 49 healthcare institutions across Australia.

Principal clinical manifestation and outcomes are collected from related clinical datasets. Consecutive isolates from distinct bacteraemic episodes in patients <18 years were analysed. To account for changes over time, trends were assessed in three-year time periods. Minimum inhibitory concentration (MIC) interpretation was as per EUCAST 2022 rules using the AMR for R Package (v2).

RESULTS

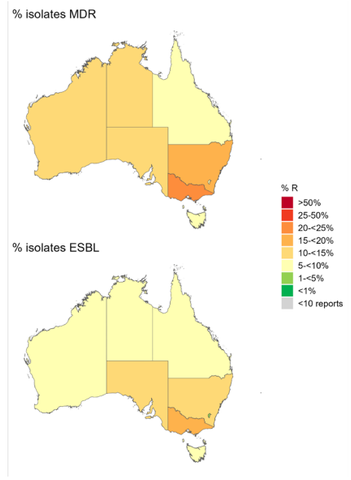
There were 902 gram-negative isolates reported from 867 bacteraemia episodes in 2020-2021; 800 Enterobacterales (88.7%), 61 *Pseudomonas aeruginosa* (6.8%) and 41 (4.5%) *Acinetobacter* spp. The median age was 1 year (0 – 7 years); 18.2% were from neonates. After 30 days from collection, 5.2% of patients had died - 27.6% of patients who died had a multi-drug resistant (MDR) organism.

Of the 800 Enterobacterales, 47.3% were *Escherichia coli*, 15.3% were *Klebsiella pneumoniae* complex and 13.3% were *Enterobacter cloacae* complex. Resistance in Enterobacterales to ciprofloxacin was 13.2%, 12.9% to ceftazidime/ceftriaxone and 11.6% to gentamicin/tobramycin. Overall, 149 (18.6%) of the 800 Enterobacterales isolates were identified as MDR; MDR isolates were more likely to be hospital-onset (p: <0.01) associated with a device-related infection (p: <0.01) and were more frequent in patients with febrile neutropenia.

Of the 61 *P. aeruginosa* reported, 19.7% were resistant to piperacillin-tazobactam, 13.1% resistant to cefepime/ceftazidime, 9.8% to ciprofloxacin and 3.3% to carbapenems. Three *P. aeruginosa* were MDR (4.9%).

Forty-one isolates of *Acinetobacter* spp. were reported but none were resistant to carbapenems or classified as MDR.

There were 108 Enterobacterales isolates with an MIC of ≥2 mg/L for ceftazidime and/or ceftriaxone; 48 *E. coli*, 25 *K. pneumoniae* complex, 23 *E. cloacae* complex*, six other Enterobacterales species and 10 *A. baumanii* complex.



*In *Enterobacter*, cefepime MICs of greater than 0.25 mg/L suggest that an isolate of this genus harbours an ESBL

CONCLUSION

Regional differences were noted in the gram-negative isolates causing bacteraemia. There were significant differences in the susceptibility patterns were observed between jurisdictions with a high proportion of resistant Enterobacterales observed in Victoria.

It is important to continue monitoring AMR in Gram-negative isolates in the paediatric population to provide targeted treatment in the local context.

AGAR Kids Group:
Jan Bell, Chris Blyth, Penelope Bryant, Anita Campbell, Louise Cooley, Geoff Coombs, Denise Daley, Jon Iredell, Adam Irwin, Alison Kesson, Brendan McMullan, Morgyn Warner, Phoebe Williams

Staphylococcus aureus Bacteraemia in Paediatric Patients From Across Australia, 2020-2021

Anita Williams[1], *Geoffrey Coombs*[2,3,4], *Denise Daley*[3,4], *Shakeel Mowlaboccus*[2,3], *Christopher Blyth*[1,5,6,7], *on behalf of the AGAR Kids Group**

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BACKGROUND

Staphylococcus aureus bacteraemia (SAB) is associated with significant morbidity and mortality, frequently affecting neonates, Indigenous children and children admitted to hospital. SAB can result in bone and joint infections, complicated skin and soft tissue infection, lower respiratory tract infections, and metastatic complications.

Since 1986, the Australian Group on Antimicrobial Resistance (AGAR) has captured clinical and microbiological data to monitor changes in antimicrobial resistance in *S. aureus* isolates.

METHOD

Demographic data, date of blood culture collection, genus and species of the bacteria isolated, and relevant antimicrobial susceptibility test results are collated from 30 participating laboratories servicing 49 healthcare institutions across Australia.

Principal clinical manifestation and outcomes are collected from related clinical datasets. Consecutive isolates from distinct bacteraemic episodes in patients <18 years were analysed. To account for changes over time, trends were assessed in three-year time periods. Minimum inhibitory concentration (MIC) interpretation was as per EUCAST 2022 rules using the AMR for R Package (v2).

RESULTS

There were 607 *S. aureus* isolates reported from patients aged <18 years; 13.2% were methicillin-resistant (MRSA) (n: 78) and 5.6% were MDR (n: 34).

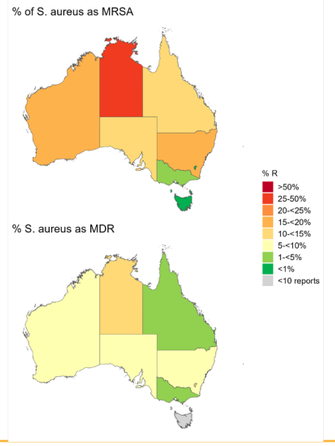
The median age was 6.0 years (1-11.5), and 8.4% of reports were from neonates. Most SAB episodes were community-onset (n: 478, 78.7%) and monomicrobial (n: 563, 92.8%).

In children <1 year the most frequent clinical manifestation were device-related infections without metastatic focus (n:30/148, 20.3%), whereas in children 1-17 years osteomyelitis/septic arthritis infections were more frequent (n: 235/459, 51.2%).

MRSA were most frequently reported in patients aged 1-4 years, and from hospital-onset infections. The NT reported the highest proportion of S. aureus isolates that were MRSA (45%) and there were no MRSA isolates reported in the ACT or Tasmania. The most frequently isolated MRSA strain was the Panton-Valentine leucocidin-positive ST93-IV clone.

Overall, 13.2% of *S. aureus* were resistant to erythromycin, 12.4% to clindamycin, and 5.3% to ciprofloxacin, with resistance to these antibiotics higher in MRSA isolates than methicillin-susceptible isolates (22.5%, 18.8%, and 16.3% respectively).

	Tested	Resistant	%	95% CI	
Clindamycin	607	75	12.4	9.8	15.2
MRSA	80	15	18.8	10.9	29
Ciprofloxacin	607	32	5.3	3.6	7.4
MRSA	80	13	16.3	8.9	26.2
Erythromycin	607	80	13.2	10.6	16.1
MRSA	80	18	22.5	13.9	33.2
Co-trimoxazole	601	0	0.0		



CONCLUSION

Regional differences in *S. aureus* were noted; there was a clear disproportion in the geographic distribution of MRSA episodes reported across Australia, and the over representation from the Northern Territory is found in both adults and children. A more detailed investigation in the geographic distribution of MRSA in paediatrics is planned proposed and it is hypothesised that there will be a higher proportion of MRSA across the north of Australia which has previously been reported in the literature.

AGAR Kids Group:
Jan Bell, Chris Blyth, Penelope Bryant, Anita Campbell, Louise Cooley, Geoff Coombs, Denise Daley, Jon Iredell, Adam Irwin, Alison Kesson, Brendan McMullan, Morgyn Warner, Phoebe Williams

ASA24 BEST POSTER AWARDEES

DIVERSITY OF *VAN* OPERONS IN VANCOMYCIN VARIABLE *ENTEROCOCCUS FAECIUM* CAUSING BACTERAEMIA FROM AUSTRALIA, 2016-2020

Form AN[1,*], Coombs GW[1,2,3], Shoby P[1], Daley DA[2,3], Mowlaboccus S[1,2,3]

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Aim

To characterise the genetic diversity of vancomycin-variable *Enterococcus faecium* (VVEfm) causing bacteraemia in Australia and test the effect of vancomycin exposure on VVEfm.

Background

The increasing prevalence of vancomycin-resistant *E. faecium* (VREfm) is a global health concern. VVEfm are phenotypically vancomycin-susceptible *E. faecium* isolates that possess a *van* gene. Some VVEfm can revert to a vancomycin-resistant phenotype when exposed to vancomycin, *in vitro* and *in vivo*, posing a challenge for the treatment of *E. faecium* infections.

Methods

VVEfm causing bacteraemia in Australia during 2016-2020 were identified from the Australian Enterococcal Surveillance Outcome Program. Whole genome sequencing (WGS) was performed on the Illumina® NextSeq™ 500 platform. Various bioinformatics tools were used to identify the sequence type (ST) of each isolate and analyse the *van* operon. Vancomycin susceptibility testing was initially performed using the Vitek® 2 or the BD Phoenix™ and confirmed by broth microdilution. The vancomycin MIC was interpreted using the EUCAST breakpoints (susceptible: ≤4 mg/L; resistant: >4 mg/L). Exposure to vancomycin was performed in overnight broth culture using a 2-fold daily increase in vancomycin concentration. VVEfm revertant mutants underwent WGS and compared their genome to their parent strain.

Diversity of *vanA* operons

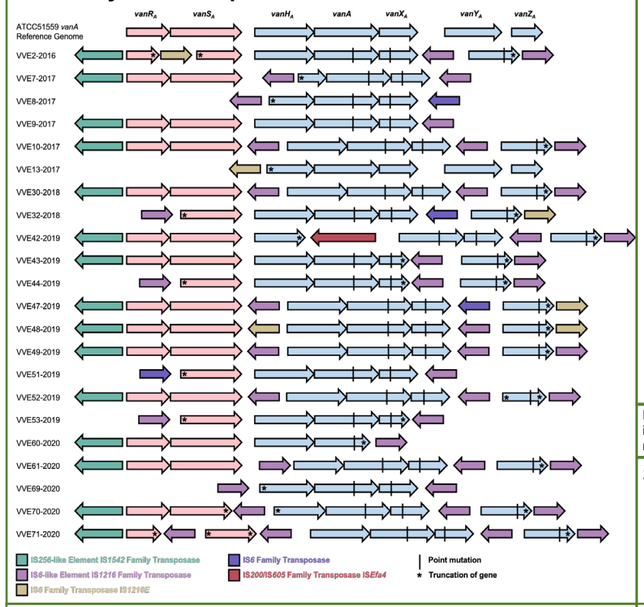

Figure 1: The diversity of *vanA* operons found within the *vanA*-positive VVEfm isolates. Each isolate has its own unique combination of IS element, point mutations, and gene truncation/absence.

Diversity of *vanB* operons

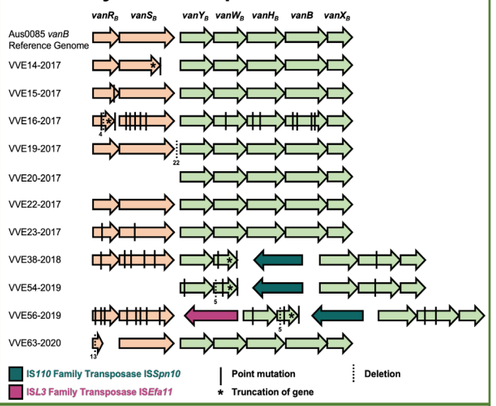

Figure 2: The diversity of *vanB* operons found within the *vanB*-positive VVEfm isolates. Each isolate has its own unique combination of IS element, point mutations, deletions, and gene truncation/absence.

Sequence Type (ST) Diversity

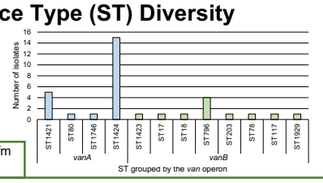

Figure 3: VVEfm ST diversity

Results

A total of 33 VVEfm isolates were identified, of which 22 (66.7%) were *vanA*-positive and 11 (33.3%) were *vanB*-positive. The *vanA*-positive isolates belonged to four STs, two of which were represented by more than one isolate, ST1424 (n=15) and ST1421 (n=5) (Figure 3). The *vanB*-positive isolates belonged to eight STs, of which only ST796 (n=4) was represented by more than one isolate (Figure 3). All *vanA* operons harboured at least one insertion sequence (IS) (IS*1542*, IS*1216E*, IS*1216*, IS6, IS*200*/IS*605*, and IS*Efa4*), as well as truncated or absent genes (Figure 1). Except for one isolate that possessed an intact *vanB* operon, the *vanB* operons harboured either point mutations, IS elements (IS*110* and IS*L3*), truncated or absent genes (Figure 2). Twelve isolates (36.4%), including 10 *vanA*-positive and 2 *vanB*-positive VVEfm, became vancomycin-resistant on exposure to vancomycin. At least a 256-fold increase in vancomycin MIC was observed in the vancomycin-resistant mutants. Some VVEfm revertant mutants showed changes in the *van* operon explaining the increase in vancomycin resistance.

Conclusion

vanA- and *vanB*-positive VVEfm causing bacteraemia in Australia are genetically diverse, some of which can revert to a vancomycin-resistance phenotype in the presence of vancomycin. More analysis is needed on the VVEfm revertant mutants.

MELBOURNE PATHOLOGY

A comparison of methods for the screening and detection of CRE/CPE/CRO/CPO in the laboratory

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Background

- Carbapenem resistance in the form of carbapenemases is primarily due to horizontal transfer of genes through plasmids and/or integrons, allowing for the easy transfer of genes between bacteria[1]. The increasing emergence of carbapenem resistance in gram negative bacilli results in limited therapeutic options and carries significant infection control issues. This has resulted in the necessity for health care facilities to screen for Carbapenem Resistant Enterobacterales (CRE)/Carbapenemase Producing Enterobacterales (CPE)/ Carbapenem Resistant Organisms (CRO)/Carbapenemase Producing Organisms (CPO) in at risk patients[2].
- Several methods exist for the detection of CRE/CRO/CPE/CPO including the Carbapenemase Inhibition Method (CIM), the modified CIM (mCIM), Selective and Differential Media, phenotypic detection of enzyme activity (e.g. Carba NP), Lateral Flow Assays (e.g. Carba 5), and Carbapenemase gene PCR both commercial and in house. These differ in their ease of use and cost.

Aim

- To determine if the currently employed method of detection by this laboratory is sufficient/efficient enough for the detection of CRE/CPE/CRO/CPO.
- To compare the performance and cost effectiveness of several methods of detection of CRE/CPE/CRO/CPO against the currently employed method which consists of a combination of ChromID ESBL media and CIM.
- To evaluate the mCIM as a method for in-house confirmation of possible Carbapenemase Resistant/Producing *Pseudomonas aeruginosa* prior to being sent to a reference laboratory.

Method

- 29 isolates with confirmed (by whole genome sequencing) carbapenemase genes were used to compare the CIM against the mCIM, and ChromID ESBL Agar against ChromID Carb/Oxa (Carba Smart) Agar, as well as to verify the accuracy and ease of use of the Carba 5 test kit.
- The CIM and mCIM are phenotypic methods used to detect carbapenemase activity by incubating a meropenem disc in a solution of organism for several hours before applying the disc to a lawn plate of *E.coli ATCC 25922*. Zones can be read as in Figure 2 with detailed instructions in the CLSI M100 document[3]
- ESBL ChromID® media (bioMérieux) is a selective chromogenic medium designed for the isolation of organisms with expressed ESBL genes, whilst Carba Smart ChromID® media (bioMérieux) is comprised of 2 selective chromogenic medium (in a split plate) designed for the isolation of organisms with carbapenem resistance[4].
- The Carba 5 test by NG Biotech is a qualitative lateral flow immunoassay which can detect KPC, IMP, VIM, NDM, and OXA-48-like carbapenemase enzymes[5]
- 4 control isolates were used to determine the efficacy of each method as well. These were well characterized ATCC strains (see Table 1).

Results

The isolates used in testing were assigned numbers 1 through 29, these numbers are used to distinguish isolates from one another in the following tables. The numbers assigned to stock control organisms are not the same as those assigned to the testing isolates.

Table 1: Stock Control Organisms

	Control Organisms							
	Organism	Gene		CIM	mCIM	CARBA 5	ESBL	CARB	OXA
1	*Klebsiella pneumoniae ATCC BAA 1705*	KPC		POSITIVE	POSITIVE	KPC	GROWTH	GROWTH	NO GROWTH
2	*Klebsiella pneumoniae ATCC BAA 1706*	NO GENE		NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	GROWTH	NO GROWTH
3	*Escherichia coli ATCC 35218*	NO GENE		NEGATIVE	NEGATIVE		NO GROWTH	NO GROWTH	NO GROWTH
4	*Pseudomonas aeruginosa ATCC 27853*	NO GENE		NOT VALID	NEGATIVE				

Several ATCC strain organisms were used as controls. *Klebsiella pneumoniae ATCC BAA 1705* and *ATCC BAA 1706* were used for each comparison/evaluation as both a positive and negative control. *Escherichia coli ATCC 35218* was also used as a negative control to ensure the CIM Vs mCIM and media comparison data was valid. *Pseudomonas aeruginosa ATCC 27853* was only used in the evaluation of CIM Vs mCIM.

Table 2: Carba 5

ISOLATE NUMBER	ORGANISM	GENE	CARBA 5
1	*Klebsiella pneumoniae*	OXA-48	OXA
2	*Escherichia coli*	NDM-5	NDM
3	*Citrobacter freundii*	IMP-4	IMP
4	*Pseudomonas aeruginosa*	VIM-2	VIM
5	*Acinetobacter baumanii*	OXA-23	NEG
6	*Pseudomonas aeruginosa*	NDM-1 and VIM-2	NDM and VIM
7	*Klebsiella pneumoniae*	KPC-2	KPC
8	*Klebsiella pneumoniae*	KPC-3	KPC
9	*Citrobacter freundii*	IMP-4	IMP
10	*Escherichia coli*	OXA-48 LIKE OXA 181	NEG
11	*Acinetobacter baumanii*	NO GENE	NEG
12	*Enterobacter cloacae complex*	NO GENE	NEG
13	*Pseudomonas aeruginosa*	CIM NEG	NEG
14	*Klebsiella pneumoniae*	OXA-48 LIKE OXA 181	OXA
15	*Escherichia coli*	OXA-48	OXA
16	*Escherichia coli*	NDM-5	NDM

Figure 1: CARBA-5 Lateral Flow Immunoassay Test Kit[6]

All but one (Isolate 10) of the test isolates were positive for the expected carbapenemase. The manufacturers guidelines state a sensitivity and specifity of 100%. The data collected reflected a 91.7% sensitivity and 100% specificity for the isolates tested.

Table 3: CIM Vs mCIM

ISOLATE NUMBER	ORGANISM	GENE	CIM	MCIM
1	*Klebsiella pneumoniae*	OXA-48	POSITIVE	POSITIVE
2	*Escherichia coli*	NDM-5	POSITIVE	POSITIVE
3	*Citrobacter freundii*	IMP-4	POSITIVE	POSITIVE
4	*Pseudomonas aeruginosa*	VIM-2	NOT VALID	INTERMEDIATE
10	*Escherichia coli*	NDM-5	POSITIVE	POSITIVE
14	*Klebsiella pneumoniae*	OXA-48	POSITIVE	POSITIVE
18	*Pseudomonas aeruginosa*	NDM-1	NOT VALID	NEGATIVE
20	*Escherichia coli*	NDM-1	POSITIVE	POSITIVE
21	*Enterobacter cloacae complex*	IMI-1	POSITIVE	POSITIVE
22	*Klebsiella pneumoniae*	NDM-1	POSITIVE	POSITIVE
23	*Escherichia coli*	NO GENE	NEGATIVE	NEGATIVE
24	*Klebsiella pneumoniae*	NO GENE	NEGATIVE	NEGATIVE
25	*Serratia marascens*	SME-4	POSITIVE	POSITIVE
27	*Pseudomonas aeruginosa*	KPM-1	NOT VALID	POSITIVE
29	*Pseudomonas aeruginosa*	NDM-1	NOT VALID	POSITIVE

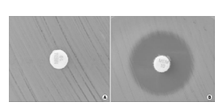

Figure 2: Image A demonstrates no zone of inhibition, indicating a positive CIM/mCIM result. Image B demonstrates a zone of inhibition >28mm, indicating a negative CIM/mCIM result

mCIM testing performed on *Pseudomonas aeruginosa* isolates demonstrated mixed results. The sensitivity and specificity for mCIM are both >99%[3]. The data collected for mCIM reflected a sensitivity of 84.6% and specificity of 100%, whilst the data collected for the CIM reflected both a sensitivity and specificity of 100%.

Table 4: ESBL Media Vs Carba Smart Media

ISOLATE NUMBER	ORGANISM	GENE	ESBL	CARB	OXA
1	*Klebsiella pneumoniae*	OXA-48	GROWTH	GROWTH	GROWTH
2	*Escherichia coli*	NDM-5	GROWTH	GROWTH	NO GROWTH
3	*Citrobacter freundii*	IMP-4	GROWTH	NO GROWTH	NO GROWTH
4	*Pseudomonas aeruginosa*	VIM-2	GROWTH	GROWTH	NO GROWTH
5	*Acinetobacter baumanii*	OXA-23	GROWTH	GROWTH	GROWTH
10	*Escherichia coli*	OXA-48 LIKE OXA 181	GROWTH	GROWTH	GROWTH
19	*Pseudomonas aeruginosa*	NDM-1	GROWTH	GROWTH	NO GROWTH
20	*Escherichia coli*	NDM-1	GROWTH	GROWTH	NO GROWTH
21	*Enterobacter cloacae complex*	IMI-1	GROWTH	GROWTH	NO GROWTH
22	*Klebsiella pneumoniae*	NDM-1	GROWTH	GROWTH	NO GROWTH
24	*Klebsiella pneumoniae*	NO GENE	GROWTH	GROWTH	NO GROWTH
27	*Pseudomonas aeruginosa*	VIM-1	GROWTH	GROWTH	NO GROWTH
29	*Escherichia coli*	ESBL	NO GROWTH	NO GROWTH	NO GROWTH

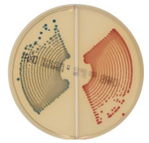

Figure 3: Growth on ChromID® CARBA SMART media[7]

ChromID ESBL® Agar demonstrated growth for all isolates with a carbapenemase gene. Isolate 28 (with a proven ESBL) failed to grow on the media, possibly due to a failure of the organism to survive for testing, as such the results for Isolate 28 for the ChromID Carba Smart® Media may also be unreliable. Excluding Isolate 28, the Carba Smart media testing demonstrated the expected growth patterns for all but 1 isolate (Isolate 3).

The sensitivity for ESBL Media from the data collected reflected a 92.3% sensitivity.
The manufacturers guidelines for Carba Smart Media state a combined sensitivity of 95.9% and combined specificity of 96.6%. The data collected reflected a combined sensitivity of 91.6% and combined specificity of 100%.

Table 5: Comparison of Methods for Concordance of Detection of Carbapenem Resistance

	Number of Isolates Tested		Concordance	Ease of Use	Turn-around time	Cost
	With known resistance genes	Without known resistance genes**		+/++/+++	+/++/+++	$/$$/$$$
CIM	12	4	100%	+	++	$
mCIM	12	4	87.50%	+	++	$
ESBL	14	3	94%	+	+++	$$
CARB/OXA	14	3	100% OXA 88% CARB	+	+++	$$
Carba 5	14	4	94%	+	+	$$$

Comparison of the CIM and mCIM demonstrated an equality in ease of use, turn-around time (although blood plates can be used, not all specimens have a blood plate at their initial culture and thus still require sub-culture as does the CIM) and cost.

The CIM and mCIM methods were equal for detection of carbapenemases in Enterobacterales; however, the performance of the mCIM for detection of carbapenemases in *Pseudomonas aeruginosa* is suboptimal. Testing on a larger number of isolates is required to confirm these results.

The Carba 5 test proved to be easy to use and had a fast turn-around time. The cost per test was the highest of all the methods compared, and had an acceptable concordance with the expected results.
In comparing the ESBL and Carba Smart media the result were relatively equal across the board for ease of use, turn-around time, cost, and their concordance. Overall there was an isolate that should have, but did not work, for both of the media types.

Discussion

- The discrepancy in the data collected for mCIM in regard to *Pseudomonas aeruginosa* demonstrates that further testing is required to evaluate the test.
- The Carba 5 test was accurate for all but 1 isolate with OXA-48-like gene.
- Turn-around time is minimal with the Carba 5 as the assay takes only 15 minutes, and the testing can be performed from Mueller Hinton, CNA, ESBL, Carba Smart, Mueller Hinton +5% Sheep blood, and MacConkey agars.
- Comparison of the ESBL and Carba Smart media showed that the media types were on a relatively equal footing for the factors being assessed. A mixed growth inoculum to determine the ability of the media to differentiate multiple organisms is ongoing.

Conclusion

- In view of the difference in ease of use, turn-around time and cost of each of the methods, no single method would address all of the different clinical scenario's that would present themselves in the laboratory. Therefore to address this, a multi-method approach is needed in the screening and confirmation of CRE/CPE/CRO/CPO's.
- Further evaluation is required for the performance of the mCIM for *Pseudomonas aeruginosa*
- Due to the cost of Carba 5 kits, it may be useful in circumstances where the results may be more clinically significant, e.g. from a blood culture or a sterile site, rather than for all suspiciously resistant isolates
- The use of Carba Smart media in the laboratory for the screening of CRE/CPE/CRO/CPO can provide an early presumptive result for infection control purposes, whereas a positive result from an ESBL plate does not necessarily indicate the presence of Carbapenem resistance and requires further workup. Sensitivity does not decrease by changing from ESBL to Carba Smart media.

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