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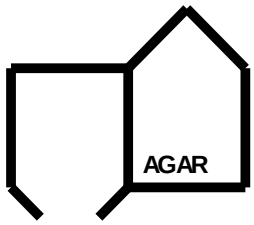

The Australian Group on Antimicrobial Resistance
http://antimicrobial-resistance.com

Project Plan

Operation of the 2023 Australian Group on Antimicrobial Resistance (AGAR) Surveillance Programmes – Additional Projects

12 May to 23 November 2023

May 2023

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1. Introduction

The Australian Group on Antimicrobial Resistance (AGAR), founded in 1986, has grown over time to achieve targeted surveillance for *Staphylococcus aureus*, *Enterococcus* species and Gram-negative bacteraemia across all Australian states and territories. As of 2020, 30 laboratories servicing 49 institutions from all Australian states and mainland territories were reporting data to AGAR (1–3).

AGAR commenced surveillance of the key gram-negative pathogens, *Escherichia coli* and *Klebsiella* species, in 1992. Surveys were conducted biennially until 2008 when annual surveys commenced, alternating between community- and hospital-onset infections. In 2004, Enterobacter species was added. In 2013, AGAR commenced the Australian *S. aureus* Sepsis Outcome Programme (ASSOP) and the *Enterobacteriaceae* Sepsis Outcome Programme (EnSOP) which focused on the collection of resistance and some demographic data on all isolates prospectively from patients with bacteraemia. In 2015, *Pseudomonas aeruginosa* and *Acinetobacter* species were added, with the program now referred to as the Gram-negative Sepsis Outcome Program (GnSOP) (1–3).

The AGAR reports feed into the key pillar objective #5 “Integrated Surveillance and Response to Resistance and Usage” of the National Antimicrobial Resistance Strategy of Australia(4). The AGAR reports allow healthcare professionals and policy makers to “use evidence-based surveillance and monitoring data to inform actions and responses to contain antimicrobial resistance” [page 11](4).

Currently, annual reports of the whole population of AGAR are produced, however previous analysis of the AGAR data comparing adult (>18 years) and paediatric (≤18 years) suggests there are lower rates of resistant organisms isolated in children, with different risk factors, antibiotic phenotypes and lower mortality rates. In 2018, the World Society for Paediatric Infectious Diseases (WSPID) recently declared that surveillance programs should present neonatal- and paediatric-specific data to assist with strengthening knowledge (5). Furthermore, various reports from Australia and Europe suggest there are differences in the burden of various organisms, not only between adults and children, but within different age groups of children. For example, Gram-negative MDR organisms were previously found to disproportionately affect children, with higher odds of death in children with an ESBL-bacteraemia vs non-ESBL bacteraemia when compared to the same ratio in adults (6). In a European study, isolated from children <1 year had less resistance than those isolated from children >1 year old (7). In a Scottish study, bacteraemia in children <1 year are more likely to be healthcare associated, whilst children aged 1-15 years are more

often likely community associated (8). These findings impact the empiric treatment guidelines and stewardship initiatives, both in hospitals and the community and highlights the value of paediatric-specific reporting of bacteraemia and antimicrobial resistance.

Payment Schedule

Estimated Date	Milestone Description	Payment Amount*
12/05/2023	Project plan	$22,000
15/06/2023	Progress report	$22,000
31/10/2023	Final report and Data	$5,500

*GST Inclusive

The isolates and metadata required for the projects will be sourced from the 2013-2021 AGAR data from all three programs (AESOP, ASSOP and GNSOP).

AGAR is a unique collaboration of clinicians and scientists from major microbiology laboratories around Australia. AGAR tests and gathers information on the level of antibiotic resistance in bacteria causing important and life-threatening infections. The group started in 1985 and at that time involved 13 teaching hospitals. It has subsequently grown to involve 40 institutions including five private laboratories. This broadening of the group has meant that not only does the group have good information as to what is happening with major pathogens in the larger teaching hospitals in each State and Territory, but now also has the ability to monitor what is happening with resistance rates in private hospitals. By standardised methodology, AGAR has been able to collect country-wide longitudinal data over a prolonged period of time. The group has also been very successful in being able to make this information available to the broader community both through publications in scientific journals and also numerous presentations at meetings and to groups around Australia and internationally. This has led to important benefits within Australia. Among these benefits has been the ability to allow more rational use of antibiotics based on known Australia-wide resistance patterns.

This one-off funding proposals will enable AGAR to establish the AGAR Kids bi-annual report, produce a report examining the previous nine years of paediatric bacteraemic data, and set up systems to improve access to the data for clinicians, researchers and policy makers.

2. Governance Arrangements

ASA, Australian Business Number 31 081 739 370, is a government endorsed charitable institution incorporated in Western Australian in 1999 (Registration Number A10076082).

Although AGAR is a working group of the ASA, the ASA Committee has delegated the authority of running AGAR to the AGAR Executive. The AGAR Executive manages the activities and operations of AGAR. ASA administers the AGAR finances, coordinates the AGAR Executive and Committee meetings and maintains the AGAR website. An AGAR representative, as recommended by the AGAR Executive, is co-opted onto the ASA Committee to provide a report on AGAR activities.

The AGAR Executive will oversee this project.

The AGAR database is stored on a secure server and is managed by an AGAR subcommittee. The AGAR Database Management Committee is a working group of AGAR and reports to the AGAR Executive.

The AGAR web application has been developed and is managed, under a service agreement, by Nexus6 Software. The AGAR database is stored on a server hosted by Bulletproof which has been externally reviewed as being security compliant.

The AGAR Database Management Committee has developed a comprehensive database governance and management plan for the operation of the 2023 AGAR antimicrobial resistance surveillance programmes.

3. Project Budget and Deliverables

1. **Project plan and evidence that work has commenced**

   Deliverable Date 12 May 2023

2. **Progress report**

   Deliverable Date 15 June 2023

3. **Final report**

   Deliverable Date 31 October 2023

4. **Manuscript**

   Deliverable Date 23 November 2023

Chief Investigators

- Ms Anita Williams – Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute
- Geoff Coombs – AGAR Chair
- Ms Jan Bell - AGAR GNSOP Scientific Officer
- Denis Daley - AGAR ASSOP/AESOP Scientific Officer
- Professor Chris Blyth – AGAR Kids Chair

On behalf of the AGAR Kids Committee

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

4. Progress to date

AGAR Kids, Ms Anita Williams and Prof Chris Blyth have been provided access to the relevant data set to enable us to meet the stated outputs.

A bi-annual report (describing paediatric data from 2020 and 2021) is in a late draft and expected to be presented for review by the AGAR Executive Group at its next meeting.

Components of the analysis of nine years of data, analysing the antimicrobial resistance trends and comparing paediatric to adult bacteraemia, has been presented at national meetings (Antimicrobials 2023, Brisbane February 2023). The abstracts of those presentations are available at the end of this document. A summary report and draft manuscript will be prepared for publication.

The data has been examined and stored in a way that will facilitate data sharing with clinicians, researchers and policy makers. Governance arrangements, through the AGAR Kids Steering Group have been formalised, ensuring approach oversight and governance.

5. Risk Management

The following scale has been used to assess the risks.

Risk Level:	Extreme risk	Detailed action/plan required
	High risk	Needs senior management attention
	Moderate risk	Specify management responsibility
	Low risk	Managed by routine procedures
Likelihood:	Almost certain	Expected in most circumstances
	Likely	Will probably occur in most circumstances
	Possible	Could occur at some time
	Unlikely	Not expected to occur
	Rare	Exceptional circumstances only
Consequence:	Severe	Would stop achievement of functional goals / objectives
	Major	Would threaten functional goals / objectives
	Moderate	Necessitating significant adjustment to overall function
	Minor	Would threaten an element of the function
	Insignificant	Lower consequence

Qualitative Risk Analysis Matrix

Likelihood	Consequences				
	Insignificant	Minor	Moderate	Major	Severe
Almost certain	M	H	H	E	E
Likely	M	M	H	H	E
Possible	L	M	M	H	E
Unlikely	L	M	M	M	H
Rare	L	L	M	M	H

Risk management plan

The following table details a high level risk assessment for this project. A more detailed risk assessment will be undertaken at the commencement of the project.

Target	What is the risk?	Consequence	Likelihood	Risk	Actions
AGAR Scientific Officers	Not collating data accurately or within the planned time frame	The additional projects will not be able to be performed by the required deliverable date.	Unlikely	High	The AGAR Chair manages the two AGAR Scientific Officers. Note: Data has already been provided
Chief Investigators	Not providing reports by the deliverable date	The additional projects will not be able to be performed by the required deliverable date.	Unlikely	Medium	Provision of reports managed by the AGAR Chair Note: Data has already been provided
Web portal - data governance	Breach of patient confidentiality	Potential harm to patient/s due to disclosure of personal information Reputational risk to ASA and AGAR	Possible	High	A comprehensive data management plan is in place that addresses privacy, security and ethics approvals management protocol is in place and includes: • arrangements for ethics and jurisdictional approval for the collection, containment, release, use and publication of any data consistent with current data sets • privacy requirements for personal information (patient date of birth, sex, postcode of residence, hospital admission and discharge date, 7- and 30-day mortality and the originating laboratory) consistent with the Privacy Act and the Privacy Amendment (Enhancing Privacy Protection) Act 2012 (Cth) (Amending Act) • arrangements to prevent re-identification of patient's arrangements for storing the data would prevent re-identification of personal data if matched or put together with to another data set data security

Target	What is the risk?	Consequence	Likelihood	Risk	Actions
					• arrangements for holding data securely on the Nexus 6 server and when in use by AGAR scientific officers, data contributor and user authorisation protocols and mechanisms for monitoring access to the database • systems and processes used for collection, analysis and storage of data and information and whether they have been designed sufficiently to ensure that the confidentiality, integrity and availability of data and information is protected Copies and dates of ethics approvals are held by AGAR for current data sets, and the purposes for which the data are provided for AGAR are addressed in the approvals Contract with web portal provider includes data privacy and security requirements. All users and staff are familiar with their obligations under the Privacy Act 1988 (Commonwealth) and the relevant state and territory privacy legislation and policies.
Web portal – maintenance and sustainability	Provider no longer able/available to provide the contracted maintenance and support services	Potential significant cost for redevelopment Potential loss of continuity of service and access to database	Possible	High	Due diligence undertaken in relation to capacity of provider to deliver the service for the contracted period as part of contracting process Contract includes requirements for provider to prepare and make available to ASA a manual in relation to web portal development processes, maintenance and operational procedures Backup arrangements in place for AGAR data

GRAM-NEGATIVE BACTERAEMIA IN PAEDIATRIC PATIENTS IN AUSTRALIA, 2013 – 2021

A. WILLIAMS[1], G. COOMBS[2,3,4], J. BELL[5], C. BLYTH[1,6,7,8],*
ON BEHALF OF THE AGAR KIDS GROUP†

1. *Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Nedlands, Western Australia, Australia*
2. *Antimicrobial Resistance and Infectious Disease (AMRID) Research Laboratory, Murdoch University, Murdoch, Western Australia, Australia*
3. *Department of Microbiology, PathWest Laboratory Medicine WA, Fiona Stanley Hospital, Murdoch, Western Australia, Australia*
4. *Australian Group on Antimicrobial Resistance, Fiona Stanley Hospital, Murdoch, Western Australia, Australia*
5. *Australian Group on Antimicrobial Resistance, Adelaide, South Australia, Australia*
6. *Department of Infectious Diseases, Perth Children's Hospital, Nedlands, Western Australia, Australia*
7. *Department of Microbiology, PathWest Laboratory Medicine WA, QEII Medical Centre, Nedlands, Western Australia, Australia*
8. *School of Medicine, The University of Western Australia, Crawley, Western Australia, Australia.*

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

Aim
To describe the microbiological and clinical characteristics of children with laboratory-confirmed Gram-negative bacteraemia across Australia between 2013 and 2021.

Background
Gram-negative bacteraemia is associated with significant morbidity and mortality. Increasing rates of antimicrobial resistance (AMR) are reported globally. Bacteraemia surveillance provides a unique opportunity to assess AMR and outcomes.
The Australian Group on Antimicrobial Resistance (AGAR) Gram-negative Surveillance Outcome Program (GnSOP) program captures clinical and microbiological data to monitor changes in AMR for key enteric Gram-negative pathogens.

Methods
Demographic data, date of culture collection, genus and species of the bacteria isolated, and relevant antimicrobial susceptibility test results are collated from 30 participating laboratories servicing 49 institutions. Principal clinical manifestation and outcomes are collected from related clinical datasets.
Enterobacterales, *Pseudomonas* spp. and *Acinetobacter* spp. isolates from distinct bacteraemic episodes in patients aged <18 years were analysed. To account for changes over time, trends were assessed in three-year time periods. MIC interpretation was as per the EUCAST 2021 rules using the AMR R Package (version 1.8.2).

Results
There were 3,259 (4.8% of total) isolates reported to AGAR from children <18 years between 2013–2021. *Escherichia coli* (1,438; 44.1%), *Klebsiella pneumoniae* (406; 12.5%) and *Salmonella* spp. (386; 11.8%) were most frequently isolated. The median age was 1 year (IQR: 0-7 years) with a slightly higher number of episodes occurring in male children (1,863; 57.2%), with a community onset (2,200; 67.5%). Urinary tract infections (556; 17.1%) were the most common focus. The median length of stay was 9 days (IQR: 4-20 days). All-cause mortality on day 30 was reported in 146 children (4.5%).
For all Gram-negative isolates, gentamicin/tobramycin resistance increased from 10.8% to 14.8% (*p*: 0.01), piperacillin-tazobactam resistance decreased from 23.4% to 18.2% (*p:* <0.01), and fluoroquinolones resistance remained consistent across the study period (18.1-23.6% *p*: 0.86). The proportion of *Enterobacterales* resistant to third generation cephalosporins increased from 9.1% to 14.8% (*p:* <0.01). Cefepime/ceftazidime resistance in *Pseudomonas* spp. remained consistent (14.8-16.1%, *p*: 0.41).

Conclusions
The increase in AMR and high mortality rate highlights the significant challenge of managing gram-negative infections in children, and the importance of reporting AGAR data specifically for children.

STAPHYLOCOCCUS AUREUS BACTERAEMIA ISOLATES IN PAEDIATRIC PATIENTS IN AUSTRALIA, 2013 – 2021

A WILLIAMS[1], G COOMBS[2,3,4], D DALEY[3,4], S MOWLABOCCUS[2,3], C BLYTH[1,5,6,7], ON BEHALF OF THE AGAR KIDS GROUP†*

1. *Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Nedlands, Western Australia, Australia*
2. *Antimicrobial Resistance and Infectious Disease (AMRID) Research Laboratory, Murdoch University, Murdoch, Western Australia, Australia*
3. *Department of Microbiology, PathWest Laboratory Medicine WA, Fiona Stanley Hospital, Murdoch, Western Australia, Australia*
4. *Australian Group on Antimicrobial Resistance, Fiona Stanley Hospital, Murdoch, Western Australia, Australia*
5. *Department of Infectious Diseases, Perth Children's Hospital, Nedlands, Western Australia, Australia*
6. *Department of Microbiology, PathWest Laboratory Medicine WA, QEII Medical Centre, Nedlands, Western Australia, Australia*
7. *School of Medicine, The University of Western Australia, Crawley, Western Australia, Australia.*

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

Aim
To describe the microbiological and clinical characteristics of paediatric patients with *Staphylococcus aureus* bacteraemia across Australia between 2013 and 2021.

Background
S. aureus bacteraemia is associated with significant morbidity and mortality in children and adults, more frequently affecting neonates, Indigenous children and children admitted to hospital. *S. aureus* bacteraemia most frequently results in bone and joint infections, complicated skin and soft tissue infection, lower respiratory infection and metastatic complications.
The Australian Group on Antimicrobial Resistance (AGAR) *S. aureus* Surveillance Outcome Program (ASSOP) program captures clinical and microbiological data to monitor changes in antimicrobial resistance in *S. aureus* isolates.

Methods
Demographic data, date of blood culture collection, genus and species of the bacteria isolated, and relevant antimicrobial susceptibility test results are collated from 30 participating laboratories servicing 49 institutions. Principal clinical manifestation and outcomes are collected from related clinical datasets. Consecutive *S. aureus* isolates from distinct bacteraemic episodes in patients <18 years were analysed. To account for changes over time, trends were assessed in three-year time periods. MIC interpretation was as per EUCAST 2022 rules using the AMR R Package (v1.8.2).

Results
There were 2,106 (9.0% of total) *S. aureus* isolates reported to AGAR from children <18 years over the 2013–2021 period. Males were more frequently affected (n=1334, 63.3%). The median age was 6 years (IQR: 0-12 years), and the median length of stay was 11 days (IQR: 7–20 days). Community-onset bacteraemia (1,646; 78%) and underlying osteomyelitis/septic arthritis (696; 39%) were most common. All-cause mortality on day 30 was reported in 30 children (1.4%), 22 children with MSSA (73.3%).
Overall, 15.5% (n: 327) of isolates were MRSA. This proportion did not change significantly over time: 13.9% [2013-15]; 17.2% [2016-2018] and 15.1% [2019-21] (17.2%; p = 0.25). The highest proportion of MRSA overall was reported from the Northern Territory (45.0%). Erythromycin, clindamycin, rifampicin and ciprofloxacin resistance was identified in 10.6%, 10.7%, 0.1% and 4.5% of paediatric MSSA isolates, and 23.2%, 16.3%, 0.3% and 14.7% of MRSA isolates.

Conclusions
The epidemiology of *S. aureus* bacteraemia in Australian children appears stable. Ongoing significant differences in the prevalence of MRSA by state is noted.