Article begins on page three of this document.

Title	The risk of resistance: what are the major antimicrobial resistance threats facing Australia?

Authors:

	Title	First name	**Mid inits**	Last name	Postnom (eg, PhD)	Position1	Address1	Position2	Address2	Tel	Email
1	Assoc. Prof.	Deborah	A	Williamson	MB ChB, PhD, BSc (Hons), MRCP, FRCPA	Deputy Director	1	Clinical Microbiologist	2		deborah.williamson@unimelb.edu.au
2	Prof.	Benjamin	P	Howden	MBBS, FRACP, FRCPA, PhD	Director	1			0383445693	bhowden@unimelb.edu.au
3	Prof.	David	L	Paterson		Professor of Medicine	3	Infectious Diseases Physician and Clinical Microbiologist	4		d.paterson1@uq.edu.au
4											
5											

Number of corresponding author:	1
Number of alternative corresponding author:	

Addresses:

	Institution		City	State		
1	Microbiological Diagnostic Unit Public Health Laboratory		Melbourne	VIC		
2	Melbourne Health		Melbourne	VIC		
3	Centre for Clinical Research, University of Queensland		Brisbane	QLD		
4	Infectious Diseases Unit, Royal Brisbane and Women's Hospital		Brisbane	QLD		
4						
5						

Postal address of first corresponding author (if different from the institutional address given above)	

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mja2.50249

Primary Keywords [Office use only]	Infectious diseases
Secondary keywords [Office use only]	Microbiology; Epidemics
Notes:	

Article details (press ctrl – 9 to enter details):

Article type	Perspective
Blurb	Collaborative systems are required to combat the rising challenge of antimicrobial resistance in health care facilities and the community

Office use

Ms. Number	mja19.00324.R3
Medical editor	Francis Geronimo
Medical editor email	fgeronimo@mja.com.au
Structural editor	Graeme Prince
Structural editor email	gprince@mja.com.au
Section/Category	Perspective (2-pp)
Strapheading	Perspective
Substrap	

Wiley – file data:

Filename for copyediting	wil_mja19.00324_ms
Accompanying graphics	
Stock images	wil_mja19.00324_im
Appendices	

Office use – history:

Event	Date
Original submission received	08/04/2019

Event	Date
Accept	30/05/2019

Proof sent to author	
Proof returned by author	
Published (date format xx/xx/xx)	05/09/19
Issue	3
Vol	211
DOI	10.5694/mja19.00324
Journal	The Medical Journal of Australia
Original article DOI (for response)	

The risk of resistance: what are the major antimicrobial resistance threats facing Australia?

Collaborative systems are required to combat the rising challenge of antimicrobial resistance in health care facilities and the community

These germs of disease have taken toll of humanity since the beginning of things—taken toll of our prehuman ancestors since life began here. But by virtue of this natural selection of our kind we have developed resisting power; to no germs do we succumb without a struggle ...

The War of the Worlds, HG Wells, 1897

In 1897, HG Wells envisaged a world where, among the chaos of war, a silent battle was occurring, with microbes emerging as victorious against an invading enemy. In this pre-antibiotic world, Darwinian selection was suggested as the main means of humankind's survival against pathogens, with a certain resignation that some individuals would inevitably succumb to the "germs of disease". Thankfully, in the mid-20th century, the introduction of antibiotics provided a transformative defence against infectious diseases, enabling lifesaving advances in medical care. However, similar to the scenario described by Wells, humanity again faces an evolutionary struggle against microbes, although in this instance, the evolutionary advantage of microbes over humankind has been greatly amplified by the global selection and dissemination of antimicrobial resistance (AMR), largely due to our misuse and overuse of antimicrobials. In our neo-Wellsian world, we face a situation where common bacterial infections may again become untreatable, and the vulnerable in society capitulate to infection.

Concurrent with the increasing use of antimicrobials over the past seven decades are other major anthropogenic changes (eg, population growth, globalisation, geopolitical instability, climate change, food insecurity) that are inextricably linked to AMR and have contributed to the complexity of the AMR phenomenon. Given the dynamic nature of the threat, it is critical to understand where and why AMR pathogens currently exist, and the risk they pose. As highlighted in a recent report to the United Nations,[1] the risk posed by AMR varies regionally according to factors such as laboratory infrastructure (including rapid diagnostics and effective surveillance), infection control in health care facilities, and antimicrobial stewardship policies (in both human and animal settings). Here, we

provide a "horizon-scanning" assessment of major emerging AMR threats facing Australia today, with a focus on highly resistant pathogens that are not yet endemic in Australian health care and community settings, and insights provided by genomic analysis. Although we discuss only four of these pathogens, additional AMR pathogens posing an emerging risk to Australia are described further in the Box.

Emerging threats in health care facilities

Health care facilities provide a fertile environment for the spread of AMR pathogens, with vulnerable patient populations existing in close quarters. Often, as measures are introduced to mitigate the impact of one AMR pathogen in health care facilities, another arises, leading to an escalation in empiric antimicrobial regimens and further potential for selection of resistance.

This situation is exemplified by the global emergence of extended-spectrum β-lactamases in Enterobacteriales in the 1980s, swiftly followed by the rise of carbapenemase-producing Enterobacteriales (CPE) in the 2000s. In addition to resistance to carbapenems (often considered last resort antimicrobials), CPE are resistant to a range of other antimicrobials, limiting treatment options to one or two less efficacious (and often more toxic) alternatives — or in some cases, no alternatives. Moreover, mortality rates of about 40% have been reported for infections caused by CPE, making these pathogens a critical public health threat.[2] Based on data from the National Alert System for Critical Antimicrobial Resistances, the number of CPE reported in Australia increased from 527 in 2017 to 603 in 2018, a relative change of 14.4%.[3] However, rather than absolute numbers, a more informative assessment of risk is the extent of CPE transmission within and between Australian health care facilities, compared with sporadic importations of CPE from overseas. One study used a combination of epidemiology and whole genome sequencing to investigate an outbreak of *Klebsiella pneumoniae* CPE in Victoria. Between 2012 and 2015, 69 patients with *K. pneumoniae* CPE were identified, with only eight patients reporting recent international travel, suggesting local CPE transmission. Rather than a single outbreak, four separate *K. pneumoniae* CPE transmission networks were identified, spanning twenty health care facilities.[4] Similarly, a whole genome sequencing-based study from Queensland characterised an outbreak of IMP-4 carbapenemase-producing *Enterobacter cloacae*, and identified dissemination of the IMP-4-containing plasmid across a range of Enterobacteriales, including a *Salmonella* isolate from a domestic cat.[5] Collectively, these studies demonstrate the necessity of applying genomic-based approaches to fully understand the complexities of CPE transmission, and to permit targeted interventions.

The most recent emerging threat in Australian health care facilities is not a bacterium but a yeast, *Candida auris*. First described in Japan in 2009, *C. auris* infections have been reported in over thirty countries, with major nosocomial outbreaks reported overseas, particularly in intensive care and other high dependence units.[6,7] Key hallmarks of outbreaks include high crude mortality rates associated with invasive infections (up to

50%); resistance to several antifungals, particularly triazole antifungals and amphotericin B; difficulties in laboratory identification; and widespread patient-to-patient transmission, facilitated by environmental contamination.[7] Phylogeographic analysis has identified four *C. auris* lineages associated with different geographical regions (South America, Africa, India/Pakistan, and South-East Asia), suggesting independent emergence of *C. auris* in each region.[6] At present, *C. auris* in Australia has been associated with overseas acquisition;[8] however, ongoing vigilance, including screening of patients with recent exposure to overseas health care facilities, is required to prevent endemicity of *C. auris* in Australia.

Emerging AMR threats in the community

Similar to AMR in health care facilities, AMR in community settings poses a major health threat, and many of the AMR pathogens designated by the World Health Organization as priority pathogens are community associated (eg, *Salmonella* spp., *Shigella* spp., *Neisseria gonorrhoeae*).[2] Given the ubiquitous nature of associated activities, two key areas where AMR poses a particular risk to society are food and waterborne infections and sexually transmitted infections.

Since late 2016, there has been an ongoing outbreak of extensively drug-resistant *Salmonella enterica* serovar Typhi in the Sindh province of Pakistan, representing the first reported epidemic due to ceftriaxone-resistant *S.* Typhi, with over 5300 cases as of December 2018.[9] Epidemiological investigations suggested the source of the outbreak as faecally contaminated municipal water (supported by the detection of *S.* Typhi DNA in community water samples), with the outbreak likely to have been expedited by low vaccination rates and high population density.[10] Genomic analysis revealed that outbreak isolates belonged to the successful drug-resistant H58 *S.* Typhi lineage, and harboured a multidrug-resistant plasmid containing CTX-M-15 extended-spectrum β-lactamases and fluoroquinolone resistance genes.[11] Of particular concern was the potential acquisition of this plasmid from *Escherichia coli*, further highlighting the propensity for AMR spread across both human and bacterial populations.[11] To date, no outbreak-associated cases have been formally reported in Australia, although cases have been reported in the United Kingdom and the United States. It is imperative that travellers to Pakistan and clinicians treating patients returning from this region are aware of these heightened health risks.

Another ominous community-based threat is the emergence of extensively drug-resistant *N. gonorrhoeae*, resistant to the two dual first line treatments, ceftriaxone and azithromycin. Between February and April 2018, three cases of extensively drug-resistant *N. gonorrhoeae* were described: one in the UK and two epidemiologically unrelated cases in Australia.[12] Of these, two (heterosexual males from the UK and Australia) reported recent travel to South-East Asia, while the other (a female) reported no recent travel outside Australia.[12] Genomic analysis revealed that all three isolates were highly related, suggesting circulation of this clone in South-East Asia, with incursions (and possible secondary transmission) into areas of low endemicity. In the face of dramatically

increasing gonorrhoea notifications in Australia (from 66.9 to 125.9 notifications per 100 000 population in 2014 and 2018, respectively),[13] a concerted national effort is required to respond to AMR in *N. gonorrhoeae*, which should include reducing the number of circulating cases, as spread of AMR is directly proportional to prevalence.

Beyond the bugs: systems-based threats from within

Along with the representative emerging threats we have focused on in this article, there remain omnipresent challenges with AMR pathogens that have established endemicity in hospital and community settings in Australia (eg, extended-spectrum β-lactamases; vancomycin-resistant Enterococci, for which we have one of the highest rates in the world; methicillin-resistant *Staphylococcus aureus*). Responding to AMR threats, both emerging and endemic, requires new approaches. Advances in genomic technology provide unparalleled opportunities to move existing surveillance systems beyond number-counting, and enable real-time information on the relatedness of hospital and community-associated AMR pathogens across jurisdictions.[14] Such information could inform both local and national responses to the emergence and spread of AMR, across both human and animal populations.[13] However, there is presently no formal national mechanism for rapid, real-time sharing and analysis of AMR-related genomic and epidemiological data across jurisdictions, creating a major risk for successful implementation of one of the pillars of the 2015–2019 National Antimicrobial Resistance Strategy — the development of nationally coordinated One Health surveillance of AMR.[15] Further, the widespread adoption of culture-independent diagnostic testing for many pathogens (eg, *N. gonorrhoeae, Salmonella* spp., *Shigella* spp.) hampers the ability of laboratories to detect AMR in these pathogens, creating a black hole in AMR surveillance. Measures such as providing incentives to request reflex laboratory cultures and development of metagenomic approaches are urgently required to mitigate the impact of culture-independent diagnostic testing.

While a high level of health care is enjoyed by most Australians, there is currently large reservoir of AMR both within Australia and at our doorstep. Global interconnectedness makes this threat greater, as AMR pathogens can be carried across borders by unsuspecting travellers. As strategies are put in place internationally (including the use of real-time genomic surveillance) to effectively prevent, detect and treat AMR pathogens, it is critical that Australia also implement nimble, cross-sectoral and collaborative systems that are fit for purpose in the 21st century.

Acknowledgements: Deborah Williamson is supported by a National Health and Medical Research Council (NHMRC) Early Career Fellowship (GNT1123854). Benjamin Howden is supported by an NHMRC Practitioner Fellowship (GNT1105905).

Competing interests: David Patterson has received research grants or honoraria for participation in advisory boards from Shionogi, MSD, Pfizer, Achaogen, Entasis Therapeutics and Accelerate Diagnostics.

Author details

Deborah A Williamson[1,2]
Benjamin P Howden[1]
David L Paterson[3,4]

1 Microbiological Diagnostic Unit Public Health Laboratory, Melbourne, VIC.
2 Melbourne Health, Melbourne, VIC.
3 Centre for Clinical Research, University of Queensland, Brisbane, QLD.
4 Infectious Diseases Unit, Royal Brisbane and Women's Hospital, Brisbane, QLD.
deborah.williamson@unimelb.edu.au
doi: 10.5694/mja19.00324

References

1 Interagency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. Report to the Secretary-General of the United Nations. April 2019. https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/ (viewed May 2019).
2 Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Inf Dis* 2018; 18: 318-327.
3 Australian Commission on Safety and Quality in Health Care. CARAlert data update 10 – 1 November 2018 to 31 December 2018. Sydney: ACSQHC, 2019. https://www.safetyandquality.gov.au/publications/caralert-data-update-10-1-november-to-31-december-2018/ (viewed Apr 2019).
4 Kwong JC, Lane CR, Romanes F, et al. Translating genomics into practice for real-time surveillance and response to carbapenemase-producing Enterobacteriaceae: evidence from a complex multi-institutional KPC outbreak. *PeerJ* 2018; 6: e4210.
5 Roberts LW, Harris PN, Ben Zakour NL, et al. Genomic investigation of an outbreak of carbapenemase-producing *Enterobacter cloacae*: long-read sequencing reveals the context of *bla*IMP4 on a widely distributed IncHI2 plasmid. *BioRxiv* 2017; doi: 10.1101/172536.
6 Eyre DW, Sheppard AE, Madder H, et al. A *Candida auris* outbreak and its control in an intensive care setting. *N Engl J Med* 2018; 379: 1322-1331.
7 Jeffery-Smith A, Taori SK, Schelenz S, et al. *Candida auris*: a review of the literature. *Clin Microbiol Rev* 2018; 31: e00029-17.
8 Heath CH, Dyer JR, Pang S, et al. *Candida auris* sternal osteomyelitis in a man from Kenya visiting Australia, 2015. *Emerg Infect Dis* 2019; 25: 192-194.
9 World Health Organization. Disease outbreak news: Typhoid fever – Islamic Republic of Pakistan. https://www.who.int/csr/don/27-december-2018-typhoid-pakistan/en/ (viewed Apr 2019).
10 Qamar FN, Yousafzai MT, Khalid M, et al. Outbreak investigation of ceftriaxone-resistant *Salmonella enterica* serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case–control study. *Lancet Infect Dis* 2018; 18: 1368-1376.
11 Klemm EJ, Shakoor S, Page AJ, et al. Emergence of an extensively drug-resistant *Salmonella enterica* serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *mBio* 2018; 9: e00105-18.
12 Jennison AV, Whiley D, Lahra MM, et al. Genetic relatedness of ceftriaxone-resistant and high-level azithromycin resistant Neisseria gonorrhoeae cases, United Kingdom and Australia, February to April 2018. *Euro Surveil* 2019; 24: 1900118.
13 Australian Government Department of Health. National Notifiable Diseases Surveillance System. http://www9.health.gov.au/cda/source/cda-index.cfm (viewed Apr 2019).
14 Williamson DA, Kirk MD, Sintchenko V, Howden BP. The importance of public health genomics to ensure health security for Australia. *Med J Aust* 2019; 210: 295-297. https://www.mja.com.au/journal/2019/210/7/importance-public-health-genomics-ensuring-health-security-australia
15 Australian Government Department of Health and Department of Agriculture and Water Resources. Implementation plan: Australia's first National Antimicrobial Resistance Strategy 2015–2019. Canberra: Commonwealth of Australia, 2016. https://www.amr.gov.au/resources/national-amr-implementation-plan (viewed

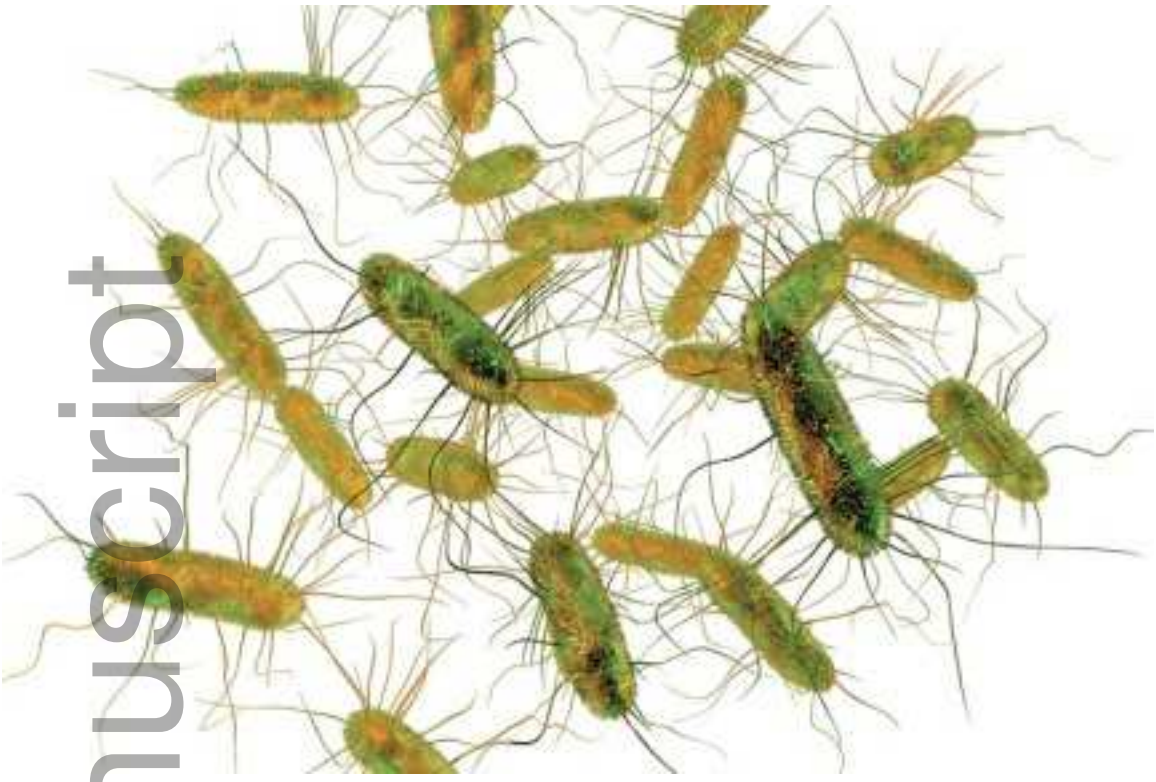
Apr 2019).

[Box]

1 Emerging antimicrobial-resistant pathogens posing clinical and public health risks to Australia

Pathogen	Frequency of occurrence*		Potential for transmission in hospitals or community[2,7]	Reported all-cause mortality with infections (range)[2]
	Australia[3]	Geographical areas with a high prevalence of AMR globally[2,7]		
Major emerging AMR threats in health care facilities				
Carbapenem-resistant *Pseudomonas aeruginosa*	Unknown	High	High	33–53%
Carbapenem-resistant *Acinetobacter baumanii*	Unknown	High	High	45–59%
Vancomycin-resistant *Staphylococcus aureus*	None reported	Low	Unknown	24–47
Carbapenemase-producing Enterobacteriaceae	High	High	High	35–54%
Candida auris	Low	High	High	0–50%[6]
Major emerging AMR threats in the community				
Cephalosporin-resistant non-typhoidal *Salmonella enterica*	Moderate	Unknown	High	Unknown
Cephalosporin-resistant *S. enterica* serovar Typhi	Low	High	High	Unknown
Ceftriaxone-resistant *Neisseria gonorrhoeae*	Low	Unknown	High	na
Multidrug-resistant *Shigella* spp.	High	High	High	na
Extensively drug-resistant *Mycobacterium tuberculosis*	Low	High	High	na

AMR = antimicrobial resistance; na = not assessed; CARAlert = National Alert System for Critical Antimicrobial Resistances. * Risk stratification: low, < 10 cases per year; moderate, 10–100 cases per year; high, ≥ 100 cases per year. Note that carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumanii* and *Candida auris* are planned for inclusion in CARAlert reporting in 2019.[3]



mja2_50249_f1.jpg