A S A

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In this issue:

SPECIAL EDITION ANTIMICROBIALS 2022

Original research E-Posters

Accepted Abstract Only submissions

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FROM THE EDITOR

Welcome to the May 2022 issue of the ASA Breakpoint Newsletter.

Although COVID-19 lead to the cancellation of the Antimicrobials 2022 conference that was scheduled to be held in Brisbane in February, many people had submitted high quality original research abstracts that would have been presented at that meeting. To support local research and the dissemination of scientific information, we dedicate this issue of the Breakpoint Newsletter to the publication of this work. We present 12 E-Posters, including the awardee of the Best Poster Award, and 30 accepted abstracts. We hold over our regular items, including the Microbiology Photo Quiz and the In The Spotlight sections for the next issue.

If you would like to contribute, have suggestions for content, or know of an author for whom their research would benefit from increased exposure, please email me on newsletter@asainc.net.au. We are also in search of images perfect for the front cover of the Newsletter. We would love to see your work. So, if you have a photo, or graphic, that would suit the Breakpoint Newsletter, please email the high definition image, with a description and your details, and we will publish your image on the cover on an upcoming issue, together with a photo credit.

Finally, make sure you tune in to the next Antimicrobials Online session, "Antifungal Agents: New Guidelines for Treatment and Future Directions" 12:30pm - 1:30pm AEST, Thursday 26th, May 2022. You can also download the Mycology Special Edition of the ASA Breakpoint Newsletter (October 2021) from the ASA website.

https://twitter.com/mikemorrison

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Front Cover: Vancomycin-resistant *Enterococcus* (VRE)
Photo Credit: Centers for Disease Control and Prevention

PRESIDENT'S REPORT

As you are aware due to the ongoing COVID pandemic the ASA Committee unfortunately had to postpone, for a second time, the Society's annual scientific meeting which was scheduled to be held 24th to 26th February 2022 at the Brisbane Convention and Exhibition Centre.

As in previous annual scientific meetings the 2022 program included six oral and two poster proffered paper sessions and members were encouraged to submit abstracts. Given the uncertainty the meeting would go ahead, we were overwhelmed with the number of abstracts received! Clearly, we are over webinars and teleconferences and are looking forward to attending a face-to-face meeting.

Rather than forwarding the abstracts to the 2023 meeting we gave the authors an opportunity to have their abstracts published in a special edition of "Breakpoint". Authors were also given the opportunity to have a poster of their research included in the special edition. I am pleased to say we are presenting 42 high quality "Breakpoint" abstracts, including 12 posters. The abstracts cover a broad range of areas reflecting the diversity of the ASA membership.

To acknowledge the work of the authors, ASA has awarded a travel grant to the best poster. Judging was preformed by three independent ASA committee members and posters were evaluated on their scientific content, presentation, originality/novelty, and ASA applicability. The grant will enable the winner to attend Antimicrobials 2023 in Brisbane and includes return economy airfare, four nights' accommodation and meeting registration. I am pleased to announce the winner of the award is Dr Shakeel Mowlaboccus for his poster "Genetic Characterisation of Linezolid Resistant *Enterococcus faecalis* Isolated in Western Australia 2016-2021".

With the improving COVID situation, not only in Australia but in many parts of the world, after a two-year hiatus, face-to-face meetings are beginning to return. I would like to remind ASA members of two meetings ASA will be hosting over the next ten months. Later this year, ASA will be co-hosting with the International Society of Antimicrobial Chemotherapy (ISAC) the **32nd International Congress of Antimicrobial Chemotherapy (ICC)** in Perth, 27th to 30th November 2022. The congress' program has almost been finalised and includes many world-leading experts in their area of research. The ICC will deliver an academic and social program that will educate, stimulate and entertain, and the Organising Committee looks forward to welcoming you. The program includes oral, and poster proffered paper sessions. Asia-Pacific young investigators who submit an abstract for the 32nd ICC are encouraged to apply for an ICC Young Investigator Travel Award. To be eligible, applicants must have received their PhD or MD within the last five years at the time of the congress and must be the presenting author (poster or oral presentation). Several awards will be made, with selection based on the quality of the abstract. Successful awardees will receive up to AUD $2,500 towards the costs of their travel to Perth and their hotel accommodation, as well as free congress registration. They will also be presented with an award certificate during the congress. For further details: https://32icc.org/

In February 2023 the ASA annual scientific meeting returns. **Antimicrobials 2023** will be in Brisbane, 23rd – 25th February at the Brisbane Convention and Exhibition Centre. The meeting's program is available at https://www.antimicrobials2023.com/ and includes six oral and two poster proffered paper sessions. Once again ASA will be providing travel awards to attend the meeting. Awards are made to ASA financial members presenting a proffered paper (oral or poster). Applicants must have current ASA membership and must have been an ASA member for at least the last 12 months. The awards consist of a return economy airfare, accommodation and conference registration up to the value of AUD2,500. Further details on the award can be found on the ASA website https://www.asainc.net.au/travel-awards/

I would also like to remind members, once again ASA will be holding Antimicrobials Online. Details of upcoming sessions can be found at https://www.antimicrobialsonline.com/. Many of the 2021 presentations are also available on the virtual platform. Please contact antimicrobials@icms.com.au if you require your login details.

Once again, I thank all those who have submitted abstract to the Society's annual scientific meeting, and I hope you find this especial edition of Breakpoint both scientifically stimulating and informative.

Professor Geoffrey Coombs
PhD, BSc (MedSc), PGrad Dip Biomed Sc, FFSc (RCPA), FASM, FISAC
President | Australian Society for Antimicrobials
Chair | Australian Group on Antimicrobial Resistance
President-Elect | International Society of Antimicrobial Chemotherapy

ASA POSTERS

ASA 2022 Travel Grant Awardee for Best Poster

Genetic Characterisation Of Linezolid-Resistant *Enterococcus faecalis* Isolated In Western Australia, 2016-2021
S. Mowlaboccus

Oral Ciprofloxacin Efficacy Against Ceftriaxone-Resistant *Escherichia coli* In A Bladder Infection Model
I. Abbott

Pandemic Positive: Rising To The Challenge To Sustain Antimicrobial Stewardship Activities
G. Grosfeld

Comparison Of Azithromycin, Tetracycline And Ertapenem Susceptibility In *Escherichia coli* Clinical Isolates At Canberra Health Services Over Time
H. Heaton

What Happened During Covid-19? Quantitative Surveillance Of Hospital Antimicrobial Use In Australia
N. Hillock

Australia & New Zealand (Anz) Study For Antimicrobial Resistance Trends (Smart): Gram-Negative Resistance In Under-Represented Surveillance Settings (2016-2019)
A. Hubber

Evaluating Antimicrobial Stewardship (AMS) Pharmacist Reviews In An Australian Multi-Site Teaching Hospital Network
J. Hughes

Long-Term Antibiotic Prescribing In The Community: 6 Years Of National Data
A. Macphail

Hidden Resistances: How Routine Whole Genome Sequencing Uncovered An Otherwise Undetected bla_{NDM-1} Gene In *Vibrio alginolyticus* Isolated From Imported Seafood
J. M. Morris

Effect Of Vancomycin Exposure On A Vancomycin Variable *Enterococcus faecium* Harbouring VanB
S. Mowlaboccus

Study Of Prescribing Patterns And Effectiveness Of Ceftolozane/Tazobactam Real-World Analysis (Spectra): Australian Utilisation And Outcomes
L. Puzniak

Antimicrobial-Impregnated Bone Cement Use In Australian Hospitals: Where Are The Gaps?
A. Teoh

Genetic Characterisation of Linezolid Resistant *Enterococcus faecalis* Isolated in Western Australia 2016-2021

S. Mowlaboccus[1,2*], D. Daley[2,3] and G. Coombs[1,2,3]

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

Introduction

Linezolid (LNZ) is an oxazolidinone antibiotic and a drug-of-last-resort used to treat infections caused by gram-positive pathogens that are resistant to multiple classes of antibiotics.

In Australia, LNZ-resistant enterococci are monitored and reported by each state and territory to the National Alert System for Critical Antimicrobial Resistances (CARAlert), as part of the AURA (Antimicrobial Use and Resistance in Australia) surveillance system.

LNZ interferes with bacterial protein synthesis by binding to the 23S rRNA on the 50S ribosomal subunit. In enterococci, resistance to LNZ can occur due to:

- **G2576T** and/or **G2505A** point mutations in **23S rRNA** gene copies
- presence of transferable genes encoding LNZ resistance
  - ***cfr*, *cfr(B)*, *optrA*, *poxtA***

Although an increasing number of linezolid-resistant *E. faecalis* (**LREfs**) has been reported worldwide, little is known about the genetic diversity and resistance mechanism of LREfs in Australia.

Aim

To determine the molecular epidemiology and resistance mechanism of 25 clinical LREfs isolated in Western Australia (WA) from 2016 to 2021.

Methods

Species Identification and Antimicrobial Susceptibility Testing

Isolates were identified as *E. faecalis* using a MALDI Biotyper® (Bruker).

Antimicrobial susceptibility testing was initially performed on the VITEK® 2 (bioMérieux) or BD™ Phoenix automated system. LNZ resistance was confirmed by the ETEST® (bioMérieux) and results were interpreted according to the CLSI breakpoints.

4 mg/L : intermediate (I) ≥ 8 mg/L : resistant (R)

Whole Genome Sequencing and Bioinformatics Analyses

Short read sequencing was performed on the NextSeq 500 Illumina platform using 150 bp paired-end chemistry.

LNZ resistance determinants were identified using LRE-Finder 1.0

Genomes were *de novo* assembled using SPAdes Genome Assembler and genetic environments were visualized in Geneious. The multilocus sequence type (ST) of each isolate was determined using the PubMLST database.

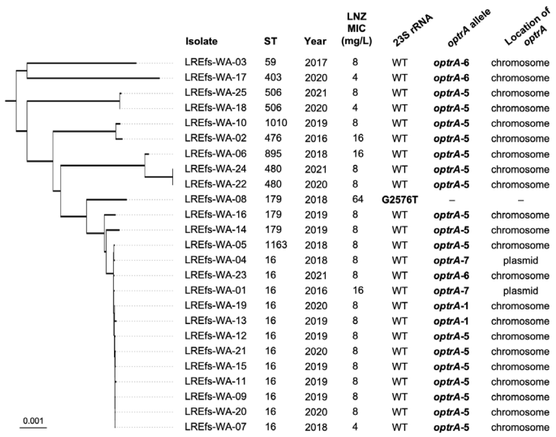
Genomes were aligned and a phylogenetic tree was constructed in MEGA and annotated in iTOL.

Results

- 88% (n=22) had a LNZ MIC of ≥ 8 mg/L
  - 3 isolates showed intermediate resistance (MIC 4 mg/L)
- Ten STs were identified and 48% (n=12) of isolates belonged to ST16.
- Most ST16 isolates had a LNZ MIC of 8 mg/L and were closely-related phylogenetically.
- LNZ resistance in 96% (n=24) of isolates was due to *optrA*
- The highest LNZ MIC (64 mg/L) was recorded in an *optrA*-negative ST179 isolate which harboured the G2576T mutation in three of the four copies of the 23S rRNA gene.

Results

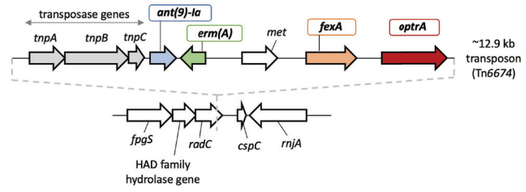
Phylogeny and resistance determinants of LREfs isolated in WA



Isolate	ST	Year	LNZ MIC (mg/L)	23S rRNA	*optrA* allele	Location of *optrA*
LREfs-WA-03	59	2017	8	WT	***optrA*-6**	chromosome
LREfs-WA-17	403	2020	4	WT	***optrA*-6**	chromosome
LREfs-WA-25	506	2021	8	WT	***optrA*-5**	chromosome
LREfs-WA-18	506	2020	4	WT	***optrA*-5**	chromosome
LREfs-WA-10	1010	2019	8	WT	***optrA*-5**	chromosome
LREfs-WA-02	476	2016	16	WT	***optrA*-5**	chromosome
LREfs-WA-06	895	2018	16	WT	***optrA*-5**	chromosome
LREfs-WA-24	480	2021	8	WT	***optrA*-5**	chromosome
LREfs-WA-22	480	2020	8	WT	***optrA*-5**	chromosome
LREfs-WA-08	179	2018	64	**G2576T**	–	–
LREfs-WA-16	179	2019	8	WT	***optrA*-5**	chromosome
LREfs-WA-14	179	2019	8	WT	***optrA*-5**	chromosome
LREfs-WA-05	1163	2018	8	WT	***optrA*-5**	chromosome
LREfs-WA-04	16	2018	8	WT	***optrA*-7**	plasmid
LREfs-WA-23	16	2021	8	WT	***optrA*-6**	chromosome
LREfs-WA-01	16	2016	16	WT	***optrA*-7**	plasmid
LREfs-WA-19	16	2020	8	WT	***optrA*-1**	chromosome
LREfs-WA-13	16	2019	8	WT	***optrA*-1**	chromosome
LREfs-WA-12	16	2019	8	WT	***optrA*-5**	chromosome
LREfs-WA-21	16	2020	8	WT	***optrA*-5**	chromosome
LREfs-WA-15	16	2019	8	WT	***optrA*-5**	chromosome
LREfs-WA-11	16	2019	8	WT	***optrA*-5**	chromosome
LREfs-WA-09	16	2019	8	WT	***optrA*-5**	chromosome
LREfs-WA-20	16	2020	8	WT	***optrA*-5**	chromosome
LREfs-WA-07	16	2018	4	WT	***optrA*-5**	chromosome

MIC (minimum inhibitory concentration) values were determined using the ETEST®. ST, sequence type; Year, year of isolation; LNZ, linezolid; WT, wild type; *optrA*-1 (Accession No. KP399637); *optrA*-5 (Accession No. KT862783); *optrA*-6 (Accession No. KT862784); *optrA*-7 (Accession No. KT862775).

- *optrA* gene was carried on a mobile genetic element in tandem with the *fexA* and erm*(A)* genes which confer resistance to chloramphenicol and erythromycin, respectively.
- In most isolates, *optrA* was **chromosomally encoded** on a transposon which also carried the *ant(9)-Ia* spectinomycin resistance gene.



- In two isolates, *optrA* was **plasmid-encoded**.

- Four variants of *optrA* were identified
  - *optrA-1*, *optrA-5*, and *optrA-6* were chromosomally encoded
  - *optrA-7* was plasmid-encoded

Conclusions

- Multiple clones of linezolid-resistant *E. faecalis* were identified including the clonal expansion of *optrA*-positive ST16.
- Resistance to linezolid could be explained by the presence of *optrA* in all isolates except the isolate with the highest linezolid MIC in which resistance to linezolid was conferred by the G2576T mutation in the 23S rRNA gene.

Acknowledgement:
We thank the Western Australian laboratories for participating in the CARAlert program and for referring the isolates.

Susceptible, increased exposure urinary breakpoints for ciprofloxacin can be raised to S ≤ 2 mg/L.

Oral Ciprofloxacin Activity Against Ceftriaxone-Resistant *Escherichia coli* in a Bladder Infection Model

INTRODUCTION

- Ciprofloxacin (CIP) achieves high urinary concentrations.
- Systemic breakpoints are currently used for the assessment of urinary isolates *Enterobacterales*:
  > S ≤ 0.25, R > 0.5 mg/L
  > ATU zone: 0.5 mg/L
- We examine if urine-specific breakpoints are supported in a bladder infection model following simulation or oral CIP treatment.

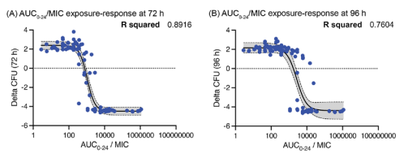
METHODS

1. CIP BMD MICs among ceftriaxone-resistant clinical *E. coli* urinary isolates (n = 93).
2. Drug-free growth assessment in selected isolates (n = 16).
   > Static incubation in different media and human urine
   > Dynamic incubation with synthetic human urine in bladder infection model
3. Urinary ciprofloxacin exposure simulated over 3-days.
   250mg daily; 500mg daily; 250mg q12; 500mg q12; 625mg q12; 750mg q12
4. PD samples: change in bacterial density by quantitative cultures.
5. PK samples: concentration of CIP measured by UHPLC-FI.
6. Exposure-response relationship and Monte Carlo simulation to determine PTA for stasis and up to 2 log kill.

RESULTS

- Modified SHU (with yeast extract added) best reflected *E. coli* growth in urine.
- *In vitro* peak and trough CIP concentrations closely matched simulation targets.
  > Bias -2.1% (95% CI: -31.4 to 27.2%)
- *E. coli* ATCC 25922 (MIC 0.008 mg/L):
  > No re-growth in all experiments
- Clinical isolates MIC 0.25-8 mg/L (n = 9):
  > At 96 h, re-growth was as follows:
  - 250mg daily: 8/9 isolates
  - 500mg daily: 5/9 isolates
  - 250mg, 500mg, 625mg q12: 4/9 isolates
  - 750mg q12: 1/9 isolate
- Clinical isolates MIC ≥ 16 mg/L (n = 6):
  > In all dosing experiments, all had re-grown by 72 h, which was maximal by 96 h.
- PTA >95% observed for 2 log kill (at 72h) and stasis (at 96h) following simulated 750 mg q12 for isolates with CIP MIC ≤ 2mg/L

Figure 1. Exposure-response relationship



E_{max} model detailing the change in bacterial density measured at (A) 72 h and (B) 96 h in response to the relative ciprofloxacin exposure (AUC_{0-24}/MIC).

DISCUSSION

- Considering a 50% urinary PK variability among individuals, *in vitro* simulation and MCS supports a ciprofloxacin UTI-specific breakpoint for a "susceptible, increased exposure" category at MIC ≤ 2 mg/L to support the use of high dose ciprofloxacin therapy (750 mg 12-hourly) against *E. coli* urinary isolates.

Figure S1. Bladder infection *in vitro* model

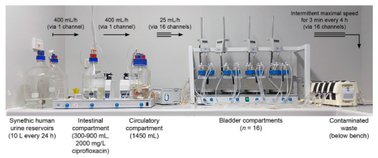
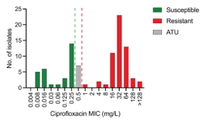


Figure S2. Ciprofloxacin MIC of ceftriaxone-resistant *E. coli* urinary isolates



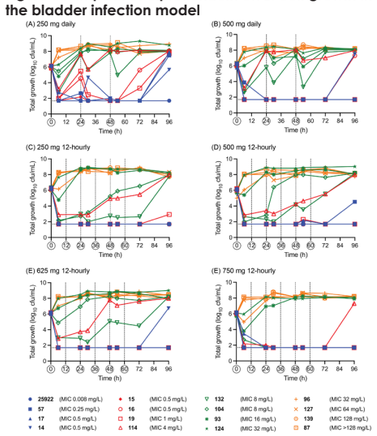
E. coli urinary clinical isolates (n = 93). CIP MIC by BMD. Wild type isolates MIC ≤ 0.064 mg/L. Susceptibility categories as per EUCAST 2022 breakpoint table.

Table S1. Change in bacterial density at 72 and 96 h following simulation of oral ciprofloxacin dosing

Strain #	CIP MIC (mg/L)	Oral ciprofloxacin dosing simulation: 250 mg daily 72 h	250 mg daily 96 h	500 mg daily 72 h	500 mg daily 96 h	250 mg BD 72 h	250 mg BD 96 h	500 mg BD 72 h	500 mg BD 96 h	625 mg BD 72 h	625 mg BD 96 h	750 mg BD 72 h	750 mg BD 96 h
25922	0.008	-	-	-	-	-	-	-	-	-	-	-	-
057	0.25	-	1.35	-	-	-	-	-	-1.52	-	-	-	-
017	0.5	-	1.74	-	-	-	-	-	-	-	-	-	-
014	0.5	-	-0.43	-	1.17	-	-	-	-	-	0.56	-	-
015	0.5	-	-	-	-	-	-	-	-	-	-	-	-
016	0.5	-0.46	1.96	-	1.08	-	-	-	-	-	-	-	-
019	1	-2.83	1.57	-	-	-3.29	-	-	-	-	-	-	-
114	4	2.27	2.18	0.86	1.79	-0.68	1.82	-0.50	1.94	1.44	1.84	-	1.26
132	8	1.92	2.00	1.47	1.69	-3.69	1.44	-0.48	2.12	-1.52	2.18	-	-
104	8	2.19	2.13	2.05	1.87	0.41	1.82	1.51	2.04	1.66	2.10	-	-
093	16	2.08	1.98	2.23	2.27	2.48	2.12	2.95	2.44	2.47	1.87	2.51	2.25
124	32	3.17	2.65	2.20	2.06	2.68	2.28	3.02	3.11	2.62	2.84	1.98	1.98
096	32	2.57	2.82	2.21	1.81	2.64	1.43	3.81	2.74	2.72	2.56	2.72	2.15
127	64	1.89	2.23	1.96	1.80	2.29	1.94	2.10	2.00	2.12	1.82	2.10	2.22
139	128	2.09	2.00	1.94	1.96	2.74	1.74	3.03	2.26	2.40	2.40	1.58	2.18
087	>128	1.96	1.91	1.77	1.88	2.51	1.81	2.14	2.01	2.29	2.29	2.10	2.18

Starting inoculum added to each bladder compartment was 10 mL of 10^6 cfu/mL. Change in bacterial density at 72 and 96 h presented.
-, indicates growth was not detected.

Figure S3. Impact of ciprofloxacin on *E. coli* growth in the bladder infection model



Total bacterial density measurements (cfu/mL). Circled time-points indicate the administration time of each dose of ciprofloxacin. LOD 50 cfu/mL.

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MONASH University

AMS thriving with the use of QI-NAPS in rural QLD hospitals despite pandemic.

*G. GROSFELD[*1], M L. AVENT[1,2], K. DAVESON[1] AND B. SMITH[1]*

1Queensland Statewide Antimicrobial Stewardship Program (QSAMSP), Statewide.AMS@health.qld.gov.au , Ph: (07) 3646 1886

2The University of Queensland, Centre for Clinical Research (UQCCR)

Pandemic Positive: rising to the challenge to sustain antimicrobial stewardship activities

Introduction

- The COVID-19 pandemic has presented challenges for sustaining Antimicrobial Stewardship (AMS) including competing priorities for resources and travel restrictions.
- The Quality Improvement National Antimicrobial Prescribing Survey (QI-NAPS) provides an audit and feedback tool that can be utilised when resources are scarce.
- The utility of QI-NAPS as an audit and feedback tool was evaluated during this resource limited time period.

Method

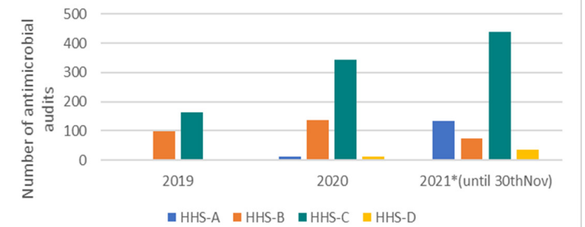
- The Queensland Statewide Antimicrobial Stewardship Program (QSAMSP) provides tele-health AMS support to four rural Hospital and Health Services (HHS's).
- Local clinicians used QI-NAPS resources to collect data during regular clinical patient reviews.
- Cases were discussed during weekly multidisciplinary AMS rounds with QSAMSP.
- Data entry and feedback to prescribers was supported by QSAMSP and Quality Improvement (QI) initiatives were identified.

Conclusion

Despite the challenges of the COVID-19 pandemic the QI-NAPS proved to be a sustainable audit and feedback tool for the rural HHS's. It also facilitated the identification and implementation of QI initiatives and monitoring of selected AMS Clinical Care Standard indicators.

Results

Figure 1. QI-NAPS usage at QSAMSP



- **Increased surveillance**: Increased numbers of antimicrobials audited across four rural HHS's (Figure 1).
- **Improvements seen**: Adherence to guidelines increased from 63% to 68% from 2019 to 2021.
- **Linking results to Quality Improvement**: Adherence to guidelines for management of Community Acquired Pneumonia improved for a HHS undertaking a project in this area.
- Supporting recommendations of the **AMS Clinical Care Standards**: monitors standards 3, 6 and 7.
- **Positive feedback:** Clinicians noted the QI-NAPS tool was efficient and easy to use, it could be incorporated into existing daily workflow, aided the clinical review process and facilitated timely feedback to prescribers.
- **Limitations:** Absence of appropriateness assessment and national benchmarking unavailable at this stage.

Queensland Statewide
Antimicrobial Stewardship Program
PRESERVING EFFECTIVE ANTIBIOTICS

Queensland Government

No change in azithromycin and tetracycline susceptibility observed from clinically significant *E. coli* isolates over the last 10 years despite common use.

Comparison Of Azithromycin, Tetracycline And Ertapenem Susceptibility In *Escherichia Coli* Clinical Isolates At Canberra Health Services Over Time.

H. HEATON[1], C. ONG[1, 2] AND K. KENNEDY[1, 2, 3]

[1] *Microbiology and Infectious Diseases Department, Canberra Health Services, Canberra ACT.*
[2] *Calvary Public Hospital, Bruce, ACT*
[3] *School of Medicine, Australian National University, Canberra ACT.*

Introduction:

E. coli frequently causes urinary tract infections and blood-stream infections. Antimicrobial resistance is increasing in *E. coli*,[1] potentially leading to a rise in carbapenem therapy.[2] Azithromycin and tetracyclines, both oral antimicrobials are widely used for non-*E. coli* infections. There are no Australian studies on azithromycin or tetracycline susceptibility in clinical *E. coli* isolates. Ertapenem testing can be used for carbapenemase surveillance. Azithromycin, tetracycline and ertapenem susceptibility changes over 2 periods ≥10 years apart was investigated.

Methods:

- Clinically significant consecutive *E. coli* isolates from urine and blood cultures at Canberra Health Services were tested.
- There were 312 isolates from 2008/2010 (150 urine and 162 blood culture) and 211 isolates from 2020 (99 urine and 112 blood culture).
- Blood culture isolates were classified as healthcare associated (HA) or community associated (CA) based on definitions endorsed by the Australian Commission on Safety and Quality in Healthcare.[3]
- Azithromycin, tetracycline and ertapenem susceptibility testing was performed using E-test method.
- Breakpoint MICs for tetracycline and ertapenem were as per CLSI M100 31st Edition. For azithromycin, *Shigella* species MIC breakpoints were used as none were available for *E. coli*.
- MICs of urine and blood culture isolates were compared between the two time periods.

Results:

- No significant change in susceptibilities of urinary or blood culture isolates (Figures 1 and 2.)
- Overall, no significant change in susceptibilities observed in all clinical isolates (Table 1.).
- Non-significant decrease in azithromycin susceptibility of CA blood culture isolates, 89.6% vs 78.3% (p=0.054) (Table 2.) and no change in susceptibilities in HA blood culture isolates.

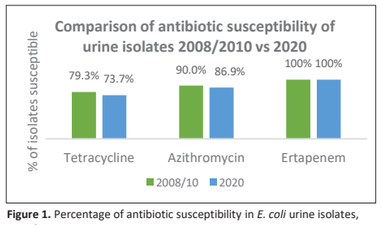


Figure 1. Percentage of antibiotic susceptibility in *E. coli* urine isolates, 2008/2010 versus 2020.

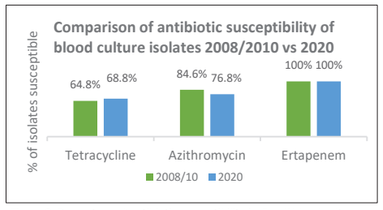


Figure 2. Percentage of antibiotic susceptibility in *E. coli* blood culture isolates, 2008/10 versus 2020.

Table 1. Antibiotic susceptibility of all *E. coli* isolates from 2008/2010 and 2020.

All Isolates	No. Of Isolates	TETRACYCLINE		AZITHROMYCIN		ERTAPENEM	
		Susceptible (%)	P value	Susceptible (%)	P value	Susceptible (%)	p value
2008/10	312	71.9	0.86	87.2	0.08	100	1.00
2020	211	71.1		81.5		100	

Table 2. Antibiotic susceptibility of HA and CA *E. coli* blood culture isolates from 2008/2010 and 2020.

Blood culture isolates	No. Of Isolates	TETRACYCLINE		AZITHROMYCIN		ERTAPENEM	
		Susceptible (%)	P value	Susceptible (%)	P value	Susceptible (%)	p value
HA 2008/10	66	53	0.12	77	0.77	100	1.00
HA 2020	52	67		75		100	
CA 2008/10	96	72.9	0.69	89.6	0.054	100	1.00
CA 2020	60	70		78.3		100	

Discussion:

Acquisition of resistance by *E. coli* often leads to limited oral antimicrobial therapeutic options. Despite common use of azithromycin and tetracyclines to treat a wide range of respiratory tract and sexually transmitted infections, this study has shown no significant change in susceptibility to azithromycin or tetracycline in clinically significant *E. coli* isolates at Canberra Health Services over a 10 year period. In addition, no change in ertapenem susceptibility was observed despite increasing use of carbapenems. Even when comparing HA and CA isolates over time, reassuringly, no substantial change was observed for any of the antimicrobials tested.

The lack of change in antimicrobial resistance observed in this study and the appeal of oral administration for azithromycin and tetracyclines supports the potential for further investigation into the utility of these antimicrobials for some *E. coli* infections.

References:

1. Coombs G, Bell J, Daley D, Collignon P, Cooley L, Gottlieb T, et al. Australian Group on Antimicrobial Resistance. Sepsis Outcome Programs 2016 Report. Sydney: Australian Commission on Safety and Quality in Health Care; 2018
2. Australian Council for Safety and Quality in Health Care (ACSQHC). AURA 2019: Third Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2019
3. Australian Council for Safety and Quality in Health Care (ACSQHC).Blood stream infection (BSI) definition. Canberra: ACSQHC; 2005

WHAT HAPPENED DURING COVID-19? ANTIMICROBIAL USE IN AUSTRALIAN HOSPITALS

National Antimicrobial Utilisation Surveillance Program | SA Health

BACKGROUND

- The National Antimicrobial Utilisation Surveillance Program (NAUSP) provides quantitative surveillance of antimicrobial use in Australian hospitals.
- The onset of the COVID-19 pandemic was accompanied by international concern regarding possible increased antimicrobial use and the potential impact on antimicrobial resistance.[1,2]

METHODS

- To examine trends in antimicrobial usage during 2020, monthly antimicrobial dispensing data for hospitals contributing to NAUSP were analysed and compared with 2019.
- Usage was converted from total grams into Defined Daily Doses (DDD) (as assigned by the WHO) and rates calculated as DDD per 1,000 Occupied Bed Days (OBD).

KEY FINDINGS

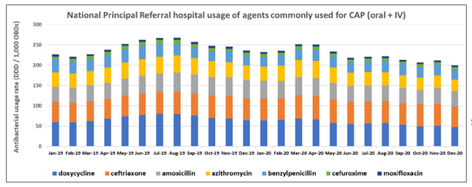
- Nationally, there was a decrease of 2.9% in total antibacterial use in hospitals contributing to NAUSP between 2019 and 2020.
- Large decreases in annual aggregate usage rates were seen for tetracyclines (20.6%), macrolides (15.5%) and β-lactamase sensitive penicillins (10.9%).
- Use of some broad-spectrum classes increased in 2020 compared to 2019, including carbapenems (up 3.1% from 14.7 DDD/1,000 OBD to 15.2 DDD/1,000 OBD) and cefepime (up 9.0% from 4.4 DDD/1,000 OBD to 4.8 DDD/OBD).

TAKE-AWAY

- **Overall antibacterial usage declined in acute care Australian hospitals in 2020 compared to 2019, however usage rates for some broad-spectrum agents increased substantially.**
- **Care must be taken when interpreting monthly usage rates due to fluctuations in hospital activity measures during the COVID-19 pandemic.**

National trends in antibacterial usage

- The total hospital aggregate antibacterial usage rate for NAUSP contributor hospitals was 859.1 DDD/1,000 OBD in 2020 (n=231) compared to 884.7 DDD / 1,000 OBDs in 2019 (n=214). This represents a decrease in the overall usage rate of 2.9%.
- Utilisation rates for antibacterials used to treat community-acquired pneumonia typically follow a seasonal trend, with higher usage in winter months. In 2020, the usual seasonal peak in winter was not apparent.[3]

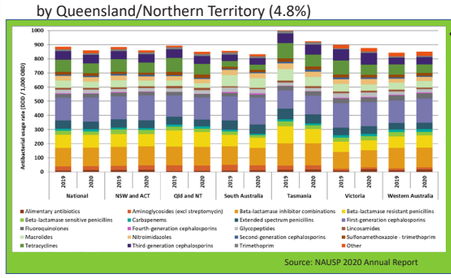


Source: Connor et al, 2022

- Substantial decreases were seen for the hospital usage of macrolides (azithro-, clarithro-, erythro-, and roxithromycin), with the national annual aggregate usage rate falling from 51.1 DDD/1,000 OBD in 2019 to 43.2 DDD / 1,000 OBDs. This is a drop of 15.5%.
- Inpatient usage of the tetracycline class of antibacterials (predominantly doxycycline) fell 20.6% between 2019 and 2020, from 86.7 DDD / 1,000 OBD to 68.8 DDD / 1,000 OBD.

State-wide trends in antimicrobial usage

- With the exception of Western Australia, total statewide hospital usage rates fell between 2019 to 2020 across all states and territories. The greatest decrease was in Tasmania (9.0%), followed by Queensland/Northern Territory (4.8%)



Source: NAUSP 2020 Annual Report

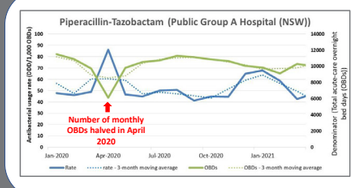
- Substantial differences in overall usage rates for the various antibacterial classes and the prescribing trends over time continue to be observed between the states and territories:
  - Carbapenem use decreased in Tasmania(-16.9%) and South Australia (-14.1%) from 2019 to 2020;
  - Use of 3rd-generation cephalosporins increased by 8.6% in Western Australia, by 6.6% in Tasmania and 4.1% in Victoria. Usage fell by 7.0% from 60.7 DDD/1,000 OBD in 2019 to 56.5 DDD/1,000 OBD in 2020 in Queensland and the Northern Territory

- Systemic antifungal use increased by 3.5% in NAUSP contributor hospitals between 2019 and 2020. Western Australia has the highest inpatient antifungal usage rate with a total annual usage rate of 45.1 DDD/1,000 OBD. The largest annual increases were seen in Queensland/Northern Territory (up 9.3%) and Victoria (up 9.0%), driven by large increases in posaconazole usage.

Reporting antimicrobial use: Challenges due to COVID-19

- Usage rates reported by NAUSP are calculated using dispensing data and are a surrogate measure for actual consumption. AMS staffing shortages and changes to hospital infrastructure to cater for the COVID-19 pandemic impacted antimicrobial data submissions in 2020, for example wards beings repurposed from sub-acute wards to COVID-19 wards, closure of surgical wards, and overflow of ICU patients into other hospital locations. These system changes should be considered when interpreting antimicrobial usage rates.

Case study: Impact of COVID-19 on reported usage rates



- As illustrated in this NSW hospital, large reductions in hospital inpatient activity to allow capacity for COVID-19 patients resulted in sudden fluctuations in reported monthly antimicrobial usage rates.
- Wider time periods (e.g. total annual usage rates) would likely provide a more appropriate metric to benchmark usage rates between hospitals during this period.

References:
1. Rawson T, Wilson RC, et al (2021). Understanding the role of bacterial and fungal infection in COVID-19. *Clin Microbiol Infect*. 27:9-11
2. Vijay S, Bansal N, et al (2021). Secondary infections in hospitalised COVID-19 patients: Indian experience. *Infect Drug Resist*, 14: 1893-1903
3. Connor E, Rasiah K, et al (2022). Utilisation of antimicrobials used to treat bacterial pneumonia in principal referral hospitals during the COVID-19 pandemic, Australia, 2020. CDI (46) https://doi.org/10.33321/cdi.2022.46.6

Acknowledgment:
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Australia and New Zealand Study for Monitoring Antimicrobial Resistance Trends (SMART): Gram-negative resistance in under-reported surveillance settings (2016-2019)

A Hubber[1*]; J Birdsall[2]; G Coombs[3]; D Drinkovic[4]; J Ellem[5]; N George[6]; T Gottlieb[2]; T Korman[7]; J Merlino[2]; S Roberts[9]; D Sahm[8]; M Tulloch[1]

[1]MSD Australia; [2]Concord Hospital, New South Wales, Australia; [3]Murdoch University, Perth, Australia; [4]North Shore Hospital, Auckland, New Zealand; [5]Westmead Hospital, New South Wales, Australia; [6]Pathology Queensland, Herston, Australia; [7]Monash Health, Victoria, Australia; [8]IHMA, Schaumburg, Illinois, USA; [9]Auckland City Hospital, Auckland, New Zealand

*an employee of Merck & Co., Inc. at the time the study was conducted

Introduction

The longitudinal **S**tudy for **M**onitoring **A**ntimicrobial **R**esistance **T**rends (SMART) has monitored in vitro susceptibility of clinical Gram-negative bacilli to antimicrobial agents since 2002 (intra-abdominal infections since 2002, urinary tract infections since 2009, respiratory tract infections (RTI) since 2015, and bloodstream infections since 2018). The SMART study adds to the body of evidence on resistance trends in Australia and New Zealand (ANZ) by contributing active surveillance data from non-blood sources.

This study aimed to describe the predominant Gram-negative pathogens in scenarios not usually reported in national surveillance, ie, ICU patients and patients hospitalised with respiratory infections. Empiric coverage was predicted for these groups. Co-resistance was assessed among resistant isolates. Finally, this analysis includes ceftolozane/tazobactam (C/T), which is not routinely tested in ANZ.

Methods

From 2016 through 2019, 9 sites across Australia and New Zealand collected up to 250 consecutive nonduplicate aerobic and facultatively anaerobic Gram-negative isolates. MICs were determined by broth microdilution as per CLSI guidelines. Testing was performed by IHMA, USA (http://ihma.com). Interpretive criteria followed EUCAST v11.0.

Results

Frequency of ICU respiratory pathogens in Australia and New Zealand

SMART sites in Australia and New Zealand provided 3,078 respiratory Gram-negative pathogens between 2016-2019, around a third of which were from ICU patients (n=1058). The major Gram-negative pathogens in local ICUs are described in **Table 1**.

Table 1. Gram-negative pathogens collected in ANZ by source and setting, 2016-2019

Organism	Respiratory (n=3078)	Respiratory, non-ICU (n=2020)	Respiratory, ICU (n=1058)	ICU, non-respiratory (n=525)	ICU, all sources (n=1583)
P. aeruginosa	32%	38%	25%	14%	18%
E. coli	15%	16%	15%	44%	25%
K. pneumoniae	11%	10%	14%	10%	13%
S. marcescens	8%	7%	8%	2%	6%
E. cloacae	5%	4%	7%	6%	7%
K. aerogenes	4%	4%	6%	2%	4%
K. oxytoca	4%	3%	5%	4%	5%
S. maltophilia	4%	4%	4%	1%	3%
P. mirabilis	2%	2%	3%	3%	3%
% of Total	86%	88%	82%	86%	84%

Dark yellow denotes >20% prevalence, mid yellow denotes 10%-19% prevalence, light yellow denotes <10% prevalence.

Probability of coverage of ICU respiratory pathogens in Australia and New Zealand

The three most common ICU respiratory infections were *Pseudomonas aeruginosa* (25%), *Escherichia coli* (15%), and *Klebsiella pneumoniae* (14%). When combined, composite susceptibilities were highest for ceftolozane/tazobactam (97.1%) and meropenem (96.9%); pip/taz was lower (84.3%). Rankings were similar when agents were assessed against 80% of the ICU respiratory Gram-negative pathogens (**Table 2**).

Table 2. Probability of empiric coverage of prevalent Gram-negative ICU respiratory pathogens, ANZ 2016-2019

ICU respiratory pathogens	Ceftolozane/ tazobactam (%S, n/N)	Piperacillin/ tazobactam[a] (%S, n/N)	Meropenem[a] (%S, n/N)	Cefepime[a] (%S, n/N)
P. aeruginosa	98.1% (208/212)	80.7% (171/212)	92.5% (196/212)	84.9% (180/212)
E. coli	96.9% (155/160)	86.3% (138/160)	100% (160/160)	86.9% (139/160)
K. pneumoniae	95.9% (139/145)	87.6% (127/145)	97.9% (142/145)	91.0% (132/145)
Combined 3 most prevalent[b]	97.1% (502/517)	84.3% (436/517)	96.9% (501/517)	87.2% (451/517)
~80% of pathogens[c]	93.5% (815/872)	82.1% (716/872)	93.5% (815/872)	88.9% (775/872)

Yellow shading denotes >90% susceptibility. [a]Susceptible includes Susceptible, Increased Exposure where applicable.
[b]Composite susceptibility of combined 3 most common RTI pathogens: *P. aeruginosa*, *E. coli*, and *K. pneumoniae*.
[c]Composite susceptibility of ~80% coverage of ICU RTI pathogens: *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *S. marcescens*, *E. cloacae*, *K. aerogenes*, *K. oxytoca*, and *P. mirabilis* (see **Table 1**). Organisms excluded from analysis due to absence of breakpoints include: *S. maltophilia* (3.4%) and *A. baumannii* (1.3%).

Reference

1. Clinical and Laboratory Standards Institute. 2019. M7: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 11th ed. Approved standards. https://clsi.org/standards/products/microbiology/documents/m07/. Accessed March 2021.

Figure 1. % Coverage of 3 most common pathogens, ICU RTI, ANZ (2016-2019) (n=517)

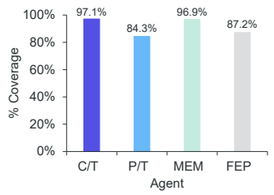
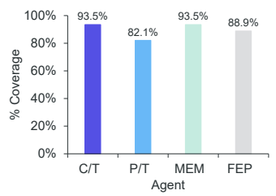


Figure 2. % Coverage of ~80% of pathogens, ICU RTI, ANZ (2016-2019) (n=872)



Co-resistance in *P. aeruginosa* resistant to first-line β-lactam agents

Co-resistance between first-line β-lactam antibiotics is common in *Pseudomonas*. Ceftolozane/tazobactam provided the most reliable in vitro activity in second-line prescribing scenarios, compared to other β-lactam antibiotics (**Table 3, Figures 3-4**).

Ceftolozane/tazobactam (C/T) demonstrated the highest activity against *Pseudomonas* resistant to possible first-line agents. In pip/taz-resistant isolates, C/T susceptibility was higher than meropenem (87.2% C/T vs 79.4% meropenem).

Table 3. Probability of coverage for *P. aeruginosa* when resistant to first-line β-lactams, ANZ (2016-2019)

Pathogen	Ceftolozane/ Tazobactam (%S, n/N)	Piperacillin/ Tazobactam (%S, n/N)	Meropenem (%S, n/N)	Cefepime (%S, n/N)
Pip/taz-resistant *P. aeruginosa*	87.2% (190/218)	n/a	79.4% (173/218)	39.4% (86/218)
Meropenem-resistant *P. aeruginosa*	69.1% (38/55)	18.2% (10/55)	n/a	30.9% (17/55)
Cefepime-resistant *P. aeruginosa*	84.6% (148/175)	24.6% (43/175)	78.3% (137/175)	n/a

All sources (RTI, IAI, UTI, BSI) and wards (ICU, Emergency Room, General Medicine, General Surgery, None Given) due to limitations of sample size.

Figure 3. % Activity against pip/taz-resistant *P. aeruginosa*, ANZ (2016-2019) (n=218)

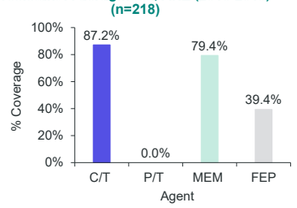


Figure 4. % Activity against meropenem-resistant *P. aeruginosa*, ANZ (2016-2019) (n=55)

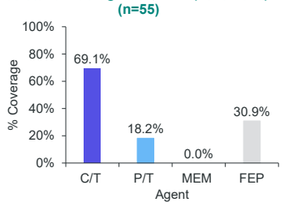
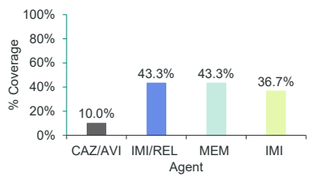


Table 4. Probability of coverage of *P. aeruginosa* when resistant to ceftolozane/ tazobactam, ANZ (2016-2019)

Pathogen	Ceftazidime/ avibactam (%S, n/N)	Imipenem/ relebactam (%S, n/N)	Meropenem (%S, n/N)	Imipenem (%S, n/N)
C/T-resistant *P. aeruginosa*	10.0% (3/30)	43.3% (13/30)	43.3% (13/30)	36.7% (11/30)

All sources (RTI, IAI, UTI) and wards (ICU, Emergency Room, General Medicine, General Surgery, None Given) due to limitations of sample size.

Figure 5. % Activity against C/T-resistant *P. aeruginosa*, ANZ (2016-2019) [n=30]



Ceftolozane/tazobactam resistance

Imipenem/relebactam (IMI/REL) and meropenem provided highest coverage of *P. aeruginosa* isolates showing resistance to ceftolozane/tazobactam.

Molecular analysis of the 30 C/T resistant *P. aeruginosa* isolates revealed presence of GES-5 (n=2), VIM-2 (n=1) enzymes, and PDC (n=29) *Pseudomonas* chromosomal-inducible cephalosporinases [data on file].

Summary and conclusions

- Ceftolozane/tazobactam and meropenem provided the most reliable activity in empiric prescribing scenarios compared to other β-lactams
- In second-line scenarios, ceftolozane/tazobactam had higher activity than meropenem for *P. aeruginosa* isolates resistant to piperacillin/tazobactam

Presented at Antimicrobials 2022, Australian Society for Antimicrobials (ASA) Annual Scientific Meeting [virtual]; March 31, 2022.

Evaluating Antimicrobial Stewardship (AMS) Pharmacist Reviews in an Australian Multi-Site Teaching Hospital Network

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[1] Pharmacy department, Monash Health, Melbourne, Australia
[2] Infectious Diseases department, Monash Health, Melbourne, Australia

Introduction

Increased antimicrobial use and misuse was anticipated with the rise of the COVID-19 pandemic[1]. To address this anticipated increase and mitigate potential antimicrobial resistance[1], Antimicrobial Stewardship (AMS) pharmacist rounds were introduced in addition to multidisciplinary AMS rounds to increase the number of reviews at a multi-site hospital network in Melbourne, Australia.

There are many benefits to incorporating AMS pharmacist reviews, however there are limited studies assessing the appropriateness and acceptance of these in practice[2,3].

Objective

To evaluate AMS pharmacist reviews of inpatient antimicrobial orders including appropriateness, type and frequency of recommendations, and acceptance of recommendations within 24 hours in comparison to those led by Infectious Diseases (ID) physicians.

Methods

AMS pharmacist reviews of adult inpatient antimicrobial orders over two time periods (April 2020 and January 2021) conducted by three pharmacists were retrospectively assessed by a panel of ID physicians (Figure 1).

Appropriateness	Reviews were classified utilising an assessment tool developed by investigators based upon the National Antimicrobial Prescribing Survey 'Guidelines to assist with the assessment of appropriateness'[4]
Acceptance Rates	Acceptance rates of AMS pharmacist recommendations within 24 hours were measured. This was then compared to those by ID physicians for the same time periods.
Type and Frequency of Recommendations	Recommendations by AMS pharmacists were grouped into similar categories and frequency noted. These were compared to the type and frequency of recommendations by ID physicians for the same time periods.

Figure 1: A summary of methods for the investigation.

Results

The ID physician panel assessed 113 AMS pharmacist reviews.

Appropriateness

- Reviews were classified overall as appropriate (optimal or adequate) in 80% of 113 assessments (figure 2).
- No reviews were deemed to be unsafe by the ID panel. Recommendations were deemed suboptimal most frequently due to missed opportunities for switching from IV to oral.

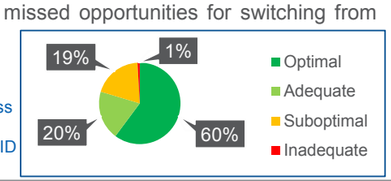


Figure 2: Appropriateness of AMS Pharmacist reviews as classified by ID Physician panel.

Acceptance rates and types of interventions

- Overall AMS pharmacist recommendations were accepted 63% (44/70) of the time (figure 3), comparable to 70% (285/406) of those involving ID physicians (p value =0.22).

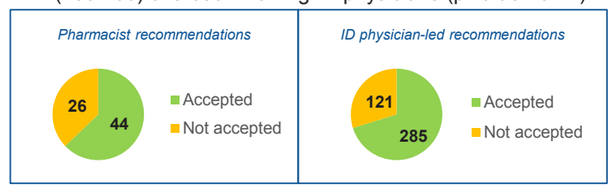


Figure 3: AMS Recommendations accepted within 24 hours for pharmacist recommendations vs ID physician-led recommendations.

- Incorrect duration was the most frequent intervention by pharmacists, followed by the need to obtain an ID approval number and incorrect dose (Table 1). These types of recommendations were accepted by prescribers more than 70% of the time.
- Unnecessary antimicrobial and IV to oral switch were often not as readily accepted as when an ID physician made the same types of recommendations (Table 1).

Type of Intervention	% of Pharmacist recommendations	Acceptance within 24 hours (Pharmacist)	Acceptance within 24 hours (ID Physician-led)
Incorrect duration (too long)	21%	73%	72%
ID approval required	16%	73%	N/A
Incorrect dose	14%	70%	72%
Unnecessary antimicrobial	13%	33%	67%
IV to oral switch	13%	33%	61%

Table 1: Most frequent AMS pharmacist interventions made and acceptance within 24 hours in comparison to ID physicians for the same interventions.

Conclusion

This research demonstrated pharmacists make appropriate AMS recommendations with overall comparable acceptance rates to ID physician AMS reviews. However improvement is required to identify oral switch opportunities, which may increase the impact of AMS pharmacist rounds further.

This investigation confirms that AMS pharmacist reviews are substantiated and can be an efficient and useful addition to AMS programs.

References

1. *Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin Microbiol Infect. 2020; 26: 808-810*
2. *Waters CD. Pharmacist-driven antimicrobial stewardship program in an institution without infectious diseases physician support. Am J Health Syst Pharm. 2015;72(6):466–8*
3. *Zhang et al. The Effectiveness of Clinical Pharmacist-Led Consultation in the Treatment of Infectious Diseases: A Prospective, Multicenter, Cohort Study. Front Pharmacol. 2020; 11: doi 70.3389/fphar.2020.575022*
4. *National Centre for Antimicrobial Stewardship. Hospital National Antimicrobial Prescribing Survey User Guide 2020. Melbourne: Melbourne Health; 2020*

March 2022, jessica.hughes2@monashhealth.org

Monash Health

3 in every 1000 Australians are prescribed long term antibiotics

Most are elderly patients prescribed antibiotics for indications other than treatment of active infection

Long term antibiotic prescribing in the community: 6 years of Australian national data

Aleece MacPhail[1,2,3], *Tony Korman*[1,2], *Ian Woolley*[1,2], *Jillian Lau*[1,2]

Background

- Long term prescribing is a target for antimicrobial stewardship[1,2]
- 75% of community prescribing in Australia is via the Pharmaceutical Benefits Scheme (PBS)[3]

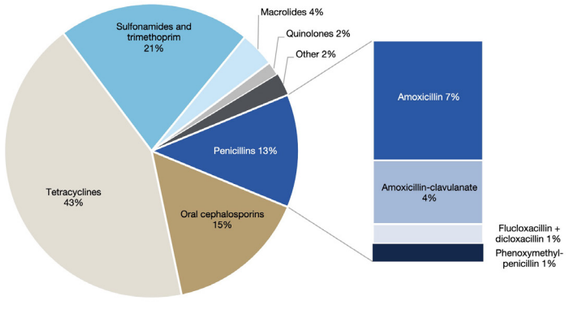
Methods

- Randomised, scaled 10% sample Australian PBS prescription data Jan 2014 – Jan 2020
- Patients identified using rolling window algorithm with 12 month look-back from each script filled
- Prescribed antibiotics >/= 12 months with </= 1 month gap between scripts dispensed
- Dispensed antibiotics >/= 90% x adjusted daily dose (ADD) x 365 days
- ADD = WHO defined daily dose +/- adjustment for specific indications

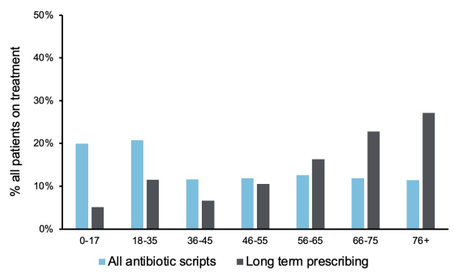
Results

- Long term antibiotics prescribed to 300/100 000 population (mean rolling annual average)
- Women (54%), age >65 years (50%)
- A minority of scripts report unique indication codes:
  - UTI prophylaxis (10 067 patients/year, 84% female, 52% aged >75)
  - Osteomyelitis (3242 patients/year)
  - Serious staphylococcal infection (1460 patients/year)

Classes of antibiotics prescribed long term



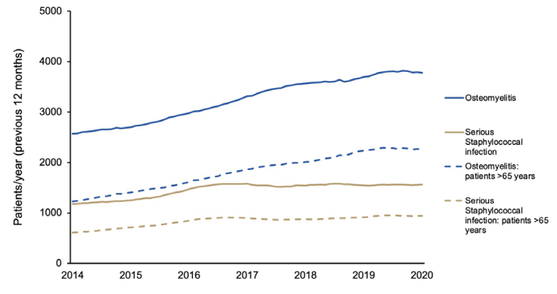
Patients prescribed long term antibiotics



Co-prescription in patients on long term antibiotics

Medication	Patients (n)	(%)
Immunomodulation		
Immunosuppressants	4,870	(6)
Corticosteroids	16,105	(21)
Symptom management		
Anti-emetics	1,665	(2.1)
Analgesics	25,508	(33)
Laxatives	5,126	(6.5)
Mental-health related drugs		
Antidepressants	24,899	(32)
Total	78,386	

Osteomyelitis and Staphylococcal infections



Conclusion

- Long term antibiotic prescribing is common
- Elderly and comorbid patients are over-represented
- Most prescribing is for prophylaxis or immunomodulation, based on antibiotic type and available PBS indications

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References: 1. Lau et al. *Life-long antimicrobial therapy: where is the evidence? JAC* 2018. 73(10): p. 2601-2612.
2. Rummukainen et al., *Antimicrobial prescribing in nursing homes in Finland: results of three-point prevalence surveys.* Infection, 2013. 41(2): p. 355-360.
3. Australian Government Department of Health PBS (2011). "Australian Statistics on Medicine 2011." https://www.pbs.gov.au/info/statistics/asm/asm-201

Monash Health

Hidden resistances: How routine whole genome sequencing uncovered an otherwise undetected bla_{NDM-1} gene in *Vibrio alginolyticus* isolated from imported seafood

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Background

- *V. alginolyticus* is a Gram-negative bacterium found worldwide in marine environments
- In humans, *V. alginolyticus:*
  - Is implicated in a range of infections due to exposure to the pathogen in the water.
  - Causes vibriosis and gastrointestinal infections due to ingestion of contaminated foods[1,2].
- Current Australia New Zealand Food Standards Code (ANZFSC) guidelines do not require imported seafood to be screened for all *Vibrio* species.
- *Vibrio spp*. are generally susceptible to antibiotics but carbapenem resistance has been reported once for *V. alginolyticus* on a plasmid (*V. alginolyticus* strain Vb1394 plasmid, pC1349)[3].

Methods

- *V. alginolyticus* strain AUSMDU00064140 was isolated in 2021in Melbourne, Australia from cooked prawns imported from Thailand and referred to the MDU PHL for identification and further characterisation.
- Phenotypes for AUSMDU00064140 were assessed by:
  - Carbapenemase inactivation method (CIM) test[4].
  - Sensititre® broth microdilution system (ThermoFisher Scientific).
- Whole genome sequencing for AUSMDU00064140 was conducted by:
  - Routine Short-read (Illumina) (with 13 additional *V. alginolyticus* isolates).
  - Long-read (Oxford Nanopore Technologies).
- Core single nucleotide polymorphism (SNP) sites (called by Snippy and SNP-sites)[5,6] informed the maximum likelihood phylogeny (IQ-TREE 2)[7] of the novel isolates against a global *V. alginolyticus* dataset (n=109).
- Genomes were screened for AMR genes using abriTAMR[8,9].
- AUSMDU00064140 complete genome was assembled by hybrid Unicycler[10,11]

Key Findings

- AUSMDU00064140 exhibited carbapenemase activity (positive CIM test) and low meropenem minimum inhibitory concentrations (MICs ≤0.5 mg/L).
- *V. alginolyticus* isolates are diverse and AUSMDU00064140 is distinct from other isolates (Fig 1).
- Multi-drug resistance (MDR, resistance to ≥3 drug classes) is rare (Fig 1).
- A full length Carbapenemase gene, bla_{NDM-1} was
- The bla_{NDM-1} is chromosomally located for AUSMDU00064140 and co-located with several AMR genes (Fig 2).
- Differs from the previously reported bla_{NDM-1} plasmid (Fig 2).

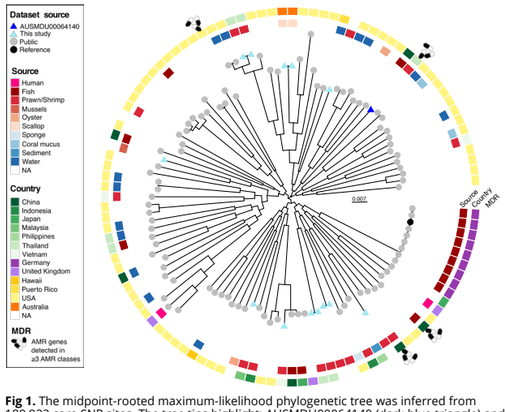

Fig 1. The midpoint-rooted maximum-likelihood phylogenetic tree was inferred from 189,922 core SNP sites. The tree tips highlight; AUSMDU00064140 (dark blue triangle) and isolates novel to this study (light blue triangles), and isolates from public repositories (grey circles) and reference, GCA_002119505.2 (black circle). Each isolate's source and country of isolation are shown according to the legend; note that the country of isolation does not necessarily represent the origin of the sample.

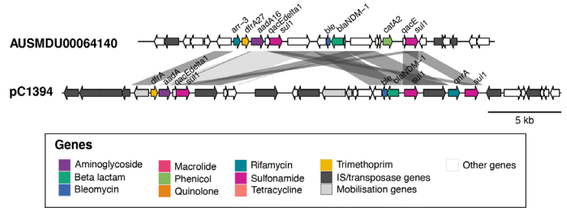

Fig 2. Nucleotide comparison of AUSMDU00064140 (chromosome 1, 775 kilobases (kb) to 800 kb region) and the previously reported bla_{NDM-1} containing-plasmid pC1394 (MH457126.1, *V. alginolyticus* strain Vb1394) (100 kb to 130 kb region). Genes, and their orientation, are indicated by arrows and coloured according to the legend; the grey connecting blocks indicate regions of > 95% nucleotide identity.

In conclusion:

The presence of ***bla*$_{NDM-1}$ in *V. alginolyticus* is concerning due to the potential for gene transmission** within hosts (gastrointestinal colonisation) and, between hosts and in the environment.

Foodborne illness due to *V. alginolyticus* and MDR *Vibrio spp*. in our food, particularly imported foods, **may be going undetected**.

Phenotypic carbapenem MIC testing alone did not detect a carbapenemase gene in this isolate, demonstrating **the value of genomics in uncovering hidden AMR determinants of public health significance**.

References and GitHub links: 1. Álvarez-Contreras, A.K., E.I. Quiñones-Ramírez, and C. Vázquez-Salinas, *Prevalence, detection of virulence genes and antimicrobial susceptibility of pathogen Vibrio species isolated from different types of seafood samples at "La Nueva Vigo" market in Mexico City.* Antonie Van Leeuwenhoek, 2021. 114(9): p. 1417-1429. 10.1007/s10482-021-01591-x **2.** Jones, E.H., et al., *Vibrio infections and surveillance in Maryland, 2002-2008.* Public Health Rep, 2013. 128(6): p. 537-45. 10.1177/003335491312800613 **3.** Zheng, Z., et al., *Identification and Characterization of IncA/C Conjugative, blaNDM-1-Bearing Plasmid in Vibrio alginolyticus of Food Origin.* Antimicrobial Agents and Chemotherapy, 2018. 62. 10.1128/AAC.01897-18 **4.** van der Zwaluw, K., et al., *The Carbapenem Inactivation Method (CIM), a Simple and Low-Cost Alternative for the Carba NP Test to Assess Phenotypic Carbapenemase Activity in Gram-Negative Rods.* PLoS ONE, 2015. 10(3): p. e0123690. 10.1371/journal.pone.0123690 **5.** Snippy https://github.com/tseemann/snippy **6.** Page, A. J., et al. (2016). SNP-sites: rapid efficient extraction of SNPs from multi-FASTA alignments. *Microbial Genomics*, *2*(4), e000056. https://doi.org/10.1099/mgen.0.000056 **7.** B.Q. Minh, et al (2020) IQ-TREE 2: New models and efficient methods for phylogenetic inference in the genomic era. Molecular Biology and Evolution, 37:1530-1534. **8.** AbriTAMR https://github.com/MDU-PHL/abritamr **9.** Feldgarden, M., et al., *AMRFinderPlus and the Reference Gene Catalog facilitate examination of the genomic links among antimicrobial resistance, stress response, and virulence.* Scientific Reports, 2021. **11**(1): p. 12728. 10.1038/s41598-021-91456-0 **10.** Wick, R. R., et al. (2017). Unicycler: Resolving bacterial genome assemblies from short and long sequencing reads. PLoS Computational Biology, 13(6). **11.** Baines, S. L., et al. (2020). Complete microbial genomes for public health in australia and the southwest Pacific. Microbial Genomics, 6(12), 1–12. https://doi.org/10.1099/mgen.0.000471

Doherty Institute
THE UNIVERSITY OF MELBOURNE
The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Effect of Vancomycin Exposure on a Vancomycin Variable *Enterococcus faecium* harbouring *vanB*

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Introduction

Clinically relevant vancomycin resistance in *Enterococcus faecium* occurs via expression of the *vanA* or *vanB* gene. The *vanA* and *vanB* genes are located on the *vanA* and *vanB* operons, respectively, which consist of an array of regulatory (*vanR*/R_B and *vanS*/S_B) and structural (*vanH-vanA-vanX-vanY-vanZ* or *vanY*$_B$-*vanW-vanH*$_B$-*vanB-vanX*$_B$) genes.

Recently, *vanA*-positive *E. faecium* with a vancomycin-susceptible phenotype have been characterised and termed **vancomycin variable *E. faecium*** (**VVEfm**). On exposure to vancomycin, VVEfm can revert to the vancomycin-resistant phenotype *in vitro* and *in vivo*, either in a vancomycin-inducible mode or constitutively.

However, *vanB*-positive VVEfm have **not** yet been described.

In Australia, **VVEfm23**, a *vanB*-positive VVEfm, was identified by the Australian Group on Antimicrobial Resistance as part of the Australian Enterococcal Sepsis Surveillance Programme. In this study, we characterised VVEfm23 and assessed its ability to revert to a vancomycin-resistant phenotype in the laboratory.

Aim

To characterise and assess the effect of vancomycin exposure on a *vanB*-positive VVEfm causing bacteraemia in Australia.

Methods

Species Identification and Antimicrobial Susceptibility Testing

VVEfm23 was identified as an *E. faecium* using the MALDI Biotyper® (Bruker) and confirmed by whole genome sequencing.

Antimicrobial susceptibility testing was initially performed on the VITEK® 2 (bioMérieux) and by ETEST® (bioMérieux). Broth microdilution was used to confirm vancomycin susceptibility of VVEfm23 and to determine the vancomycin MIC of the generated mutant. Results were interpreted according to the CLSI breakpoints.

≤4 mg/L: susceptible 4-16 mg/L: intermediate ≥ 32 mg/L: resistant

Whole Genome Sequencing and Bioinformatics Analyses

Short read sequencing was performed on the NextSeq 500 Illumina platform using 150 bp paired-end chemistry.

Genomes were *de novo* assembled using SPAdes Genome Assembler and annotated using Prokka. Genetic environments were visualized in Geneious. The multilocus sequence type (ST) was determined using the PubMLST database.

Evolution by Vancomycin Exposure

Following vancomycin MIC determination of VVEfm23 by broth microdilution, an aliquot from the well containing bacterial growth in the highest vancomycin concentration was transferred into broth containing vancomycin at double the concentration. The culture was grown overnight at 37°C and an aliquot was transferred into fresh broth containing vancomycin at double the concentration. The overnight growth followed by exposure to higher concentrations of vancomycin were repeated until growth was no longer observed. Growth from the last set of experiments were sub-cultured in the absence of vancomycin and stocked as **VVEfm23-M**

Results

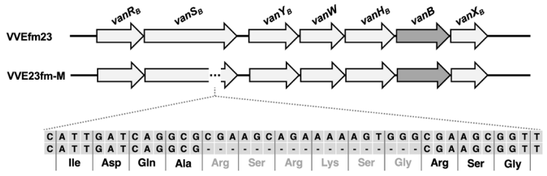
- VVEfm23 was a **ST796** (4-1-1-1-1-20-1) *E. faecium.*

Table 1. Antibiotic susceptibility profile of VVEfm23 by VITEK® 2

Susceptible	erythromycin, linezolid, teicoplanin, vancomycin
Intermediate	nitrofurantoin
Resistant	ampicillin, benzylpenicillin, ciprofloxacin

- VVEfm23 harboured a complete *vanB* operon.
- The vancomycin MIC of VVEfm23 was 1.5 mg/L by ETEST® and **1.0 mg/L** by broth microdilution.
- The vancomycin MIC of VVEfm23-M was **256 mg/L** by broth microdilution.
- The *vanB* operon of VVEfm23-M harboured an 18 bp in-frame deletion in the *vanS*$_B$ regulatory gene.
- The deleted fragment in VVEfm23-M encoded **Arg-Ser-Arg-Lys-Ser-Gly**

Figure 1. Alignment of *vanB* operons from VVEfm23 and VVEfm23-M



- No other mutations in the *vanB* operon were identified in VVEfm23-M compared to its wild-type parent, VVEfm23.
- Mutations elsewhere in the genome of VVEfm23-M were not investigated.

Conclusions

- *In vitro* exposure of a *vanB*-positive vancomycin variable *E. faecium* harbouring all *vanB* operon genes to vancomycin resulted in the isolation of a vancomycin-resistant mutant with a 256-fold increase in vancomycin MIC.
- Resistance was attributed to a deletion mutation in the *vanS*$_B$ gene which likely resulted in constitutive expression of the *vanB* operon.
- Future work is required to confirm activity of the product encoded by the truncated *vanS*$_B$.
- To our knowledge, this is the first report characterizing a *vanB*-positive vancomycin variable *E. faecium*.

Study of Prescribing Patterns and Effectiveness of Ceftolozane/Tazobactam Real World Analysis (SPECTRA): Australian Utilisation and Outcomes

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*An employee of Merck & Co., Inc. at the time the study was conducted

Introduction

Gram-negative infections cause significant morbidity and mortality. As new agents and indications become available, it is important to understand real-world use, particularly in populations that may have been excluded from registration trials.

Ceftolozane/tazobactam (C/T) was registered for use in Australia in 2015 for treatment of cIAI (in combination with metronidazole) and cUTI (1.5 g q8h). The TGA approved use in nosocomial pneumonia (3 g q8h) in 2020.

This study describes the real-world clinical use and outcomes with ceftolozane/tazobactam in the Australian subset of the multinational Study of Prescribing Patterns and Effectiveness of Ceftolozane/Tazobactam Real World Analysis (SPECTRA) registry study.

Methods

SPECTRA is a multicenter, retrospective, observational study of patients treated with C/T in Australia, Austria, Germany, Italy, Spain, and the United Kingdom. Demographics, clinical characteristics, treatment patterns, microbiological findings, and clinical outcomes (clinical success, mortality, readmission) were analysed for Australian inpatients receiving >48 hours of C/T treatment. Participating Australian hospitals are University Hospital Geelong, VIC; Alfred, VIC; Westmead Hospital, NSW; Fiona Stanley Hospital, WA; Prince Charles Hospital, QLD; and Royal Brisbane Womens and Childrens Hospital, QLD.

Results

Patient characteristics

In this interim analysis, 46 patients from 6 Australian hospitals received C/T for >48 hours between **February 2016 and November 2019** (Table 1).

Table 1. Australian patient demographics (N=46)

Patient characteristics	n or mean	% or SD
Age (years), mean (SD)	53.4	15.9
Male	33	71.7%
Renal impairment (CrCl ≤50 mL/min)	13	28.3%
Augmented renal clearance (CrCl ≥130 mL/min)	1	2.2%
ICU during current hospitalisation	21	45.6%
Mechanical ventilation	6	13.0%
Previous hospitalisations within 6 months of current infection	34	73.9%
Previous ICU stay within 6 months of current infection	8	17.4%
Previous surgery within 6 months of current infection	16	34.8%
Patient comorbidities		
At least one comorbidity	36	78.3%
Number of comorbidities, mean (SD)	2.8	2.3
Immunocompromised	25	54.3%
Diabetes mellitus	17	36.9%
Transplant	15	32.6%
Chronic pulmonary disease	13	28.3%
Cystic fibrosis (median age: 40)	11	23.9%
Heart disease	9	19.6%

Indications and microbiology

The majority of C/T use was off-label at the time of data collection, although the TGA has recently approved C/T for treatment of nosocomial pneumonia (Figure 1).

Most patients received C/T for *Pseudomonas aeruginosa* infection (84.4%) (Figure 2). Around a third of patients had polymicrobial infections (34.7%).

Treatment management

Most patients (95.7%) received an ID consult. Within each indication there was noticeable variation in treatment duration (Table 3).

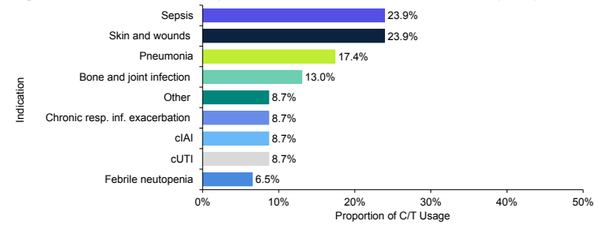
Table 2. Therapy characteristics (N=46)

Therapy characteristics	n or mean	% or SD
Prior antibiotic exposure within 30 days of index event		
Received antibiotics in past 30 days	31	67.4%
Piperacillin/tazobactam	11	23.9%
Fluoroquinolone	10	21.7%
Aminoglycoside	8	17.4%
Cephalosporin	7	15.2%
Carbapenem	7	15.2%
Polymyxin	6	13.0%
Antifungal therapy in the past 30 days	12	26.1%
Antimicrobials for *Clostridium difficile* in the past 30 days	3	6.5%
Ceftolozane/tazobactam utilisation		
Duration of C/T therapy (days), mean and median, SD	15 and 9	15
C/T empiric therapy[a,c]	8	17.8%
C/T early directed therapy[a] (0-7 days[b])	18	40.0%
C/T late directed therapy[a] (>7 days[b])	27	60.0%

Patients could receive more than one treatment in prior 30 days. [a]N=45 as date of one isolate collection missing. [b]Time from first sample from which at least one antibiotic has been tested (C/T or other) until first dost of C/T. [c]Empiric therapy assumed for treatment initiation ≤2 days post-microbiologic sample.

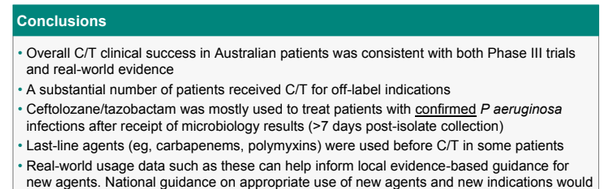
Presented at Antimicrobials 2022, Australian Society for Antimicrobials (ASA) Annual Scientific Meeting [virtual]

Figure 1. Indications for which patients received ceftolozane/tazobactam (N=46)



Note: Patients could have multiple indications. "Skin and wounds" represents mediastinitis, skin graft site infection, above-knee amputation, neck wound, chronic venous leg ulcer, post-burn soft tissue infection, scrotal wound, otitis externa, discharging thigh sinus, lower limb infection, sinusitis. "Bone and joint infections" not defined. "Other" represents infective endocarditis, bronchoalveolar lavage, ureteric calculi, infected aorta post-heart transplant. Resp. inf., respiratory infection; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection.

Figure 2. Pathogens identified in patients receiving ceftolozane/tazobactam (N=45)



Note: 45 of 46 patients had positively identified microbiological isolates. Patients could have more than one pathogen.

Table 3. Ceftolozane/tazobactam treatment duration (days) by indication

Indication	Sepsis[a]	Skin and wound	Pneumonia	BJI	Other	CRIE	cIAI	cUTI	Febrile Neutro.
N	10	11	8	6	4	4	4	4	3
Mean	8	11	13	19	30	19	22	2	6
SD	12	8	9	13	25	7	26	1	2

[a]Duration of therapy not recorded for 1 sepsis patient. BJI, bone and joint infection; CRIE, chronic respiratory infection exacerbation; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; Neutro., neutropenia; SD, standard deviation.

Ceftolozane/tazobactam dosage

Most pneumonia patients (75.0%) received an inappropriate dose of C/T (Table 4). However, these data were collected prior to TGA authorisation for use in nosocomial pneumonia as 3 g q8h dose.

Table 4. Initial dose of ceftolozane/tazobactam by indication

Dose received	cUTI/cIAI N=8	Pneumonia N=8	Other N=30	Con. sepsis[a] N=14
1.5 g q8h	**75%**	63%	67%	**50%**
3.0 g q8h	0%	**25%**	13%	**21%**
Other	25%	13%	20%	**29%**

Note: TGA-approved doses for cUTI/cIAI and nosocomial pneumonia highlighted in blue. Dose adjustments are recommended for treatment of cIAI, cUTI, and nosocomial pneumonia in patients with CrCL levels ≤50 mL/min. [a]Concomitant sepsis.

Clinical outcomes

Overall clinical success (78.5%) was consistent with both Phase III trials and real-world evidence. In-hospital mortality was zero (Table 5).

Table 5. Overall clinical outcomes

Clinical outcomes	n	%
Clinical success (N=42[a])	**33**	**78.6%**
In-hospital mortality	**0**	**0.0%**
Patient remained hospitalised 30 days post-last dose of C/T (N=43[b])	**2**	**4.7%**
30-day all-cause readmission (N=43[c])	**9**	**20.9%**
30-day infection-related readmission (N=43[c])	**3**	**7.0%**

[a]Clinical success was recorded as unknown for 4 patients. [b]Date of last dose of C/T not recorded for 1 patient and discharge date not recorded for 2 patients. [c]Readmission to hospital within 30 days of last C/T dose was recorded as unknown for 3 patients.

Conclusions

- Overall C/T clinical success in Australian patients was consistent with both Phase III trials and real-world evidence
- A substantial number of patients received C/T for off-label indications
- Ceftolozane/tazobactam was mostly used to treat patients with confirmed *P aeruginosa* infections after receipt of microbiology results (>7 days post-isolate collection)
- Last-line agents (eg, carbapenems, polymyxins) were used before C/T in some patients
- Real-world usage data such as these can help inform local evidence-based guidance for new agents. National guidance on appropriate use of new agents and new indications would aid optimal and appropriate use of new agents

ANTIMICROBIAL-IMPREGNATED BONE CEMENT USE IN AUSTRALIAN HOSPITALS: CEMENTING THE JOINTS

A Teoh, N Hillock

National Antimicrobial Utilisation Surveillance Program | SA Health

BACKGROUND

- Antibiotic-impregnated bone cement is frequently used in arthroplasty surgery to minimize the risk of infection in the prosthetic knee or hip joint.[1,2]
- The objective of this study was to gain greater insight into the use, documentation, and stock management of antibiotic-impregnated bone cement in Australian hospitals.

METHODS

- The NAUSP database was searched to identify hospitals including bone cement in their monthly data submissions.
- An online survey was distributed to all NAUSP contributors to establish which department was responsible for stock management, and pharmacist knowledge of use and documentation of bone cement.

KEY FINDINGS

- 13% of hospitals included proprietary antibiotic-impregnated bone cement in their monthly data submission to NAUSP.
- Antimicrobials that were identified by pharmacists as having been added to cement in theatre include: vancomycin, ciprofloxacin, colistin, aminoglycosides, carbapenems and antifungals.
- 53% of pharmacists who responded were unsure or find it difficult to locate documentation in the clinical notes of the bone cement used including whether antimicrobials were added.

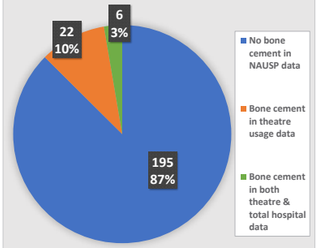
CONCLUSION

- **Consistency in the management and documentation of antimicrobial-impregnated cement would assist in surveillance of usage, help identify variations in practice and provide opportunities for quality improvement**
- **This study has illustrated a gap in pharmacist knowledge in the peri-operative setting and highlights a possible focus for future education to assist with AMS in this setting**

Antimicrobial-impregnated bone cement in NAUSP surveillance data

- The surveillance of antimicrobial usage is a key component of antimicrobial stewardship (AMS), enabling the monitoring of trends in usage, the identification of inappropriate use, and the evaluation of the effectiveness of interventions to optimise usage.
- From January 2021, the National Antimicrobial Utilisation Surveillance Program (NAUSP) data inclusions were expanded to include the use of all antimicrobials in Australian hospitals, including antimicrobial-impregnated bone cement.
- 233 hospitals submitted pharmacy dispensing data to NAUSP in 2021.[#] Of the 233 hospitals, 222 submitted granular data for theatre. Only 13% of hospitals submitted data that included antibiotic-impregnated bone cement.

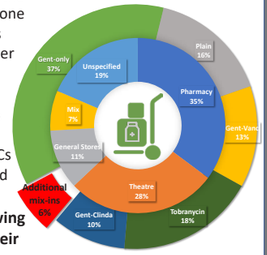
Antibiotic-impregnated bone cement included in pharmacy dispensing data: NAUSP contributing hospitals*



*Includes 222 acute hospitals that have contributed data in 2021 (excludes AIHW Public Acute Group D and Rehab / mixed sub-acute hospitals)

Survey results

- 52 responses to the online survey were received.
- Approximately one third of respondents (35%) stated that the pharmacy was responsible for the stock management of bone cement in their hospitals. At other sites, bone cement was managed by the operating theatre, the general stores, other unspecified departments, or a combination (mixed management).
- For respondents whose respective hospital pharmacies do manage antibiotic-impregnated BCs, gentamicin-and tobramycin-impregnated BC was most common. Others BCs stocked included gentamicin-clindamycin combination, and gentamycin-vancomycin combination.
- **Pharmacists who responded were aware of the following antimicrobials being added to cement in theatre at their hospitals: tobramycin, amikacin, vancomycin, ciprofloxacin, ertapenem, meropenem, colistin, daptomycin, voriconazole.**



- **53%** of the respondents reported difficulty locating details of bone cement and/or antimicrobial added to cement in patient clinical notes. ***"I know nothing about bone cement; I wouldn't know where to look or who to talk to".***
- 38% stated details would be in the theatre notes and 9% knew to look in prosthetic records.

Limitations

Response rates to the pharmacy survey was only 22% of NAUSP contributors (52/233 hospitals). The survey results therefore may not be representative of all Australian hospitals, nor representative of pharmacists specialised in the peri-operative clinical setting.

Opportunities for quality improvement

- There appears to be wide variation in the clinical use and management of antimicrobial-impregnated bone cement in Australian hospitals. Routinely used proprietary products vary between hospitals with the majority utilising cement with pre-added aminoglycoside (either gentamycin or tobramycin).
- Pharmacists identified a number of broad-spectrum agents added to bone cement in theatre, however the frequency of use and the usual amount added is not clear. There is a lack of strong evidence to determine optimal practice in this setting. Further research to determine routine practice of orthopaedic surgeons would assist in developing consensus-based guidelines.
- There is an opportunity for clinical pharmacists to increase their understanding of antimicrobials added to bone cement, in particular, the stability of antimicrobials in bone cement, how and where it is documented, and the recommended antimicrobial and dose that decreases infection risk but does not compromise the joint stability. This could lead to improved care in patients who undergo arthroplasty procedures.

Government of South Australia
SA Health

References:
1. Kleppel, D, Storton J, et al (2017). *Antibiotic bone cement's effect on infection rates in primary and revision total knee arthroplasties.* World J Orthop, 8 (12): 946-55
2. Mayer, M, Naylor J, et al (2017). *Evidence base and practice variation in acute care processes for knee and hip arthroplasty surgeries.* PLoS ONE 12(7): e0180090

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POSTER ABSTRACTS

ORAL CIPROFLOXACIN EFFICACY AGAINST CEFTRIAXONE-RESISTANT *ESCHERICHIA COLI* IN A BLADDER INFECTION MODEL

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Aim: Provide *in vitro* data to support ciprofloxacin breakpoints specific for urinary tract infections (UTIs).

Background: Oral ciprofloxacin is an important antimicrobial for antimicrobial-resistant uropathogens. Ciprofloxacin achieves higher urinary concentrations compared to plasma, which may promote increased efficacy against isolates with reduced susceptibility. Urine-specific breakpoints, however, do not exist.

Methods: 15-clinical ceftriaxone-resistant *E. coli* urinary isolates were selected with a range of ciprofloxacin MICs (0.25-512mg/L). *E. coli* ATCC 25922 was also selected (MIC 0.008 mg/L). A dynamic bladder infection model simulated oral ciprofloxacin administration over 3-days, generating urinary exposures following different dosing schedules: 250mg daily, 500mg daily, 250mg 12-hourly, 500mg 12-hourly, 750mg 12-hourly. Human urodynamics was simulated by continuous inflow of synthetic human urine (25 mL/h) and intermittent 4-hourly bladder voiding. Bacterial starting inoculum was 10 mL of 10^6 cfu/mL. Bacterial density was determined at 0, 6, 24, 30, 48, 54, 72 and 96-h. Ciprofloxacin concentrations, measured by LC-MS, were measured at peak concentration on third day from each bladder compartment, and representative peak and trough samples from 3-bladders each day, and at 72-h and 96-h.

Results: Following the 5 dosing schedules (ciprofloxacin exposure range: $AUC_{0\text{-}24}$ 1500-9000 mg/L.h), *E. coli* ATCC 25922 was killed in all experiments, while all clinical isolates with ciprofloxacin MIC ≥ 4mg/L had maximal re-growth at 96-h. Of the 6 clinical isolates with MIC 0.25-1mg/L, none re-grew at 72-h except following 250mg daily. Re-growth at 96-h in these 6-isolates was: 5/6 after 250mg daily, 2/6 after 500mg daily, 1/6 after 250mg 12-hourly, 500mg 12-hourly and 750mg 12-hourly. A post-exposure rise in ciprofloxacin MIC was noted in one isolate following 250mg 12-hourly (MIC 0.5 mg/L to 8 mg/L at 96-h). E_{max} model (Fig. 1) describing exposure ($AUC_{0\text{-}24}$/MIC) and response (change in cfu/mL at 96 h) targets for stasis, 1-log and 2-log kill were: 2310, 3094 and 4116, respectively.

Conclusions: This *in vitro* model does not support a ciprofloxacin UTI-breakpoint >2 mg/L, despite simulation of high-dose administration. Whereas isolates with MIC ≤1mg/L were more reliably killed following 12-hourly dosing at 250mg, 500mg and 750mg. Emergence of resistance was rare.

PANDEMIC POSITIVE: RISING TO THE CHALLENGE TO SUSTAIN ANTIMICROBIAL STEWARDSHIP ACTIVITIES

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Aim: Evaluated the utility of the Quality Improvement National Prescribing Survey (QI-NAPS) as an audit and feedback tool during resource limited time periods.

Background: The COVID-19 pandemic has presented challenges including competing priorities for resources and travel restrictions. The QI-NAPS provides an audit and feedback tool that can be utilised when resources are scarce and has demonstrated greater uptake in remote and regional facilities.

Methods: The Queensland Statewide Antimicrobial Stewardship Program (QSAMSP) supports Antimicrobial Stewardship (AMS) activities in four rural Hospital and Health Services (HHS's) where there are no onsite infectious diseases/clinical microbiologist consultants. Local clinicians used QI-NAPS resources to collect data during regular clinical patient reviews. Cases were discussed weekly during multidisciplinary telehealth AMS rounds with QSAMSP. Data entry and feedback to prescribers was supported by QSAMSP and Quality Improvement (QI) initiatives were identified.

Results: Data entry records from the online portal were used to assess uptake of the QI-NAPS in four rural HHS's. Data was exported to Microsoft Excel format to assess adherence to guidelines from 2019 to 2021. Numbers of antimicrobials audited in QI-NAPS increased particularly from 2020 (Figure 1). Adherence to guidelines increased from 63% to 68% from 2019 to 2021 respectively which was comparable to national rates. The management of community acquired pneumonia at one HHS was identified as a QI initiative and QI-NAPS results showed improved adherence to guidelines from 50% to 86%. Feedback from clinicians included that the tool was efficient and easy to use, it could be incorporated into existing daily workflow, aided the clinical review process and facilitated timely feedback to prescribers. Limitations included absence of appropriateness assessment and national benchmarking being unavailable. The QI-NAPS facilitated monitoring for three out of the eight AMS Clinical Care standard indicators (use of guidelines, documentation and review of therapy).

Conclusions: Despite the challenges of the COVID-19 pandemic the QI-NAPS proved to be a sustainable audit and feedback tool which also facilitated the identification and implementation of QI initiatives and monitoring of selected AMS Clinical Care standard indicators.

COMPARISON OF AZITHROMYCIN, TETRACYCLINE AND ERTAPENEM SUSCEPTIBILITY IN *ESCHERICHIA COLI* CLINICAL ISOLATES AT CANBERRA HEALTH SERVICES OVER TIME.

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Aim: To assess the change in susceptibility patterns of clinically significant *Escherichia coli* isolates to azithromycin, tetracycline and ertapenem at Canberra Health Services over time.

Background: *E. coli*, a Gram-negative bacillus that colonises the human gastrointestinal tract is a frequent cause of urinary tract infections and the most common blood-stream infection. The Australian Group on Antimicrobial Resistance (AGAR) have shown increasing antimicrobial resistance in *E. coli*. Azithromycin is widely used to treat respiratory tract infections, bacterial gastroenteritis and sexually transmitted infections. There have been no large-scale studies on the *in vitro* activity of azithromycin on clinical *E. coli* isolates in an Australian population.

Methods: This was a laboratory-based descriptive study at Canberra Health Services Microbiology Laboratory in which azithromycin, tetracycline and ertapenem susceptibility testing was performed on 513 previously stored clinically significant *E. coli* isolates. Susceptibility testing was performed using the E-test method. Breakpoint minimum inhibitory concentrations (MIC) for tetracycline and ertapenem were as per Clinical and Laboratory Standards Institute (CLSI) M100 31st Edition. For azithromycin, *Shigella* species breakpoints were used as there are no specified MIC breakpoints. MIC's of urinary and blood culture isolates from 2008/2010 and 2020 were compared.

Results: Of the urinary isolates from 2020 (n=99), 86.9% were susceptible to azithromycin and 73.7% to tetracycline. When compared to 2008/2010 (n=150), there was no significant change in susceptibility with 90% of urinary isolates susceptible to azithromycin (p=0.44) and 79.3% to tetracycline (p=0.30). Blood cultures isolates in 2020 (n=112) showed a decrease susceptibility to azithromycin, however, this was not significant with 76.8% of blood culture isolates in 2020 susceptible and 84.6% in 2008/2010 (n=162) (p=0.10). Susceptibility of blood culture isolates to tetracycline in 2020 was 68.8%, compared to 64.8% susceptible in 2008/2010 (p=0.5). There was no change in ertapenem susceptibility observed.

Conclusions: Despite widespread use of azithromycin and tetracyclines in Australia for various indications, there was no significant change in susceptibility to these antibiotics observed from clinically significant *E. coli* isolates over the last 11 years.

WHAT HAPPENED DURING COVID-19? QUANTITATIVE SURVEILLANCE OF HOSPITAL ANTIMICROBIAL USE IN AUSTRALIA

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Background: The onset of the COVID-19 pandemic was accompanied by international concern regarding possible increased antimicrobial use and the potential impact on antimicrobial resistance. In addition to potential changes in prescribing patterns, fluctuating changes in hospital activity and the establishment or repurposing of existing wards to cater for COVID-19 patients had the potential to impact antimicrobial usage trends.

Aim: To examine trends in antimicrobial usage in Australian hospitals during 2020 and identify any changes in usage rates during the waves of the COVID-19 pandemic.

Method: Monthly antimicrobial dispensing and distribution data for Australian hospitals contributing to NAUSP were analysed for 2020 and compared with 2019. Antimicrobial usage was converted from total grams into Defined Daily Doses (DDDs) assigned by the WHO. Usage rates were calculated as DDDs per 1,000 Occupied Bed Days.

Results: Total antimicrobial usage decreased by 2.9% in 2020 compared to 2019 in hospitals contributing to NAUSP. Large decreases in annual aggregate usage rates were seen for tetracyclines (-20.6%), macrolides (-15.5%) and β-lactamase sensitive penicillins (-10.9%). Use of some broad-spectrum classes increased in 2020 compared to 2019, notably carbapenems (up 3.1% from 14.7 DDD / 1,000 OBD to 15.2 DDD / 1,000 OBD) and fourth-generation cephalosporins (up 9.0% from 4.4 DDD/1,000 OBD to 4.8 DDD/1,000 OBD).

Conclusion: AMS staffing shortages and changes to hospital infrastructure to cater for the COVID-19 pandemic impacted antimicrobial data submissions to NAUSP. These system changes should be considered when interpreting antimicrobial usage rates. While this introduced some uncertainty with regards to consistency in reporting, overall aggregate data suggests that antimicrobial usage decreased in Australian hospitals in 2020.

AUSTRALIA & NEW ZEALAND (ANZ) STUDY FOR ANTIMICROBIAL RESISTANCE TRENDS (SMART): GRAM-NEGATIVE RESISTANCE IN UNDER-REPRESENTED SURVEILLANCE SETTINGS (2016-2019)

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Aim: This study aimed to describe the predominant Gram-negative pathogens and evaluated empiric coverage in settings not commonly reported in national surveillance, namely ICU patients and hospitalised patients with respiratory infections.

Background: Empiric therapy decisions are based upon a combined prediction of infecting pathogens and local susceptibilities, adapted to patients' characteristics. This analysis included ceftolozane/tazobactam (C/T), which is not routinely tested in Australia or New Zealand.

Methods: Data were collected from ANZ SMART hospitals/ laboratory networks (2016-2019). MIC testing was performed by broth microdilution (EUCAST v.11).

Results: From 2016-2019 ANZ SMART sites provided 3078 respiratory Gram-negative pathogens; around a third of these isolates were from ICU patients (n=1058). In the same period, 524 non-respiratory Gram-negative pathogens were collected from ICU patients.
The most common respiratory Gram-negative pathogens were *Pseudomonas aeruginosa* (32%), *Escherichia coli* (15%), *Klebsiella pneumoniae* (11%), *Serratia marcescens* (8%) and *Enterobacter cloacae* (5%). Rank-order prevalence was maintained between ICU and non-ICU respiratory pathogens for these pathogens. These species were also the major pathogens in the ICU-setting. Against the three most common ICU RTIs, composite susceptibilities were highest for ceftolozane/tazobactam (97.1%) and meropenem (96.9%), whereas piperacillin/tazobactam susceptibility was markedly lower (84.3%). Rankings were similar when agents were assessed against 80% of the ICU respiratory Gram-negative pathogens. Ceftolozane/ tazobactam showed the highest susceptibilities against ICU respiratory Gram-negative pathogens resistant to possible first-line agents; against piperacillin/tazobactam-resistant isolates C/T was higher than meropenem (87.2% C/T versus 79.4% meropenem).

Conclusion: Ceftolozane/tazobactam and meropenem provided the most reliable activity in empiric prescribing scenarios compared to other β-lactams. In adjustment scenarios, C/T had higher activity than meropenem for *P. aeruginosa*.

EVALUATING ANTIMICROBIAL STEWARDSHIP (AMS) PHARMACIST REVIEWS IN AN AUSTRALIAN MULTI-SITE TEACHING HOSPITAL NETWORK

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Aim: To evaluate Antimicrobial Stewardship (AMS) pharmacist reviews of inpatient antimicrobial orders including appropriateness, type and frequency of recommendations, and acceptance of recommendations within 24 hours in comparison to those led by Infectious Diseases (ID) physicians.

Background: To increase the number of antimicrobial reviews, AMS pharmacist ward rounds were introduced in addition to multidisciplinary AMS rounds at a multi-site hospital network in Melbourne, Victoria. There are many benefits to independent AMS pharmacist reviews, however there are limited studies assessing the appropriateness and acceptance of these reviews.

Methods: AMS pharmacist reviews of adult inpatient antimicrobial orders over defined time periods were retrospectively assessed by a panel of ID physicians for appropriateness. Reviews were classified utilising an assessment tool developed based upon the National Antimicrobial Prescribing Survey (NAPS) 'Guidelines to assist with the assessment of appropriateness'. Acceptance rates of pharmacist recommendations were measured and compared with those involving an ID physician during the assessed periods.

Results: Pharmacy recommendations were appropriate in 80% of 113 assessments. Of appropriate recommendations, 76% were optimal and 24% were adequate. Recommendations were deemed suboptimal most frequently due to missed opportunities for switching from IV to oral. Incorrect duration was the most frequent intervention by pharmacists at 21%, followed by the need to obtain an ID approval number (16%) and incorrect dose (14%). More than 70% of these types of recommendations were accepted by prescribers.
AMS pharmacist recommendations were accepted within 24 hours 63% (44/70) of the time, comparable to 70% (285/406) of AMS recommendations involving ID physicians (p value =0.22).

Conclusions: This small investigation of AMS pharmacist reviews demonstrated pharmacists make appropriate recommendations with comparable acceptance rates to multidisciplinary reviews. Improvements in identifying oral switch opportunities may develop the impact of AMS pharmacist rounds further. This investigation confirms that AMS pharmacist reviews are substantiated and can be an efficient and useful addition to AMS programs.

LONG-TERM ANTIBIOTIC PRESCRIBING IN THE COMMUNITY: 6 YEARS OF NATIONAL DATA

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Aim: To quantify and describe community prescribing of continuous long-term antibiotics in Australia

Background: Prolonged or indefinite courses of antibiotics are sometimes prescribed for suppression of chronic infection, prophylaxis of infection, or non-infective indications. Risks of long-term prescribing include antimicrobial resistance, drug adverse effects and cost. In Australia, 75% of community prescribing is funded by the Pharmaceutical Benefits Scheme (PBS).

Methods: A randomised 10% sample of PBS prescription data from 2014-2020 was analysed. "Long term prescribing" was defined as continuous prescribing of >/= 12 months. Patients prescribed long-term antibiotics were identified using a rolling window algorithm with 12 month look-back from each script provided. Patient demographics, prescriber type, antibiotic type and antibiotic indication data were described.

Results: Long-term oral antibiotics were prescribed to 82 383 individual patients per year (339/100 000 population mean yearly rolling average; 54% female). 50% of patients were aged >65 years (Figure 1) 68% of prescribers were General Practitioners. The most frequently prescribed long-term antibiotics (average patients/year) were doxycycline (34 410), trimethoprim-sulfamethoxazole (19 630), cefalexin (14 280), amoxycillin (6 260) and minocycline (5 540). Broad-spectrum oral antibiotics of interest were amoxicillin-clavulanate (3320 patients/year) and ciprofloxacin (1410 patients/year). Classes of antibiotics most frequently prescribed were tetracyclines (43% of antibiotics prescribed long term), sulfonamides/trimethoprim (21%), cephalosporins (15%), and penicillins (13%) (Figure 2). A minority of scripts reported unique indication codes. These included: "urinary tract infection prophylaxis" (10 067 patients/ year, 84% female, 52% aged >75); "Osteomyelitis" (3242 patients/ year) and "serious staphylococcal infection" (1460 patients/year). Long-term prescribing under the indications osteomyelitis and serious staphylococcal infection rose 47% and 33% respectively over the study period, primarily in patients aged >65 years. Patients on long term antibiotics were co-prescribed analgesia (30%), antidepressants (30%), corticosteroids (20%), and immunosuppressive drugs (6%). (Table 1)

Conclusions: In any given year, 1/300 Australians are prescribed long-term continuous antibiotics subsidised by the PBS. Elderly and comorbid patients are over-represented. A better understanding of indications for long-term prescribing is needed. Antimicrobial stewardship and polypharmacy may be important in this group.

HIDDEN RESISTANCES: HOW ROUTINE WHOLE GENOME SEQUENCING UNCOVERED AN OTHERWISE UNDETECTED *BLA*$_{NDM-1}$ GENE IN *VIBRIO ALGINOLYTICUS* ISOLATED FROM IMPORTED SEAFOOD

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Aim: To investigate and describe the antimicrobial resistance (AMR) mechanisms of a carbapenemase-producing *Vibrio alginolyticus* isolate, identified by routine genomic surveillance from imported prawns.

Background: *V. alginolyticus* is a Gram-negative bacterium found worldwide in marine, estuarine and coastal environments, able to cause vibriosis in a range of marine vertebrates, invertebrates, and humans. There have been reports of multidrug resistance (MDR, resistance to ≥3 drug classes) in *Vibrio* species, including *V. alginolyticus*, but carbapenem resistance is rare, previously reported only once for *V. alginolyticus* on a plasmid (*V. alginolyticus* strain Vb1394 plasmid, pC1349).

Methods: Routine short-read whole genome sequencing (WGS) was conducted for *V. alginolyticus* strain AUSMDU00064140, in addition to thirteen other *V. alginolyticus* isolates identified at Microbiological Diagnostic Unit, Public Health Laboratory (MDU PHL). Phylogenetic comparisons of the novel isolates were performed against a global *V. alginolyticus* dataset (n=109), and all isolates were screened for AMR genes using the abriTAMR tool. The complete genome was assembled for the carbapenemase-producing isolate, AUSMDU00064140, using both long-read and short-read sequencing data.
Phenotypic carbapenemase detection was performed using the carbapenemase inactivation method (CIM) test for AUSMDU00064140, in addition to antimicrobial susceptibility testing using a commercial broth microdilution panel.

Results: Phenotypic testing of AUSMDU00064140 showed evidence of carbapenemase activity (positive CIM test), despite low meropenem MICs (MIC ≤0.5 mg/L). Genomic analyses confirmed the presence of a full-length carbapenemase gene, *bla*$_{NDM-1}$, located on the chromosome, unlike the first report of a *bla*$_{NDM-1}$ in *V. alginolyticus* located on the plasmid, pC1349. Ten additional acquired AMR genes (belonging to seven AMR classes) were detected on the chromosome of AUSMDU00064140, of which several are co-located with the *bla*$_{NDM-1}$ gene. AUSMDU00064140 is phylogenetically distinct from all other *V. alginolyticus* isolates analysed. MDR was only identified in four of the *V. alginolyticus* isolates across the dataset.

Conclusions: The presence of *bla*$_{NDM-1}$ in *V. alginolyticus* is concerning due to the potential for gene transmission within hosts (gastrointestinal colonisation) and, between hosts and the environment. Phenotypic carbapenem MIC testing alone did not detect a carbapenemase gene in this isolate, demonstrating the value of genomics in uncovering hidden AMR determinants of public health significance.

GENETIC CHARACTERISATION OF LINEZOLID-RESISTANT *ENTEROCOCCUS FAECALIS* ISOLATED IN WESTERN AUSTRALIA, 2016-2021

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Aim: To determine the molecular epidemiology and resistance mechanism of linezolid-resistant *Enterococcus faecalis* isolated in Western Australia from 2016 to 2021.

Methods: A total of 25 linezolid-resistant *E. faecalis* were included in the study. Isolates were identified as *E. faecalis* using matrix-assisted laser desorption ionization (MALDI Biotyper). Resistance to linezolid was confirmed by the Etest®. MIC results were interpreted using the CLSI breakpoints (S: ≤2 mg/L; I/R: ≥4 mg/L). Whole genome sequencing was performed on the NextSeq® 500 platform (Illumina, USA) and raw sequence reads were assembled using SPAdes. Assembled contigs were used to determine the multi-locus sequence type (ST). Linezolid resistance determinants were identified using the LRE-finder tool.

Results: Of the 25 isolates, 72% (n=18) had a linezolid MIC of 8 mg/L and the remainder had an MIC of 4 mg/L (n=3), 16 mg/L (n=3) and 64 mg/L (n=1). A total of ten STs were identified and 48% (n=25) of isolates belonged to ST16 whilst the remainder belonged to ST179 (n=2), ST480 (n=2), ST506 (n=2), ST59 (n=1), ST403 (n=1), ST476 (n=1), ST895 (n=1), ST1010 (n=1) and ST1163 (n=1). Most ST16 isolates had an MIC of 8 mg/L and were phylogenetically related. The isolate with the highest linezolid MIC belonged to ST179 and harboured the G2576T mutation in three of the four copies of the 23S rRNA gene. Linezolid resistance in the remaining isolates could be explained by the presence of the *optrA* gene which encodes an ATP-binding cassette F protein that mediates resistance to both phenicols and oxazolidinones through target protection. The *optrA* gene was carried on a mobile genetic element which also harboured the *fexA* and *erm(A)* genes which confer resistance to chloramphenicol and erythromycin, respectively. The *cfr*, *cfr(B)* and *poxtA* genes conferring resistance to linezolid were not identified.

Conclusions: Multiple clones of linezolid-resistant *E. faecalis* were identified including the clonal expansion of *optrA*-positive ST16. Resistance to linezolid could be explained by the presence of *optrA* in all isolates except the isolate with the highest linezolid MIC in which resistance to linezolid was conferred by the G2576T mutation in the 23S rRNA gene.

EFFECT OF VANCOMYCIN EXPOSURE ON A VANCOMYCIN VARIABLE *ENTEROCOCCUS FAECIUM* HARBOURING VANB

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Aim: To characterise and assess the effect of vancomycin exposure on a *vanB*-positive vancomycin variable *Enterococcus faecium* causing bacteraemia in Australia.

Methods: Vancomycin MIC was determined using the broth microdilution method and results were interpreted using the CLSI breakpoints (susceptible: ≤4 mg/L; intermediate: 8-16 mg/L; resistant: ≥32 mg/L). Exposure to vancomycin was performed in overnight broth culture using a 2-fold daily increase in vacomycin concentration. Whole genome sequencing was performed on the NextSeq® 500 platform (Illumina, USA) and raw sequence reads were assembled using SPAdes. Assembled contigs were annotated using Prokka and the *van* operons were visualised and aligned using Geneious Prime.

Results: VVEfm23 is a vancomycin-susceptible *vanB* harbouring *E. faecium* isolate identified in the Australian Enterococcal Sepsis Outcome Program (AESOP) survey carried by the Australian Group on Antimicrobial Resistance (AGAR). VVEfm23, a ST796 *E. faecium*, harboured a complete *vanB* operon consisting of the $vanR_B$, $vanS_B$, $vanY_B$, $vanW_B$, $vanH_B$, *vanB* and $vanX_B$ genes but had a low vancomycin MIC of 1.0 mg/L. After exposing VVEfm23 to a daily increase in concentration of vancomycin, the vancomycin-resistant mutant VVEfm23-M was isolated. In contrast to its wild-type parent, VVEfm23-M had a vancomycin MIC of 256 mg/L. A nucleotide alignment of the *vanB* operon of VVEfm23 and VVEfm23-M identified an 18-bp in-frame deletion in the $vanS_B$ regulatory gene of the mutant. The deleted fragment encoded a six amino acid sequence (Arg-Ser-Arg-Lys-Ser-Gly) which may play an important role in the regulation of the *vanB* operon. No nucleotide differences were identified elsewhere in the *vanB* operons.

Conclusions: *In vitro* exposure of a *vanB*-positive vancomycin variable *E. faecium* harbouring all *vanB* operon genes to vancomycin resulted in the isolation of a vancomycin-resistant mutant with a 256-fold increase in vancomycin MIC. Resistance was attributed to a deletion mutation in the $vanS_B$ gene.

STUDY OF PRESCRIBING PATTERNS AND EFFECTIVENESS OF CEFTOLOZANE/TAZOBACTAM REAL-WORLD ANALYSIS (SPECTRA): AUSTRALIAN UTILISATION AND OUTCOMES

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Aim: This study evaluates real-world clinical use and outcomes among Australian patients treated with ceftolozane/tazobactam (C/T).

Background: C/T has demonstrated efficacy and safety in registration trials, yet eligibility criteria often limit translation of trial results into clinical practice.

Methods: SPECTRA is a multicenter, retrospective, observational study of patients treated with C/T in Australia, Austria, Germany, Italy, Spain and United Kingdom. Demographics, clinical characteristics, treatment patterns, microbiological findings and clinical outcomes (clinical success, mortality, readmission) were analysed for Australian patients admitted with >48 hours of C/T treatment.

Results: There were 46 Australian patients from six hospitals receiving C/T for >48 hours [Table 1]. The predominant sites of index infection were skin and wounds (24%), sepsis (24%), pneumonia (17%) and bone and joint infection (13%). Approximately one third (36%) of patients were then diagnosed with sepsis and 11% with septic shock. Two thirds of patients (67%) had additional antibacterial exposure in the 30 days prior to receipt of C/T; 15% received carbapenems and 17% an aminoglycoside. Most (96%) received an ID consult. The top Gram-negative pathogens were *Pseudomonas aeruginosa* (84%) and *Escherichia coli* (16%); around a third were polymicrobial infections (35%). 30-day all-cause readmission was 21% and 7% were infection-related. 79% were considered clinical success and in hospital mortality was zero.

Conclusion: Despite the complexity of these real-world patients, the majority had favourable clinical outcomes that are similar to results of controlled clinical trials.

ANTIMICROBIAL-IMPREGNATED BONE CEMENT USE IN AUSTRALIAN HOSPITALS: WHERE ARE THE GAPS?

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Background: Antimicrobial-impregnated bone cement is frequently used in arthroplasty surgery to minimise the risk of infection in prosthetic knee or hip joints. There is a lack of clarity regarding the routine management and documentation of antimicrobial-impregnated bone cement in Australian hospitals.

Aim: The objective of this study was to gain greater insight into the use, documentation and stock management of antimicrobial-impregnated bone cement in Australian hospitals.

Methods: The National Antimicrobial Utilisation Surveillance Program (NAUSP) database was searched to identify hospitals submitting bone cement data in their monthly data contributions. An online survey was distributed to all hospitals registered with NAUSP, regarding the management of bone cements, the antimicrobial agents commonly added by surgeons, and the method of documentation in the clinical notes.

Results: 13% (28/233) hospitals include proprietary antibiotic-impregnated bone cement in NAUSP data submissions. 35% of survey respondents reported that bone cements were included in their pharmacy inventories. Where bone cements were not managed by pharmacy, they were managed by operating theatres directly, general stores, other unspecified departments, or a combination (mixed management). Apart from commercially pre-loaded antibiotic bone cements (gentamicin, tobramycin, clindamycin or vancomycin), respondents reported knowing of nine antimicrobials added intra-operatively. 53% of respondents were unable to find clinical information regarding bone cement in patient notes.

Discussion: These results suggest there is wide variability in the management, use and documentation of antimicrobial-impregnated bone cement in Australian hospitals. Management of antimicrobial-impregnated bone cements by pharmacy and their inclusion in routine antimicrobial surveillance would assist in understanding current practice, facilitate the development of guidelines to optimise clinical use and assist in identification of inappropriate use. Standardisation of documentation in clinical notes would assist participation in clinical audits or national surveys (such as the National Antimicrobial Prescribing Survey (NAPS)) which aim to ensure appropriate use of antimicrobials in this setting.

ABSTRACT ONLY

— Analysis of Antimicrobial Resistance Trends for the Port Moresby General Hospital in 2020

— Silver Lining of COVID-19: The Unexpected Reduction of Commonly Used Antibiotics for Children in Western Australia

— Utilising Health Belief Model to Assess Antimicrobial Awareness of Western Australian Parents: A Qualitative Study

— Genomics of *Neisseria gonorrhoeae* Lineages Associated with Decreased Susceptibility to Extended Spectrum Cephalosporins and Mosaic *penA* Alleles in Australia

— Simulating Mono and Combination Therapy of Meropenem and Amikacin Against *Pseudomonas aeruginosa* Bacteraemia in Patients Using the Hollow-Fiber Infection Model

— The Antimicrobial Use and Resistance in Australia (AURA) Surveillance System

— Critical Antimicrobial Resistances: CAR-Alert Reports from 2016 to 2021

— The Australian Group on Antimicrobial Resistance Report from the Gram-Negative Sepsis Outcome Program (GNSOP) 2020 – Susceptibility Data

— The Australian Group on Antimicrobial Resistance Report from the Gram-Negative Sepsis Outcome Program (GNSOP) – 2013-2020

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— 2020 Australian Enterococcal Sepsis Outcome Programme (AESOP) Comparative Genomics of *Enterococcus faecium* Causing Bacteraemia

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— Carbapenemase Genes in Enterobacterales from the Agar Gram-Negative Sepsis Outcomes Programme 2017-2020

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— Antimicrobial Restrictions and Use of High Importance Antimicrobials – Survey Results from Australian Veterinarians

— Evaluation Of Vitek2 And Etest for Penicillin and Ceftriaxone Susceptibility Testing for *Streptococcus pneumoniae*

— Molecular Epidemiology of Pencillin-Susceptible *Staphylococcus aureus* Causing Bacteraemia in Australia, 2020

ANALYSIS OF ANTIMICROBIAL RESISTANCE TRENDS FOR THE PORT MORESBY GENERAL HOSPITAL IN 2020

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Aim: To provide antimicrobial resistance data for the Port Moresby General Hospital (PMGH).

Background: In the fight against antimicrobial resistance (AMR), the generation of annual cumulative antibiograms are important to guide empirical antimicrobial therapy for the management of infections, support antimicrobial stewardship strategies and infection prevention and control measures. PMGH is a 1,200 bed, level 6 referral hospital in Papua New Guinea (PNG). The hospital's yearly admissions average 24,000. The only functional clinical Microbiology laboratory in Papua New Guinea (PNG) is at the PMGH, Pathology department.

Methods: Data on all sample referred to the lab in 2020 was collected, including: patient demographics, and the date and ward of sample collection. Antimicrobial susceptibility testing (AST) was performed using disk diffusion, zone diameter readings were recorded and clinical breakpoints from of European Committee on Antimicrobial Susceptibility Testing (EUCAST v9) were used for interpretation.

Results: In 2020, a total of 11,113 samples were received by the lab. Of these, 3,428 were culture positive and subjected to AST. Methicillin-resistant *Staphylococcus aureus* (MRSA) rates of 33% to 65% were observed across all groups (adult and paediatric, outpatient and inpatient wards). The highest MRSA rate (69%, n=169/246) was observed in inpatients, but overall rates were consistent with those observed in 2018 and 2019. Suspected extended-spectrum beta-lactamase (ESBL), based on ceftriaxone susceptibility, was observed in 26% and 31% of *Klebsiella* spp, and 68% and 50% of *Escherichia coli* from urine and non-urine cultures, respectively. These rates were also consistent with those observed in 2018 and 2019. Vancomycin resistant *Enterococcus* was identified in 17% (8/46) of all enterococci recovered.

Conclusions: Comparison of the AMR trends observed in 2020 were similar to those in 2018, and 2019, with variation of ~5-7% in rates for MRSA, ESBL and VRE. Antimicrobial resistance is now a priority agenda for the National Health Department of PNG, and this represents the 3rd year in which PMGH has been able to generate antibiogram data. This will help PNG assess the reality of its AMR situation and be proactive in addressing the issue.

SILVER LINING OF COVID-19: THE UNEXPECTED REDUCTION OF COMMONLY USED ANTIBIOTICS FOR CHILDREN IN WESTERN AUSTRALIA

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Aim: Our study assessed whether the COVID-19 pandemic has had an impact on commonly used antibiotics among children by comparing antibiotics dispensing between January to December 2016-2020.

Background: In primary care, there is much concern regarding the prescribing of antimicrobials to children and more specifically, the overuse of antibiotics for self-limiting illnesses in children. Within the ongoing COVID-19 pandemic, the occurrence of respiratory tract infections caused by other infectious agents is of interest. While several studies have been done to identify antibiotic use in hospitals during the COVID-19 pandemic, there is a lack of studies investigating how the pandemic affected antibiotic use in the community. With the impact of COVID-19 transmission mitigation measures, increased media, and public attention the outlook of community acquired infections might have been altered and subsequently might have an effect on antibiotic consumption in the community.

Methods: The study was based on national pharmacy claims data from Pharmaceutical Benefit Scheme (PBS) through Services Australia Services. Four commonly used antibiotics with paediatric preparations were included in this analysis (Amoxicillin, Amoxcillin+Clavunalate Potassium, Cefaclor, Cefalexin). A time-analysis was done to determine the pattern and trends in antibiotic dispensing.

Results: There were about 3,543,925 antibiotic dispensing recorded over the study period. There was a 3% increase in antibiotic dispensing from 2016 to 2017. In 2018, there was a decrease of 3.5% in antibiotics dispensed and 1.9% reduction in antibiotic dispensing in 2019 was noted. During the pandemic period of 2020 antibiotic dispensing substantially dropped by 23% which equates to 167,491 lesser antibiotics dispensed compared to 2019. However, dispensing patterns remains unchanged and typically peaks during winter period and increases during periods when there is an increased with respiratory viral activities.

Conclusion: Overall, there is a reduction of commonly used antibiotics for children in Western Australia during COVID-19 pandemic. However, the dispensing pattern of antibiotics during influenza season has remained over the last five years and unchanged even with COVID-19 pandemic. Our study showed the temporal relationship between viral respiratory activity and antibiotic prescription in children which may indicate inappropriate antibiotic prescribing among children.

UTILISING HEALTH BELIEF MODEL TO ASSESS ANTIMICROBIAL AWARENESS OF WESTERN AUSTRALIAN PARENTS: A QUALITATIVE STUDY

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Aim: Our study aims to determine local factors that promote or prevent responsible use of antibiotics for their children among parents in Perth, Western Australia.

Background: Children are commonly prescribed with antibiotics during illness and one of largest consumers of antibiotics. Parents as the main healthcare decision maker for their children are important group to be targeted in promoting responsible antibiotic use and preventing antimicrobial resistance (AMR). Understanding parentals' attitude and exploring their decision making whether to use antibiotics play a vital role in informing interventions that are aimed to encourage responsible antibiotic use for their children.

Methods: A qualitative and explorative research design of focus group discussions (FGD) was used in this study. In total, twenty-six parents participated in four (FGD) in this study. The Health Belief Model was used to provide a theoretical framework to explore how parents perceive antibiotic and their likelihood engaging in judicious use of antibiotics for their children. The FGDs were audio-recorded and were transcribed verbatim and was analysed using the constructs of Health Belief Model.

Results: Participants agreed that antimicrobial resistance is a serious public health problem. However, participants agreed that they did not have enough knowledge and awareness of AMR to assess the risks of their children developing antimicrobial resistant organism infection and did not perceive the likelihood of their children developing antimicrobial resistant infections. Participants acknowledged that "time" is their greatest barrier in engaging in judicious of antibiotics. They have identified antibiotics as a "quick-fix" for their children and will help them to return back to normal routine. Participants acknowledged that having previously managed their child's illness has increased their confidence in managing their child's illness and also linked their positive and negative experiences with their GPs to engage in judicious use of antibiotics.

Conclusion: Our study identified factors that promote or prevent responsible use of antibiotics among children in community setting. The study also found parents lack of understanding of antimicrobial resistance and barriers in engaging in judicious use of antibiotics. Targeting these barriers will be essential in modifying misconceptions and promoting antimicrobial awareness. Incorporating parent empowerment, participation in decision-making regarding antibiotics and maintaining a positive relationship with healthcare provider may be important strategies to encourage appropriate use of antibiotics in children.

GENOMICS OF *NEISSERIA GONORRHOEAE* LINEAGES ASSOCIATED WITH DECREASED SUSCEPTIBILITY TO EXTENDED SPECTRUM CEPHALOSPORINS AND MOSAIC *PENA* ALLELES IN AUSTRALIA

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Aim: To determine the prevalence and mechanisms of decreased susceptibility (DSC) to extended specrum cephalosporins (ESCs) in our local setting.

Background: Reports of resistance to ESCs, the last remaining option for empiric first-line treatment of gonorrhoea, are of great concern. DSC to ESCs is primarily mediated by mosaic *penA* alleles. Globally, several Multi-locus Sequence Types (MLSTs) are associated with elevated minimum inhibitory concentrations (MICs) to ESCs, including Sequence Type (ST)7363.

Methods: We undertook a phenotypic and genomic analysis of *Neisseria gonorrhoeae* isolates in Victoria, Australia from 2015 to 2020. Further, we focused on ST7363 and combined our data with 572 ST7363-associated isolates from Victoria, Australia (2017-2020) and 724 global ST7363-associated isolates (1993-2020) obtained from Pathogenwatch.

Results: Between 2015 and 2020, 178 isolates displayed decreased susceptibility (n=175) or resistance (n=3) to ceftriaxone in Victoria, Australia. Additionally, of these isolates, 147 showed decreased susceptibility (n=106) or resistance (n=37) to cefixime. Whole genome sequencing showed that the three most common MLSTs were ST7363 (n=62), ST1901 (n=25) and ST7827 (n=21). Four isolates with mosaic *penA* 60 alleles had the highest ceftriaxone MICs (median of 0.44 µg/mL), however weren't associated with any specific lineage. Conversely, isolates with mosaic *penA*-10 (n=76/178, 42.7%) and mosaic *penA*-34 (n=22/178, 12.4%) alleles had the highest cefixime MICs (median of 0.25 µg/mL and 0.13 µg/mL respectively) and were primarily associated with ST1901 and ST7363. Phylogenomic analysis of Australian and global ST7363-associated isolates revealed at least four ST7363 lineages, with distinct antimicrobial resistance profiles. Lineage 1 was the most geographically diverse, lineage 2 was associated primarily with Japanese isolates (n=201/204) and lineages 3 and 4 were Australian-specific. Bayesian analysis of two large, Australian-specific sub-lineages: 2.4 (mosaic *penA*-34) and 4.1 (mosaic *penA*-92) predicted that the most recent common ancestor emerged in 2011 and 2016 respectively.

Conclusions: Consistent with global reports, we showed that ST7363 was associated with elevated cephalosporin MICs in Victoria, Australia. Additionally, we identified novel, Australian-specific lineages and sub-lineages of ST7363, some of which have only emerged within the last decade. These results highlight the need for continued whole genome sequencing based AMR surveillance on a local, national, and international scale.

SIMULATING MONO AND COMBINATION THERAPY OF MEROPENEM AND AMIKACIN AGAINST *PSEUDOMONAS AERUGINOSA* BACTERAEMIA IN PATIENTS USING THE HOLLOW-FIBER INFECTION MODEL

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Background: debate continues as to the role of combination antibiotic therapy for the management of *Pseudomonas aeruginosa* infections.

Aim: we studied meropenem and amikacin as mono- and combination therapy against susceptible and resistant *P. aeruginosa* isolates from bacteremic patients and compared the extent of bacterial killing and suppression of resistance.

Methods: we used a dynamic *in vitro* hollow-fiber infection model with three *P. aeruginosa* isolates from patients (meropenem MICs from 0.25 to 64 mg/L) simulating a bacteremia, with an initial inoculum ~ 1×10^5 CFU/mL, and the expected pharmacokinetics of critically ill patients.

Results: maximal bacterial killing was similar for both monotherapy and combination therapy isolates susceptible to meropenem and amikacin, although the combination regimen achieved a more rapid reduction in bacterial density killing. In addition, the combination regimen as well as meropenem monotherapy were able to sustain bacterial killing throughout the seven-day treatment course whereas regrowth of bacteria occurred with amikacin monotherapy after 12 hours. In contrast, for the *P. aeruginosa* isolate resistant to meropenem (but susceptible to amikacin) only the combination therapy was able to achieve extensive initial bacterial killing, although bacterial regrowth was evident after 32 hours.

Conclusions: Combination therapy using both amikacin and meropenem for the initial empiric management of *P. aeruginosa* infections offers some *in vitro* advantages over meropenem monotherapy particularly for immunocompromised patients. Given that optimized dosing of individual antibiotics in combination can maximize potential synergy against some isolates, future studies should explore the conditions for benefit of combination therapy against *P. aeruginosa*.

THE ANTIMICROBIAL USE AND RESISTANCE IN AUSTRALIA (AURA) SURVEILLANCE SYSTEM

BELL, J., *on behalf of the Group Australian Group on Antimicrobial Resistance (AGAR).*

Background: The Antimicrobial Use and Resistance in Australia (AURA) Surveillance System was established by the Australian Commission on Safety and Quality in Health Care (the Commission) to provide a coordinated approach to the collection, analyses and reporting of antimicrobial resistance (AMR) and antimicrobial use (AU) data for human health.

Methods: The Commission established a strategic framework to guide the development of the broadest possible scope of AMR and AU surveillance and achieve comprehensive voluntary data collection through collaborative partnerships. The development and operational processes were underpinned by a data governance framework; robust data collection and analyses; clinical and technical expertise across the subject matter; a commitment to timely reporting; and, effective relationships with the public and private sectors, across community and acute organisations.

Results: The extent of surveillance and reporting made possible through AURA has enabled data and information accessible in a range of forms for many audiences. The most recent comprehensive report was the *Fourth Australian report on antimicrobial use and resistance in human health: AURA 2021*, along with several companion documents for specific audiences. AURA 2021 provides a broad range of vital data, such as the decline in overall use of antibiotics in the community annually since 2015, but Australia continues to prescribe antimicrobials at much higher rates than most European countries. In 2019, just over 10 million people had a least one antimicrobial dispensed in the community. AURA 2021 provides detailed resistance data on 13 priority organisms, with additional data on a number of critical resistances to last-line antimicrobial agents. Common pathogens, such as *E. coli*, are becoming increasingly resistant to major drug classes, and some organisms are resistant to last-resort treatments.

Conclusions: AURA has successfully delivered a comprehensive and integrated picture of the burden of resistance and AU in Australia, and regular reporting of patterns and trends in AMR and AU to inform clinical policy and practice, and national and local programs to prevent and contain AMR. There has been significant growth in the breadth and scope of AMR and AU surveillance in Australia through AURA, informing improved decision-making at the clinician, organisation, state and territory and national levels. The integrated approach to considering resistance surveillance, alongside antimicrobial use and appropriateness data has been a further benefit in ensuring data for action.

CRITICAL ANTIMICROBIAL RESISTANCES: CAR-ALERT REPORTS FROM 2016 TO 2021

BELL, J., *on behalf of the Group Australian Group on Antimicrobial Resistance (AGAR).*

Background: The National Alert System for Critical Antimicrobial Resistances (CARAlert) was established in March 2016 by the Australian Commission on Safety and Quality in Health Care for the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System. CARAlert provides timely communication on critical antimicrobial resistances (CARs) to health departments in each state and territory to inform infection prevention and control strategies.

Methods: CARAlert uses established laboratory testing and confirmation systems to capture data on CARs – resistances to last line antimicrobials that are uncommon or rare, but with the capacity to become established in Australia. Laboratories that confirm CARs enter results into a national database at the time of confirmation.

Results: From 1 April 2016 to 17 December 2021, a total of 8,444 CARs was reported. Carbapenemase-producing *Enterobacterales* (CPE) has been the most prevalent CAR reported annually, except in 2017 when azithromycin non-susceptible *Neisseria gonorrhoeae* (ANSNG) dominated. Although CPE reports declined nationally following a peak in 2019, there has been notable variation between jurisdictions. Reports from Victoria decreased 1.5-fold from 2020 to 2021; and there was a slight increase in Queensland. The vast majority of CPE were IMP- and NDM-types. In 2021, IMP-types comprised 60% of all CPE reported, and one-quarter were NDM-types; however, there was considerable regional variation. Multidrug-resistant *Shigella* species increased rapidly from 2018. This CAR was ranked second to CPE in 2020; and was ranked fifth overall in 2021, when the lowest number was reported since 2016. ANSNG declined steadily annually after it peaked in 2017; in 2021, reports decreased slightly compared to 2020 and were similar to 2016. Daptomycin non-susceptible *Staphylococcus aureus* reports increased from 2016. In 2021, reports from Queensland increased slightly, but remained steady or decreased in other jurisdictions Carbapenemase-producing *Pseudomonas aeruginosa* have been reported in low but increasing numbers. There were 16 reports of *Enterobacterales* with transmissible resistance to colistin (*mcr-1.1*) and 12 reports of *Candida auris*.

Conclusions: Several CARs are detected in Australia on a regular basis. In 2021, lower numbers were reported for most CARs, compared with previous years; there was notable variation between jurisdictions, and evidence of local outbreaks of carbapenemase-producing organisms.

THE AUSTRALIAN GROUP ON ANTIMICROBIAL RESISTANCE REPORT FROM THE GRAM-NEGATIVE SEPSIS OUTCOME PROGRAM (GNSOP) 2020 – SUSCEPTIBILITY DATA

BELL, J., *on behalf of the Group Australian Group on Antimicrobial Resistance (AGAR).*

Background: The Australian Group on Antimicrobial Resistance (AGAR) Gram-negative Sepsis 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: In the 2020 bacteraemia survey, 30 laboratories servicing 49 institutions across Australia, including 11 regional or district hospitals from north-west Western Australia, collected up to 200 *Enterobacterales*, *P. aeruginosa* and *Acinetobacter* spp. MICs were determined using Vitek® 2 (BioMérieux) or Phoenix™ (BD). The results were analysed using CLSI and EUCAST breakpoints (January 2021).

Results: Of 8,752 gram-negative isolates, four genera (*Escherichia,* 55.8%; *Klebsiella*, 17.8%, *Pseudomonas*, 8.8%; *Enterobacter*, 5.3%), accounted for 87.7%. For *E. coli* and *K. pneumoniae*, the percentage resistance in 2020 was similar to 2019 for all antimicrobial agents tested, although ampicillin resistance in *E. coli* decreased by 3.2 percentage points. For *E. cloacae* complex, the percentage resistance to all key antimicrobials, except ciprofloxacin, increased slightly in 2020, Resistance to ceftriaxone was found in 13.4% of *E. coli*; and 8.6% of *K. pneumoniae*. For *E. coli* bacteraemia, ciprofloxacin resistance was 16.1% (15.1% for community onset (CO), 21.8% for hospital onset (HO) episodes). In 2020, ESBL phenotypes were found in 14.7% of *E. coli* and 10.0% of *K. pneumoniae* complex and were more common in HO patients. CTX-M genes were prevalent in both *E. coli* (83.8%) and *K. pneumoniae* (70.4%) with an ESBL phenotype. Overall prevalence of carbapenemase genes among *Enterobacterales* was 0.36% (28/7,871), mostly carrying bla_{IMP-4}. It was 0.39% (3/771) for *P. aeruginosa* and 0.9% (1/110) for *Acinetobacter* species. For HO bacteraemia caused by *E. cloacae* complex, the rate increased to 4.3%. Of 579 referred isolates sequenced, *mcr*-1.1 was detected in one *E. coli*.

Conclusions: Australia ranks towards the middle in rates of resistance to third-generation cephalosporins in *E. coli*, compared with European Antimicrobial Resistance Surveillance Network (EARS-Net) data, and is now similar to that of the European Union and European Economic Area average. Carbapenem resistance attributable to acquired carbapenemase genes is still uncommon in patients with bacteraemia in Australia.

THE AUSTRALIAN GROUP ON ANTIMICROBIAL RESISTANCE REPORT FROM THE GRAM-NEGATIVE SEPSIS OUTCOME PROGRAM (GNSOP) – 2013-2020

BELL, J., *on behalf of the Group Australian Group on Antimicrobial Resistance (AGAR).*

Background: In 2013, AGAR began the ongoing *Enterobacterales* Sepsis Outcome Program (EnSOP), which focused on the prospective collection of resistance and demographic data on all isolates from patients with documented bacteraemia. In 2015, *Pseudomonas aeruginosa* and *Acinetobacter* species were added, and the program evolved into the Gram-negative Sepsis Outcome Program (GNSOP). Survey objectives were to monitor resistance (co-resistance and multi-resistance), and to detect critical emerging antimicrobial resistance (AMR). Trends in key antimicrobial resistances are presented.

Methods: Participating laboratories servicing institutions from each State and mainland Territories of Australia, collected either all or up to 200 isolates from different patient bacteraemia episodes. AGAR has increased the number of institutions from 26 in 2013 to 46 in 2018 and 49 in 2020. 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 54,530 *Enterobacterales* have been studied since 2013; with 4,358 *P. aeruginosa* and 623 *Acinetobacter* spp. since 2015. Over the past five years (2016–2020), significantly increasing trends in fluoroquinolone- and third-generation cephalosporin (3GC) resistance was observed in both Victoria and the NT, although both rates have stabilised since 2019. Aminoglycoside resistance increased in the NT and decreased in WA. There was a significantly increasing trend in fluoroquinolone resistance in *K. pneumoniae* complex isolates from the NT, although the rate has stabilised over the past three years. 3GC resistance also increased in the NT from 2.6% in 2016 to 27.0% in 2020. Although an increasing aminoglycoside resistance trend was noted in all data from NSW, this was not observed when only data from institutions consistently reporting for all five years were included.
Conclusions: AGAR data show a longitudinal trend of increasing *E. coli* resistance to key anti-gram-negative antimicrobial agents, such as ceftriaxone and ciprofloxacin. 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.

THE AUSTRALIAN GROUP ON ANTIMICROBIAL RESISTANCE REPORT FROM THE GRAM-NEGATIVE SEPSIS OUTCOME PROGRAM (GNSOP) 2020 – CLINICAL OUTCOMES

BELL, J., *on behalf of the Group Australian Group on Antimicrobial Resistance (AGAR).*

Background: The Australian Group on Antimicrobial Resistance (AGAR) Gram-negative Sepsis Outcome Programme (GNSOP) 2020 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 sepsis outcomes.

Methods: Thirty laboratories servicing 49 institutions across Australia, including 11 regional or district hospitals from north-west Western Australia, collected either all or up to 200 isolates from different patient bacteraemia episodes.

Results: Of 8,752 gram-negative episodes *Enterobacterales* accounted for 89.9%, *P. aeruginosa* (8.8%) and *Acinetobacter* species (1.3%). The proportion of males was 52.9%, and 4.8% were from children (<18 years). Overall, 77.7% of episodes were designated community-onset (CO). Urinary tract infection was the most frequent principal clinical manifestation for both CO (50.2%) and HO (22.4%) episodes caused by *Enterobacterales*. For *P. aeruginosa*, urinary tract infection (23.0%) and febrile neutropenia (20.6%) were the most common HO association. Device-related bacteraemia accounted for 5.1% (CO, 3.4%; HO, 11.1%) of all GNSOP episodes in 2020. A little under one-half (43.9%) of patients with gram-negative bacteraemia had a length of hospital stay of less than seven days (CO, 51%; HO 20%). The 30-day all-cause mortality for gram-negative bacteraemia was 11.4% (9.7% in *E. coli*, 12.5% in *K. pneumoniae* complex, and 15.5% in *P. aeruginosa*). A significant difference in 30-day all-cause mortality between CO and HO was seen with *E. coli* bacteraemia (8.6% vs 14.9%; p<0.01). Nationally, one-quarter of *E. coli* (ranging from 14.9% in South Australia to 39.1% Northern Territory) and 12.1% of *K. pneumoniae* complex would be classed as multi-resistant, resistant to three of five key antimicrobial groups, revealing little change from the 2019 survey. Multi-resistance in *P. aeruginosa* remains low (3.8%).

Conclusions: Gram-negative sepsis is common in Australia and continues to be a significant cause of mortality. The AGAR data show a longitudinal trend of increasing *E. coli* resistance to key anti–gram negative antimicrobial agents, such as ceftriaxone and ciprofloxacin. Although there was little change since 2019, ciprofloxacin resistance is now at 21.8% in HO bacteraemia.

QUINOLONES ARE NO LONGER SUITABLE FOR TYPHOIDAL SALMONELLA

BELL, J., *on behalf of the Group Australian Group on Antimicrobial Resistance (AGAR).*

Background: *Salmonella* Typhi and *Salmonella* Paratyphi (together called 'typhoidal *Salmonella*') are the causes of enteric fever. In Australia, almost all cases have been acquired overseas. Antimicrobial therapy is essential to cure, with azithromycin and ceftriaxone now listed as empirical first-line therapy due to increasing ciprofloxacin resistance.

Methods: Data from pathology services contributing data to the Australian Passive AMR Surveillance (APAS) System, the AGAR Gram-negative Sepsis Outcome Program (GNSOP), and from Sullivan Nicolaides Pathology were extracted for the period 2015 to 2020. Analyses were conducted only when the proportion of isolates that were tested against a single antimicrobial was at least 75%. To minimise the impact of duplicate testing, only data from the first isolate, per patient, per year were used. Ciprofloxacin resistance was defined as MIC > 0.06 mg/L.

Results: Rates of resistance to ciprofloxacin in typhoidal *Salmonella* species isolated from blood have increased from 43% in 2015 to 81% in 2020, peaking at 87% in 2019. In 2020, compared to 2019, there was a two-fold increase in resistance to ampicillin (2019, 8.1%, 2020, 15.5%), third-generation cephalosporins (2.7%, 3.8%), and trimethoprim–sulfamethoxazole (7.0%, 13.3%). Azithromycin was not routinely tested; however, some acquired resistance was observed. Increased resistance may in part be due to the implementation of recent changes to fluoroquinolone interpretative guidelines by both CLSI (2013) and EUCAST (2014). AGAR data from 2019–20 have shown that all typhoidal *Salmonella* resistant to ciprofloxacin harboured known mutations in the QRDR region. Two extensively-drug resistant S. Typhi were reported in 2019, both isolated from children with recent history of travel to Pakistan.

Conclusions: High rates of resistance to ciprofloxacin in typhoidal *Salmonella* species mean that, as stated in current national guidelines, ciprofloxacin should no longer be used as empirical treatment for infections caused by these species. Ciprofloxacin may have a role as oral stepdown therapy if susceptibility of the infecting strain is confirmed. Routine testing of azithromycin should now be recommended, given observed acquired resistance. Continued monitoring for third-generation resistance is also essential.

ANTIMICROBIAL USAGE IN THE THEATRE & RECOVERY SETTING IN AUSTRALIAN HOSPITALS

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Aim: To analyse antimicrobial usage for the first time in the theatre and recovery setting of Australian hospitals participating in the National Antimicrobial Utilisation Surveillance Program (NAUSP).
Background: Appropriate surgical antimicrobial prophylaxis is an important factor in reducing surgical infections, however prolonged or inappropriate usage is common. From January 2021, the NAUSP Portal enabled granular/stratified data submission and reporting of antimicrobials administered to patients in theatre and recovery relative to theatre presentation/case numbers. To date, hospitals have not been able to measure nor monitor trends involving the volume of antimicrobials used in this area.

Methods: Monthly antimicrobial dispensing records for 193 Australian hospitals with stratified theatre & recovery data were analysed for the period January to June 2021. Aggregate usage rates for each state and territory including both public and private facilities were extracted. Grams of antimicrobial agents used were converted into the WHO assigned metric Defined Daily Dose (DDDs). Using the activity metric Theatre Cases/Presentations, a standardised usage rate was calculated (DDDs per 1,000 theatre cases).

Results: Cefazolin, metronidazole, gentamicin, vancomycin and flucloxacillin were common to all state and territories' top-10 most used agents, and account for 90.9% of theatre use nationally (by rate). Beyond these five antimicrobials, subtle differences were observed between states, along with public and private facilities. Statewide usage rates ranged from 214.2 DDD/1,000 theatre cases to 349.7 DDD/1,000 theatre cases. Oral agents are used infrequently in the theatre setting.
Conclusions: Preliminary data from January to June 2021 demonstrates differences in state-based antimicrobial usage in theatre and recovery. Usage of agents not routinely used for surgical prophylaxis may indicate non-prophylactic indications. Monitoring of usage in the theatre setting relative to theatre cases provides hospitals with additional data to implement local AMS initiatives and complements data on appropriateness of usage in this setting.

GENOMIC CHARACTERISATION OF CC398 MRSA CAUSING SEVERE DISEASE IN AUSTRALIA

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Background and Aim: Complex (CC) 398 livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) has been reported worldwide in a variety of food-animal species. Although CC398 is synonymous with LA-MRSA, community-associated MRSA (CA-MRSA) variants have emerged, including the Panton-Valentine leukocidin (PVL)-positive ST398-V and ST398 single locus variant ST1232-V, and the PVL-negative ST398-V clones. To determine if ten CC398 MRSA bacteraemia episodes recently identified in Australia were due to LA-MRSA or CA-MRSA CC398, comparative genomic analysis was performed.

Methods: The isolates were sourced from the Australian Group on Antimicrobial Resistance *S. aureus* surveillance program and episodes occurred across Australia. Whole genome sequencing (WGS) was performed using the Illumina NextSeq® 500. Isolates were classified into previously described clades.

Results: Phylogenetic comparison of the ten CC398 bacteraemia isolates with previously published CC398 MRSA whole-genome sequences identified the Australian CC398 isolates were closely related to the human-associated II-GOI clade, and the livestock-associated IIa clade. The identified CC398 MRSA clones included:
- Five cases of PVL-positive ST1232-V (5C2&5) isolated from patients living across Australia. Although previously reported in Europe, the clone is mainly associated with people from south-east Asia. Only two cases were epidemiologically linked to Asia, suggesting a spill over of the clone has occurred in the Australian community.
- Three cases of PVL-negative community-associated ST398-V (5C2&5) isolated from patients living in Queensland and Victoria. A highly virulent clone initially reported in China; only one case could be linked to travel to Asia.
- Two cases of PVL-negative livestock-associated ST398-V (5C2&5) isolated from patients living in Queensland and South Australia.

Conclusions: Our findings demonstrate the importance of using WGS and comparing the sequences to international sequences to distinguish between CC398 CA- and LA- MRSA and to determine the isolates' origin. Furthermore, our findings suggest CC398 CA-MRSA has become established in the Australian community and ST398-V (5C2&5) LA-MRSA is now widespread in Australian piggeries. Our study emphasizes the need of national one health antimicrobial resistance surveillance programs to assist in monitoring the ongoing epidemiology of MRSA and other clinically significant antimicrobial resistant organisms.

2020 AUSTRALIAN ENTEROCOCCAL SEPSIS OUTCOME PROGRAMME (AESOP)

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Aim: To determine the antimicrobial resistance of enterococcal bacteraemia in Australia, and to characterise the molecular epidemiology of the *E. faecium* isolates.

Methods: Susceptibility testing was performed using Vitek® 2 (bioMérieux, France) or BD Phoenix™ (Becton Dickinson, USA) automated microbiology systems. Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were utilised for interpretation. Characterisation of *E. faecium* was performed by whole genome sequencing (WGS) on the NextSeq® 500 platform (Illumina, USA).

Results: Of the 1,230 episodes of enterococcal bacteraemia collected by thirty nine institutions, 93.9% were caused by *E. faecalis* (54.2%) or *E. faecium* (39.7%). Vancomycin non-susceptibility was reported in 32.6% of *E. faecium* and 0.2% of *E. faecalis*. Overall 35.2% of *E. faecium* harboured *vanA* or *vanB* genes. For the *vanA/vanB* positive *E. faecium*, 38.8% harboured *vanA*, 60.6% harboured *vanB*, and 0.6% harboured both *vanA* and *vanB*. *E. faecium* consisted of 71 multi-locus sequence types (STs) and 81.7% of isolates were classified into eight major STs. All eight STs were grouped within clonal complex 17. The most prevalent ST was ST17. Thirty day all-cause mortality was not significantly different for *E. faecium* and *E. faecalis* (19.6% and 17.3% respectively, p=0.4) or for vancomycin-resistant and vancomycin-susceptible *E. faecium* episodes (19.8% and 19.4% respectively, p=0.9). Where data was available, length of stay (LOS) from blood culture collection to discharge was calculated. Overall 22.8% of patients had a LOS >30 days. There was a significant difference in mean LOS between *E. faecium* and *E. faecalis* episodes (34 and 22 days respectively [p<0.0001]) and in mean LOS between vancomycin susceptible and non-susceptible *E. faecium* (31 and 39 days respectively [p=0.02])

Conclusions: AESOP 2020 has shown enterococcal bacteraemia in Australia is frequently caused by *vanA* or *vanB E. faecium* with considerable clonal diversity. The percentage of vancomycin-resistant *E. faecium* bacteraemia isolates in Australia is significantly higher than most European countries participating in the EARS-NET program. *E. faecium* is a significant cause of healthcare-associated sepsis and the emergence of multiple multi-resistant hospital-adapted STs remains a major infection control issue in Australian hospitals.

2020 AUSTRALIAN *STAPHYLOCOCCUS AUREUS* SEPSIS OUTCOME PROGRAMME (ASSOP)

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Aim: To determine the antimicrobial resistance of *Staphylococcus aureus* bacteraemia (SAB) isolates in Australia and characterise the molecular epidemiology of the methicillin-resistant isolates.

Methods: Susceptibility testing was performed using the Vitek® 2 (bioMérieux, France) or BD Phoenix™ (Becton Dickinson, USA). Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were utilised for interpretation. Characterisation of methicillin-resistant *S. aureus* (MRSA) was performed by whole genome sequencing (WGS) on the NextSeq® 500 platform (Illumina,USA).

Results: A total of 2,734 SAB episodes from 39 institutions were reported, 79.7% of which were community-onset. Overall 17.6% were methicillin-resistant. Apart from the β-lactams and erythromycin, resistance in methicillin-sensitive *S. aureus* (MSSA) was rare. In addition to the β-lactams approximately 33% of MRSA were resistant to erythromycin and ciprofloxacin, 13% resistant to tetracycline and gentamicin and 4% to cotrimoxazole. Vancomycin, linezolid and teicoplanin resistance was not detected using CLSI breakpoints.Of the healthcare-associated MRSA, two clones predominated: ST22-IV [2B] (EMRSA-15) and ST239-III [3A] (Aus-2/3 EMRSA). However 85% of methicillin-resistant SAB were due to community-associated (CA) clones. Although polyclonal, 77.3% of CA clones were classified into eight major sequence types (STs); ST93-IV [2B] (Queensland CA-MRSA), ST5-IV [2B], ST45-V [5C2&5], ST1-IV [2B] (WA1), ST30-IV [2B], ST8-IV [2B], ST97-IV [2B] and ST78-IV [2B]. Overall 43.9% of CA-MRSA isolates were Panton-Valentine leucocidin (PVL) positive. Thirty day all-cause mortality was not significantly different for MRSA and MSSA (14.2% and 13.3% respectively, p=0.6). Where available, length of stay (LOS) from blood culture collection to discharge was calculated. Overall 24.7% of patients had a LOS >30 days. There was no significant difference in mean LOS between MSSA and MRSA (19 days and 20 days, p=0.4) and community- and hospital-onset MRSA (19.8 and 21 days respectively, p=0.5). There was a signficant difference in mean LOS between community- and hospital-onset MSSA (18 and 22 days respectively, p=0.001)

Conclusion: ASSOP 2020 demonstrated antimicrobial resistance in SAB in Australia is a significant problem. 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.

FIXATION OF ANTIMICROBIAL RESISTANCE GENES IN BACTERIAL CHROMOSOMES

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Aim: To define the extent of chromosomal AMR gene carriage in Gram-negative bacteria in Australia.

Background: Antimicrobial resistance (AMR) genes in Gram-negative organisms commonly disseminate on plasmids, but critical AMR genes are increasingly reported on bacterial chromosomes. If this leads to a permanent change in multiple species and strains, restricting antibiotic use (the primary policy setting globally) will be largely powerless to reverse the threat of AMR.

Methods: Whole genome sequencing (WGS) was performed by the Antimicrobial Resistance Laboratory (Microbial Genomics Reference Laboratory, CIDMLS, ICPMR) at Westmead Hospital using the Illumina NextSeq™ 500 platform. Data were analysed using a modification of the Nullarbor bioinformatic pipeline, followed by a custom AMR-specific pipeline which includes a read-based search using ARIBA against the CARD and NCBI databases. Ambiguities, potential multiple gene copies/ variants and gene location (plasmid or chromosomal) were checked manually by mapping reads to reference genes using Geneious software.

Results: Our analysis of short-read WGS data for 2019 and 2020 isolates from the Gram-negative Sepsis Outcome Program (Australian Group on Antimicrobial Resistance, AGAR GNSOP) revealed that the most prevalent AMR genes conferring resistance to widely-used extended-spectrum β-lactam antibiotics (ESBL, $bla_{CTX\text{-}M}$ genes) are mostly found on the chromosome in some major pandemic lineages of *Escherichia coli* (Table 1), the most predominant pathogen isolated from sepsis episodes in Australia (55.5% and 55.8% in 2019 and 2020, respectively).

Conclusion: Our results indicate that some global epidemic bacterial strains might be permanently incorporating AMR genes into their core genome. The chromosomal fixation of AMR genes will have enormous implications for antibiotic use policies as the view that less antibiotic use will allow AMR to vanish might not be valid in the near future.\

IMPACT OF EXPIRED STOCK ON ANTIMICROBIAL SURVEILLANCE IN RURAL HOSPITALS: IMPLICATIONS AND CHALLENGES FOR STEWARDSHIP

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Background: Quantitative surveillance of antimicrobial use is a useful stewardship tool, providing information on usage trends and allowing benchmarking between similar healthcare settings. The National Antimicrobial Utilisation Surveillance Program (NAUSP) monitors antimicrobial use in Australian hospitals enabling facilities to identify overprescribing or unexpected changes in prescribing. Low or variable patient numbers in smaller, more remote hospitals can result in substantial usage rate fluctuations.

Aim: To investigate the impact of expired stock on antimicrobial usage rates in smaller, more remote hospitals.

Method: Antimicrobial usage rates (Defined Daily Doses (DDDs) per 1000 Occupied Bed Days (OBDs)) were calculated using monthly dispensing data and hospital activity data from 12 rural South Australian facilities for January 2018 to December 2020. Usage rates were re-calculated excluding expired stock to estimate the impact on usage rates, and to quantify stock wastage.

Results: Between 2018 and 2020, the average monthly aggregate usage rate for all 12 hospitals was 650 DDD / 1,000 OBDs. Removing expired stock from usage data resulted in an average reduction in aggregate usage rate of 37 DDD / 1,000 OBDs (5.7%) over the 3-year period. Analysis by Australian Institute of Health and Welfare peer group demonstrated that exclusion of expired stock reduced average monthly usage rates by 6.0% for Public Acute Group C sites, and 10.6% for Public Acute Group D and Very small hospitals.

Discussion: Replacement of expired, un-used stock may account for a substantial proportion of perceived antimicrobial usage in rural and remote hospitals, particularly for agents infrequently prescribed. Interpretation of antimicrobial usage rates in smaller, more remote facilities should consider the challenges of stock management in these sites and acknowledge that a substantial proportion of reported antimicrobial usage may be attributed to stock replenishment. The results also highlight the challenges of antimicrobial surveillance in small sites across Australia.

2020 AUSTRALIAN ENTEROCOCCAL SEPSIS OUTCOME PROGRAMME (AESOP) COMPARATIVE GENOMICS OF *ENTEROCOCCUS FAECIUM* CAUSING BACTERAEMIA

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Aim: To determine the distribution of antimicrobial resistance (AMR) and virulence genes in the major *E. faecium* clones causing bacteraemia in Australia in 2020.

Methods: Whole genome sequencing (WGS) was performed on the NextSeq® 500 platform (Illumina, USA). Raw sequence reads were assembled using SPAdes. The Resfinder and VFDB databases were used to identify AMR and virulence genes, respectively.

Results: Of the 488 *E. faecium* isolates causing bacteraemia collected by thirty-nine institutions, 96.3% (n=470) were successfully sequenced. Although 71 multi-locus sequence types (STs) were identified, 81.7% (n=384) of isolates were grouped into eight major STs represented by ³10 isolates: ST17 (n=116), ST1424 (n=94), ST80 (n=52), ST796 (n=47), ST78 (n=34), ST1421 (n=20), ST555 (n=11) and ST117 (n=10). Overall, 41.1% (n=158) of isolates harboured at least one vancomycin resistance gene of which 61 harboured *vanA* only, 93 harboured *vanB* only, one harboured *vanD* only, and three harboured both *vanA* and *vanB*. Most of the *vanA*-positive and *vanB*-positive isolates belonged to ST1424 and ST796, respectively. The *vanD*-positive isolate belonged to ST17 and all three *vanAB*-positive isolates belonged to ST796. The aminoglycoside resistance genes *aac(6')-Ii*, *aph(2'')-Ih*, *aph(3')-IIIa*, *ant(9)-Ia* and *ant(6)-Ia* were identified in 99.2%, 79.4%, 43.0%, 29.2% and 19.0% of isolates respectively. The macrolide resistance genes *msr(C)*, *erm(B)*, *erm(A)*, *erm(T)* and *erm(C)* were identified in 98.7%, 73.4%, 28.9%, 16.9% and 0.5% of isolates, respectively. The tetracycline resistance genes *tet(M)*, *tet(L)*, *tet(S)* and *tet(O)* were identified in 54.4%, 36.7%, 1.6% and 0.3% of isolates, respectively. The trimethoprim resistance genes *dfrG* and *dfrF* were identified in 69.0% and 6.8% of isolates, respectively. We investigated the distribution of thirteen virulence genes associated with adhesion and biofilm formation including *acm* (99.0%), *ecbA* (84.1%), *esp* (3.6%), *fnm* (96.6%), *hyl* (38.5%), *orf1481* (98.4%), *ptsD* (94.3%), *sagA* (97.1%), *scm* (15.1%), *sgrA* (88.8%), *swpA* (99.0%), *swpB* (84.9%) and *swpC* (94.8%). Each virulence gene was identified in at least one isolate from each major ST except the *esp* and *hyl* genes which were not detected in ST80/ST1421 and ST117/ST796 isolates, respectively.

Conclusions: WGS has detected the distribution of AMR and virulence genes within the major clones of *E. faecium* causing bacteraemia in Australia.

MOLECULAR CONFIRMATION OF *ESCHERICHIA COLI* CLASSIFIED AS FOSFOMYCIN-RESISTANT BY THE REVISED EUCAST MIC BREAKPOINT

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Background: In *Escherichia coli* fosfomycin resistance occurs through the presence of *fos* genes which encode fosfomycin inactivating enzymes, or by mutations in proteins important for the uptake (GlpT, Ptsl, UhpA, Uhpt, CyaA) or action (MurA) of fosfomycin. Recently we published two Australian cross-sectional studies which identified and characterised fosfomycin-resistant uncomplicated UTI *E. coli* isolated in females >12 years of age. Although 15 of the 2,056 isolates were classified fosfomycin-resistant by disk diffusion, only five isolates had a fosfomycin MIC above the 2020 EUCAST breakpoint of >32 mg/L. In 2021 EUCAST revised the fosfomycin MIC breakpoint when using the standard oral dose of 3 g for treatment of uncomplicated UTIs from >32 to >8 mg/L. In the two Australian studies six isolates classified as fosfomycin-resistant by disk diffusion had an MIC of 16 or 32 mg/L.

Methods: Whole genome sequencing was performed on the six isolates with an MIC of 16 or 32 mg/L (EC6 to EC11) to identify genetic factors responsible for fosfomycin resistance. To identify known fosfomycin-resistant associated mutations, the amino acid sequences of GlpT, Ptsl, UhpT, UhpA, CyaA and MurA for each isolate were aligned to the fosfomycin-susceptible *E. coli* K-12 reference strain.

Results: Six unrelated multi-locus sequence types were identified. Although none of the six isolates harbored a *fos* gene, all possessed the previously described GlpT E448K mutation. In two isolates, EC7 and EC9, the UhpA and/or UhpT membrane transporter proteins were absent. In addition to the E448K mutation, the GlpT L297F, E443Q and Q444E mutations and the CyaA S352T mutation were detected in EC8 and EC11.

Conclusion: Using the revised breakpoint of >8 mg/L, fosfomycin resistance determinants were identified in six isolates previously classified as fosfomycin susceptible. Although the prevalence of fosfomycin resistance in *E. coli* in Australia remains relatively low at only 0.5% and chromosomally encoded mutations are less likely to undergo horizontal gene transfer, to minimise the emergence and spread of resistance it is recommended that fosfomycin in Australia continue to be reserved for the treatment of uncomplicated *E. coli* UTI in patients when the standard first-line drugs are not an option.

2020 AUSTRALIAN STAPHYLOCOCCAL SEPSIS OUTCOME PROGRAMME (ASSOP) COMPARATIVE GENOMICS OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* CAUSING BACTERAEMIA

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Aim: To determine the distribution of antimicrobial resistance (AMR) and toxin genes in the predominant methicillin-resistant *S. aureus* (MRSA) clones causing bacteraemia in Australia in 2020.

Methods: Whole genome sequencing (WGS) was performed on the NextSeq® 500 platform. Raw sequence reads were assembled using SPAdes. The Resfinder database was used to identify AMR genes. An in-house database was used to identify toxin genes.

Results: Of the 481 MRSA identified by thirty-nine institutions, 94.8% (n=456) were successfully sequenced. Of the sequenced isolates, 79.6% (n=363) were grouped into two predominant healthcare-associated clones, ST22-IV (n=59) and ST239-III (n=7), and eight predominant community-associated clones, ST93-IV (n=98), ST5-IV (n=59), ST45-V (n=50), ST1-IV (n=29), ST30-IV (n=21), ST8-IV (n=16), ST97-IV (n=14), and ST78-IV (n=10). The beta-lactam resistance genes *mecA* and *blaZ* were identified in 100% and 93.9% of isolates respectively. More than half (58.1%) of the isolates harboured at least one other AMR gene (Table 1). The *lukF/S-PV* PVL (Panton-Valentine leukocidin) encoding genes were identified in 42.7% of isolates including 52.1% of community-associated clones. All ST93-IV isolates were PVL-positive whilst 49.1% and 75.0% of ST5-IV and ST8-IV, respectively, were PVL-positive. A variety of enterotoxins were identified including the *egc* cluster [*seG+sel+seM+seN+seO+seU*] which was identified in 49.3% of isolates. However, the *egc* cluster was absent in ST1-IV, ST78-IV, ST8-IV, ST93-IV, ST97-IV, and ST239-III. The IEC (immune evasion cluster) genes *seA*, *seP*, *sak*, *chp* and *scn* were identified in 6.6%, 5.8%, 96.4%, 81.5% and 96.7% of isolates. The type B IEC was identified in 74.9% of isolates whilst 9.1%, 6.3%, 5.8%, 0.3% and 0.3% of isolates harboured a type E, F, D, C and G IEC respectively. No IEC genes were detected in 3.3% of isolates.The *eta* gene encoding the exfoliative toxin A was identified in two ST5-IV isolates. The *tsst* gene encoding the toxic shock syndrome toxin was identified in 15 isolates from ST1-IV, ST5-IV, ST8-IV, or ST22-IV.

Conclusions: WGS has detected the distribution of AMR and toxin genes within the predominant clones of MRSA causing bacteraemia in Australia. Of concern is the ongoing emergence of the multi-resistant community-associated clone ST45-MRSA-V and the incidence of PVL-positive CA-MRSA.

NON-FAECIUM, NON-FAECALIS ENTEROCOCCAL SEPSIS IN AUSTRALIA

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Aim: To determine the antimicrobial resistance of bacteraemia from non-*faecium,* non-*faecalis* enterococci in Australia, and to characterise the epidemiology of the these isolates.

Methods: Susceptibility testing was performed using Vitek® 2 (bioMérieux, France) or BD Phoenix™ (Becton Dickinson, USA) automated microbiology systems. Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were utilised for interpretation.

Results: Between 2013 and 2020, AGAR collected 441 non-*faecium*, non-*faecalis* enterococcal isolates from bacteraemia cases from 39 institutions across Australia. The most common species were the intrinsically vancomycin-resistant *E. casseliflavus* (n=148) and *E. gallinarum* (n=120), and *E. avium* (n=79). Penicillin resistance was observed in 24 isolates (5.4%) from multiple species, with *E. raffinosus* being the most common species (15 isolates). The 30-day all-cause mortality for all species combined was 11.1% which is significantly lower than the 2020 30-day all-cause mortality *for E. faecium* (19.5%) and *E. faecalis* (17.4%). The mean age of patients with non-faecium, non-faecalis bacteraemia was not different to those who had bacteraemia from *E. faecium* and *E. faecalis* (mean age = 66.7 years). The majority of cases were from community onset (74.8%). Biliary tract infection was the most common clinical manifestation (49.8%) followed by non-biliary intraabdominal infection (n=13.6%). Urinary tract infection was the primary clinical manifestation in only 3.4% of episodes.

Conclusions: Non-*faecium*, non-*faecalis* enterococci are a significant cause of sepsis. While they have a lower mortality rate compared to other enterococcal species, they typically have different clinical manifestations and can be vancomycin resistant.

IMPACT OF A COMBINATION OF NCL195 AND SUB-INHIBITORY CONCENTRATIONS OF COLISTIN IN TREATING GRAM-NEGATIVE INFECTIONS

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Background: The increasing incidence of multidrug-resistant (MDR) bacterial pathogens in health care settings has led to a decrease in treatment options and continues to generate global health concerns. In particular, drug discovery for the treatment of MDR-Gram-negative bacterial (GNB) infections in comparison to MDR-Gram-positive (GPB) bacterial infections has been hampered due to the presence of an outer membrane in GNB, which prevents antibiotics from gaining entry to reach their targets.

Aim: We previously demonstrated *in vitro* activity for NCL195 against MDR-GPB and *in vitro* synergistic activity of NCL195 + colistin combination against MDR-GNB pathogens. We have also reported promising *in vivo* efficacy against MDR-GPB pathogens when administered via the systemic route. This study aims to examine the efficacy of oral treatment with NCL195 against *Staphylococcus aureus* sepsis and also against *Escherichia coli* sepsis in the presence of low concentrations of colistin in bioluminescent mouse models.

Methods: A bioluminescent mouse *S. aureus* sepsis challenge model was used to test the efficacy of NCL195 against GPB and bioluminescent *E. coli* sepsis challenge models were developed to examine the efficacy of NCL195 + colistin combination against GNB. After infection, mice were treated on four occasions at 4 h intervals on the first day of trials.

Results: Administration of four oral doses of 50 mg/kg NCL195 (4 h apart) resulted in significantly reduced *S. aureus* loads and longer survival times than vehicle-only treated mice. Simultaneous administration of four oral doses of 50 mg/kg NCL195 and four intraperitoneal (IP) doses of colistin at 0.125 mg/kg, 0.25 mg/kg or 0.5 mg/kg 4 h apart resulted in dose-dependent significant reduction in colistin-susceptible *E. coli* loads compared to treatment with colistin alone at similar concentrations. Correspondingly, co-administration of four oral doses of 50 mg/kg NCL195 and four IP doses of colistin at 0.5 mg/kg, 1 mg/kg or 2 mg/kg resulted in dose-dependent significant reduction in colistin-resistant *E. coli* loads compared to treatment with colistin alone at similar concentrations.

Conclusions: NCL195 is a viable candidate for further development for specific treatment of MDR-GPB and GNB infections either as a stand-alone antibiotic or in combination with sub-inhibitory concentrations of colistin.

OUTPATIENT ANTIMICROBIAL THERAPY PROGRAM AND VANCOMYCIN DOSING: HOW WILL PATIENT MODELLING CHANGE CURRENT PRACTICE?

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Aim: To compare pharmacokinetic/pharmacodynamic target parameters utilising Bayesian predictions to steady state concentrations (Css) for patients on continuous vancomycin infusions receiving Out Patient Antimicrobial Therapy (OPAT).

Background: Vancomycin is a first-line antibiotic for methicillin-resistant *Staphylococcus aureus* (*MRSA*) infections. The area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio is proposed as a therapeutic drug-monitoring parameter. Clinical efficacy as predicted by this measure is not established for patients on OPAT where vancomycin treatment is provided as a continuous infusion. Current practices suggest a target C_{SS} of 15-25mg/L as vancomycin achieves effect in a concentration dependent manner. Calculation of the AUC_{24} for this drug may better represent the therapeutic doses that are required.

Method: A retrospective single centre study was conducted at a tertiary hospital on adult patients on OPAT receiving vancomycin infusions for *MRSA* infection. Patient demographics, clinical outcomes, vancomycin dosing and serum concentrations were documented. Retrospective Bayesian modelling - Individually Designed Optimum Dosing Strategies (ID-ODS) utilising the Goti model - was performed to predict the likelihood of achieving target pharmacokinetic / pharmacodynamic parameters. Modelled Bayesian data was compared to OPAT patient data.

Results: Fifteen patients, 87% male, average age 58, were evaluated. For the OPAT data, 53% (8/15) achieved target C_{SS} on enrolment to the program. On average 4 vancomycin concentrations, and 7.7 inpatient days and 9.8 OPAT days were required to reach target C_{SS}. 5/15 (33%) patients suffered an Acute Kidney Injury and 1 patient failed therapy. The average Bayesian AUC/MIC was 613 mg.h/L with C_{SS} 25 mg/L. Retrospective Bayesian modelling demonstrated on median 250 mg/24hr lower doses than administered on OPAT was required (R^2=0.72). which achieved AUC_{24}/MIC average 435 (range 405 to 460) mg.h/L and Cmin average 18.4 (range 16.8 to 20.4) mg/L.

Conclusion: Current vancomycin OPAT dosing methods require prolonged periods to achieve target C_{SS}, with several patients suffering significant renal dysfunction. Bayesian modelling can assist in obtaining more timely target parameters at lower doses, which may beget fewer adverse effects. Utilisation of personalised predictive modelling may optimise vancomycin prescribing, achieving earlier appropriate patient therapeutic concentrations as compared to empiric dosing regimens.

CARBAPENEMASE GENES IN ENTEROBACTERALES FROM THE AGAR GRAM-NEGATIVE SEPSIS OUTCOMES PROGRAMME 2017-2020

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Aim: To examine genetic contexts of, plasmid vehicles and strains carrying carbapenemase genes in isolates from the Australian Group on Antibiotic Resistance (AGAR) Gram-negative Sepsis Outcome Programme **(**GNSOP) 2017-2020.

Background: Resistance to last-line carbapenem antibiotics, an increasing problem, is often due to carbapenemases encoded by various β-lactamase (*bla*) genes. AGAR GNSOP collects blood isolates from sites across Australia and since 2017, those resistant to carbapenems have undergone whole genome sequencing (WGS)

Methods: Genomic DNA from Enterobacterales isolates with meropenem MIC >0.125 mg/L (Phoenix) or >0.25 mg/L (Vitek) was sequenced (Illumina NextSeq™ 500, Microbial Genomics Reference Laboratory, Westmead Hospital). Sequences were assembled and analysed using modified versions of the Nullarbor pipeline, including species confirmation, sequence typing (ST) and detection of resistance genes (ABRicate, ARIBA AMRFinder, CARD). Carbapenemase gene contexts were examined and, if possible, linked to plasmids.

Results: About ~0.3% (n=20-30) of Enterobacterales submitted each year were sequenced as carbapenem resistant. The most common carbapenemase gene, bla_{IMP-4} (n=59) was found mainly in the *Enterobacter cloacae* complex (n=39, >17 ST, but 9 ST190 from one site 2019-20), and *Klebsiella* spp. (n=15, >11 ST) and associated mostly with HI2 or M type plasmids. $bla_{OXA-181}$ was found in *K. pneumoniae* (n=8, 6 ST), and *E. coli* (n=6, 5 ST), mostly on X3 plasmids. Five isolates had the related bla_{OXA-48} gene, likely carried by different plasmid types. Different bla_{NDM} variants, mainly bla_{NDM-1} and bla_{NDM-4} in *K. pneumoniae* (n=3 of each) and bla_{NDM-5} in *E. coli* (n=5), were found in different contexts in different ST. bla_{KPC-2} and bla_{KPC-3} were each detected in a pair of *K. pneumoniae* from the same site, ST258 in 2017 and ST307 in 2018, likely all on related plasmids.

Conclusions: Levels of carbapenemase genes detected in GNSOP isolates are low and have not changed greatly 2017-20. As expected, bla_{IMP-4} was the most common, apparently spreading mainly on known plasmid types. $bla_{OXA-181}$ genes appear to be spreading on one main plasmid type, while different bla_{NDM} variants in different contexts and different ST suggest different sources. Rare bla_{KPC} genes were associated with a known plasmid type in global high-risk clones.

THE GENETIC CHARACTERISATION OF ANTIMICROBIAL RESISTANCE IN AUSTRALIAN BOVINE RESPIRATORY DISEASE PATHOGENS

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Aim: To determine if the resistance to macrolide and tetracycline antibiotics discovered in Australian *Pasteurella multocida* and *Mannheimia haemolytica* isolates from bovine respiratory disease cases is encoded on a small transmissible plasmid.

Background: Bovine Respiratory Disease (BRD) is the leading cause of death in feedlot cattle, resulting in annual economic losses of approximately AUD $40 million. As of 2020, low levels of antimicrobial resistance to macrolides and tetracycline have been detected in Australian feedlots.

Methods: Four *P. multocida* isolates and one *M. haemolytica* isolate, exhibiting resistance to tetracycline (*tet*(R)-*tet*(H), *tet*(Y)), macrolides (*msr*(E), *mph*(E)) and dual resistance to both tetracycline and macrolides were subjected to spontaneous plasmid loss and plasmid curing experiments in either one or two rounds, using 100 mg and 50 mg of Acridine Orange, respectively. Following this, plasmids were extracted and profiled using DNA electrophoresis, restriction digestion, and back-transformation into three sensitive strains via electroporation.

Results: Plasmid curing was successful for three of four resistant *P. multocida* isolates, and spontaneous plasmid loss was successful for one resistant *P. multocida* isolate, however neither technique was successful when applied to the *M. haemolytica* isolate. Macrolide resistance was lost quicker than tetracycline resistance in most cases. Single and double plasmids were extracted successfully and profiled from all four *P. multocida* isolates. Plasmid maps established from bioinformatics studies and plasmid sequencing confirmed the approximate size for each plasmid encoding either macrolide (~7 kb and ~7.7 kb) or tetracycline (~4.5 kb) resistance.

Conclusion: It was confirmed that the resistance carried by *P. multocida* isolates is plasmid-mediated, however it is uncertain if the resistance carried by *M. haemolytica* is plasmid-mediated, as resistance was not lost in curing and spontaneous loss experiments, and a plasmid could not be extracted. Due to the restriction digest profiles, it is also confirmed that the resistances for tetracycline and macrolide are carried on separate plasmids. These results will inform the industry's antimicrobial stewardship programme, and may change how macrolides and tetracycline are used in feedlots until an effective vaccine is developed.

Acknowledgements: This project is sponsored in part by Meat and Livestock Australia and the Davies Livestock Research Centre.

SYNERGISTIC BETA LACTAM COMBINATIONS FOR TREATING MULTIDRUG-RESISTANT TUBERCULOSIS

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Aim: This study aimed to investigate the antimycobacterial activity of various beta-lactam drug combinations with novel beta-lactamase inhibitors

Background: Currently, tuberculosis (TB) is a leading cause of death from an infectious disease, and is one of the top ten causes of death worldwide. The rapid growth and expansion of multidrug-resistant tuberculosis (MDR-TB) has worsened the consequences of the TB pandemic, adversely impacting the treatment and management of disease. However, the costs and risks associated with novel drug discovery have severely limited treatment options for MDR-TB patients, who require long-term multidrug treatment. Identifying synergistic drug interactions is key to designing effective drug combinations for MDR-TB.

Methods: Repurposing existing antimicrobials can rapidly accelerate clinical application of treatments for MDR-TB. Based on minimum inhibitory concentration (MIC), oral bioavailability, and commercial availability, five beta lactams, two beta lactam inhibitors, and three second-line TB drugs were selected for combination in vitro testing against *Mycobacterium tuberculosis* H37Rv and clinical MDR-TB isolates. Resazurin and crystal violet assays were used to quantify drug efficacy. Chou-Talalay calculations were performed to identify drug synergy, and Chou-Martin calculations were performed to quantify drug dose reduction index (DRI).

Results: Of the two beta lactam inhibitors tested, avibactam and clavulanate, clavulanate was found to be much more effective at inhibiting the mycobacterial growth when used in combination with penicillin V, flucloxacillin, cephradine, cefdinir, tebipenem, cephalexin and cefadroxil. All combinations of beta lactams were strongly antagonistic except for cefdinir/cephradine with clavulanate, which was strongly synergistic and allowed for a 2.3-fold DRI for cefdinir and a 22.8-fold DRI for cephradine. Similarly, combining beta lactams with the second-line TB drugs moxifloxacin, levofloxacin or linezolid resulted in antagonistic effects. Finally, combining cefdinir/cephradine with clavulanate was highly effective against clinical isolates of MDR-TB *in vitro*.

Conclusion: This study identified cefdinir/cephradine with clavulanate as a potent and synergistic drug combination with strong *in vitro* activity against MDR-TB.

INVASIVE PNEUMOCOCCAL DISEASE ANTIMICROBIAL SUSCEPTIBILITY TESTING INTER-LABORATORY QUALITY ASSURANCE

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Aim: To assess the inter-laboratory reproducibility of *S. pneumoniae* minimum inhibitory concentration (MIC) data generated by the four laboratories contributing data for national surveillance.

Background: Invasive Pneumococcal Disease (IPD) due to *Streptococcus pneumoniae* commonly presents as pneumonia, septicemia, or meningitis. Penicillin or a third-generation cephalosporin is used for treatment. Susceptibility of *S. pneumoniae* to these agents has recently been added to the Commonwealth Surveillance of Invasive Pneumococcal Disease program which is undertaken by four laboratories in Australia. Reproducibility of antimicrobial susceptibility testing across reference laboratories is an important pre-requisite to ensure effective national surveillance of IPD.

Methods: Eight isolates of *S. pneumoniae* with MICs spanning low to high MICs to ceftriaxone and penicillin were selected for inclusion and distributed to each laboratory for susceptibility testing by the E-test® method and CLSI breakpoint interpretations.

Results: The ceftriaxone MIC values obtained by the four laboratories for 6/8 the isolates were within a single two-fold dilution of each other. Two isolates exhibited MICs across three two-fold dilutions. For penicillin, the MIC values obtained for all 8 of the isolates were all within a single two-fold dilution of each other. Interpretations were all classified correctly according to CLSI breakpoints.

Conclusion: These findings are within the accepted variation for antimicrobial susceptibility testing and will allow laboratories to review AST processes as part of ongoing quality assurance activities. These results validate the reproducibility of MIC data generated by the four laboratories contributing data to the Commonwealth Surveillance of Invasive Pneumococcal Disease program, ensuring confidence in surveillance of antimicrobial resistance in IPD samples.

ANTIMICROBIAL RESTRICTIONS AND USE OF HIGH IMPORTANCE ANTIMICROBIALS – SURVEY RESULTS FROM AUSTRALIAN VETERINARIANS

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Aim: To explore the use of antimicrobials with high importance to human health in veterinary medicine and determine levels of agreement around restrictions being placed on this use.

Background: Use of high importance antimicrobials (HIAs) in food-producing animals in Australia is largely restricted to macrolides, streptogramins (of which only virginiamycin is used) and third generation cephalosporins (in individual pigs or cattle only). So there is some room for improvement but less so than in the companion animal and equine sectors. Use of high importance antimicrobials in companion animals including exotics and equine practice is quite widespread and there is a gap in knowledge around reasonable use across all sectors of veterinary practice.

Methods: An online survey was distributed to veterinarians working in Australia in clinical and non-clinical roles. The survey was distributed via social media and email from June to December 2020.

Results: The survey was completed by 322 veterinarians with the majority (70.5%) working in general practice. Of the 278 veterinarians working in clinical practice, 49% had heard of the Australian Strategic and Technical Advisory Group rating system, and 19% used a traffic light system for antimicrobial importance in their workplace. Overall, 61% of participants disagreed that veterinarians should be able to prescribe HIAs without restrictions, while 35% agreed with the statement. If there were to be restrictions, there was most agreement for restricting high importance antimicrobials (73%). Participants were asked about the appropriateness of various restrictions if they were to be placed on the use of HIAs. There was most agreement (81%) for use to only be allowed after culture and susceptibility testing confirmed that the pathogen was resistant to all low and medium rated antimicrobials that could be used to treat the case.

Conclusions: Respondents generally disagreed that veterinarians should be able to use high importance antimicrobials without restriction. However, any restrictions implemented must be done in a way that is; practical; maintains animal welfare; and addresses veterinarians' concerns surrounding the costs of culture and sensitivity, off-label prescribing of human and compounded products, and the need for further education around antimicrobial use amongst veterinarians.

EVALUATION OF VITEK2 AND ETEST FOR PENICILLIN AND CEFTRIAXONE SUSCEPTIBILITY TESTING FOR *STREPTOCOCCUS PNEUMONIAE*

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Aim: To evaluate benzylpenicillin and ceftriaxone Minimum Inhibitory Concentrations (MICs) determined by bioMerieux Vitek2® and E test compared with broth microdilution (BMD) for *Streptococcus pneumoniae* isolates.

Background: A warning was issued in 2019 by EUCAST against the use of gradient tests for benzylpenicillin MIC for *S. pneumoniae* due to MIC underestimation, and recommended use of BMD. The underestimation MIC by E test evaluation for *S pneumoniae* has been well demonstrated in small sample sizes. In a study performed by EUCAST Development Laboratory, 57% of all gradient test MICs performed on 20 isolates were 1-3 dilutions below the BMD MICs. There have been no larger studies to date determining reliability of both VITEK2 and E test susceptibility methods for *S. pneumoniae* using EUCAST methods and breakpoints. In previous studies using CLSI breakpoints and methods, Vitek2® had significant minor errors for β-lactam antibiotics.

Methods: Evaluation of penicillin and ceftriaxone MIC determined by broth microdilution (Sensititreä), E test and Vitek2® was performed to date on 78 of 200 stored *S. pneumoniae* isolates against both meningitis and non-meningitis breakpoints. Errors were classified as Very Major (VME) for false susceptibility, Major Errors (ME) for false resistant, and minor errors (mE) for all other discrepant results.

Results: A total of n=40 (25.6%) errors were detected across E Test and Vitek2® susceptibility methods and isolates (Table 1). Significant minor errors were observed for non-meningitis breakpoints: n=18 (11.5%) E test and n=10 (6%) Vitek2® results had minor errors, defined as a result in which either method reported an isolate intermediate and the other method reported the result as susceptible or resistant (Table 3). For meningitis breakpoints, n=9 (11.5%) E test ceftriaxone readings were false susceptible (VME); n=2 (2.5%) of these 9 isolates also tested falsely susceptible on Vitek2®. Only one VME occurred in the benzylpenicillin readings for E test and meningitis breakpoints (Table 2). Errors were observed exclusively in intermediate and resistant *S. pneumoniae* isolates based on reference broth microdilution susceptibility.

Conclusions: Vitek2® and E test underestimate MICs for intermediate and resistant *S. pneumoniae* isolates. This effect was more pronounced for ceftriaxone compared with benzylpenicillin.

MOLECULAR EPIDEMIOLOGY OF PENCILLIN-SUSCEPTIBLE *STAPHYLOCOCCUS AUREUS* CAUSING BACTERAEMIA IN AUSTRALIA, 2020

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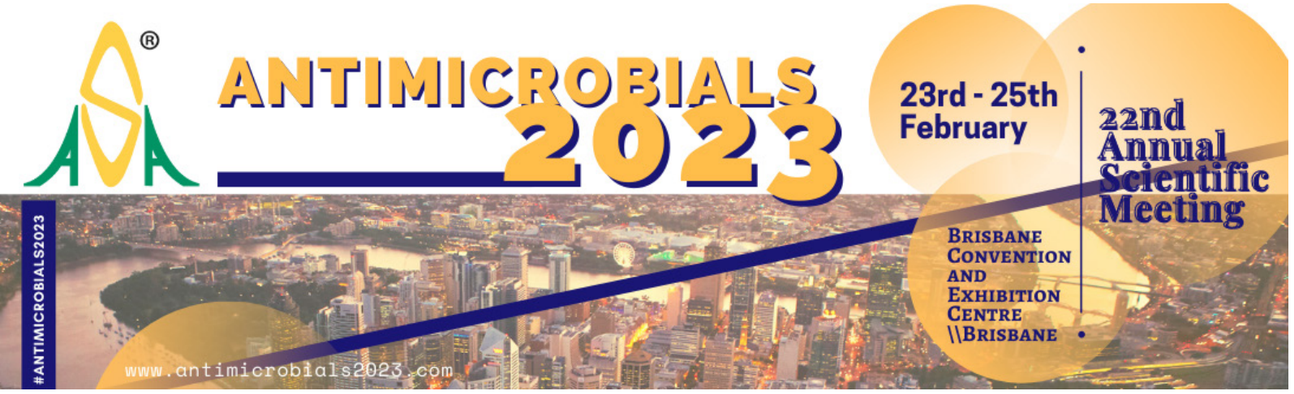
Background and Aim: *Staphylococcus aureus* penicillin susceptibility may be in a period of renaissance. The Australian Group on Antimicrobial Resistance (AGAR) reported approximately one in six *S. aureus* bacteraemia (SAB) episodes in Australia in 2020 were penicillin susceptible. To determine the population structure of penicillin-susceptible *S. aureus* (PSSA) causing bacteraemia in Australia and to assess the presence of *blaZ* in the PSSA population we performed whole genome sequencing (WGS) on PSSA SAB isolates from the AGAR 2020 Australian Staphylococcal Sepsis Outcome Program (ASSOP).

Methods: WGS was performed on the NextSeq® 500 platform (Illumina, USA) and raw sequence reads were assembled using SPAdes. The PubMLST database was used to determine the multi-locus sequence type (ST) and cloncal complex (CC) of each isolate. The Resfinder database was used to identify the *blaZ* gene.

Results: A total of 479 PSSA isolates were sequenced. We identified 89 different STs and eight different CCs. Representing 32% (n=154) of isolates, the predominant CC was CC5 which consisted of six different STs: ST5 (n=128), ST6 (n=16), ST3628 (n=6), ST5189 (n=2), ST2967 (n=1) and ST3724 (n=1). The *blaZ* gene was detected in 9.4% (n=45) of isolates. Although the *blaZ*-positive isolates belonged to 23 different STs, only four STs had more than one isolate – ST582 (n=10), ST5 (n=8), ST3911 (n=5) and ST34 (n=3). All ST582 and ST3911 PSSA isolates harboured the *blaZ* gene. The following ten STs were identified only once in our collection and each isolate harboured *blaZ*: ST9, ST25, ST1104, ST5059, ST7251, ST7255, ST7262, ST7273, ST7276, and ST7283. The *blaZ* was intact in 32 isolates, including the ST582 and ST3911 isolates, and truncated due to a nonsense mutation in 13 isolates.

Conclusions: WGS has shown high genetic diversity exists among PSSA isolates causing bacteraemia in Australia. Furthermore, the *blaZ* gene has been detected in 9.4% of *S. aureus* classified phenotypically as penicillin susceptible. Future work is required to investigate the expression of the beta-lactamase in *blaZ*-positive PSSA isolates when using phenotypic susceptibility methods.



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