Disease burden, associated mortality and economic impact of antimicrobial resistant infections in Australia

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The Lancet Regional Health - Western Pacific 2022;27: 100521
Published online xxx
https://doi.org/10.1016/j.lanwpc.2022.100521

Summary

Background The growing spread of antimicrobial resistance (AMR) is accepted as a threat to humans, animals and the environment. This threat is considered to be both country specific and global, with bacteria resistant to antibiotic treatment geographically dispersed. Despite this, we have very few Australian estimates available that use national surveillance data supplemented with measures of risk, to generate reliable and actionable measures of AMR impact. These data are essential to direct policies and programs and support equitable healthcare resource utilisation. Importantly, such data can lead to implementation of programs to improved morbidity and mortality of patients with a resistant infection.

Methods Using data from a previous case-cohort study, we estimated the AMR-associated health and economic impact caused by five hospital-associated AMR pathogens (*Enterococcus spp.*, *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *S. aureus*) in patients with a bloodstream, urinary tract, or respiratory tract infection in Australia in 2020. We estimated disease burden based on the counterfactual scenario in which all AMR infections were replaced by no infection.

We used a population-level simulation model to compute AMR-associated mortality, loss of quality-adjusted life years and costs.

Findings In 2020, there were 1,031 AMR-associated deaths (95% uncertainty interval [UI] 294, 2,615) from the five resistant hospital-associated infections in Australia. The greatest odds of dying were from respiratory infections (ceftazidime-resistant *P. aeruginosa*) and bloodstream infections, both resulting in high hospital and premature death costs. MRSA bacteraemia contributed the most to hospital costs (measured as bed-days) as patients with this infection resulted in additional 12,818 (95% UI 7246, 19966) hospital bed-days and cost the hospitals an extra $24,366,741 (95%UI $13,774,548, $37,954,686) per year. However, the cost of premature death from five resistant pathogens was $438,543,052, which was by far greater than the total hospital cost ($71,988,858). We estimate a loss of 27,705 quality-adjusted life years due to the five AMR pathogens.

Interpretation These are the first Australian estimates of AMR-associated health and economic impact. Country-level estimates of AMR impact are needed to provide local evidence to better inform programs and health policies to reduce morbidity and mortality associated with infection. The burden in hospital is likely an underestimate of the impact of AMR due to community-associated infections where data are limited, and the AMR burden is high. This should now be the focus of future study in this area.

Funding TMW was supported by the Australian Partnership for Preparedness Research on Infectious Disease Emergencies (APPRISE) (grant number GNT1116530) Fellowship.

Keywords: Antimicrobial resistance; Australia; Health; Quality-adjusted life years; Costs

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Research in context

Evidence before this study

Accurate estimates of the burden of antimicrobial resistance (AMR) provide the foundation for planning and prioritizing health. Recently published global estimates demonstrate that the burden is higher than the previously estimated 700,000 deaths per year due to AMR. In fact, as many as 1.3 million people died world-wide in 2019 because of an AMR infection. These estimates are critical in supporting global efforts but are less useful for national efforts in combating AMR.

National estimates of impact are important to describe and highlight variations and inequalities. These are key resources necessary to use when developing strategies to reduce infections and improve health outcomes for people with resistant pathogens. Additionally, accurate estimates of impact within a population can support a more equitable approach to resource allocation by drawing focus on regions of greatest risk of infection.

Previous studies have reported the impact of AMR on patients, healthcare and society and shown geographically variable estimates and future projections of AMR impact. Clusters of hotspots of risk factors converging with surveillance blind spots have been identified, contributing to under-representation of some of the most at risk remote-dwelling populations in Australia.

The first Australian report of antimicrobial use and resistance in human health was published in 2016. Despite much effort in coordinating monitoring of AMR across the country, there are only state-wide estimates of AMR-associated impact. They show that in Queensland hospitals an estimated 1693 patients' infections (8.3%, n=20,469) are due to antibiotic-resistant bacteria, resulting in 717 hospital bed-days and an estimated cost of US$1.6 million to the Australian healthcare system. Currently, there are no national estimates quantifying the AMR-associated burden in Australia.

Added value of this study

We provide the first national estimate of the health and economic impact of AMR in Australia using local Australian data. We used population-level surveillance data and applied rigorous, un-biased estimates of AMR-associated morbidity and mortality generated from data linkage studies. We then assessed the impact of AMR on patient morbidity and Australian healthcare cost using a population-based simulation model. We assessed scenarios for future impact of AMR by exploring regions across Australia that had low AMR prevalence ('best-case') and those with high AMR prevalence ('worst-case') for each of the pathogens and sites of infection. The large variation in AMR impact between high and low AMR prevalence regions provides evidence to support decision making on representative surveillance and data infrastructure required.

Implications of all the available evidence

Country-level estimates of the AMR are needed to inform national AMR strategy and implementation plans. For these estimates, local data needs to be representative of the population, especially in a country which is large, geographically and demographically diverse such as Australia. This study provides further evidence of the importance and feasibility of enhancing surveillance infrastructure and processes, particularly to include the impact of AMR in the primary health/community sector and more broadly under the One Health approach. Together with current efforts in monitoring AMR in hospitals, only then can we truly determine a more complete burden of human AMR.

Introduction

Each year an estimated 5 million people die with an antimicrobial resistant (AMR) infection, a number greater than the number of deaths from HIV/AIDS and malaria combined.[1] These recent global estimates are likely an under-representation of the true global burden as approximately 2 billion people live in countries with insufficient diagnostic capacity and/ or surveillance to detect many of these AMR pathogens.[2] If rates of AMR continue to grow, as it is expected to, greater numbers of people globally will be affected and die due to AMR.

Australia is not immune to the impact of AMR and rates of resistance to several pathogens are of particular concern.

Escherichia coli (E. coli), where resistances to common agents used for treatment continue to increase; resistance to third-generation cephalosporins (3GC) (ceftriaxone or cefotaxime) has increased from 9.7% in 2016 to 12% in 2019 in Australia.[3,4] Patterns also show high geographical heterogeneity.[5] Rates of 3GC resistant *E. coli* range from 7% in the south to 18% in the north, whilst resistance to fluoroquinolones is more uniform across the country (11-15%).[4,6] Hospital data shows that the rate of inappropriate prescribing for ceftriaxone in Australia has increased in the past two years from 25% to 29%.[3,4] There were sporadic reports of ceftriaxone-resistant gonorrhoea in 2019.[4]

Outbreaks of vancomycin−resistant *E. faecium* (VRE) have been common in hospitals for decades. Australia has one of the highest rates of VRE in the world and resistance rates have been above 40% since 2016.[7] Importantly, patients with a VRE infection require treatment with agents that are usually reserved such as teicoplanin or daptomycin.

Other notable resistant pathogens in Australia include *Acenitobacter baumannii* (*A. baumanni*), where resistance has remain below 5% in hospitals,[4] however the pathogen can cause severe community-acquired pneumonia.[8] Strains of community-onset non-multidrug resist strains are believed to be closely related to multidrug resistant *A. baumanni* stains from geographically distant international locations suggesting global spread of the bacteria.

Progress has been made in reducing methicillin-resistant *Staphylococcus aureus* (MRSA) infections in hospitals by almost half (41% in 2013 to 20%)[9] by implementing antimicrobial stewardship and infection control procedures including hand hygiene programs.[10] However, MRSA is still particularly problematic and rising in the north of Australia. There are clusters of very high MRSA (35% of *S. aureus* isolates overall and 37% in blood cultures) suggestive of community transmission, and co-resistance with second-line antibiotics such as clindamycin (35%) presenting a significant impediment to oral treatment and increased risk of more severe infections.[5,11]

In contrast to evidence of very high levels of AMR in Australia (likely compounded by chronic disease and complex socio-demographic factors),[12] international estimates of the Australian burden do not reflect these geographical variations and Australia is considered a low-AMR region with an average 10% resistance to eight key bacterial pathogens.[13] One limitation of these data is that they rely on contributions from only a select number of studies. This usually does not include local data for all jurisdictions and can mask the variations in country prevalence. Clusters of hotspots of risk factors and potential infection converging with surveillance blind spots have been identified, which has led to under-representation of some of the most at risk remote-dwelling populations in Australia in available data.[14]

With the prevalence of infections disproportionately spread across the country it is important that appropriate antibiotic stewardship and infection prevention and control measures are tailored to local conditions.[5,12,15] Accurate estimates of AMR burden at a local level are also required.

To address these gaps, we used estimates of AMR-associated morbidity and mortality to inform a more accurate population-based model to determine the health and economic burden of AMR infection in Australian hospitals.

Methods

Study design

We updated the Health and Economic Modelling of AMR in Australia (HEMAA) population-level simulation model (referred to as "the simulation model")[16] to determine the Australian healthcare burden of five clinically-important organisms, namely *Enterococcus spp., E. coli, K. pneumoniae, P. aeruginosa* and *S. aureus*.

The model parameters were updated with recently published state-wide Queensland healthcare-associated morbidity and mortality estimates[17] and 2021 cost estimates (Table 1, Supplementary S1-S5). Using these components, we estimated disease burden based on one counterfactual. The counterfactual of AMR-associated morbidity and mortality is based on the alternative scenario in which all AMR infections were replaced by no infection.[18]

Health parameters used in the simulation model

AMR incidence, morbidity and mortality were obtained from a published multi-site, retrospective case-cohort study.[17] These estimates were used to model the number of AMR infections, length of hospital stay, years of life and quality-adjusted life years lost due to AMR infections in Australia (Table 1). Further details of input parameters used for each of the five organisms are presented in supplementary Tables S1–S5.

Below is a brief overview of the case-cohort study design from which our simulation model estimates were drawn.

The case-cohort study by Lee et al (2020) collected all Queensland acute-care hospital admissions between 1 January 2012 and 30 December 2016.[17] The methods of this study have been previously published.[17] Briefly, incidence of infection and resistance parameters were derived from a database of clinical isolates linked hospital admissions for all patients in Queensland,

Model parameter	Metric	Data source
Incidence of infection	Incidence of resistant + susceptible infection per 10,000 patient bed-days	Case cohort study[17]
Resistance	Number of resistant isolates / total isolates tested represented as proportion (%)	
Length of stay (LOS)	The number of hospital days for patients with a resistant infection	
AMR-associated mortality	The odds of dying due to resistant infection compared to odds of dying in uninfected control patients, represented as odds ratio (OR)	
Years of life lost and Quality Adjusted life Years (QALYs)	The average years a person would have lived if they had not died prematurely due to AMR infection, adjusted for age-related quality of life, represented as QALYs	Case cohort study[17]; Australian Institute of Health and Welfare[19]
Healthcare costs	Accounting cost of a hospital bed-day, represented in Australian dollars (AUD)	Independent Hospital Pricing Authority[20]
Premature mortality costs	The utility value of lost QALYs due to premature death	Australian Institute of Health and Welfare[19]

***Table 1*: Parameters included in the population-level simulation model.**

Incidence of infection (resistant + susceptible) 10,000 patient bed-days	Resistance, %	LOS, days (95%CI)	Odds ratio of mortality (95%CI)
E. coli	3GCR	3GCR	3GCR
BSI: 3.4 (2.9, 6.3)	BSI: 7.65 (6.56, 8.75)	BSI: 2.34 (2.21, 2.48)	BSI:3.06 (1.2, 6.81)
UTI: 51.1 (49.9, 100.9)	UTI: 5.0 (4.77, 5.23)	UTI: 1.01 (0.87, 1.14)	UTI: 0.52 (0.3, 0.85)
K. pneumoniae	3GCR	3GCR	3GCR
BSI: 2.0 (1.7, 3.7)	BSI: 3.95 (2.92, 4.99)	BSI:7.27 (7.13,7.41)	BSI: 2.23 (0.33, 8.97)
UTI: 13.8 (12.9, 26.8)	UTI: 4.96 (4.52, 5.4)	UTI:2.29 (2.1, 2.48)	UTI:0.92 (0.38, 1.89)
S. aureus	MRSA	MRSA	MRSA
BSI: 5.7 (5.2, 10.9)	BSI: 14.01 (12.92, 15.11)	BSI: 7.96 (7.79, 8.13)	BSI:3.34 (1.91, 5.53)
UTI: 2.8 (2.4, 5.3)	UTI: 16.3 (14.64, 17.95)	UTI: 1.44 (1.29, 1.6)	UTI: 1.43 (0.62, 2.89)
P. aeruginosa	Ceftazidime resistant	Ceftazidime resistant	Ceftazidime resistant
BSI: 1.6 (1.3, 2.9)	BSI: 8.07 (6.46, 9.68)	BSI: 5.04 (4.9, 5.17)	BSI:3.86 (1.07, 11.00)
UTI: 20.1 (19.1, 39.2)	UTI: 17.4 (16.54, 18.27)	UTI: 2.04 (1.87, 2.22)	UTI:1.3 (0.82, 1.97)
RTI: 11.1 (10.3, 21.4)	RTI:8.5 (8.03, 8.97)	RTI: 1.51 (1.34, 1.67)	RTI:3.03 (2.1, 4.26)
E. faecium	VRE	VRE	VRE
BSI: 0.6 (0.4, 1.0)	BSI: 40.19 (35.45, 44.93)	BSI: 2.04 (1.73, 2.34)	BSI:5.01 (2.26, 10.39)
UTI: 4.2 (3.7, 7.8)	UTI: 44.43 (42.59, 46.27)	UTI: 1.43 (1.27, 1.58)	UTI:1.23 (0.78, 1.84)

***Table 2*: Published estimates[17] used in the study population-level simulation model.**
BSI: Bloodstream infection; UTI: Urinary tract infection; RTI: Respiratory tract infection; 3GCR: third-generation cephalosporin resistant; VRE: vancomycin-resistant *E. faecium*; MRSA: methicillin-resistant *Staphylococcus aureus*.

Australia.[21] This database provides antimicrobial susceptibilities for all 170 Queensland public hospitals networked by 35 laboratories that collect specimens from district laboratories in rural, large, regional as well as metropolitan teaching hospitals. The data included the first clinical isolate from a patient infected with any one of the included organisms. An estimated 160,000 infections are recorded each year in this database, excluding infection control screens with contributing sites from blood, urine, respiratory and other sites (swabs, operational specimens, tissue, fluid, and pus).[21]

In the case-cohort study,[17] antibiotic susceptibility results were provided as European Committee on Antimicrobial Susceptibility Testing interpreted values (resistant, intermediate, and susceptible). All resistant and intermediate results were regarded as "resistant" for the purpose of phenotype analysis. Third-generation cephalosporin (3GC) resistance was inferred from ceftazidime and ceftriaxone resistance, and methicillin resistance in Staphylococcus aureus (*S. aureus*) was inferred from resistance to flucloxacillin.

We used data for 5 exposure groups from multiple sites (BSI, UTI, RTI)

1. 3GC-resistant (3GCR) *K. pneumoniae* BSI, UTI
2. 3GC-resistant (3GCR) *E. coli* BSI, UTI
3. Ceftazidime-resistant *P. aeruginosa,* BSI, UTI, RTI
4. Methicillin-resistant *S. aureus* (MRSA), BSI, UTI
5. Vancomycin-resistant *E. faecium* (VRE), BSI, UTI

BSI was defined as a positive blood culture present >48 hours after hospital admission. A UTI was defined as a patient having a urine culture >48 hours after hospital admission with no more than two species of organisms identified and a count of $>10^5$ colony-forming units of bacteria per milliliter in a urine specimen. RTI was defined as a positive P. aeruginosa smear or culture and a count of $>10^4$ colony-forming units per milliliter from lung tissue or pleural fluid present >48 hours after admission.

The estimates of LOS and odds ratio of mortality for each of the five AMR pathogens of interest used in our population-level simulation model were drawn from the case-cohort study which adjusted for potential confounding variables such as age, sex, admission year, time from admission to infection, hospital peer-group and remoteness, and comorbidities as additional covariates in their analysis. Authors used multi-state modelling to adjust for time-dependent bias (Table 2).[17] The multi-state survival model used by Lee et al (2020) included four states: uninfected, infected, discharged alive and died in hospital. Patients entered the model through the "uninfected" state. Transition between states was determined by transition hazards (α), accounting for both time-dependent and competing risk natures of the events.[17]

In the absence of other state-wide or national data linkage studies in Australia, we used the published incidence rate, proportion resistance of isolates and odds ratio of mortality due to AMR pathogens estimates[17] in our simulation model. In doing so, we assumed the

estimates of AMR health impact have remained constant between the published date range (2012–2016) and 2020. Importantly, Lee et al (2020)[17] estimates of rates of resistant all fell between the rates of resistance published in AURA 2021 reporting the national AMR surveillance program.[4]

Queensland incidence rate and proportion resistant (Table S1-S5) was extrapolated to the Australian population using the most recently published estimates of the number of patient bed-days in Australian hospitals (n= 20,257,957 million).[22] We used the number of patient bed-days in Australia to estimate the number of infections for each of the five AMR pathogens in Australia. We computed this using the following equation:

$$\text{Number of infections in Australia} = \text{Incidence} * \text{Proportion resistant} * 20,257,957$$

Using the number of infections, we applied the infection-attributable LOS (Table S1–S5) to compute the number of hospital bed days in Australia, according to the following formula:

$$\text{Number of hospital bed} - \text{days in Australia} = \text{Number of infections} * \text{length of stay (LOS)}$$

Lastly, the number of infections, odds of death (Table S1–S5) and the published proportion of deaths amongst admitted hospital patients (5.7%)[17] was used to compute the number of AMR-associated deaths according to the following formula:

$$\text{Number of AMR} - \text{associated deaths in Australia} = \text{Number of infections} * [(\text{odds ratio} * 5.7) - 5.7]$$

Enumeration of years of life lost and quality-adjusted life years in Australia

We calculated the years of life lost by using life expectancy in Australia[23] and computing the age of death of patients with each of the five AMR infections.[17] Years of life lost were adjusted by age-related utility weights[23] to calculate the quality-adjusted life years (QALYs). Loss of one QALY equates to a loss of one year of life in perfect health and provides a measure of AMR impact due to premature death. This was computed with the following formula:

$$\text{Loss of QALYs due to death} = \text{Utility weight} * \text{Expected years of life lost}$$

Economic parameters used in the population-level simulation model

The costs of AMR in Australian hospitals is presented separately as hospital costs and cost of premature death.

Hospital costs were calculated by computing the number of AMR infections in Australia, length of hospital stay and the cost of a bed-day. We enumerated the number of bed days due to AMR infection using published estimates (Table 2) and applied the value of a hospital bed-day in Australia ($1901/ bed day).[20]

The cost of premature death is a measure of the number of AMR deaths combined with the value of lost QALYs. The economic cost of mortality due to resistance was calculated based a willingness to pay per QALY of $29,274.[19]

All costs were calculated in Australian dollars (AUD). Costs, including cost of premature death, discounted at 3.5%.

Estimating uncertainty in the model

Uncertainties in the model parameters were included by fitting prior statistical distributions and making 10,000 random picks from all distributions. The method of moments was used to estimate the model parameters for γ and β distribution (Tables S1–S5). A γ distribution was fitted to LOS data to reflect the skew typical of this type of information, and a β distribution to describe uncertainty about the true value of a rate and resistance probability. A log-normal distribution was used for mortality measures. The results of the simulations show the uncertainty in estimates.

Estimating high and low AMR prevalence scenarios

To determine the impact of AMR in a high and low prevalence setting, we used prevalence of AMR from Australia's national AMR surveillance program - Antibiotic Usage and Resistance in Australia (AURA).[4] This national program provides Australia-wide aggregated estimates of resistance across all states and territories, providing a snapshot of resistance across the country.

Ethics

The original two studies[16,17] used in this study are published with full ethical approvals. This study did not require further ethical approval as no new patient level data was accessed or used. Written approval was provided for the release of region level data from the AURA program pertaining to the high and low prevalence of AMR.

Role of funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Health burden

In 2020, the five analysed pathogens resulted in 21,663 AMR infections in Australia (95% UI 12113, 33746). The

highest number of infections were in patients with a urinary infection, which contributed to 70% (n = 15,160 infections) of the total hospital burden. The remaining infections included respiratory tract *P. aeruginosa* (16%; n = 3446) and blood stream infection (BSI) which contributed 14% (n = 3057) of the total number of AMR infections in Australian hospitals.

Using published measures of AMR-associated odds of dying (odds ratio,[17] Table S1-5), we estimated that there were 2121 (95%UI 691, 5906) extra people dying each year in Australian hospitals because of a resistant infection (Table 3). The highest number of hospital deaths was in patients with a ceftazidime-resistant *P. aeruginosa* respiratory infection (n = 922, 95%UI 397, 1720), followed by 3GC-resistant *E.coli* BSIs (n = 260, 95% UI 18, 1077). Lee et al (2021) showed that the odds of dying from a resistant *K. pneumoniae* UTI was almost equal to the odds of dying in the control/uninfected patient population (OR= 0.9; 95%CI 0.38, 1.89 [Table S2]), and similarly for resistant *E.coli* (OR=0.5; 95%CI 0.3, 0.89, [Table S1]). The lack of significantly increased odds of death in both *E. coli* and *K. pneumoniae* AMR UTIs compared to control patients did not result in any additional deaths in our analysis (Table 3).

The average age at death of patients with an AMR infection ranged from 53 years for 3GC-resistant *K. pneumoniae* BSI to 71 years for VRE UTIs (Table 4). Patients with a 3GC-resistant *K. pneumoniae* BSI, a ceftazidime-resistant *P. aeruginosa* BSI and UTI, died earliest. These three patient groups each lost an estimated 15 year of life in good health (i.e. quality-adjusted life years, QALYs) and an average of 30 years of life (Table 4). Patients with a MRSA BSI lost on average 28 years of life, and an estimated 14.5 QALYs. The total loss of life for the included infections was 27,705 quality-adjusted life years.

Organism	Number of infections (95%UI)	Number of deaths (95%UI)
3GCR *E. coli* BSI	524 (293, 825)	70 (5, 296)
3GCR *E. coli* UTI	5179 (2902, 8008)	0
3GCR *K. pneumoniae* BSI	161 (85, 266)	20 (5, 101)
3GCR *K. pneumoniae* UTI	1392 (771, 2183)	0
MRSA BSI	1611 (911, 2506)	228 (76, 501)
MRSA UTI	939 (527, 1477)	29 (0, 117)
Ceftazidime-resistant *P. aeruginosa* BSI	265 (144, 427)	54 (3, 180)
Ceftazidime-resistant *P. aeruginosa* RTI	3446 (1936, 5335)	411 (177, 774)
Ceftazidime-resistant *P. aeruginosa* UTI	3922 (2213, 6113)	73 (0, 246)
VRE BSI	496 (274,784)	90 (28, 195)
VRE UTI	3728 (2057, 5822)	56 (0, 205)
Total	21663 (12,113, 33,746)	1031 (294, 2615

***Table 3*: Estimated annual health burden of AMR infections in 2020, Australia.**
PBD: patient bed days; 3GCR: third-generation cephalosporin resistant; MRSA: methicillin-resistant *Staphylococcus aureus*, VRE: vancomycin-resistant *E. faecium*, BSI: bloodstream infection; UTI: urinary tract infection; RTI: respiratory tract infections, UI: uncertainty intervals.

	Age at death (SD)	YLL/infection	Lost QALYs/infection	Total QALYs lost	QALYs lost /10,000*
3GCR *E. coli* BSI	61(20.6)	24.21	13.06	3395	1.68
3GCR *E. coli* UTI	68 (20.1)	19.26	11.01	0	0
3GCR *K. pneumoniae* BSI	53 (17.2)	31.17	15.45	865	0.43
3GCR *K. pneumoniae* UTI	66 (18.8)	20.70	11.46	0	0
MRSA BSI	56 (23.2)	28.71	14.46	1041	0.51
MRSA UTI	71 (17.4)	15.97	9.29	752	0.37
Ceftazidime-resistant *P. aeruginosa* BSI	54 (24.6)	30.47	15.12	1859	0.92
Ceftazidime-resistant *P. aeruginosa* RTI	60 (21.9)	25.32	13.42	12370	6.11
Ceftazidime-resistant *P. aeruginosa* UTI	68 (19.5)	18.72	15.05	2558	1.26
VRE BSI	61 (14.9)	24.39	13.06	2416	1.19
VRE UTI	71 (17.1)	16.82	9.71	2446	1.21
Total				27,705	

***Table 4*: Estimated years of life and quality-adjusted life years lost due to AMR infections, Australia.**
3GCR: third-generation cephalosporin resistant; MRSA: methicillin-resistant *Staphylococcus aureus*, VRE: vancomycin-resistant *E. faecium*, BSI: bloodstream infection; UTI: urinary tract infection; RTI: respiratory tract infections, UI: uncertainty intervals, AUD: Australian dollars* patient bed days (hospital population). YLL: years of life lost.

Organism	LOS (95%UI)	Hospital costs AUD (95% UI)	Premature mortality cost AUD (95% UI)
3GCR *E. coli* BSI	1226	$2,331,455	$ 26,841,346
	(683, 1952)	(1298900, $3710182)	($1785903, $113191757)
3GCR *E. coli* UTI	5227	$9,936,130	0
	(2863, 8259)	($5441984, $15701081)	
3GCR	1172	$2,228,686	$ 9,233,084
K. pneumoniae BSI	(616, 1941)	($1170703, $3690599)	($0, $ 45661523
3GCR	3185	$6,053,935	0
K. pneumoniae UTI	(1755, 5021)	($3335954, $9545555)	
MRSA BSI	12,818	$24,366,741	$ 96,551,242
	(7246, 19966)	($13774548, $37954686)	($32060855, $ 212073885
MRSA UTI	1353	$2,571,962	$21,950,132
	(754, 2157)	($1433925, $4099885)	($13049213, $87749865)
Ceftazidime-resistant	1336	$2,540,257	$ 23,804,876
P. aeruginosa BSI	(726, 2149)	($1379668, $4085261)	($1208018, $ 79475606)
Ceftazidime-resistant	5204	$9,892,433	$ 181,003,565
P. aeruginosa RTI	(2899, 8188)	($5510956, $15566109)	($78005482, $ 340995680)
Ceftazidime-resistant	8007	$15,220,906	$ 28,786,073
P. aeruginosa UTI	(4454, 12643)	($8466204, $24,033,789)	($0, $ 96489234)
VRE BSI	1012	$1,924,208	$ 34,575,034
	(547, 1647)	($1040513, $3131419)	($10677129, $74731089)
VRE UTI	5336	$10,143,051	$ 15,797,700
	(2917,8440)	($5545878, $16044292)	(0, $ 58117278)
Total	45,876	$71,988,858	$438,543,052
	(25460, 70214)	($48399233, $137562858)	($13686600, $1108485917)

***Table 5*: Estimated annual hospital and mortality costs due to AMR infections, Australia 2020.**
3GCR: third-generation cephalosporin resistant; MRSA: methicillin-resistant *Staphylococcus aureus*, VRE: vancomycin-resistant *E. faecium*, BSI: bloodstream infection; UTI: urinary tract infection; RTI: respiratory tract infections, UI: uncertainty intervals; LOS: length of stay.
[a]Value of quality adjusted life year (QALY): $29,274 AUD.[19]

Economic burden

In 2020, we estimate an additional 45,876 hospital bed days (95% UI 25460, 70214) were taken up by patients with resistant infections. Patients with a MRSA BSI stayed in hospital the longest (extra 12,818 (95% UI 7246, 19966) bed days), costing the healthcare system an additional AUD$24 million (95%UI $13,774,548, $37,954,686) per year. The total hospital cost attributable to the five resistant infections were $72 million (95%UI $48,399,233, $137,562,858) in 2020.

The combined costs of AMR-associated premature death were $439 million (95%UI $136,786,600, $1,108,485,917) (Table 5). We found that patients with a ceftazidime-resistant *P. aeruginosa* RTI contributed almost half of the total premature death cost (41%, AUD$181,003,565) of the five included pathogens. Patients who had a bloodstream infection caused by the five resistant pathogens, each lost estimated 13–15 years of quality life due to premature death (Table 4) which amounted to AUD$191 million (cost of premature mortality in all BSIs, Table 5). Patients with a resistant urinary infection (caused by *E.coli, K. pneumoniae, S. aureus* and *P. aeruginosa*) lost an average of 11 QALYs per infection (Table 4) and an estimated cost of $67 million per year (cost of premature mortality in all UTIs, Table 5).

High and low prevalence of AMR in Australia

We sourced regional-level data from AURA (Antimicrobial Usage and Resistance in Australia) to identify areas with the highest and lowest AMR prevalence in 2020.[4] These data revealed that AMR prevalence is variable across Australia with infections. Analysis of data on MRSA and VRE bloodstream infections revealed that some infections were highly prevalent (VRE: 64.2%; MRSA: 48.8%) in some regions and very low in other regions (VRE 7.9%; MRSA:5.5%) in 2020. For infections such as third generation cephalosporin resistant *E.coli* BSI, the regional difference between the highest and lowest prevalence were smaller at 19.8% compared to 6%, respectively (Table 6).

We used these estimates of high and low AMR prevalence for each infection group, to model scenarios for the Australia-wide hospital burden using current observed, rather than predicted AMR prevalence. We firstly assumed it might be possible for all regions to observe infection rates on par with the currently highest

Organism		Worst case-high AMR prevalence, (95%CI)	Best case- low AMR prevalence, (95%CI)
3GCR *E. coli* BSI	Resistance, %	19.8% (16.96, 22.64)	6% (4.32, 7.68)
	number of isolates	*n* = 197	*n* = 201
	Number of infections	1345 (747, 2162)	410 (213, 682)
	Extra deaths	184 (12, 789)	55 (4, 250)
	Extra hospital days	3147 (1739, 5065)	959 (498, 1600)
	Hospital cost, AUD	$5,982,267 ($3305674, $9628303)	$1,823,382 (947288, $3042011)
3GCR *E. coli* UTI	Resistance, %	13.3% (12.74, 13.86)	5.1% (4.94, 5.26)
	number of isolates	*n* = 3680	*n* = 19169
	Number of infections	13,743 (7673, 21503)	5285 (2984, 8215)
	Extra deaths	0	0
	Extra hospital days	13,876 (7656, 21957)	5338 (2955, 8513)
	Hospital costs, AUD	$26,378,997 ($14553831, $41741105)	$10,147,651 ($5617252, $16183897)
3GCR	Resistance, %	27% (19.70, 34.29)	3.7% (2.32, 5.07)
K. pneumoniae BSI	number of isolates	*n* = 37	*n* = 189
	Number of infections	1105 (566, 1837)	152 (74, 264)
	Extra deaths	139 (36, 711)	19 (0, 96)
	Extra hospital days	8034 (4127, 13312)	1102 (536, 1921)
	Hospital costs, AUD	$15,271,828 ($7846376, $25307002)	$2, 095,755 ($1018087, $3652213)
3GCR	Resistance, %	8% (6.55, 9.45)	3.2% (2.76, 3.63)
K. pneumoniae UTI	number of isolates	*n* = 351	*n* = 1640
	Number of infections	2240 (1225, 3617)	897 (494, 1429)
	Extra deaths	0 (0, 371)	0
	Extra hospital days	5129 (2797, 8312)	2053 (1121, 3309)
	Hospital costs, AUD	$9,750,931 ($5316376, $15801525)	$3,902,408 ($2,130,416, $6290122)
MRSA BSI	Resistance, %	48.8% (43.28, 54.32)	5.5% (3.48, 7.52)
	number of isolates	*n* = 82	*n* = 127
	Number of infections	5,614 (3140, 8857)	639 (311, 1111)
	Extra deaths	788 (257, 1728)	88 (27, 127)
	Extra hospital days	44,682 (24954, 70386)	5084 (2467, 8836)
	Hospital costs, AUD	$89,941,290 ($47437029, $133804486)	$9,663,943 ($4689142, $16796712)
MRSA UTI	Resistance, %	24.5% (23.33, 25.67)	8.3% (5.64, 10.95)
	number of isolates	*n* = 1356	*n* = 108
	Number of infections	1407 (795, 2209)	479 (246, 814)
	Extra deaths	44 (0, 179)	15 (0, 61)
	Extra hospital days	2024 (1126, 3208)	690 (347, 1178)
	Hospital costs, AUD	$3,847,292 ($2139660, $6099113)	$1,310,820 ($659749, $2240290)
Ceftazidime-resistant	Resistance, %	12.1%(8.82, 15.38)	1.0% (0.99, 1.99)
P. aeruginosa BSI	number of isolates	*n* = 99	*n* = 101
	Number of infections	396 (206, 660)	33 (7, 81)
	Extra deaths	82 (4, 273)	7 (0,27)
	Extra hospital days	1998 (1039, 3331)	166 (38, 409)
	Hospital costs, AUD	$3,798,926 ($1975683, $6333053)	$315,634 ($71535, $778090)
Ceftazidime-resistant	Resistance, %	23.9%(22.49, 25.31)	8.1% (7.43, 8.75)
P. aeruginosa RTI	number of isolates	*n* = 920	*n* = 1776
	Number of infections	9,719 (5482, 15150)	3302 (1854, 5232)
	Extra deaths	1149 (491, 2186)	389 (167, 743)
	Extra hospital days	14,663 (8221, 23204)	4982 (2796, 7986)
	Hospital costs, AUD	$27,873,439 ($15627912, $44111126)	$9,470,446 ($5315503, $3523878)
Ceftazidime-resistant	Resistance, %	12.3% (10.35, 14.24)	2.3% (1.44, 3.16)
P. aeruginosa UTI	number of isolates	*n* = 285	*n* = 306
	Number of infections	2773 (1512, 4386)	517 (252, 904)
	Extra deaths	51 (0, 169)	10 (0,33)
	Extra hospital days	5656 (3057, 9008)	1056 (511, 1854)
	Hospital costs, AUD	$10,752,971 ($5811202, $17123842)	$2,007,363 ($970642, $3523878)

Table 6 *(Continued)*

Organism		Worst case-high AMR prevalence, (95%CI)	Best case- low AMR prevalence, (95%CI)
VRE BSI	Resistance, %	64.2% (59.88, 68.52)	7.9% (3.52, 12.28)
	number of isolates	*n* = 123	*n* = 38
	Number of infections	798 (449, 1234)	98 (41, 188)
	Extra deaths	144 (44, 307)	18 (5, 43)
	Extra hospital days	1628 (891, 2584)	199 (82, 389)
	Hospital costs, AUD	$3,095,643	$378,840
		($1694607, $4913053)	($156109, $739661)
VRE UTI	Resistance, %	57.3% (53.44, 61.16)	6.4% (4.61, 8.19)
	number of isolates	*n* = 164	*n* = 187
	Number of infections	4795 (2678, 7463)	537 (283, 892)
	Extra deaths	71 (0, 264)	18(0, 32)
	Extra hospital days	6858 (3776, 10778)	767 (399, 1293)
	Hospital costs, AUD	$13,037,690	$1,458,521
		($7178984, $20489747)	($758872, $2457402)

***Table 6*: Health and economic impact of AMR in Australia: worst- and best-case scenarios.**

reported regions. We called this the "worst case scenario". We also looked to see what would happen if all regions were able to reduce their rates to be on par with the currently reported lowest regional rates. We called this the national "best case scenario" (Table 6).

For the best-case scenario where AMR prevalence ranges from 1% (ceftazidime-resistant *P. aeruginosa* BSI) to 8.3% (MRSA UTI), we estimate that Australia will have 12,349 AMR infections per year, which result in 601 deaths and cost the healthcare system an estimated AUD $42,574,763 (hospital costs only, does not include the cost of premature death).

In a worst-case scenario where the prevalence of AMR is the highest identified in the country the proportion of isolates that are resistant ranges from 8% (3GC-resistant *K. pneumoniae*) to 57.3% (VRE UTI). In high AMR prevalence we estimate 43,935 AMR infections per year would result in 3,306 AMR deaths and additional AUD$209,731,274 healthcare costs.

Discussion

This study reports the first national estimates of the health and economic burden directly attributable to AMR in Australia, simulating data (pre-COVID-19) from local surveillance. The estimated burden associated with resistant infections across five bacteria was 1031 (294, 2615) deaths in 2020. This is greater than the number of deaths caused by influenza which was reported as 953 in 2019.[24] The majority of these deaths are preventable.

In addition to excess annual hospital stays costing the Australian health system AUD$24 million, premature deaths are resulting in AUD$439 million (95% UI $137 million, $1.18 billion) in costs due to loss of quality-adjusted life years.

We also report the mortality and cost impact observed by comparing regions of high and low prevalence of AMR. For this simulation we used 2020 AMR prevalence data from the Australian national surveillance program[25] and report geographical variation of AMR across Australia, similar to previously reported trends using 2019 data[4] and in northern Australia.[5] Such geographical variation in AMR may be attributed to several contextual factors that are critical to the Australian setting. Firstly, national surveillance data are drawn from population which reside across major capital cities and small remote-dwelling settings in a geography that spans 4000km east to west and 3200 kms north to south. The populations being surveyed therefore are varied and patient level characteristics, healthcare conditions, access to health services and health seeking behaviour would contribute to important differences in rates of AMR.[12] Whilst the national surveillance system aims to maximise geographical coverage of both community and acute sector to achieve greater representation, regional and rural areas fall outside of surveillance reach.[14] Whilst it is important to note that there are inevitably biases or potential for errors in interpretation of surveillance data,[26] using observed real-life AMR prevalence data to determine a best and worst-case scenario is justified. These data provide insight into the pace of resistance spread in Australia and reduces the need for a 'one-size-fits-all' approach. Interestingly regions with low resistance for one pathogen also displayed low resistance for other pathogens, meaning high and low AMR regions did not coincide. For example, regions with low 3GCR-*E.coli* BSI also displayed a low rate of MRSA BSI. Similarly, region with high proportion of MRSA BSI had a high rate of 3GCR-*E.coli* BSI and 3GCR-*K.pneumoniae* BSI. One large state in Australia had the highest rate of AMR for *E.coli, K. pneumoniae, P. aeruginosa* and *E. faecium* UTIs. This region contributed 66% of the overall AMR data to the national surveillance system,[4] raising an important issue that a representative sample of the population is

critical for surveillance systems.[14] This pattern was not clear for *P. aeruginosa* respiratory infections included in our study.

Analysis of best and worst-case AMR prevalence scenarios shows that if Australia acts quickly and reduces the number of infections there are considerable health and economic benefits. In a scenario where the highest identified AMR prevalence currently reported in Australia is observed nationally, we would have 43,935 AMR infections per year and 2652 AMR-associated deaths, a doubling of the current estimated impact. In a best-case scenario (where the lowest identified AMR prevalence currently reported in Australia is observed nationally) the impact would be reduced to match our estimates with approximately 619 deaths avoided yearly, resulting in substantial savings. The hospital costs would range from AUD$42 million in best case scenario to AUD $210 million in worst case scenario. The represents a difference, and possible saving of $168 million. This shows there is a strong economic argument for investing in interventions that reduce the spread of AMR. There is a need for programs to reduce AMR infection rates to ensure Australia sees best case scenario prevalence. It is cost effective to reduce infections with money saved from deaths attributable to AMR able to be redirected to programs to reduce infections. This is currently a lost opportunity to maximise resource allocation within the Australian healthcare system.

Comparisons with previous estimates

Despite the importance of AMR as a public health threat, the scarcity of a robust and accepted approach to assess its burden is known. Quantifying the burden of AMR is a challenge and encompasses various methodologies that aim to measure the impact on the patient, their use of healthcare system and contribution to society. Part of the challenge stems from uncertainty regarding the *best way to measure AMR in* humans.[27] For example, the O'Neil report estimated 10 million deaths a year due to AMR by 2050,[28] whilst more recent burden of disease study reports an estimated 5.27 million (95% UI 3.26–8.15) deaths and 207 million (135–304) DALYs in 2019 due to 88 resistant bacteria–drug combinations.[1] The equivalent numbers attributable to resistance, were 1.36 million (0.823–2.16) deaths and 52.8 million (34.1–79.0) DALYs.[1] This highlights the need for establishing standardised and feasible approaches to determining the burden of AMR,[29] to ensure estimates are reliable and result in meaningful action.[30]

In Australia, the OECD population-based model reported that an average of 290 people die each year due to infections from eight resistant bacteria.[13] We provide an estimate which is 4-fold higher. Our figure is still likely to be an underestimation as our analysis was based on only five hospital-associated resistant bacteria, namely *E. coli, S. aureus, K. pneumoniae* and *P. aeruginosa*.

The main difference in estimates derived by the OECD[13] and our model is likely explained by a difference in model parameters used to generate estimates of impact. Firstly, we used incidence data from a statewide surveillance program that include both tertiary health hospitals and smaller regional hospitals that service populations across a diverse demographic and large geographical region (1.85 million km^2). We used these surveillance data and published estimates of risk (LOS and mortality) to extrapolate to the Australian population.

Secondly, we used these surveillance data to determine resistance patterns in patients with both invasive and non-invasive infections including bloodstream, urinary and respiratory tract infection. This approach is likely to reduce sampling bias, which results from including resistance data from blood cultures that are taken from invasive infections only. Unlike the OECD report that extrapolated BSI proportions to infections at other sites, we used incidence data from BSI, UTI and RTIs in our model.

Lastly, our model used estimates of length of stay and mortality derived from a case-cohort multi-state model that adjusts for not only patient-level comorbidities but importantly, it adjusts for timing of infections and occurrence of competing risks, which are important considerations in hospital-based studies.[31] Additionally, we report uncertainty intervals for all estimates of AMR impact included in our model (LOS, mortality and costs), providing the scientific community much needed confidence around baseline infection rates and mortality estimates.[30]

Limitations

It is likely that the health and economic burdens reported here, pre-COVID are an underestimate of the true impact. We used the loss of healthy years by measuring premature death and QALYs. We did not consider any other societal cost, but acknowledge that these are likely to be greater than direct healthcare cost and should be enumerated in the future.[32] We also did not consider the financial cost that covers a range of health services, health infrastructure (i.e. hospital buildings) and disease prevention. In 2019, the Australian government spent $185.4 billion on healthcare, equating to $7,486 per person.[33] It is important to note that AMR is a complex disease and its effect on people and healthcare system is complex. There can be many reasons why a disease may have a large human cost but a low health spending. For example, premature death creates a severe cost to society and the family in lost wages but may well save healthcare costs. With this conservative approach we were not able to capture the value of interventions that may avert future infection, which would be useful to explore in other studies. We were also not able to account for resistance that bacteria may acquire

in the future. Approaches to costing have been explored but no data are yet available.[34,35]

In the absence of Australian estimates of morbidity and mortality attributable to AMR, we used estimates from Queensland to project to the Australian population. These data may be limited in how they represent the entire Australian population. In particular, patient characteristics, quality of healthcare, health-seeking behaviour and other factors are varied across the country and no single State or Territory dataset is truly representative of the entire country. It should be noted however that all states and territories must comply with national infection prevention and control guidelines, and hospitals throughout the country are accredited against national standards which include infection control and AMS requirements.[36] As such infection control and AMS programs do not vary dramatically between jurisdictions — rather between rural facilities and metropolitan hospitals.[4] We used data from Queensland, which is the second largest state in Australia and has an AMR surveillance network that covers the entire state with district laboratories in rural, large, regional as well as metropolitan teaching hospitals. The number of hospital-associated infections recorded each year in the Queensland database (160,000 per year) is similar to the estimated national incidence of hospital-associated infections of 165,000 infections.[37] Due to data access limitations, the estimates used in our population-level simulation model, do not include private hospitals or primary healthcare and are thus likely to under-estimate the impact in these sectors. However, we show that the estimates of AMR prevalence used in our baseline population-level simulation model all fall between the AMR prevalence for the high and low prevalence presented in Table 6, except for ceftazidime resistant *P. aeruginosa* UTI. In this infection group, baseline estimates are higher (Table S417.4%; 95%CI 16.5, 18.27) than the high prevalence scenario reported in passive surveillance data (Table 6 12.3%; 95%CI 10.35, 14.24). This may reflect a difference in the testing of ceftazidime *P. aeruginosa* in our dataset which originated from Queensland state-wide surveillance, compared to the national surveillance system. Ceftazidime is not routinely tested in regional laboratory groups and may contribute the difference in rates.

It is possible there may have been changes in infection and AMR since 2016. Australia has developed a national action plan to address antimicrobial resistance and started to report baseline data for antimicrobial resistance and antimicrobial use.[4] This surveillance data has shown that change has been very slow, and despite antimicrobial stewardship being a hospital accreditation requirement very little has changed. No large policy interventions have been implemented during this time in either antimicrobial stewardship or infection control[38]; with the last major program (the National Hand Hygiene Initiative) being implemented in 2009. Regardless there are likely lessons to be learned from regions with low and high rates, which is why we hypothesised and modelled best and worst-case scenarios.

In conclusion the health and economic burden of AMR in Australia is significant. The level of this impact will differ significantly depending on the future prevalence of AMR. Interventions aimed at decreasing the spread of AMR and preventing infections represent an opportunity for more effective resource allocation within the healthcare system.

Contributors

Teresa Wozniak conceived and designed the study with advice from Lisa Hall and Greg Merlo. All authors planned and performed the analyses and interpreted the data. Teresa Wozniak prepared the manuscript with contributions from all authors. Teresa Wozniak, Greg Merlo and Lisa Hall have accessed and verified the underlying data and model.

Data sharing statement

The authors confirm that the data (model inputs and parameters) supporting the findings of this study are available within the article and its supplementary materials.

Declaration of interests

The authors declare no conflict of interest.

Acknowledgment

We acknowledge the support and contribution of the Australian Commission of Safety and Quality in Health Care and the AURA Surveillance System in the provision of data. We would also like to thank Ms Jan Bell and Professor John Turnidge, from the AURA team, for their input in interpreting national surveillance data.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100521.

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