JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlae202

JAC-Antimicrobial Resistance

Antimicrobial resistance–attributable mortality: a patient-level analysis

Ioannis Baltas[1,2]*, Timothy Miles Rawson [3,4,5], Hamish Houston [2], Louis Grandjean[1] and Gabriele Pollara[2,6]

[1]Infection, Immunity & Inflammation Department, UCL Institute of Child Health, London, UK; [2]Department of Clinical Microbiology, University College London Hospitals NHS Foundation Trust, London, UK; [3]National Institute for Health Research Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, London, UK; [4]Centre for Antimicrobial Optimisation, Imperial College London, London, UK; [5]David Price Evans Infectious Diseases & Global Health Group, The University of Liverpool, Liverpool, UK; [6]Division of Infection & Immunity, University College London, London, UK

*Corresponding author. E-mail: ioannis.baltas.20@ucl.ac.uk
@GreekDoc

Received 14 September 2024; accepted 26 November 2024

Background: The impact of antimicrobial resistance (AMR) on death at the patient level is challenging to estimate. We aimed to characterize AMR-attributable deaths in a large UK teaching hospital.

Methods: This retrospective study investigated all deceased patients in 2022. Records of participants were independently reviewed by two investigators for cases of AMR-attributable deaths using a newly proposed patient-level definition.

Results: In total, 758 patients met inclusion criteria. Infection was the underlying cause of death for 11.7% (89/758) and was implicated in the pathway that led to death in 41.1% (357/758) of participants. In total, 4.2% (32/758) of all deaths were AMR-attributable. Median time from index sample collection to death was 4.5 days (IQR 2–10.5 days). The majority of AMR-attributable deaths (56.3%, 18/32) were associated with intrinsic resistance mechanisms, primarily by *Enterococcus faecium* (20.7%), Enterobacterales carrying repressed chromosomal ampicillinase Cs (AmpCs) (14.7%) and *Pseudomonas aeruginosa* (11.8%), whereas a minority (43.7%, 14/32) had acquired resistance mechanisms, primarily derepressed chromosomal AmpCs (11.8%) and ESBLs (8.8%). The median time to effective treatment was 32 h 15 min (no difference between subgroups). Only 62.5% (20/32) of AMR-attributable deaths had infection recorded on the death certificate. AMR was not recorded as a cause of death in any of the patients.

Conclusions: Infection and AMR were important causes of death in our cohort, yet they were significantly underreported during death certification. In a low-incidence setting for AMR, pathogen-antimicrobial mismatch due to intrinsic resistance was an equally important contributor to AMR-attributable mortality as acquired resistance mechanisms.

Introduction

Antimicrobial resistance (AMR) is a global health concern and was declared a top 10 threat to human health by the WHO in 2019.[1] It refers to the ability of microorganisms, especially bacteria, to resist or to become tolerant to antimicrobials, because of either acquired or intrinsic resistance mechanisms.[2] AMR can cause pathogen-antimicrobial mismatch, making treatment of infections delayed or ineffective, a scenario strongly linked to elevated mortality.[3,4] Quantifying the total number of deaths caused by AMR is important for accurate epidemiological monitoring of drug-resistant infections with the highest burden of disease, guiding new diagnostics, treatments and guidelines, as well as raising awareness on the magnitude of the problem among relevant stakeholders, including governments and the public.

Despite established national vital statistic registries in many countries, how many people die of antibiotic-resistant infections remains difficult to determine. This is largely due to incomplete

© The Author(s) 2024. Published by Oxford University Press on behalf of British Society for Antimicrobial Chemotherapy.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

Downloaded from https://academic.oup.com/jacamr/article/6/6/dlae202/7928505 by University College London (inactive) user on 19 February 2025

AMR-related data entry during completion of the medical certificate of cause of death (MCCD), from which national statistics are derived.[5] Challenges may include lack of microbiological testing to detect AMR, low physician awareness to attribute infection-related deaths to AMR and limitations in existing coding systems to record AMR at the time of death.[5] For these reasons, quantification of the total number of AMR-attributable deaths through vital statistics registries is likely inaccurate.

To address this limitation, large-scale modelling studies have attempted to estimate the total number of AMR-attributable deaths by defining them based on the counterfactual scenario whereby drug-resistant infections are replaced by drug-sensitive infections.[6–9] This approach relies on *a priori* knowledge of antibiotic-resistant infection rates, as well as precise case fatality ratios for antibiotic-sensitive and antibiotic-resistant infections. However, these estimates cannot be reliably extrapolated for all possible combinations of pathogens, antimicrobials and infection sites.[10] Moreover, the primary driver of mortality from AMR is dependent on the timing and antimicrobial activity of prescribed antibiotics.[11,12] Population-level modelling does not account for these factors, indicating that patient-level assessments are more likely to inform the true contribution of AMR on patient mortality.

In this study, we sought to quantify the proportion of deaths attributable to AMR over 1 year in a major UK academic centre. We propose and deploy a new patient-level definition of AMR-attributable death that focuses on treatment delay due to resistance and describe the patient cohorts, pathogens and resistance mechanisms most frequently involved.

Methods

Ethical approval

The study was approved by the Audit and Research Committee in the Department of Clinical Microbiology, University College London Hospitals. Requirement for regional ethics committee review was waived as this was a retrospective review of routine clinical data analysed for service development.

Study setting

This study was conducted in University College London Hospitals NHS Foundation Trust (UCLH), a tertiary teaching hospital in central London, with a total inpatient bed capacity of 1022 beds. The Trust acts as a referral centre for haematology and haematopoietic cell transplantation in North and East London and West Essex, being one of the largest blood diseases treatment centres in Europe. It also hosts the Hospital of Tropical Diseases and the National Hospital for Neurology and Neurosurgery. Pathology services in UCLH, including microbiology, virology and parasitology, are provided by the Health Services Laboratories (HSL), a state-of-the-art diagnostic laboratory accredited by the UK National External Quality Assessment Service. HSL uses the most recent EUCAST guidelines (version 12 and version 13 for the two study years) for antimicrobial susceptibility testing.

Study population

We reviewed the records of all patients who died as inpatients at UCLH between 1 January 2022 and 31 December 2022. Eligible patients were identified through the local medical examiner office registry. Patients without available data on the cause of death as recorded on the MCCD were excluded. No other exclusion criteria applied.

Data sources and measurement

All data were collected from computerized medical records (Epic Systems Corporation, Verona, WI, USA and WinPath Enterprise, Clinisys, Woking, UK).[13] Ethnicity was recorded as white, Asian, black, mixed or other as defined in the 2021 UK Census. The Index of Multiple Deprivation was calculated according to participants' postcodes. Causes of death as described on the MCCD were collected using ICD-10 codes and grouped in categories as suggested by the Office of National Statistics.[14] The Underlying Cause of Death (UCOD) and Multiple Causes of Death (MCD) were determined according to WHO methodology.[15]

In accordance with WHO guidelines, the UK MCCD has two sections for recording causes of death. Part 1 consists of three lines to record the pathway of morbid events leading to death, where the UCOD is the condition that initiates this sequence. Part two of the death certificate is designated for conditions that contribute to death but do not have a significant direct relationship to the underlying cause. The MCD approach includes all medical conditions listed on the death, including those in part one and part two. If two discreet pathologies are given as the UCOD, they are considered equally responsible for the patient's death and 0.5 deaths are recorded for each pathology. This is to avoid scenarios in which the total number of UCODs is greater than the number of participants who died. Infection was recorded as the UCOD if it was the condition on the MCCD that initiated the sequence of events that led to death, otherwise it was considered to be in the pathway that led to death if it was recorded in section 1 but was not the UCOD.

AMR-attributable death definition

To the best of our knowledge, there is no previously established patient-level definition of an AMR-attributable death. The following definition was proposed and used in this study:

An AMR-attributable death is recorded when:

1. There is a positive microbiological sample (excluding screening samples) for a pathogen within 28 days of death.

AND

2. Two independent investigators agree that:
   a. At the time of death there was an active infection at the site where the pathogen in 1) was identified.

   AND

   b. The infection contributed (but was not necessarily solely responsible) to the patient's death.

   AND

3. There was a clinically significant delay in *in vitro* effective antimicrobial therapy because of the pathogen's resistance profile.

Clinically significant treatment delay was set at 1 h for patients with septic shock at the time of sample collection, at 6 h for patients with sepsis and at 24 h for patients with infections without sepsis and septic shock.[12,16,17] The Third International Consensus Definitions for Sepsis and Septic Shock were used.[18] The 28 day window was adopted from the US FDA recommendations for mortality endpoints of acute infections.[19,20]

Data collection

To apply the definition of AMR-attributable deaths, all participant cases were linked to local microbiological results within 28 days of death. Medical records of patients with any positive microbiological sample

Downloaded from https://academic.oup.com/jacamr/article/6/6/dlae202/7928505 by University College London (inactive) user on 19 February 2025

within 28 days of death were then independently reviewed by two study investigators (I.B., T.M.R.), who recorded cases of AMR-attributable deaths using the study definition. In case of disagreement, a third investigator (G.P.) reviewed the case and acted as the tiebreaker. Cases of AMR-attributable deaths were then further divided into acquired resistance–attributable deaths and intrinsic resistance–attributable deaths, depending on whether the treatment delay was due to an acquired or intrinsic resistance mechanism for that particular pathogen as described by EUCAST.[21] Intrinsic resistance mechanisms were defined as the ones leading to EUCAST-defined expected phenotypes, whereas all others were considered acquired.[21] In the absence of knowing the time of infection onset for all cases, time to effective treatment was calculated as the difference between the sample collection time and the administration of the first *in vitro* effective antimicrobial.

Statistical analysis

Statistical analysis was performed using SPSS v29 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians with IQRs, categorical variables as percentages. Univariable comparisons were made using the Mann–Whitney *U* test for continuous variables and Pearson's chi-squared test for categorical variables, as appropriate. We calculated 95% CIs using 10 000 bootstrap samples. The level of statistical significance was set at 0.05. No formal power analysis was performed as all available patients were enrolled. This study has been reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[22]

Results

Cohort characteristics

There was a total of 815 deaths recorded in the study centre during the study period. MCCD details were available for 93% (758/815) of patients, which were included in the final analysis. Cohort characteristics are described in Table 1. The median age was 72 years (IQR 61–83) and there was a slight male predominance (54.6%, 414/758). The majority of patients were of white ethnicity (53%, 402/758) and levels of deprivation were low (53.6%, 404/758 in the two least-deprived quintiles, Table 1). Most patients were admitted under medical inpatient teams during their final admission (58.8%, 446/758), followed by oncology (16.6%, 126/758), haematology (15.8%, 120/758) and surgery (12.5%, 95/758). Only 4.1% (31/758) of patients were admitted to intensive care.

Table 1. Cohort characteristics[a]

Variable	All deaths $N=758$	AMR-attributable deaths $n=32$	Non-AMR-attributable deaths $n=726$	P
Age	72 (61–83)	67 (54–74)	73 (62–84)	0.01
Sex				
Male	414 (54.6%)	15 (46.9%)	399 (55%)	0.37
Female	344 (45.4%)	17 (53.1%)	327 (45%)	
Ethnicity				
White	402 (53%)	14 (44%)	388 (53.4%)	0.12
Asian	57 (7.5%)	1 (3%)	56 (7.7%)	
Black	37 (4.9%)	1 (3%)	36 (5%)	
Mixed	9 (1.2%)	0 (0%)	9 (1.2%)	
Other	59 (7.8%)	1 (3%)	58 (8%)	
Not stated/not known	194 (25.6%)	15 (47%)	179 (24.7%)	
Index of Multiple Deprivation quintile[b]				
1st (least deprived)	141 (18.7%)	9 (28.1%)	132 (18.3%)	0.08
2nd	263 (34.9%)	5 (15.6%)	258 (35.8%)	
3rd	185 (24.6%)	8 (25%)	177 (24.5%)	
4th	104 (13.8%)	8 (25%)	96 (13.3%)	
5th (most deprived)	60 (8%)	2 (6.3%)	58 (8.1%)	
Number of specialties during final admission	1 (1–1)	1 (1–1)	1 (1–1)	1
Medicine	446 (58.8%)	19 (59.4%)	427 (58.8%)	0.95
Surgery	95 (12.5%)	2 (6.3%)	93 (12.7%)	0.27
Intensive care	31 (4.1%)	1 (3.1%)	30 (4.1%)	1
Haematology	120 (15.8%)	9 (28.1%)	111 (15.3%)	0.06
Oncology	126 (16.6%)	3 (9.3%)	123 (16.9%)	0.26
Infectious diseases	53 (7%)	1 (3.1%)	52 (7.2%)	0.72
Emergency medicine	18 (2.4%)	0 (0%)	18 (2.5%)	0.37
Paediatrics	3 (0.4%)	0 (0%)	3 (0.4%)	1
Psychiatry	1 (0.1%)	0 (0%)	1 (0.1%)	1

[a]Continuous variables are presented as median (IQR), categorical variables as *n* (%).
[b]$n=753$.

Downloaded from https://academic.oup.com/jacamr/article/6/6/dlae202/7928505 by University College London (inactive) user on 19 February 2025

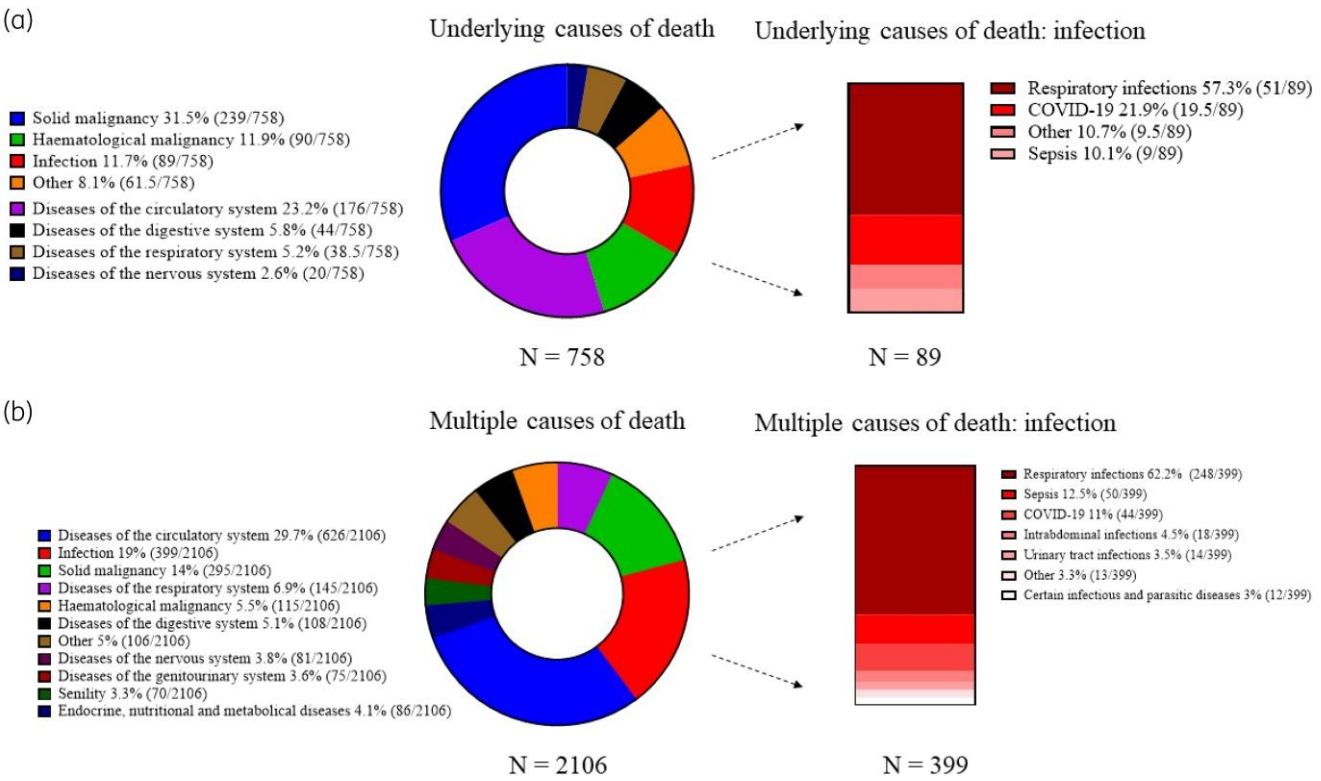

Figure 1. Causes of death in all study patients, recorded using ICD-10 codes according to WHO methodology. If two discreet pathologies were given as the underlying cause of death, they were considered equally responsible for the patient's death and 0.5 deaths were recorded for each pathology. (a) All underlying causes of death and infections recorded as underlying causes of death. (b) All multiple causes of death and infections recorded as multiple causes of death.

Infection as a documented cause of death

Infection was the UCOD for 11.7% (89/758) of patients but was implicated in the pathway that directly led to death in 41.1% (357/758) of cases (Figure 1a). The most common infections as the UCODs were respiratory tract infections (57.3%, 51/89). A median of three MCDs (IQR 2–4) were recorded on the MCCD in this patient cohort. Infection was the second commonest cause of death (19%, 399/2106), behind only diseases of the circulatory system (29.7%, 626/2106, Figure 1b). Other common causes of death included solid malignancies (14%, 295/2106), diseases of the respiratory system (6.9%, 145/2106), haematological malignancies (5.5%, 115/2106) and diseases of the digestive system (5.1%, 108/2106). The most common infections contributing to death were infections of the respiratory system (62.5%, 248/399), sepsis (12.5%, 50/399), COVID-19 (11%, 44/399), intra-abdominal infections (4.5%, 18/399) and infections of the urinary tract (3.5%, 14/399).

AMR-attributable deaths

In total, 36.5% (277/758) of patients had a least one positive microbiological sample within 28 days of death. Detailed review of these cases identified that 4.2% (32/758) of patients had an AMR-attributable death according to our prespecified study definition. The median time from sample collection to death was 4.5 days (IQR 2–10.5 days). Cohort characteristics are described in Table 1. Patients with AMR-attributable deaths were younger (median age 67 versus 72, $P=0.01$) and were more commonly under haematology, although the difference did not reach statistical significance (28.1% versus 15.3%, $P=0.06$, Table 1). No other significant differences were observed.

Within AMR-attributable deaths, the majority (56.3%, 18/32) were intrinsic resistance–attributable deaths, and the minority (43.7%, 14/32) were acquired resistance–attributable deaths. The leading causes of intrinsic resistance–attributable deaths were *Enterococcus faecium* (38.9%, 7/18), Enterobacterales carrying repressed chromosomal ampicillin Cs (AmpCs; 27.7%, 5/18) and *Pseudomonas aeruginosa* (22.2%, 4/18). A variety of acquired resistance mechanisms were detected among AMR-attributable death cases, including four deaths (28.7%, 4/14) due to resistance from derepressed chromosomal AmpCs, three deaths (21.4%, 3/14) from plasmid-encoded ESBLs and only one death (7.1%, 1/14) due to a carbapenemase producer (Figure 2).

The median time to effective treatment from sample collection was 32 h 15 min for all AMR-attributable deaths and did not differ significantly between subgroups (36 h 32 min for acquired resistance–attributable deaths compared with 30 h 49 min for intrinsic resistance–attributable deaths, $P=0.31$). Only 62.5% (20/32) of AMR-attributable deaths had infection recorded within the pathway that led to death on the MCCD, and AMR was not recorded as a cause of death in any of these patients.

Downloaded from https://academic.oup.com/jacamr/article/6/6/dlae202/7928505 by University College London (inactive) user on 19 February 2025

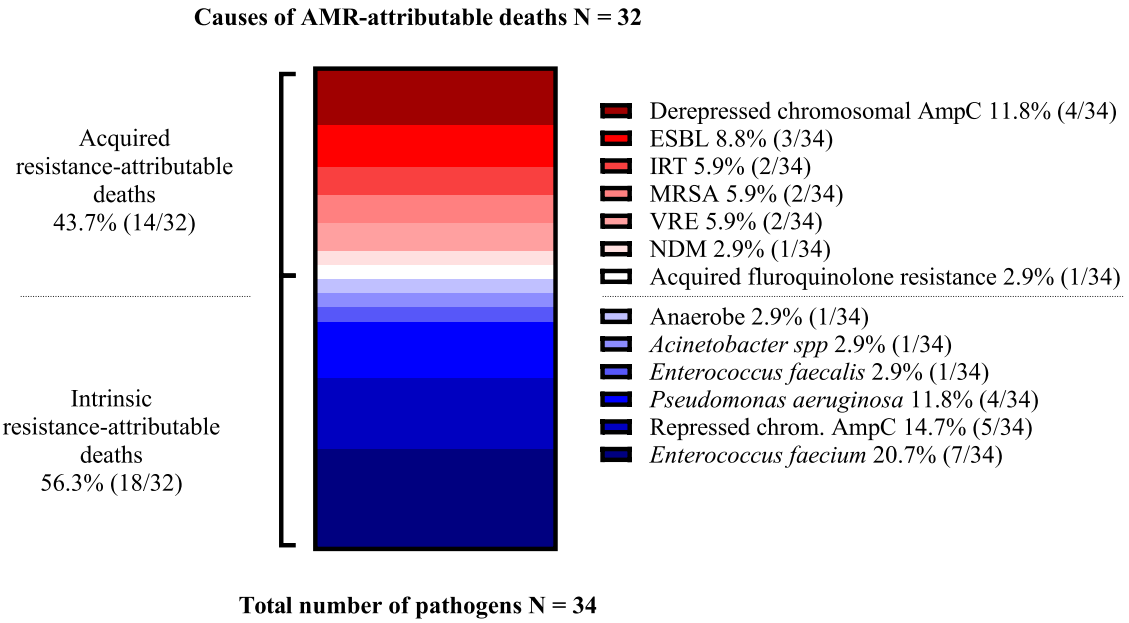

Figure 2. Causes of AMR-attributable deaths, presented within subgroups of acquired resistance–attributable deaths and intrinsic resistance–attributable deaths. Causes within each subgroup are sorted by frequency. Two patients had more than one pathogen isolated. AmpC, ampicillinase C; AMR, antimicrobial resistance; IRT, inhibitor-resistant TEMs; NDM, New Delhi metallo-β-lactamase.

Discussion

In this study, we performed a patient-level analysis to determine the burden of AMR on mortality using a newly proposed definition focusing on treatment delay due to pathogen/antimicrobial mismatch. In our local setting, AMR was responsible for 4.2% of all deaths in 2022. We interpreted this to be a significant proportion, given that over the same time period in this cohort diseases of the respiratory system accounted for 5.2% of all deaths. Suboptimal antimicrobial therapy due to intrinsic resistance mechanisms leading to death was more frequently observed compared with acquired resistance mechanisms. Most strikingly, we found significant underreporting of infection as a cause of death (37.5%, 12/32 of cases not recorded), and AMR was not documented on the MCCD in any patient including in the 14 deaths due to acquired resistance.

AMR is conventionally associated with acquired antimicrobial resistance genes (ARGs), carried in plasmids or other mobile genetic elements.[23] This is reflected in the predominance of microbes producing β-lactamases and other acquired resistance mechanisms in the current WHO AMR critical priority pathogen list.[24] However, evidence does not support pathogens carrying ARGs to be more virulent than susceptible pathogens.[25,26] Excess mortality is instead attributed to treatment delays.[11,12,16,17] Some pathogens with expected resistant phenotypes, like *P. aeruginosa* (intrinsically resistant to amoxicillin/clavulanic acid and earlier generation cephalosporins), *E. faecium* (intrinsically resistant to cephalosporins) and Enterobacterales with repressed chromosomal AmpCs (intrinsically resistant to amoxicillin/clavulanic acid and second-generation cephalosporins) can also lead to treatment delay.[21] Our study reaffirms that in low-AMR-incidence settings, intrinsic resistances can be as impactful on mortality, indicating that in these settings prevention of AMR-attributable deaths should also focus on rapid pathogen identification and sufficiently broad empirical treatment regimens that cover pathogens with intrinsic resistances.

Our study also highlights the broader underestimation of infection and AMR, independent of the resistance mechanism, in the pathway that leads to death. This was noted despite the rigorous medical examiner process in place in England, through which all deaths are reviewed by an independent senior medical doctor that requires agreement on the cause of death with the responsible medical team.[27] Although not formally analysed in our cohort, it was particularly evident to the case assessors that doctors prioritized chronic conditions, like malignancies, rather than acute conditions, like infections, as the cause of death on the MCCD, a phenomenon that has been previously described.[28,29] It is likely that infections contribute to death in the context of chronic conditions. For this reason, it is important to quantify this disease burden and support AMR national actions plans by highlighting the potential benefit of future infection preventative measures, such as improved prophylaxis or vaccines.

Strengths of our study include the unique study design with access to patient-level data including death certification data, which are rarely available. Data collection was facilitated by a state-of-the-art electronic medical record, which supported data accuracy. We used an *a priori* definition for AMR-attributable deaths, which was independently applied after careful case review by two expert investigators, who reached agreement for all cases in a blinded fashion, although interobserver variability using Cohen's kappa was not formally assessed.

Our single-centre study was limited by a small sample size, leading to low total numbers of AMR-attributable deaths. More importantly, our results might not be representative for all

Downloaded from https://academic.oup.com/jacamr/article/6/6/dlae202/7928505 by University College London (inactive) user on 19 February 2025

hospitals, even in low-AMR settings, especially given our large haematology patient population, who are at higher risk for infections from *E. faecium* and *P. aeruginosa*.[30] Treatment delay was calculated from sample collection rather than symptom onset and is also dependent on local empirical guidelines, which include cefuroxime, amoxicillin/clavulanic acid and aminoglycosides for many infections in non-haematology patients in our centre. Hospitals that use antipseudomonal agents or glycopeptides in their empirical regimens might experience lower rates of intrinsic resistance–attributable deaths than we observed, but risk development of AMR and higher numbers of acquired resistance–attributable deaths instead. We were unable to access 7% of MCCDs due to confidentiality purposes, therefore we cannot assess for systematic differences of patients excluded. Yet, they represent less than 10% of the total sample size and are unlikely to have had a high impact. Lastly, our definition of AMR-attributable death is limited by the need for a microbiological culture result, but this is a diagnostic process that is not universally performed in the context of a suspected infection and has even lower sensitivity if delayed after the commencement of antimicrobial therapy. Additionally, we did not have access to eligible microbiological results outside our institution, although we anticipate the impact of this to be small, as almost 75% of microbiological samples were collected within 10 days of death at our hospital. Therefore, it is likely we underestimated the true number of AMR-attributable deaths in our cohort overall. Future use of molecular and genomic assessments of microbiological causes of infection may better estimate the association between specific resistance mechanisms and death.

In conclusion, infection and AMR were important causes of death in our cohort, yet they were significantly underreported during death certification. In a low-incidence setting for AMR, deaths due to intrinsic resistance were equally important contributors to AMR-attributable mortality. Both timely pathogen identification and rapid antimicrobial susceptibility testing are key for reducing AMR-attributable mortality.

Acknowledgements

We thank the GOSH/ICH Biomedical Research Centre for supporting this study.

Funding

This study was supported by a Wellcome Trust grant (CDA 226007/Z/22/Z) to L.G. and a National Institute of Allergy and Infectious Diseases of the National Institutes of Health award (R01AI146338) to L.G.

Transparency declarations

I.B. reports investigator-initiated research funding from Shionogi B.V. for research on Gram-negative infections outside the submitted work; honoraria from Shionogi B.V. and Menarini UK; and participating in an advisory board for GSK on the UK subscription model for antimicrobials outside the submitted work. All remaining authors report no conflicts of interest.

References

1 Walsh TR, Gales AC, Laxminarayan R *et al*. Antimicrobial resistance: addressing a global threat to humanity. *PLoS Med* 2023; **20**: e1004264. https://doi.org/10.1371/journal.pmed.1004264

2 Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol* 2018; **4**: 482–501. https://doi.org/10.3934/microbiol.2018.3.482

3 Kadri SS, Lai YL, Warner S *et al*. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. *Lancet Infect Dis* 2021; **21**: 241–51. https://doi.org/10.1016/S1473-3099(20)30477-1

4 Baltas I, Stockdale T, Tausan M *et al*. Impact of antibiotic timing on mortality from gram-negative bacteraemia in an English district general hospital: the importance of getting it right every time. *J Antimicrob Chemother* 2021; **76**: 813–9. https://doi.org/10.1093/jac/dkaa478

5 Temkin E, Carmeli Y. Zero or more: methodological challenges of counting and estimating deaths related to antibiotic-resistant infections. *Clin Infect Dis* 2019; **69**: 2029–34. https://doi.org/10.1093/cid/ciz414

6 Antimicrobial Resistance Collaborators. The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis. *Lancet Reg Health Am* 2023; **25**: 100561. https://doi.org/10.1016/j.lana.2023.100561

7 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399**: 629–55. https://doi.org/10.1016/S0140-6736(21)02724-0

8 European Antimicrobial Resistance Collaborators. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. *Lancet Public Health* 2022; **7**: e897–913. https://doi.org/10.1016/S2468-2667(22)00225-0

9 de Kraker ME, Lipsitch M. Burden of antimicrobial resistance: compared to what? *Epidemiol Rev* 2022; **43**: 53–64. https://doi.org/10.1093/epirev/mxab001

10 Dunachie SJ, Day NP, Dolecek C. The challenges of estimating the human global burden of disease of antimicrobial resistant bacteria. *Curr Opin Microbiol* 2020; **57**: 95–101. https://doi.org/10.1016/j.mib.2020.09.013

11 Baltas I, Stockdale T, Tausan M *et al*. Long-term outcome and risk factors for late mortality in gram-negative bacteraemia: a retrospective cohort study. *J Glob Antimicrob Resist* 2021; **25**: 187–92. https://doi.org/10.1016/j.jgar.2021.03.019

12 Rüddel H, Thomas-Rüddel DO, Reinhart K *et al*. Adverse effects of delayed antimicrobial treatment and surgical source control in adults with sepsis: results of a planned secondary analysis of a cluster-randomized controlled trial. *Crit Care* 2022; **26**: 51. https://doi.org/10.1186/s13054-022-03901-9

13 Dutey-Magni P. Ramses: R package for antimicrobial stewardship and surveillance. R package version 0.4.3. https://ramses-antibiotics.web.app/articles/Ramses.html

14 Office for National Statistics. User guide to mortality statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017#cause-of-death-coding

15 Piffaretti C, Moreno-Betancur M, Lamarche-Vadel A *et al*. Quantifying cause-related mortality by weighting multiple causes of death. *Bull World Health Organ* 2016; **94**: 870–9. https://doi.org/10.2471/BLT.16.172189

16 Kumar A, Roberts D, Wood KE *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of

Downloaded from https://academic.oup.com/jacamr/article/6/6/dlae202/7928505 by University College London (inactive) user on 19 February 2025

survival in human septic shock. *Crit Care Med* 2006; **34**: 1589–96. https://doi.org/10.1097/01.CCM.0000217961.75225.E9

17 Liu VX, Fielding-Singh V, Greene JD *et al*. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med* 2017; **196**: 856–63. https://doi.org/10.1164/rccm.201609-1848OC

18 Singer M, Deutschman CS, Seymour CW *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; **315**: 801–10. https://doi.org/10.1001/jama.2016.0287

19 Food and Drug Administration, U.S. Department of Health and Human Services. Hospital-acquired bacterial pneumonia and ventilator associated bacterial pneumonia: developing drugs for treatment guidance for industry. https://www.fda.gov/media/79516/download

20 Food and Drug Administration, U.S. Department of Health and Human Services. Complicated urinary tract infections: developing drugs for treatment guidance for industry. 2018. https://www.fda.gov/media/71313/download

21 European Committee on Antimicrobial Susceptibility Testing. Expert rules and expected phenotypes. https://www.eucast.org/expert_rules_and_expected_phenotypes

22 Von Elm E, Altman DG, Egger M *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X

23 Holmes AH, Moore LSP, Sundsfjord A *et al*. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016; **387**: 176–87. https://doi.org/10.1016/S0140-6736(15)00473-0

24 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 Infect Dis* 2018; **18**: 318–27. https://doi.org/10.1016/S1473-3099(17)30753-3

25 Cepas V, Soto SM. Relationship between virulence and resistance among gram-negative bacteria. *Antibiotics (Basel)* 2020; **9**: 719. https://doi.org/10.3390/antibiotics9100719

26 Beceiro A, Tomás M, Bou G. Antimicrobial resistance and virulence: a successful or deleterious association in the bacterial world? *Clin Microbiol Rev* 2013; **26**: 185–230. https://doi.org/10.1128/CMR.00059-12

27 Fletcher A. *National Medical Examiner's Good Practice Series No. 9—recording antimicrobial resistance on the Medical Certificate of Cause of Death*. Royal College of Pathologists, 2022. https://www.rcpath.org/static/5677cccb-e4c2-450d-aaea199035bc3828/bd98e91c-f134-49b0-965c7076b0a8f5bf/Good-Practice-Series-Recording-antimicrobial-resistance-on-the-Medical-Certificate-of-Cause-of-DeathFinal.pdf

28 Govindan S, Shapiro L, Langa KM *et al*. Death certificates underestimate infections as proximal causes of death in the US. *PLoS One* 2014; **9**: e97714. https://doi.org/10.1371/journal.pone.0097714

29 Désesquelles A, Demuru E, Pappagallo M *et al*. After the epidemiologic transition: a reassessment of mortality from infectious diseases among over-65s in France and Italy. *Int J Public Health* 2015; **60**: 961–7. https://doi.org/10.1007/s00038-015-0704-9

30 Baltas I, Kavallieros K, Konstantinou G *et al*. The effect of ciprofloxacin prophylaxis during haematopoietic cell transplantation on infection episodes, exposure to treatment antimicrobials and antimicrobial resistance: a single-centre retrospective cohort study. *JAC Antimicrob Resist* 2024; **6**: dlae010. https://doi.org/10.1093/jacamr/dlad143.010

Downloaded from https://academic.oup.com/jacamr/article/6/6/dlae202/7928505 by University College London (inactive) user on 19 February 2025