



**Australian Government**  
**Department of Health**

# COMMUNICABLE DISEASES INTELLIGENCE

2019 Volume 43  
<https://doi.org/10.33321/cdi.2019.43.37>

## **Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2017**

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# Communicable Diseases Intelligence

ISSN: 2209-6051 Online

This journal is indexed by Index Medicus and Medline.

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Communicable Diseases Intelligence (CDI) is a peer-reviewed scientific journal published by the Office of Health Protection, Department of Health. The journal aims to disseminate information on the epidemiology, surveillance, prevention and control of communicable diseases of relevance to Australia.

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Office of Health Protection  
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# Australian Group on Antimicrobial Resistance (AGAR) Australian Gram-negative Sepsis Outcome Programme (GNSOP) Annual Report 2017

Jan M Bell, Thomas Gottlieb, Denise A Daley and Geoffrey W Coombs

## Abstract

The Australian Group on Antimicrobial Resistance (AGAR) performs regular period-prevalence studies to monitor changes in antimicrobial resistance in selected enteric Gram-negative pathogens. The 2017 survey was the fifth year to focus on blood stream infections, and included Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter* species.

Seven thousand nine hundred and ten isolates, comprising Enterobacterales (7,100, 89.8%), *P. aeruginosa* (697, 8.8%) and *Acinetobacter* species (113, 1.4%), were tested using commercial automated methods. The results were analysed using Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (January 2018). Of the key resistances, non-susceptibility to the third-generation cephalosporin, ceftriaxone, was found in 11.3%/11.3% of *Escherichia coli* (CLSI/EUCAST criteria), 8.8%/8.8% of *Klebsiella pneumoniae*, and 5.7%/5.7% of *K. oxytoca*. Non-susceptibility rates to ciprofloxacin were 12.1%/18.0% for *E. coli*, 4.4%/11.2% for *K. pneumoniae*, 1.3%/3.5% for *K. oxytoca*, 3.0%/8.5% for *Enterobacter cloacae* complex, and 5.1%/9.8% for *P. aeruginosa*. Resistance rates to piperacillin-tazobactam were 2.8%/5.9%, 3.7%/7.3%, 9.6%/11.0%, 22.5%/27.6%, and 6.4%/13.2% for the same five species respectively. Twenty-seven isolates from 25 patients were shown to harbour a carbapenemase gene: 12 *bla*<sub>IMP</sub> (11 patients), five *bla*<sub>OXA-181</sub> (four patients), three *bla*<sub>OXA-23</sub>, two *bla*<sub>NDM</sub>, two *bla*<sub>KPC</sub>, two *bla*<sub>VIM</sub>, and one *bla*<sub>GES</sub>.

Keywords: Australian Group on Antimicrobial Resistance (AGAR); antibiotic resistance; bacteraemia; gram-negative; *Escherichia coli*; Enterobacter; Klebsiella

## Introduction

Emerging resistance in common pathogenic members of the Enterobacterales is a world-wide phenomenon and presents therapeutic problems for practitioners, both in the community and in hospital practice. The Australian Group on Antimicrobial Resistance (AGAR) commenced surveillance of the key Gram-negative pathogens, *Escherichia coli* and *Klebsiella* species in 1992. Surveys have been conducted biennially until 2008 when annual surveys commenced, alternating between community- and hospital-onset infections ([http://www.agargroup.org/sur-](http://www.agargroup.org/surveys)

[veys](http://www.agargroup.org/surveys)). In 2004, another genus of Gram-negative pathogens in which resistance can be of clinical importance, *Enterobacter* species, was added. *E. coli* is the most common cause of community-onset urinary tract infection; *Klebsiella* species are less common but are known to harbour important resistances. *Enterobacter* species are less common in the community, but of high importance due to intrinsic resistance to first-line antimicrobials in the community. Taken together, the three groups of species surveyed are considered to be valuable sentinels for multi-resistance and emerging resistance in enteric Gram-negative bacilli. In 2013 AGAR com-

menced 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, and the program referred to as the Gram-negative Sepsis Outcome Program (GNSOP).

Resistances of particular interest include resistance to  $\beta$ -lactams due to  $\beta$ -lactamases, especially extended-spectrum  $\beta$ -lactamases, which inactivate the third-generation cephalosporins that are normally considered reserve antimicrobials. Other resistances of interest are to agents important for treatment of these serious infections, such as gentamicin; and resistance to reserve agents such as ciprofloxacin, meropenem and colistin.

The objectives of the 2017 surveillance program were to:

1. Monitor resistance in Enterobacteriales, *P. aeruginosa* and *Acinetobacter* species isolated from blood cultures taken from patients presenting to the hospital or already in hospital
2. Examine the extent of co-resistance and multidrug resistance in the major species
3. Detect emerging resistance to newer last-line agents such as carbapenems
4. Characterise the molecular basis of resistance to third-generation cephalosporins, quinolones, amikacin and carbapenems

## Methods

### Study design

From 1 January to 31 December 2017, 36 laboratories across Australia collected either all or up to 200 isolates from different patient episodes of bacteraemia.

### Species identification

Isolates were identified using the routine method for each institution; Vitek<sup>®</sup>, Phoenix<sup>™</sup> Automated Microbiology System, or where available mass spectrometry (MALDI-ToF).

### Susceptibility testing

Testing was performed by two commercial semi-automated methods, Vitek 2 (BioMérieux, France) or Phoenix (Becton Dickinson, USA), which are calibrated to the ISO reference standard method of broth microdilution. Commercially available Vitek AST-N246 and AST-N247, or Phoenix NMIC-203 and NIMC-404 cards were utilized by all participants throughout the survey period. The CLSI M100<sup>1</sup> and EUCAST v8.0<sup>2</sup> breakpoints from January 2018 have been employed in the analysis. For analysis of cefazolin, breakpoints of  $\leq 4$  mg/L for susceptible,  $\geq 8$  mg/L for resistant were applied due to the restricted minimum inhibitory concentration (MIC) range available on the commercial cards, recognising that the January 2018 breakpoint is actually susceptible  $\leq 2$  mg/L.

### Molecular confirmation of resistances

*E. coli*, *Klebsiella* spp., *Proteus* spp. and *Salmonella* spp. with ceftazidime or ceftriaxone MIC > 1 mg/L, or cefoxitin MIC > 8 mg/L; any other Enterobacteriales with cefepime MIC > 1 mg/L; all isolates with ciprofloxacin MIC > 0.25 mg/L; all isolates with meropenem MIC > 0.25 mg/L; all isolates with amikacin MIC > 32 mg/L, and all isolates with colistin MIC > 2 mg/L were referred to a central laboratory (University of Adelaide) for molecular confirmation of resistance.

All referred isolates were screened using real-time polymerase chain reaction (PCR) platform (LC-480) and published primers for the presence of  $bla_{TEM}$  and  $bla_{SHV}$ , CTX-M-type genes (groups 1, 2, 9, 8/25), plasmid-borne AmpC ( $bla_{CIT}$ ,  $bla_{DHA}$ ,  $bla_{EBC}$ ,  $bla_{ACC}$ ,  $bla_{FOX}$ ,  $bla_{MOX}$ ), and carbapenemases genes ( $bla_{IMP}$ ,  $bla_{NDM}$ ,  $bla_{KPC}$ ,  $bla_{OXA-48-like}$ ,  $bla_{VIM}$ ,  $bla_{GES}$ ,  $bla_{SME}$ ,  $bla_{IMI}$ ).<sup>3-5</sup>

PCRs was also used to detect *bla*<sub>IMP</sub> types, known plasmid-mediated quinolone resistance mechanisms (*qnr*, efflux [*qepA*, *oqxAB*] and *aac* (6′)-*Ib-cr*), aminoglycoside ribosomal methyltransferases (*armA*, *rmtB*, *rmtC*, *rmtF*), and mobile colistin resistance genes (*mcr-1*, *mcr-2*, *mcr-3*).<sup>6–11</sup> All referred *E. coli* were examined for membership of the O25b-ST131 clone.<sup>12</sup> All isolates with demonstrated carbapenemase activity and any amikacin resistant isolates were also screened for OXA-23-like, -24, and -58 carbapenemases.<sup>13</sup>

All isolates with carbapenemase activity were subjected to whole genome sequencing using the Illumina MiSeq platform. Data were analysed using the Nullarbor bioinformatic pipeline.<sup>14</sup> The pipeline was used to identify the multi-locus sequence type and the resistome.

## Results

The species isolated, and the numbers of each are listed in Table 1. Enterobacterales accounted for 89.8%, followed by *P. aeruginosa* (8.8%) and *Acinetobacter* species (1.4%). Of the Enterobacterales, three genera—*Escherichia* (61.6%), *Klebsiella* (19.9%) and *Enterobacter* (6.3%)—contributed 87.8% of all isolates. Major resistances and non-susceptibilities for the top six ranked species are listed in Table 2. Non-susceptibility (which includes both intermediately resistant and resistant isolates) has been included for some agents because these figures provide information about important emerging acquired resistances. Multiple acquired resistances by species are shown in Table 3. Multi-resistance was detected in 21.9% of *E. coli* isolates, 10.4% of *K. pneumoniae*, and 18.6% of *E. cloacae* complex. A more detailed breakdown of resistances and non-susceptibilities by state and territory is provided in the online AGAR report.

### *Escherichia coli*

Moderately high levels of resistance to ampicillin (and therefore amoxicillin) were maintained (53.0%/54.4%, CLSI/EUCAST criteria), with

**Table 1. Number and proportion of species isolated, blood cultures, 2017**

Species	Percentage (n)
<i>Escherichia coli</i>	55.2 (4,370)
<i>Klebsiella pneumoniae</i>	12.7 (1,001)
<i>Pseudomonas aeruginosa</i>	8.8 (697)
<i>Enterobacter cloacae</i> complex	5.5 (433)
<i>Proteus mirabilis</i>	3.0 (235)
<i>Klebsiella oxytoca</i>	2.9 (229)
<i>Serratia marcescens</i>	2.1 (167)
<i>Salmonella</i> species (non-typhoidal)	1.7 (134)
<i>Klebsiella aerogenes</i>	1.3 (105)
<i>Morganella morganii</i>	1.1 (85)
<i>Klebsiella variicola</i>	0.9 (72)
<i>Acinetobacter baumannii</i> complex	0.8 (65)
<i>Citrobacter freundii</i>	0.7 (56)
<i>Citrobacter koseri</i>	0.5 (43)
<i>Salmonella</i> species (typhoidal)	0.4 (31)
<i>Raoultella ornithinolytica</i>	0.2 (14)
<i>Pantoea agglomerans</i>	0.2 (14)
<i>Acinetobacter</i> species	0.2 (12)
<i>Acinetobacter lwoffii</i>	0.1 (11)
Other species (total n = 42)	1.7 (136)
<b>Total</b>	<b>7,910</b>

lower rates for amoxicillin-clavulanic acid (13.6%/– intermediate, 8.4%/– resistant). Non-susceptibility to third-generation cephalosporins was low (ceftriaxone 11.3%/11.3%, ceftazidime 6.3%/11.1%). Moderate levels of resistance were detected to cefazolin (22.8%/22.8%) and trimethoprim–sulfamethoxazole (31.2%/31.2%). Ciprofloxacin non-susceptibility was found in 12.1%/18.0% of *E. coli* isolates. Resistance to gentamicin (8.4%/8.5%), piperacillin-tazobactam (2.8%/5.9%) and cefepime (5.1%/8.7%) was low. Eleven isolates (0.3%) had elevated meropenem MICs ( $\geq 0.5$  mg/L). For the strains with extended-spectrum  $\beta$ -lactamase (ESBL) phenotype, ciprofloxacin and gentamicin resistance was found in 56.5%/64.2% and 35.5%/35.6% respectively.

Table 2. Non-susceptibility and resistance rates for the top six ranked species tested, 2017

Antimicrobial	Category <sup>a</sup>	E. coli (%)		K. pneumoniae (%)		P. aeruginosa (%)		E. cloacae complex (%)		K. oxytoca (%)		P. mirabilis (%)	
		CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST
Ampicillin	I	1.4	-	b	b	na	na	b	b	b	b	0.4	-
	R	53.0	54.4	b	b	na	na	b	b	b	b	16.6	17.0
Amoxicillin-clavulanic acid (2:1) <sup>c</sup>	I	13.6	na	4.1	-	na	na	b	b	3.5	-	5.5	-
	R	8.4	-	5.3	-	na	na	b	b	8.3	-	2.6	-
Piperacillin-tazobactam	R	2.8	5.9	3.7	7.3	6.4	13.2	22.5	27.6	9.6	11.0	0.0	1.3
Cefazolin	R	22.8	22.8	12.5	12.5	na	na	b	b	67.1	67.1	18.5	18.5
Cefoxitin	R	3.7	/	5.6	/	na	na	b	b	2.2	/	0.4	/
Ceftriaxone	NS	11.3	11.3	8.8	8.8	na	na	27.9	27.9	5.7	5.7	2.1	2.1
Ceftazidime	NS	6.3	11.1	5.8	8.6	9.3	9.3	24.9	28.2	0.0	0.4	1.3	3.0
Cefepime	NS	5.1	8.7	4.0	6.9	3.3	6.5	6.9	14.5	0.4	0.9	1.3	1.3
Meropenem	NS	0.1	0.1	0.8	0.8	7.9	7.9	2.3	2.3	0.0	0.0	0.0	0.0
Ciprofloxacin	NS	12.1	18.0	4.4	11.2	5.1	9.8	3.0	8.5	1.3	3.5	3.4	6.8
Gentamicin	R	8.4	8.5	4.4	4.9	2.0	3.9	6.9	7.4	0.4	0.4	3.4	4.7
Trimethoprim-sulfamethoxazole	R	31.2	31.1	16.1	15.7	na	na	20.1	19.9	3.5	3.5	14.9	14.9
Nitrofurantoin	R	0.8	0.8	23.1	/	na	na	10.6	/	1.8	/	b	b

a R = resistant, I = intermediate, NS = non-susceptible (intermediate + resistant), using criteria as published by the CLSI [2018] and EUCAST [2018].

b Considered largely intrinsically resistant due to natural  $\beta$ -lactamases; - no intermediate category; / no breakpoints defined; na = not applicable (testing not recommended)

c For EUCAST interpretation, the clavulanate is fixed at 2 mg/L, rather than a 2:1 ratio used in CLSI guidelines. As all susceptibility test cards used have a 2:1 ratio of clavulanate no EUCAST category has been applied.

Table 3. Multiple acquired resistances by species, 2017

Species	Number of acquired resistances (EUCAST breakpoints)													Cumulative %		
	Non-multi-resistant						Multi-resistant									
	0	1	2	3	Cumulative %	4	5	6	7	8	9	10	11		12	13
<b>Total</b>	4,293	1,688	636	669	360	268	189	125	134	100	71	41	12	0	0	
<i>E. coli</i>	%	39.3	14.8	15.6	8.4	78.1	6.2	4.4	2.9	3.1	1.7	1.0	0.3	0.0	0.0	21.9
<i>K. pneumoniae</i> <sup>a</sup>	983	701	114	40	26	19	11	12	19	10	26	4	1	na	na	
%	71.3	11.6	4.1	2.6	89.6	1.9	1.1	1.2	1.9	1.0	2.6	0.4	0.1			10.4
<i>E. cloacae</i> complex <sup>b</sup>	350	199	36	11	39	30	8	14	6	5	2	na	na	na	na	
%	56.9	10.3	3.1	11.1	81.4	8.6	2.3	4.0	1.7	1.4	0.6					18.6
<i>P. mirabilis</i>	231	130	57	14	12	8	4	2	1	0	3	0	0	0	na	
%	56.3	24.7	6.1	5.2	92.2	3.5	1.7	0.9	0.4	0.0	1.3	0.0	0.0	0.0		7.8
<i>K. oxytoca</i> <sup>a</sup>	221	59	115	19	16	8	4	0	0	0	0	0	0	0	na	
%	26.7	52.0	8.6	7.2	94.6	3.6	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0		5.4
<i>Salmonella</i> species (non-typhoidal)	127	110	14	2	0	1	0	0	0	0	0	na	na	na	na	
%	86.6	11.0	1.6	0.0	99.2	0.8	0.0	0.0	0.0	0.0	0.0					0.8
<i>S. marcescens</i> <sup>b</sup>	126	115	5	4	2	0	0	0	0	0	0	na	na	na	na	
%	91.3	4.0	3.2	1.6	100	0.0	0.0	0.0	0.0	0.0	0.0					0.0
<i>K. aerogenes</i> <sup>b</sup>	102	48	8	3	35	6	1	0	1	0	0	na	na	na	na	
%	47.1	7.8	2.9	34.3	92.2	5.9	1.0	0.0	1.0	0.0	0.0					7.8

a Antibiotics included: amoxicillin-clavulanate, piperacillin-tazobactam, ceftazidime, ceftaxime, gentamicin, amikacin, ciprofloxacin, nitrofurantoin, trimethoprim, meropenem; na = not applicable  
 Antibiotics excluded: ampicillin (intrinsic resistance), tobramycin, norfloxacin, nalidixic acid, trimethoprim-sulfamethoxazole (high correlation with antibiotics in the included list)

b Antibiotics included: piperacillin-tazobactam, ceftaxime, ceftazidime, cefepime, gentamicin, amikacin, ciprofloxacin, trimethoprim, meropenem  
 Antibiotics excluded: ampicillin, amoxicillin-clavulanate, ceftazolin, and ceftoxitin (all four due to intrinsic resistance); also excluded were ticarcillin-clavulanate, tobramycin, norfloxacin, nalidixic acid, trimethoprim-sulfamethoxazole (high correlation with antibiotics in the included list).

Most of the *E. coli* strains with ESBL genes harboured genes of the CTX-M type (408/536 = 76%). Fifty-three percent of *E. coli* with CTX-M group 1 types were found to belong to sequence type 131 (O25b-ST131). ST131 accounted for 57% of *E. coli* ESBL phenotypes that were ciprofloxacin resistant (MIC >1 mg/L), and only 5% of ciprofloxacin susceptible ESBL phenotypes.

### *Klebsiella pneumoniae*

*K. pneumoniae* showed slightly higher levels of resistance to piperacillin-tazobactam compared with *E. coli*, but lower rates of resistance to amoxicillin-clavulanic acid, cefazolin, ceftriaxone, ceftazidime, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole. Ten (1.0%) *K. pneumoniae* isolates had elevated meropenem MICs (see below). ESBLs were present in 77 of 95 (81%) presumptively ESBL-positive isolates of *K. pneumoniae*, 67 (87%) of which were confirmed to be of the CTX-M type.

### *Enterobacter cloacae* complex

Acquired resistance was common to piperacillin-tazobactam (22.5%/27.6%) ceftriaxone (27.9%/27.9%), ceftazidime (24.9%/28.2%) and trimethoprim-sulfamethoxazole (20.1%/19.9%) among *E. cloacae* complex isolates. Cefepime resistance was less than 15%; ciprofloxacin and gentamicin resistance were both less than 10%. Twenty-one (4.9%) *E. cloacae* complex strains had elevated meropenem MICs.

### Carbapenemase resistance

Overall, 27 isolates (25 patients) in thirteen institutions from five states/territories were found to harbour a carbapenemase gene. *bla*<sub>IMP-4</sub> was detected in 12 isolates: *E. cloacae* (eight), *K. pneumoniae* (three), and *E. coli* (one) – one *E. cloacae* and one *K. pneumoniae* were from the same patient. *bla*<sub>OXA-181</sub> was detected in four *E. coli* and one *K. pneumoniae* – one *E. coli* and one *K. pneumoniae* from the same patient. *bla*<sub>OXA-23</sub> was detected in three *A. baumannii*; *bla*<sub>NDM-1</sub> was detected in two *K. pneumoniae*; *bla*<sub>KPC-2</sub> was detected in one *K. pneumoniae* and

*bla*<sub>KPC-3</sub> in one *E. coli*; *bla*<sub>VIM-1</sub> was detected in one *E. cloacae* and *bla*<sub>VIM-5</sub> in one *P. aeruginosa*; and *bla*<sub>GES-5</sub> was detected in one *P. aeruginosa*.

### Discussion

AGAR has been tracking resistance in sentinel enteric Gram-negative bacteria since 1992. From 2008, surveillance was segregated into hospital-versus community-onset infections. The last year of hospital-onset only surveillance was 2011.<sup>15</sup> In 2013, the first survey of antimicrobial resistance among Enterobacterales isolates from bacteraemic patients through Australia was conducted using an approach similar to that conducted by the European EARS-Net program. 2017 was the fifth survey of antimicrobial resistance among Enterobacterales, and the third for *P. aeruginosa* and *Acinetobacter* spp. from bacteraemic patients through Australia.

CTX-M-producing *E. coli* and *Klebsiella* species and gentamicin- and ciprofloxacin-resistant *E. coli* continued to be a problem in patients with bacteraemia. Of concern is the high proportion of *E. coli* that belong to the O25b-ST131 clone. Carbapenem resistance attributable to acquired carbapenemases are still uncommon in patients with bacteraemia in Australia, although seven different types (IMP, KPC, NDM, OXA-181, OXA-23, VIM, and GES) were detected from thirteen of the participating institutions. Compared with many other countries in our region, resistance rates in Australian Gram-negative bacteria are still relatively low,<sup>16</sup> but similar to those observed in 2017 in many Western European countries.<sup>17</sup>

Multi-resistance is being increasingly observed, especially in *E. coli* and *E. cloacae* complex, both of which have multi-resistance rates (as defined by AGAR) above 18%. This is likely to drive more broad-spectrum antibiotic use, and increase the resistance selection pressure for important reserve classes, especially the carbapenemases.

## Acknowledgments

This study was funded by a grant from the Australian Commission on Safety and Quality in Healthcare.

Members of the AGAR in 2017 were:

### Australian Capital Territory

Peter Collignon and Susan Bradbury,  
Canberra Hospital

### New South Wales

Thomas Gottlieb and Graham Robertson,  
Concord Hospital

Rodney Givney and Ian Winney,  
John Hunter Hospital

James Branley and Linda Douglass,  
Nepean Hospital

Peter Huntington, Royal North Shore Hospital

Sebastiaan van Hal and Alicia Beukers, Royal  
Prince Alfred Hospital

Jock Harkness and David Lorenz, St Vincent's  
Hospital Sydney

Jon Iredell and Andrew Ginn,  
Westmead Hospital

Peter Newton and Melissa Hoddle,  
Wollongong Hospital

### Northern Territory

James McLeod, Alice Springs Hospital

Rob Baird and Jann Hennessy,  
Royal Darwin Hospital

### Queensland

Enzo Binotto and Bronwyn Thomsett,  
Pathology Queensland Cairns Base Hospital

Graeme Nimmo and Narelle George, Pathology  
Queensland Central Laboratory, Royal Brisbane  
and Women's Hospital

Clare Nourse Pathology Queensland Lady  
Cilento Children's Hospital

Petra Derrington and Cheryl Curtis, Pathology  
Queensland Gold Coast Hospital

Robert Horvath and Laura Martin, Pathology  
Queensland Prince Charles Hospital

Naomi Runnegar and Joel Douglas, Pathology  
Queensland Princess Alexandra Hospital

Jennifer Robson and Georgia Peachey, Sullivan  
Nicolaidis Pathology

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Morgyn Warner and Kija Smith, SA Pathology,  
Royal Adelaide Hospital and Women's and  
Children's Hospital

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Louise Cooley and David Jones,  
Royal Hobart Hospital

### Victoria

Denis Spelman and Rose Bernhard,  
Alfred Hospital

Paul Johnson and Frances Hurren,  
Austin Health

Tony Korman and Despina Kotsanas, Monash  
Health, Monash Medical Centre and Monash  
Children's Hospital

Andrew Daley and Gena Gonis, Royal Women's and Children's Hospital

Mary Jo Waters and Lisa Brenton,  
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