

The Australian Group on Antimicrobial Resistance (AGAR)



Geoffrey Coombs^{A,B,E}, Denise Daley^C and Jan Bell^D, on behalf of the Australian Group on Antimicrobial Resistance

^AAntimicrobial Resistance and Infectious Diseases Laboratory, School of Veterinary and Life Sciences, Murdoch University, Murdoch, WA 6150, Australia

^BDepartment of Microbiology, PathWest Laboratory Medicine-WA, Fiona Stanley Hospital, Murdoch, WA 6150, Australia

^CAustralian Group on Antimicrobial Resistance, Fiona Stanley Hospital, Murdoch, WA 6150, Australia

^DThe University of Adelaide, Adelaide, SA 5005, Australia

^EEmail: G.Coombs@murdoch.edu.au

The Australian Group on Antimicrobial Resistance (AGAR) is a collaboration of clinicians and scientists working in diagnostic medical microbiology laboratories located across Australia. The group gathers information on the level of antimicrobial resistance (AMR) in bacteria causing important and life threatening infections and is a key component of Australia's response to the problem of increasing AMR. It defines where Australia stands with regard to antimicrobial resistance in human health.

History and governance

AGAR commenced in 1985 and at that time involved 13 teaching hospitals. It has subsequently grown to involve 40 institutions including five private laboratories (Table 1). This broadening of AGAR 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 also has the ability to monitor what is happening with resistance rates in private hospitals and the community. Initially funded by Eli Lilly Pharmaceuticals, from 2003 AGAR has received funding from the Australian Government Department of Health to perform its AMR surveillance programs. Although AGAR is a working group of the Australian Society for Antimicrobials (ASA), the ASA Committee delegates the authority of running AGAR to the AGAR Executive.

AGAR is a key component of the Australian Commission on Safety and Quality in Health Care's (ACSQHC) Antimicrobial Use and Resistance in Australia (AURA) Surveillance System. AURA provides essential information to develop and implement strategies to prevent and contain AMR in human health and improve antimicrobial use across hospital, residential care and community health-care settings. AGAR complements two other AMR surveillance programs that contribute to AURA: the National Alert System for Critical Antimicrobial Resistances (CARAlert) and Australian Passive Antimicrobial Resistance Surveillance (APAS).

Surveillance programs

Historically, AGAR performed 'snap shot' targeted AMR surveillance programs that initially focused on antimicrobial resistance in *Staphylococcus aureus* and over time was broadened to include studies on *Escherichia coli*, *Enterobacter* species, *Klebsiella* species, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Enterococcus* species.

Since 2013 AGAR has primarily focused on performing 'ongoing' targeted AMR surveillance programs on bloodstream infections and conducts three annual programs:

- *Staphylococcus aureus* (ASSOP – Australian Staphylococcal Sepsis Outcome Program)
- *Enterococcus* species (AESOP – Australian Enterococcal Sepsis Outcome Program)

Table 1. 2017 participating members of AGAR.

| Institution | AGAR members |
|--|---|
| Alfred Hospital, Vic | Denis Spelman and Rose Bernhard |
| Alice Springs Hospital, NT | James McLeod |
| Austin Hospital, Vic | Paul Johnson and Frances Hurren |
| Canberra Hospital, ACT | Peter Collignon and Susan Bradbury |
| Concord Hospital, NSW | Thomas Gottlieb and Graham Robertson |
| John Hunter Hospital, NSW | Rod Givney and Ian Winney |
| Joondalup Hospital, WA | Shalinie Perera and Ian Meyer |
| Lady Cilento Children's Hospital, Qld | Clare Nourse and Janet Wallace |
| Launceston General Hospital, Tas | Pankaja Kalukottege and Kathy Wilcox |
| Monash Children's Hospital, Vic | Tony Korman and Despina Kotsanas |
| Monash Health (Monash Medical Centre), Vic | Tony Korman and Despina Kotsanas |
| Nepean Hospital, NSW | James Branley and Linda Douglass |
| Pathology Queensland Cairns Base Hospital, Qld | Enzo Binotto and Bronwyn Thomsett |
| Pathology Queensland Central Laboratory, Qld | Graeme Nimmo and Narelle George |
| Pathology Queensland Gold Coast Hospital, Qld | Petra Derrington and Cheryl Curtis |
| Pathology Queensland Prince Charles Hospital, Qld | Robert Horvath and Laura Martin |
| Pathology Queensland Princess Alexandra Hospital, Qld | Naomi Runnegar and Joel Douglas |
| PathWest Laboratory Medicine – Remote WA | Michael Leung |
| PathWest Laboratory Medicine – WA, Fiona Stanley Hospital | David McGeachie and Denise Daley |
| PathWest Laboratory Medicine – WA, Princess Margaret Hospital for Children | Chris Blyth |
| PathWest Laboratory Medicine – WA, Queen Elizabeth II Hospital | Ronan Murray and Jacinta Bowman |
| PathWest Laboratory Medicine – WA, Royal Perth Hospital | Owen Robinson and Geoffrey Coombs |
| Royal Darwin Hospital, NT | Rob Baird and Jann Hennessy |
| Royal Hobart Hospital, Tas | Louise Cooley and David Jones |
| Royal North Shore Hospital, NSW | Peter Huntington |
| Royal Prince Alfred Hospital, NSW | Sebastian van Hal and Alicia Beukers |
| Royal Children's Hospital, Vic | Andrew Daley and Gena Gonis |
| SA Pathology, Flinders Medical Centre, SA | Kelly Papanaooum and Xiao Chen |
| SA Pathology, Royal Adelaide Hospital, SA | Morgyn Warner and Kija Smith |
| SA Pathology, Women's and Children's Hospital, SA | Morgyn Warner and Kija Smith |
| St John of God Hospital, Murdoch, WA | Sudha Pottumarthy-Boddu and Fay Kappler |
| St Vincent's Hospital, Melbourne, Vic | Mary Jo Waters and Lisa Brenton |
| St Vincent's Hospital, Sydney, NSW | Jock Harkness and David Lorenz |
| Sullivan Nicolaides Pathology, Qld | Jennifer Robson and Georgia Peachey |
| Westmead Hospital, NSW | Jon Iredell and Andrew Ginn |
| Wollongong Hospital, NSW | Peter Newton and Melissa Huddle |

- Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter* species (GNSOP – Gram negative Sepsis Outcome Program)

The sepsis programs' activities are overseen by three program committees which have the key advisory role of ensuring the highest quality of results is collected within an AGAR surveillance program. The program committees:

- analyse the clinical data collected in the AGAR surveillance program with the aim of producing peer reviewed publications;
- organise additional research activities related to the surveillance program; and
- provide scientific advice to the AGAR Executive on matters that are related to the surveillance program.

Each year the AGAR laboratories collect all *S. aureus* and *Enterococcus* species isolates and up to 200 isolates of Enterobacterales, *Acinetobacter* species and *P. aeruginosa* from unique patient episodes of bacteraemia. Approval to conduct the prospective data collection, including de-identified demographic data, is given by the research ethics committees associated with each participating hospital.

All AGAR laboratories obtain basic laboratory information for each patient episode plus varying demographic information, depending on the level at which they are enrolled in the program. There are two levels of AGAR enrolment: Bronze and Silver. At Bronze level, participating laboratories provide date of collection, date of birth, sex, postcode and admission date. At Silver level, participating laboratories provide discharge date, device-related infection, principal clinical manifestation, outcome at seven and 30 days, and, if applicable, date of death.

Isolates are identified to species level using the routine method for each institution. This includes the Vitek® and Phoenix™ automated microbiology systems, and, if available, mass spectrometry (MALDI-TOF).

Susceptibility testing is performed using two commercial semi-automated methods: Vitek 2 (bioMérieux) and Phoenix (BD), which are calibrated to the ISO (International Organization for Standardization) reference standard method of broth microdilution. CLSI and EUCAST breakpoints are used in the analysis.

The AGAR data is submitted by AGAR laboratories using a web application portal. AGAR complies with all relevant privacy legislation and data security provisions.

Detailed annual reports on each program can be found on the AGAR website (www.agargroup.org). Reports are also published in the Australian Government Department of Health Communicable Diseases Intelligence (CDI) journal. An annual amalgamated report is produced by the ACSQHC and is available on their website (<https://www.safetyandquality.gov.au/antimicrobial-use-and-resistance-in-australia/agar/>).

In 2017, 11 562 episodes of bacteraemia across Australia were included in the AGAR programs.

ASSOP

The objectives of ASSOP are to determine the proportion of *Staphylococcus aureus* bacteraemia (SAB) isolates in Australia that are antimicrobial resistant, with particular emphasis on susceptibility to methicillin and to characterise the molecular epidemiology of the methicillin-resistant isolates.

Key findings from the 2017 ASSOP:

- A total of 2515 SAB episodes were reported, of which 77% were community onset. One in five of all episodes were methicillin resistant (19%)
- The 30-day all-cause mortality was 14.8% with a significant difference between methicillin-resistant (MRSA) (18.9%) and methicillin-sensitive *S. aureus* (MSSA) (13.9%) mortality, as well as community-onset (13.8%) and hospital-onset *S. aureus* bacteraemia (18.3%)
- There is an increasing rate of community-associated MRSA (CA-MRSA) bacteraemia, and in Australia CA-MRSA dominate MRSA bacteraemia
- With the exception of the β -lactams and erythromycin, antimicrobial-resistance in MSSA was rare. However, in addition to the β -lactams approximately 40% of MRSA were resistant to erythromycin and ciprofloxacin and approximately 15% resistant to cotrimoxazole, tetracycline and gentamicin. When applying the EUCAST breakpoints, teicoplanin resistance was detected in five *S. aureus* isolates. Resistance was not detected for vancomycin and linezolid
- Three healthcare-associated MRSA (HA-MRSA) clones were identified of which EMRSA-15 (ST22-IV) was the major clone. The majority of EMRSA-15 episodes arose in the community, which is consistent with the prevalence of this clone in residential care facilities in Australia
- Thirty-nine CA-MRSA clones were identified. The Queensland clone (ST93-IV) that harbours the Panton-Valentine leucocidin (PVL) associated genes has become the dominant CA-MRSA clone and is now seen throughout Australia; it is the most common CA-MRSA clone in Queensland, Western Australia and the Northern Territory
- Overall, 49.7% of CA-MRSA isolates harboured the PVL associated genes

AESOP

The objectives of AESOP are to determine the proportion of *E. faecalis* and *E. faecium* bacteraemia isolates demonstrating antimicrobial resistance with particular emphasis on:

- Assessing susceptibility to ampicillin
- Assessing susceptibility to glycopeptides
- Monitoring the molecular epidemiology of *E. faecium*

Key findings from the 2017 AESOP:

- A total of 1,137 episodes of enterococcal bacteraemia were reported; the majority (95.3%) of episodes were caused by *E. faecalis* or *E. faecium*
- The majority of *E. faecalis* bacteraemia were community-onset (71.3%), while in *E. faecium* bacteraemia only 30.1% were community onset

- The combined 30-day all-cause mortality was 20.3%
- There was significant difference in 30-day all-cause mortality between *E. faecalis* (14.3%) and *E. faecium* (27.7%)
- Overall 50.9% of *E. faecium* harboured *vanA* or *vanB* genes or both, with 50% of vancomycin-resistant *E. faecium* bacteraemias due to *vanA*; this type of vancomycin resistance has emerged rapidly in the past six years, particularly in New South Wales, where it is now the dominant genotype
- There were 64 *E. faecium* multilocus sequence types (STs), of which ST17, ST1421, ST796, ST1424, ST80, ST555, ST203, ST18, and ST78 were the nine most frequently identified
- *vanA* genes were detected in nine STs, and *vanB* genes were detected in 12 STs. Two STs harboured *vanA* and *vanB* genes. The clonal diversity varied across Australia
- The percentage of *E. faecium* bacteraemia isolates resistant to vancomycin is now much higher in Australia than in all European countries

GNSOP

The objectives of the 2017 surveillance program are to:

- Monitor resistance in Enterobacteriales, *P. aeruginosa* and *Acinetobacter* species isolated from blood cultures taken from patients presenting to the hospital or already in hospital
- Study the extent of co-resistance and multidrug resistance in the major species
- Detect emerging resistance to last-line agents such as carbapenems and colistin
- Examine the molecular basis of resistance to third-generation cephalosporins, quinolones and carbapenems
- Monitor the epidemiology of *E. coli* sequence type 131

Key findings from the 2017 GNSOP:

- A total of 7910 episodes of gram-negative bacteraemia were reported, including Enterobacteriales (89.8%), *Pseudomonas aeruginosa* (8.8%) and *Acinetobacter* species (1.4%). Three genera – *Escherichia* (61.6%), *Klebsiella* (19.9%) and *Enterobacter* (6.3%) – contributed 87.8% of all Enterobacteriales bacteraemias
- The all-cause 30-day mortality for gram-negative bacteraemia was 12.5% (10.1% in *E. coli*, 20.6% in *P. aeruginosa*)
- Over 11% of *E. coli* isolates causing community-onset bacteraemia, which accounted for 84% of all *E. coli* bacteraemia cases, were ceftriaxone resistant
- Extended-spectrum β -lactamase (ESBL) phenotypes were found in 12.6% of *E. coli* and 9.8% of *Klebsiella pneumoniae* and are more common in hospital onset episodes. The CTX-M type gene was present in 76.1% of *E. coli* with an ESBL phenotype
- Increasing fluoroquinolone non-susceptibility in *E. coli* is a continuing concern and is most striking in hospital-onset bacteraemia, with a change from 16.1% to 21.1% between 2013 and 2017
- Fluoroquinolone resistance is commonly linked to cephalosporin resistance caused by ESBLs of the CTX-M type. O25b-ST131 accounted for 57.3% of *E. coli* ESBL phenotypes that were ciprofloxacin resistant
- Very low levels of carbapenemase-producing Enterobacteriales (CPE) bacteraemia was observed (0.1% in *E. coli* and 0.7% in *K. pneumoniae*), although the *Enterobacter cloacae* complex hospital-onset figure is higher at 3.6%
- The rate of colistin resistance – when tested for, but excluding species with intrinsic resistance – was 0.9% (7/752). No mobile colistin resistance genes were detected among all referred isolates

Individual 2017 program reports can found on the AGAR website. An amalgamated 2017 report will be available on the AGAR and the ACSQHC websites in the first half of 2019.

By using standardised methodology AGAR has been able to collect ongoing AMR data on what is happening in Australia over long periods 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.

For further information on AGAR and its activities please contact Denise Daley, info@agargroup.org.au.

Reference laboratories

AGAR gratefully acknowledges the Australian Centre for Antimicrobial Resistance Ecology, The University of Adelaide, South Australia for the molecular characterisation of gram-negative isolates; and the Antimicrobial Resistance Reference Laboratory, Centre for Infectious Diseases and Microbiology Laboratory Services, Westmead Hospital, for performing whole genome sequencing on carbapenemase-producing isolates.

AGAR also gratefully acknowledges Dr Stanley Pang and Ms Yung Thin Lee at the Antimicrobial Resistance and Infectious Disease Laboratory, School of Veterinary Life Science, Murdoch University, Western Australia for performing the whole genome sequencing on *E. faecium* and MRSA isolates.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

The AGAR programs are funded by the Department of Health via the Australian Commission on Safety and Quality in Health Care and the Australian Society for Antimicrobials.

Biographies

Professor Geoffrey Coombs, PhD, is Chair of Public Health and Murdoch University and Senior Clinical Scientist at PathWest Laboratory Medicine, WA. In addition he is the AGAR Chairman. His major research interest is on antimicrobial resistance and molecular epidemiology of *S. aureus* and *Enterococcus faecium*.

Denise Daley is the AGAR Scientific Officer for the Australian Staphylococcus and Enterococcus Sepsis Outcome Programs (ASSOP and AESOP).

Jan Bell is the AGAR Scientific Officer for the Gram Negative Sepsis Outcome Program.