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Leveraging existing data to improve antimicrobial resistance-related mortality estimates for Australia

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ABSTRACT

Antimicrobial resistance (AMR) is a global pandemic, however, estimating its burden is a complex process. As a result, many countries rely on global estimates to infer burden within their own setting. With a growing number of recent publications quantifying AMR burden in Australia, and an expansion of surveillance programs, enumerating AMR mortality for Australia is feasible. We aimed to leverage existing published data to assess methodological factors contributing to the considerable variation in AMR-related mortality and provide two reliable estimates of AMR mortality in Australia. This is a necessary step towards generating meaningful measures of AMR burden in Australia.

Keywords: all-cause mortality, antimicrobial resistance, associated mortality, attributable mortality, Australia, burden of disease, epidemiology, mortality.

Introduction

Although more people die of resistant infections than HIV and malaria,[1] antimicrobial resistance (AMR) is still considered a silent pandemic. Estimating the global burden of AMR is a complex process that requires the collection of high-quality, microbiology and clinical data[2] to assess AMR-related mortality.[3]

Estimating the number of antimicrobial resistance-related deaths

There are three proposed approaches to enumerating the number of AMR-related deaths. The first approach, termed 'all-cause mortality', measures the number of people who have died with a resistant infection. All-cause mortality does not compare against any other patient group and there is no way of knowing whether the death was caused by the infection. The second method, termed 'AMR-attributable mortality', measures the number of patients who have died with a resistant infection compared with the number of patients who have died with an antimicrobial-susceptible infection. The third method, termed 'AMR-associated mortality', measures the number of patients who have died with a resistant infection compared with the number of patients who have died with no infection. The three methods have conceptual and technical challenges, the most fundamental of which is to define what is meant by the burden or harm caused by AMR.[2]

The number of antimicrobial resistance-related deaths in Australia

In Australia, since 2018 five peer-reviewed publications reporting on Australia-wide estimates of AMR mortality have been published.[1,4–7] We assessed these publications for their scope and methodological approaches (Table 1).

The Organisation for Economic Co-operation and Development (OECD) estimated that between 2015 and 2050 there would be 2.4 million deaths globally and 10,150 deaths in Australia over a period of 15 years,[4] equating to 290 deaths per year. The authors developed a strategic public health planning for AMR model to quantify AMR-attributable mortality.

Table 1. Published AMR-related deaths in Australia.

Publication	Number and type of antibiotic–bacteria pairs	Methodological approaches; mortality measure	Number of deaths per year, (95% UI)
Organisation for Economic Co-operation and Development (OECD)[4]	Eight pairs: • 3GCR *E. coli*, • FR *E. coli*, • 3GCR KP, • carbapenem-resistant KP, • carbapenem-resistant PA, • penicillin-resistant SP, • MRSA, • VRE.	Monte Carlo, Markov and microsimulation using 2015 AMR data and projecting to 2050. Mortality measure: AMR-attributable	290 (UI not reported)
Global Burden of Disease[1]	88 pairs, including (refer to study for full list): • 3GCR *E. coli*, • FR *E. coli*, • 3GCR KP, • FR KP, • FR *Salmonella typhi*, • FR *Shigella* sp., • 3GCR *N. gonorrhoea*, • MRSA, • penicillin-resistant SP, • MDR *M. tuberculosis*	Case fatality ratios were modelled for the pathogens and infectious syndromes using all available and published data. The pathogens for each infectious syndrome were determined by prevalence and expert opinion. The data were analysed using a meta-analytic mixed effects structure. Mortality data available only for Australasia. Mortality measure: AMR-associated and AMR-attributable	No estimates of deaths in Australia
Wozniak *et al.*[6]	Five pairs: • 3GCR *E. coli*, • 3GCR KP, • ceftazidime-resistant PA, • MRSA, • VRE.	Simulation of Queensland mortality rates based on 2012–2016 linked data,[8] to the Australian hospital population. Mortality measure: AMR-associated	1031 (294–2615)
MPTConnect-CSIRO[5]	Four pairs:[9] • ESBL *E. coli*, • ESBL KP, • MRSA, • VRE.	Extrapolation of Australian hospital mortality rate based on 2019 AGAR 2021 data,[9] which is 209 deaths from 27 hospitals or 29.3% of beds in Australia. This is then scaled up to approximate all-cause mortality across all Australian hospitals. Mortality measure: all-cause	713 (UI not reported)
	88 pairs as described[1]	Australasia mortality rates based on Global Burden of Disease 2019 data,[1] extrapolated to the 2019 Australian population. Mortality measure: AMR-attributable and AMR-associated	Attributable: 1648 (1090–2384) Associated: 5276 (4768–10,120)
WHO, Western-Pacific Region report[7]	MRSA only Six organisms: • *E. coli*, • KP, • SP, • *E. faecalis*, • *H. influenzae*, • PA.	Simulation model using linear projections of resistance rates, population from 2020 to 2030. Source of AMR data from Australia is not reported. No mention of which resistance profile was modelled other than MRSA. Cumulative excess AMR-related deaths reported for 10 year period (2020–2030). Mortality measure: AMR-attributable	2970 (UI not reported) Taken from 10 year estimates of the number of deaths (n = 29,703)

3GCR, third generation cephalosporin-resistant; AGAR, Australian Group on Antimicrobial Resistance; *E. coli, Escherichia coli*; *E. faecalis, Enterococcus faecalis*; ESBL, extended-spectrum beta-lactamase; FR, fluoroquinolone-resistant; *H. influenzae, Haemophilus influenzae*; KP, *Klebsiella pneumoniae*; *M. tuberculosis, Mycobacterium tuberculosis*; MDR, isoniazid and rifampicin co-resistance; MRSA, methicillin-resistant *Staphylococcus aureus*; *N. gonorrhoea, Neisseria gonorrhoea*; PA, *Pseudomonas aeruginosa*; SP, *Streptococcus pneumoniae*; UI, uncertainty interval; VRE, vancomycin-resistant *Eenterococcus faecium*.

This model is a computational technique that combines Monte Carlo simulation, Markov modelling and microsimulation. For the Australian estimates, data were sourced from the 2017 Antimicrobial Usage and Resistance in Australia (AURA) program for eight resistant bacteria.[10] Input data to model the health impact caused by the resistant

pathogens, including the increased risk of death, were extracted from the literature.[11]

The Global Burden of Disease study estimated in 2019 that there were 5 million AMR-associated deaths and 1.27 million AMR-attributable deaths globally.[1] The number of deaths in Australia was aggregated into the Australasian region and combined with AMR estimates from Asia-Pacific countries for 88 antibiotic–bacteria combinations. The authors did not report Australia-only estimates of mortality. Predictive statistical modelling was based on broad modelling components, including infection-related deaths, resistance rates and excess risk of death or duration of infection due to AMR.

To date, the only peer-reviewed publication estimating Australia-wide mortality reported 1031 AMR-associated deaths per year.[6] The authors used population-level estimates generated from a data-linkage[8] study to report the risk of dying for patients with a resistant compared with antimicrobial-susceptible infection, and uninfected patients.

In 2022 an Australian report[5] used the Global Burden of Disease study[1] to estimate 1648 AMR-attributable deaths per year and 5276 AMR-associated deaths per year for 88 antibiotic–bacteria combinations in Australia.[5] The authors also extrapolated the 30 day all-cause mortality reported by the Australian Group on Antimicrobial Resistance (AGAR)[9] from 27 hospitals, to the wider Australian hospital population, and estimated 713 all-cause deaths per year for four antibiotic–bacteria combinations.

Last, a recent report by the World Health Organization for the Western-Pacific region estimated 29,703 AMR-attributable deaths in Australia between 2020 and 2030, equating to 2970 deaths per year.[7] The authors modelled published parameters and provided a sensitivity analysis but did not reference or report the data source or list which antimicrobial resistance profiles were assessed for *Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae, Enterococcus faecalis, Pseudomonas aeruginosa* and *Haemophilus influenzae*.

Overall, the five published studies produced six AMR-related mortality estimates, ranging from 290[4] to 5276[5] deaths per year. Given the large variation in the number of resistant bacteria that were modelled (88 versus four antibiotic–bacteria pairs), and differences in methodological approaches including all-cause, AMR-attributable and AMR-associated mortality, it is not feasible to combine such heterogeneous estimates.

Therefore, to our knowledge there are only two reliable estimates of AMR mortality in Australia, in which Australian prevalence and risk of death data are used.[5,6] The first report[5] estimates 713 all-cause deaths per year for four antibiotic–bacteria combinations (extended-spectrum beta-lactamase (ESBL) *E. coli*, ESBL *K. pneumoniae*, vancomycin-resistant *Enterococcus faecium* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA)) extracted from the AGAR hospital data.[9] The second peer-reviewed publication[6] estimates 1034 AMR-associated deaths per year for five antibiotic–bacteria combinations (third generation cephalosporin-resistant (3GCR) *E. coli,* MRSA, 3GCR *K. pneumoniae*, ceftazidime-resistant *P. aeruginosa*, and VRE). Other than the methodological approach used to estimate mortality (all-cause[9] and AMR-associated[6]), there are a number of important differences in the data collected that may explain the discrepancies in the number of deaths enumerated. The AGAR hospital data[9] reported bloodstream infections, while Wozniak *et al.*[6] considered mortality from bloodstream, urinary and respiratory infections and the inclusion of *P. aeruginosa* infections. *Pseudomonas* lung infections are responsible for a large number of deaths,[12] potentially accounting for the discrepancy between the 713[5] and 1034[6] estimates.

Currently, we lack Australian estimates of deaths caused by AMR beyond the five specific combinations of antibiotic–bacteria examined in the two hospital-based studies.[5,6] Not knowing the burden of AMR in the community poses a significant challange in understanding disease transmission and spread, given that some of these infections are highly prevalent and readily transmissible in both hospital and community settings.[13] Studies reporting on AMR acquired in the community demonstrate that in Australia, community-associated resistant infections contribute approximately 30% of the total burden of AMR in hospitalised patients.[14] Numerating community-acquired AMR mortality is critically needed to complement estimates from the hospital setting and to capture the true impact of AMR in Australia.

A way forward

It is evident that there is a need for accurate estimates of AMR-related deaths in Australia. However, these estimates need to be supported by a transparent and explicit explanation of the methodology used, with standard terminology, and drawn from a sample of the population that represents the population at risk. The definition of relevant health states for AMR infections and the use of these to quantify AMR deaths, as either AMR-associated and/or AMR-attributable death counterfactual scenarios, is critical. A key requirement is a representative, harmonised (and standardised) repository of surveillance data linked to clinical outcomes.

Rather than collecting new data, data collection methods should be aligned with the primary clinical purpose, while considering secondary use, in this case to quantify AMR-related deaths. By repurposing existing surveillance and clinical data, this approach minimises the workload on data collectors while considering data for secondary use. The Department of Health and Aged Care has recently funded Sparked to drive the adoption of national data standards and to allow the reuse of data collected for clinical purposes, for decision support, analytics and other secondary uses. Important work has also commenced to establish a data model and common indications to standardise how

antimicrobials are evaluated for appropriateness, funded by the Medical Research Future Fund National Centre for Antimicrobial Stewardship Digital Health Program. Similar efforts are now needed to standardise AMR surveillance data and allow the reuse of data to measure AMR impact. The HOTspots Surveillance Response Program, the Australian Passive AMR Surveillance System, and AGAR already collect both surveillance and clinical data with the support of the AURA program. The challenge will be to address obstacles in data exchange, and data sharing to enable expansion and collaboration between these programs.

There is genuine enthusiasm from stakeholders across government, academia and industry to find solutions for data reuse and sharing. The establishment of the Australian Centre for Disease Control is an opportunity to assess whether legislative arrangements could be leveraged for data linkage, and to use a multisectoral approach to facilitate some of these solutions to address the AMR challenge collaboratively.

Ethics

Ethics approval was not required for this study.

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Data availability. The data that support this study will be shared upon reasonable request to the corresponding author.

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