

Improving the estimation of the global burden of antimicrobial resistant infections

Direk Limmathurotsakul PhD^{1,2}, Susanna Dunachie PhD^{1,2}, Keiji Fukuda MD³, Nicholas A. Feasey PhD⁴, Iruka N. Okeke PhD⁵, Alison H. Holmes FRCP⁶, Catrin E. Moore PhD⁷, Christiane Dolecek FRCP^{1,2}, H. Rogier van Doorn PhD^{2,8}, Nandini Shetty FRCPATH⁹, Alan D. Lopez PhD¹⁰, Sharon J. Peacock FRCP¹¹, Surveillance and Epidemiology of Drug Resistant Infections Consortium (SEDRIC)

¹ Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, 10400, Thailand

² Centre for Tropical Medicine and Global Health, University of Oxford, OX3 7FZ, UK

³ School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Sassoon Road, Pokfulam, Hong Kong

⁴ The Malawi Liverpool School Wellcome Trust Clinical Research Programme, Blantyre, Malawi

⁵ Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria

⁶ Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0HS, UK

⁷ Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, OX3 7LF, UK

⁸ Oxford University Clinical Research Unit, National Hospital for Tropical Diseases, 78 Giai Phong, Hanoi, Viet Nam

⁹ National Infection Service, Public Health England, 61 Colindale Avenue, Colindale London, NW9 5EQ, UK

¹⁰ School of Population and Global Health, University of Melbourne, Melbourne, Victoria, 3010, Australia

¹¹ London School of Hygiene and Tropical Medicine, London, WC1E 7HT, UK

Word count of summary: 200 (Unstructured: 150-200 words)

Word count of main text: 2,902 (limit 3000 words)

Summary

Estimating the global burden of disease from infections caused by pathogens that have acquired antimicrobial resistance (AMR) is critical for resource allocation and to inform AMR action plans at national and global levels. However, the lack of robust and accepted methodology to determine burden is widely acknowledged. Here, we discuss the underlying assumptions, characteristics, limitations and comparability of the approaches used to date to quantify mortality from AMR bacterial infections. We demonstrate that the global burden of AMR estimated in the O'Neill Review and the Global Burden Disease 2016 study are not comparable because of their different methodological approaches, assumptions and data used to generate them. Neither analytical framework is adequate, and we conclude that a new approach to the estimation of deaths caused by AMR infection is needed. This will require the development of mechanisms to systematically collect a clinical dataset of sufficient breadth and quality to support the accurate assessment of burden, combined with decision-making and resource allocation for interventions against AMR. We define key actions required and call for innovative thinking and solutions to address these.

Text

Antimicrobial resistance (AMR) occurs when microorganisms (including bacteria) change in ways that render the drugs used to treat the infections they cause ineffective.¹ Estimating premature mortality and the burden of disease due to AMR is critical, both to decide on resource allocation for interventions against AMR^{2,3} and to inform the implementation of action plans at global and national levels.² With robust methods and reliable estimates, individual countries could track trends, determine the impact of actions on AMR, and compare these with others. It is also crucial for policy makers to be able to compare the impact of AMR infections with other major communicable diseases such as HIV/AIDS, malaria and tuberculosis, as well as non-communicable diseases with a large global impact, including heart disease and cancer.

The Review on AMR chaired by Jim O'Neill estimated that around 700,000 deaths each year globally may be from infections with AMR bacterial infections, including multidrug-resistant and extensively drug-resistant tuberculosis.⁴ The Global Burden of Disease (GBD) 2016 study estimated that around 126,000 people died of multidrug-resistant and extensively drug-resistant tuberculosis in 2016, but the number of people who died of other drug-resistant bacterial infections, malaria and HIV were not estimated separately.⁵ National estimates of mortality from AMR bacterial infections have also been published for the United States (US),⁶ Europe^{7,8} and Thailand,^{9,10} among others. A direct comparison of these estimates is not possible because each used different approaches and data sources, including which types of infections were considered, when preparing the estimates.

Despite the importance of AMR as a public health threat, the lack of a robust and accepted methodological approach to assess its burden is widely acknowledged.^{2,11-14} The burden of AMR can be measured using many parameters, including mortality, morbidity, economic cost and resource utilization.^{1,12} Here, we limit discussion to mortality from AMR, drawing on a combination of published evidence and expert opinion. We compare and discuss general underlying assumptions, characteristics, limitations and comparability of the approaches that have been used to quantify mortality from AMR bacterial infections in a country or globally.⁴⁻¹⁰ We also propose general guiding principles and potential approaches for improving these estimates in the future. We focused on the approaches used by the O'Neill Review⁴ and the GBD study⁵ because of the availability of their estimates of global mortality from AMR and their high impact on national and international stakeholders.

What is the cause of death?

Determining the cause of death can be complicated. Patients often die from a combination of underlying conditions, co-morbidities, and acute complications, like a drug-resistant infection, that ultimately results in death.^{15,16} It is often hard to decipher which of these initiated the train of events that resulted in death. Put simply, did the patient die because of a drug-resistant infection or did the patient die while having a drug-resistant infection? The International Classification of Diseases (ICD)¹⁷ is the global standard that is widely used to promote international comparability in the collection, processing, classification and presentation of mortality statistics. Globally, healthcare systems document all of a patient's medical conditions using ICD codes, and certifying physicians record the sequence on the International Medical Certificate of Causes of Death. This information is then coded by a trained ICD coder to select the underlying cause of death. Information about comorbidities, the presence of sepsis,^{18,19} etc, can be determined from the combination of underlying and non-underlying (i.e. immediate

or intermediate) causes listed on the death certificate, which are collectively known as “multiple causes of death”.¹⁷ Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, and the final common pathway to death from most infectious diseases.^{18,19} Nonetheless, the global standard for mortality statistics is to select only one main underlying cause of death as “a single cause of death”, regardless of how many conditions are reported in medical records or death certificates.

Challenges with applying the ICD principle (using a single cause of death for mortality statistics) is best illustrated with examples.

1) An elderly patient is admitted to hospital due to ischaemic heart disease and cardiogenic shock. The patient has a history of chronic kidney failure. During hospitalization, the patient is intubated and develops a hospital-acquired pneumonia and sepsis. Blood cultures are positive for carbapenem-resistant *Acinetobacter baumannii*. The patient dies of multiple organ failure, including acute on chronic kidney failure. One doctor might conclude that the cause of death in this case was infection with a carbapenem-resistant *A. baumannii*, while another might conclude that the underlying cause of death was chronic kidney disease, not the infection or heart disease. However, using the ICD principle,¹⁷ the cause of death recorded in the national mortality statistics would be “heart disease” (Figure 1A).

2) A patient with HIV/AIDS and community-acquired multidrug-resistant non-typhoidal *Salmonella* (NTS) infection; they would be recorded in national statistics on causes of death as having died from “HIV/AIDS” (Figure 1B).

To put it simply, the ICD principle relies on the assumption that there is only one cause of death,¹⁷ when particularly for complex illnesses, the cause of death is often the interplay between two or more major morbid conditions. Assigning a single cause of death according to the ICD principles means that the majority of hospital-acquired infections and an unknown proportion of community-acquired bacterial infections do not feature in statistics as a cause of death because of the presence of an underlying condition that led to the original hospital admission.

The application of rules and procedures of the ICD to certify and code causes of death data may still be diagnostically inaccurate due to the subjective nature of ICD certification practices, the limited training provided to physicians or medical coders, and cultural differences that can influence their judgement even after the training.^{20,21} Death certificates, which collectively form the basis of a nation’s civil registration and vital statistic system, are frequently filled in by non-medical staff or by medical officers who did not participate in direct patient care, and who often have received little if any formal training in how to correctly fill in a death certificate.^{22,23} Not surprisingly, the diagnostic accuracy of death certificate data is often very poor and inadequate to guide public policy.²⁴ Improving accuracy requires uniform application of the ICD principles in force by well-trained physicians or medical coders.

As the ICD principle is not perfect, some countries have been improving mortality statistics for specific infectious diseases using different approaches. For example, the increasing incidence of serious infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* in England and Wales led the Department of Health and Social Care to mandate that deaths caused by MRSA or *C. difficile* should be recorded as text on the death

certificate. The Office for National Statistics (ONS) has been storing the text of death certificates together with ICD codes on a database since 1993.²⁵ Mention of MRSA or *C. difficile* as text anywhere on the death certificate was classified as deaths involving MRSA or *C. difficile*.²⁵ The ONS could therefore access and publish data on deaths involving MRSA and *C. difficile* stratified by sex, age group and whether the death occurred in hospital or elsewhere.^{26,27}

What is all-cause mortality and attributable mortality?

Another approach is to measure mortality from AMR infections in a representative population and then use that measurement to estimate mortality in a larger population. Two such approaches are measurements of all-cause mortality and attributable mortality.

All-cause mortality (e.g. in-hospital mortality, 30- or 90-day mortality) is frequently used to quantify the burden of specific diseases and AMR infections.^{9,12,13,26,27} Measuring all-cause mortality is objective because the measurement does not involve determining what the single main underlying cause of death for each patient is. In addition, all-cause mortality can be categorized by resistant pathogens and infection type. It is challenging to collect these data from ICD coded death certificates, as described above; rather, this is best studied in representative populations to determine all-cause mortality and then apply these mortality to established infection rates.⁹ It is important to note that this measure of mortality includes deaths caused or contributed by other underlying and intermediate causes. To take account of this potential error, all-cause mortality is noted as 'deaths involving AMR infection' by ONS, UK.^{26,27}

Attributable mortality (generally assessed by the counterfactual approach)²⁸ can be used to estimate how many deaths would not have occurred in the absence of the disease or condition of interest. Counterfactual, as the term suggests, is an artificial (i.e. not factual) distribution of exposure of the population to a certain hazard that would result in the theoretical minimum disease burden from that exposure. So for tobacco smoking, for example, the counterfactual approach would assume that 100% of the population had never smoked.

It is probably true that if the hypothetical patient described in Figure 1A did not have ischemic heart disease, they would not have died. If, however, they still had ischemic heart disease but the hospital-acquired infection had been prevented, or the causative bacterium had not been resistant, they might not have died. Likewise, the second patient (Figure 1B) might not have died if their bacterial infection had been prevented or if the bacterium had not been resistant.

The mortality attributable to AMR can be calculated based on the (counterfactual) assumption that deaths would not have occurred if the AMR infection had not occurred or if the causative organisms had been antimicrobial-susceptible.^{6,8,29} Specifically, the attributable mortality (mortality difference) is the comparison of mortality between patients with the respective AMR bacterial infection and patients without the infection or patients infected with a susceptible infection, factoring out the risk of death resulting from the underlying co-morbidity. Figure 2 shows a simple diagram of how mortality attributable to AMR was calculated in the O'Neill Review and the US CDC Antibiotic Resistant Threats Report based on this assumption.^{6,29} Specifically, an attributable mortality was applied to estimates of the number of bacterial infections in order to estimate the number of excess deaths due to AMR. The appendix of a recent publication estimating attributable deaths caused by AMR bacterial infections in the EU

in 2015 provides a review of research articles estimating attributable mortality in different clinical settings worldwide.⁸

Characteristics, limitations and underlying assumptions of different approaches

Characteristics of the models used for estimating the global burden of AMR in the O'Neill Review and by the GBD 2016 study are shown in Table 1. Because of the principle of a single underlying cause embodied in the ICD, AMR could be part of many different causes of death, including almost all infectious diseases.⁵ The assumptions used for the AMR Review⁴ by KPMG²⁹ and RAND³⁰ and to estimate the future burden of AMR infections with HIV, malaria, tuberculosis and other bacterial infections are not discussed here.

The most important limitation of the O'Neill Review and the GBD 2016 study is the lack of data from both high-income countries and lower and middle-income countries (LMICs). For the O'Neill Review,^{4,31} the estimated 700,000 deaths attributable to AMR infection was based on the attributable mortality for bacterial infections reported from the US CDC,⁶ and the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA),⁷ and attributable mortality for multi and extensively drug-resistant tuberculosis reported from WHO estimations.³² This is mainly because surveillance data on outcomes of AMR and mortality attributable to AMR are close to non-existent. For the GBD 2016 approach, mortality from AMR was calculated only for multi and extensively drug-resistant tuberculosis, and not for any other pathogen. Moreover, the quality and availability of mortality data used in the GBD was often very poor, with vital registration data from many countries being less than 70% complete and a high proportion of 'garbage codes' (ICD codes that cannot be main or underlying causes of death), such as 'heart failure' or senility.⁵ These data were shown in the data visualization but were not used in the model estimation.⁵

Other major limitations are not separating the burden of community-acquired and hospital-acquired AMR infection (infection origin), and limiting the range of organisms and antibiotics to which they have become resistant. Separating infection origin is important for policy makers since prevention and interventions to reduce the burden of AMR in these two settings are different. For example, controlling AMR in hospitals would require improved hospital hygiene, hand hygiene, patient screening, decontamination, isolation and antibiotic stewardship to reduce colonization pressure and cross-transmission of AMR organisms in the hospitals.^{33,34} Controlling AMR infection in the community is multifaceted and could involve improved community hygiene, water and sanitation, improved care of chronic conditions such as ulcers and the presence of long-term urinary catheters, reduced overuse and misuse of antibiotics in both humans and animals in the community, control of antibiotic waste in the environment, etc.^{35,36}

The advantages and disadvantages of three different approaches (the underlying cause of death, all-cause mortality and attributable mortality) to estimate the burden of AMR are summarized in Table 2. The reliability of the attributable mortality approach used by the O'Neill Review has been widely debated.^{37,38} Concerns include the assumptions made, data availability, use of data that are biased towards tertiary care hospitals, data extrapolation, and the potential that their calculated attributable mortality is poorly estimated in the source data.^{37,38} In addition, the use of complex terminology such as attributable mortality creates a barrier to understanding by healthcare providers, stakeholders and the wider public. It is also unclear whether attributable mortality should be compared with drug-susceptible infection or

patients without infection. This relates to the current debate and on-going research on whether or not actions on AMR would result in an overall reduction in burden rather than simply be replaced with antimicrobial-susceptible infections.³⁹⁻⁴²

What would be required to solve the problem?

A new, more inclusive approach to estimate deaths caused by AMR infection is needed (Table 3). While the burden of AMR as estimated by disability-adjusted life-years (DALYs) using the GBD DALY model is more appropriate to measure the full health (fatal and non-fatal) consequences of AMR, estimating deaths caused by AMR infection is still likely to be better understood by policy makers and healthcare providers for purposes of quantification and monitoring intervention impact. Drug-resistant tuberculosis is already in the GBD 2016. To describe the impact of AMR infection more accurately and comprehensively, adding drug-resistant bacterial infections should be considered, possibly using the attributable mortality approach as applied more generally for risk factors such as tobacco smoking⁴³ or alcohol use⁴⁴ in the GBD.

Whatever approach is adopted, the analysis should clearly separate the burden of community-acquired infections from hospital-acquired infections, and include the global priority list of antibiotic-resistant bacteria reported by the WHO.⁴⁵ Health systems around the world will need to have the capability and capacity to reliably detect these priority pathogens, and link microbiological data to clinical outcome data in order to inform the model. This will mean boosting both diagnostic and clinical bacteriology capacity globally, particularly in resource-limited settings where routine testing is underused or unavailable, and links between laboratory and clinical services and information systems are weak. This will in turn have the added benefit of enhancing local, national and global surveillance for resistance.

Availability of data describing incidence and prevalence of AMR infections in LMICs will be improved over time as more countries enroll and submit data to the WHO Global Antimicrobial Resistance Surveillance System (GLASS), which is collecting and reporting data on AMR globally.⁴⁶ It is important to note that the initial phase of GLASS did not include the routine collection of mortality outcomes and other parameters required for modeling AMR burden. The data required for estimating the burden of AMR will need to be generated for the next phase of AMR surveillance and other mechanisms, including research and the pharmaceutical industry. In addition, training for physicians in how to correctly certify causes of death, and a better understanding of how infectious diseases, sepsis^{18,19} and AMR infection have been recorded as the main or intermediate causes of death in LMICs are needed.

Quality and availability of data on ICD coded causes of death from national vital registration systems also need to be improved to support the more reliable estimation of the burden of infectious diseases, sepsis and AMR. Training in correct certification of causes of death using the ICD rules should be prioritized by policy makers. The current version of the ICD in use (ICD-10) does not have specific codes for all priority antibiotic-resistant bacterial infections, and hence the burden of these pathogens requires a counterfactual approach, implying the availability of prevalence data on resistance and data and approaches to measure excess mortality risks in resistant versus susceptible cases. The 11th Revision of the ICD released in 2018 does include a wide range of codes to describe AMR infection, and the use of the new codes complementary with multiple approaches (Table 3) could assist in improving estimations of the burdens of AMR infection.⁴⁷

In conclusion, the global burden of AMR estimated in the O'Neill Review and the GBD 2016 study cannot be compared due to the very different methodological approaches, assumptions and data used to generate them. Neither analytical framework is adequate. A new, more inclusive approach to estimate deaths caused by AMR infection is needed. In addition, a systematic and comprehensive approach is required to gather data of sufficient breadth and quality to support the accurate assessment of burden, combined with decision-making and resource allocation for interventions against AMR both at national and global levels. This requires renewed efforts to stimulate innovative thinking and solutions.

Acknowledgements

We thank Carmem L. Pessoa Da Silva and Jean Patel for comments on the manuscript. We thank Anthony McDonnell and Jeremy Knox for comments and reviews on the models used by the AMR review. We thank Ghada Zoubiane, Francesca Chiara and Wellcome Trust Drug-resistant infections team for their technical and administrative support. SEDRIC is supported by the Wellcome Trust Drug Resistant Infection Priority Programme. The funders had no involvement in the content, writing or submission of the paper.

Contributors

DL and SJP prepared the initial draft of this Viewpoint, which SD, KF, NAF, INO, AHH, CEM, CD, HRVD, NS and AL revised.

Conflicts of interests

We declare that we have no conflicts of interest.

References

1. WHO. Antimicrobial resistance. Geneva: WHO; 2018. <https://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance> (accessed 1 Jun 2018)
2. WHO. Global Action Plan on Antimicrobial Resistance. Geneva: WHO; 2015. http://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1 (accessed 1 Jun 2018).
3. WHO. Library of National Action Plans 2018. Geneva: WHO; 2018 <http://www.who.int/antimicrobial-resistance/national-action-plans/library/en/> (accessed 1 Jun 2018).
4. O'Neill, J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Review on antimicrobial resistance. 2014. <https://amr-review.org> (accessed 1 Jun 2018)
5. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**(10100): 1151-210.
6. CDC. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: US Department of Health and Human Services, Center of Disease and Infection Control, 2013. <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf> (accessed 1 Jun 2018)
7. ECDC and EMEA Joint Working Group. ECDC/EMA Joint Technical Report. The bacterial challenge: time to react. 2009. http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (accessed 1 Jun 2018)

8. Cassini A, Hogberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; **19**(1): 56-66.
9. Phumart P, Phodha T, Thamlikitkul, V, et al. Health and economic impacts of antimicrobial resistance in Thailand. *J Health Serv Res Pol* 2012; **358**(9): 352-60.
10. Lim C, Takahashi E, Hongsuwan M, et al. Epidemiology and burden of multidrug-resistant bacterial infection in a developing country. *Elife* 2016; **5**.
11. Hay SI, Rao PC, Dolecek C, et al. Measuring and mapping the global burden of antimicrobial resistance. *BMC Med* 2018; **16**(1): 78.
12. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. *Clin Microbiol Infect* 2016; **22**(5): 416-22.
13. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible *Enterobacteriaceae* and *Staphylococcus aureus* in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. *Euro Surveill* 2016; **21**(33).
14. Naylor NR, Atun R, Zhu N, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrob Resist Infect Control* 2018; **7**: 58.
15. Wheller L, Rooney C, Griffiths C. Death certification following MRSA bacteraemia, England, 2004-05. *Health Stat Q* 2009; (41): 13-20.
16. McEwen LN, Kim C, Haan M, et al. Diabetes reporting as a cause of death: results from the Translating Research Into Action for Diabetes (TRIAD) study. *Diabetes Care* 2006; **29**(2): 247-53.
17. Handbook of Vital Statistics Systems and Methods: Legal, Organisational and Technical Aspects, United Nations Studies in Methods, Glossary, Series F, No. 35, United Nations, New York 1991.; 1991.
18. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**(8): 801-10.
19. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med* 2016; **193**(3): 259-72.
20. Office for National Statistics. Death Certification Reform: A case study of the potential impact on mortality statistics, England and Wales. 2015.
<http://www.ons.gov.uk/ons/rel/subnational-health2/death-certification-reform---a-case-study-on-the-potential-impact-on-mortality-statistics/england-and-wales/stb-deathcertification.html> (accessed 12 Feb 2019)
21. Jones G, Taright N, Boelle PY, et al. Accuracy of ICD-10 codes for surveillance of *Clostridium difficile* infections, France. *Emerg Infect Dis* 2012; **18**(6): 979-81.
22. Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *Int J Epidemiol* 2000; **29**(3): 495-502.
23. Shamsuddin K, Lieberman E. Linking death reports from the Malaysian Family Life Survey-2 with birth and death certificates. *Med J Malaysia* 1998; **53**(4): 343-53.
24. Rampatige R, Mikkelsen L, Hernandez B, Riley I, Lopez AD. Hospital cause-of-death statistics: what should we make of them? *Bull World Health Organ* 2014; **92**(1): 3-A.
25. Office for National Statistics. Deaths involving MRSA: England and Wales: 2007 to 2011. 2012.
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsinvolvingmrsaenglandandwales/2012-08-22> (accessed 1 Jun 2018)
26. Office for National Statistics. Deaths involving MRSA: England and Wales. 2014.
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsinvolvingmrsaenglandandwales> (accessed 1 Jun 2018)
27. Office for National Statistics. Deaths involving *Clostridium difficile*. 2017.
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsinvolvingclostridiumdifficilereferencetables> (accessed 1 Jun 2018)

28. Murray CJ, Lopez AD. On the comparable quantification of health risks: lessons from the Global Burden of Disease Study. *Epidemiology* 1999; **10**(5): 594-605.
29. KPMG. The global economic impact of anti-microbial resistance 2014. London: KPMG; 2014. <https://home.kpmg.com/content/dam/kpmg/pdf/2014/12/amr-report-final.pdf> (accessed 1 Jun 2018)
30. RAND. Estimating the economic costs of antimicrobial resistance 2014. Cambridge: RAND; 2014. <https://pdfs.semanticscholar.org/a2dc/3c112c37e9e4e5a15c7235b3f61f53c4337a.pdf> (accessed 1 Jun 2018)
31. Hall WM, A., O'Neill, J. Superbugs: an arm race against bacteria: Harvard University Press; 2018.
32. WHO. Antimicrobial resistance: global report on surveillance 2014. Geneva: WHO; 2014. <http://www.who.int/antimicrobial-resistance/publications/surveillancereport/en/> (accessed 1 Jun 2018)
33. Weinstein RA. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. *Emerg Infect Dis* 2001; **7**(2): 188-92.
34. Dancer SJ. Controlling hospital-acquired infection: focus on the role of the environment and new technologies for decontamination. *Clin Microbiol Rev* 2014; **27**(4): 665-90.
35. Alividza V, Mariano V, Ahmad R, et al. Investigating the impact of poverty on colonization and infection with drug-resistant organisms in humans: a systematic review. *Infect Dis Poverty* 2018; **7**(1): 76.
36. O'Neill J. Antimicrobials in agriculture and the environment: reducing unnecessary use and waste. 2014. <https://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf> (accessed 12 Feb 2019).
37. de Kraker ME, Stewardson AJ, Harbarth S. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050? *PLoS Med* 2016; **13**(11): e1002184.
38. Abat C, Rolain JM, Dubourg G, Fournier PE, Chaudet H, Raoult D. Evaluating the Clinical Burden and Mortality Attributable to Antibiotic Resistance: The Disparity of Empirical Data and Simple Model Estimations. *Clin Infect Dis* 2017; **65**(suppl_1): S58-S63.
39. Ammerlaan HS, Harbarth S, Buiting AG, et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. *Clin Infect Dis* 2013; **56**(6): 798-805.
40. Mostofsky E, Lipsitch M, Regev-Yochay G. Is methicillin-resistant *Staphylococcus aureus* replacing methicillin-susceptible *S. aureus*? *J Antimicrob Chemother* 2011; **66**(10): 2199-214.
41. David MZ, Cadilla A, Boyle-Vavra S, Daum RS. Replacement of HA-MRSA by CA-MRSA infections at an academic medical center in the midwestern United States, 2004-5 to 2008. *PLoS One* 2014; **9**(4): e92760.
42. Kim L, McGee L, Tomczyk S, Beall B. Biological and Epidemiological Features of Antibiotic-Resistant *Streptococcus pneumoniae* in Pre- and Post-Conjugate Vaccine Eras: a United States Perspective. *Clin Microbiol Rev* 2016; **29**(3): 525-52.
43. GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet* 2017; **389**(10082): 1885-906.
44. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018; **392**(10152): 1015-35.
45. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva: WHO; 2017. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf (accessed 1 Jun 2018).

46. WHO. Global antimicrobial resistance surveillance system (GLASS) Report Early Implementation 2016-2017. Geneva: WHO; 2018.
<http://apps.who.int/iris/bitstream/handle/10665/259744/9789241513449-eng.pdf?sequence=1> (accessed 1 Jun 2018).
47. WHO. ICD-11 update. Geneva: WHO; 2017.
http://www.who.int/classifications/2017_10_ICD11_Newsletter.pdf?ua=1 (accessed 1 Jun 2018).
48. Knight LA, Cree IA. Quality assurance and good laboratory practice. *Methods Mol Biol* 2011; **731**: 115-24.
49. Turner P, Fox-Lewis A, Shrestha P, et al. Microbiology Investigation Criteria for Reporting Objectively (MICRO): a framework for the reporting and interpretation of clinical microbiology data. *BMC Med* 2019; **17**(1): 70.

Table 1: Characteristics of models used by the Review on AMR and the GBD 2016

	Review on AMR ^{4 *}	GBD study 2016 ⁵
Main principle	Counterfactual analysis or attributable mortality (i.e. estimating how many deaths would not have occurred if all causative pathogens were not antimicrobial resistant)	International Classification of Diseases (ICD) principle ¹⁷ (there can only be a single cause of death for each case).
Main assumptions used in the model estimating the current burden of antimicrobial resistance (AMR) **	<ul style="list-style-type: none"> - Attributable mortality was estimated by comparing case fatality rate of people with infections caused by pathogens with AMR characteristics versus those with non-AMR characteristics or versus patients without infections. - Attributable mortality for drug-resistant bacterial infections in the US and the Europe was based on a report of US CDC⁶ and a report of ECDC/EMEA,⁷ respectively. Attributable mortality for drug-resistant bacterial infections per 100,000 population in all other countries is assumed to be equal to that observed in the US,⁶ except for tuberculosis, where global resistance estimates were used. 	<ul style="list-style-type: none"> - Total number of deaths from each cause in each country was estimated using the Cause of Death Ensemble model (CODEm).⁵ - Sepsis and unspecified infections were considered as intermediate causes of death and garbage codes, respectively, and cannot be the true cause of death - Data from countries with a high percentage of garbage codes as causes of death were not represented in the model - Data from countries with completeness lower than 70% were not represented in the model
Source of data	Reports from WHO, ³² ECDC/EMEA ⁷ and US CDC. ⁶	Vital registration (including ICD code data or death certification), national and subnational verbal autopsy and surveillance systems for specific causes
Studied AMR pathogens	Tuberculosis (multidrug-resistant and extensively drug-resistant) and other bacterial infections included in a report of US CDC ⁶ and a report of ECDC/EMEA. ⁷	Tuberculosis (multidrug-resistant and extensively drug-resistant)

* The model used for the Review on AMR⁴ by KPMG²⁹ and RAND³⁰ to estimate the future burden of AMR infections with HIV, malaria, tuberculosis and other bacterial infections are not discussed here. The 700,000 deaths every year were estimated from deaths attributable to AMR infections with tuberculosis and other bacterial infections.⁴

** AMR is defined as the ability of a microorganism (including bacteria, viruses, fungi and parasites) to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it where it normally would have. As a result, standard treatments become ineffective against AMR infection and associated with a higher risk of complications and death.

Table 2. Advantages and disadvantages of different data sources and approaches used to estimate burden of AMR

	Advantage(s)	Disadvantage(s)	Example *
Data sources			
International Classification of Diseases (ICD) code data	<ul style="list-style-type: none"> - A common source of data in high-income countries - Can be applied more rigorously with better codes 	<ul style="list-style-type: none"> - Requires judgement in applying - Non-trained medical staff often apply ICD codes 	GBD study 2016, ⁵ and reports from The Office for National Statistics (ONS), the United Kingdom ^{26,27}
Death certificate data from vital registration systems	A common source of data worldwide	<ul style="list-style-type: none"> - Difficulties in implementing standardized reporting resulting in variable validity - May be applied by someone without direct care of patients 	GBD study 2016 ⁵
National and international reports (such as WHO, ECDC and UNAIDS)	Official data from the countries where data is available	<ul style="list-style-type: none"> - May need to extrapolate data available from high-income countries to low and middle-income countries (LMICs) due to data unavailability in LMICs - Data available may be biased towards tertiary-care hospitals 	O'Neill Review on AMR ⁴ , GBD study 2016 ⁵ and a report of ECDC/EMEA ^{7,8}
Research data	<ul style="list-style-type: none"> - Can have Good Laboratory Practice (GLP)⁴⁸ - Can have pre-defined study design, collect required data and comply with reporting guidelines⁴⁹ 	<ul style="list-style-type: none"> - May need to extrapolate data available from high-income countries to LMICs - Data available may be biased towards tertiary-care hospitals 	O'Neill Review on AMR, ⁴ GBD study 2016, ⁵ a report of US CDC, ⁶ a report of ECDC/EMEA ^{7,8} and two studies from Thailand ^{9 10}
Approaches			
Estimating a single cause of death using the ICD principle	<ul style="list-style-type: none"> - Can cover all diseases evaluated (e.g. 246 causes of death in GBD 2016)⁵ - Consistent methods applied to all diseases evaluated 	Majority of hospital-acquired infections and an unknown proportion of community-acquired bacterial infections may not be counted as cause of death	GBD study 2016 ⁵
Estimating all-cause mortality (e.g. in-hospital)	Easy to standardize	Other causes of death may be included	A study from Thailand, ⁹ and reports of The Office for

mortality, 30-day mortality and 90-day mortality)			National Statistics (ONS), the United Kingdom ^{26,27}
Estimating attributable mortality	<ul style="list-style-type: none"> - Specific to AMR - Can be used to directly estimate the economic cost of AMR 	<ul style="list-style-type: none"> - Hard to accurately measure - Hard to understand; for example, what does attributable to AMR mean (e.g. comparison of drug-resistant infection versus drug-susceptible infection, or drug-resistant infection versus patients without infection)?** 	O'Neill Review on AMR, ⁴ a report of US CDC, ⁶ a report of ECDC/EMA ^{7,8} and a study from Thailand ¹⁰

* GBD study 2016 used ICD code data, death certificates and data from international reports and surveillance systems for specific causes.⁵

** The mortality attributable to AMR represents the total number of deaths that would not have occurred if all causative organisms had been antimicrobial-susceptible.

Table 3. Key actions to improve the estimation of the global burden of AMR infections

Strengthen health systems	<ul style="list-style-type: none"> • Increase country capability and capacity to: <ol style="list-style-type: none"> 1. reliably detect the global priority list of antibiotic-resistant bacteria reported by the WHO⁴⁵ 2. document clinical outcomes and link to laboratory data 3. train in correct certification of causes of death using the ICD rules 4. improve the quality and availability of ICD coded mortality data from vital registration systems, and the data required to determine attributable mortality (including prevalence of resistance and excess mortality risks) 5. systematically utilize data generated within country 6. share the data required to estimate the burden of AMR infections with international organizations or make the data open-access • Consider mandatory notification (similar to statutory notifiable diseases) for AMR infection
Increase confidence in the quality of data used to estimate burden of AMR infections	<ul style="list-style-type: none"> • Develop and use standardized guidelines for data capture and reporting of AMR infections, together with details on those collecting data (e.g. clearly describe population being sampled and laboratory practice being performed) • Improve understanding of how infectious diseases, sepsis^{18,19} and AMR infection are recorded as the main, immediate or intermediate causes of death in LMICs • Design and implement prospective studies to generate parameters to inform AMR burden estimation (e.g. AMR attributable mortality)
Improve the methodological approaches used to estimate burden	<ul style="list-style-type: none"> • Develop improved methodological approaches to estimate deaths caused by AMR infection • New methods need to be robust, reliable, sustainable and plausible to policy makers and healthcare providers • Include the burden caused by the global priority list of antibiotic-resistant bacteria reported by the WHO⁴⁵ • Consider separating the burden of community-acquired infections and hospital-acquired infections

Figure 1. Hypothetical death certificate for a deceased patient (1A) with ischaemic heart disease, hospital-acquired pneumonia, carbapenem-resistant *Acinetobacter baumannii* bacteraemia, and sepsis-related organ failures, and a deceased patient (1B) with HIV/AIDS and multidrug-resistant non-typhoidal *Salmonella* infection.

1A

To Be Completed By: MEDICAL CERTIFIER	29. ACTUAL OR PRESUMED DATE OF DEATH (MO/Day/Yr)	30. ACTUAL OR PRESUMED TIME OF DEATH	31. WAS MEDICAL EXAMINER OR CORONER CONTACTED? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
	<p align="center">CAUSE OF DEATH</p> <p>32. Part I. Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.</p>			Approximate interval: Onset to death
	<p>IMMEDIATE CAUSE (final disease or condition resulting in death) → a. sepsis Due to (or as a consequence of):</p> <p>Sequentially list conditions, if any, leading to the cause listed on line a. Enter the UNDERLYING CAUSE (disease or injury that initiated the events results in death) LAST</p> <p>b. <i>Acinetobacter</i> bacteraemia Due to (or as a consequence of):</p> <p>c. Hospital-acquired pneumonia Due to (or as a consequence of):</p> <p>d. Ischaemic heart disease Due to (or as a consequence of):</p>			
<p>Part II. Enter other <u>significant conditions contributing to death</u> but not resulting in the underlying cause given in PART I</p> <p align="center">Chronic kidney disease</p>				

1B

To Be Completed By: MEDICAL CERTIFIER	29. ACTUAL OR PRESUMED DATE OF DEATH (MO/Day/Yr)	30. ACTUAL OR PRESUMED TIME OF DEATH	31. WAS MEDICAL EXAMINER OR CORONER CONTACTED? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
	<p align="center">CAUSE OF DEATH</p> <p>32. Part I. Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.</p>			Approximate interval: Onset to death
	<p>IMMEDIATE CAUSE (final disease or condition resulting in death) → a. sepsis Due to (or as a consequence of):</p> <p>Sequentially list conditions, if any, leading to the cause listed on line a. Enter the UNDERLYING CAUSE (disease or injury that initiated the events results in death) LAST</p> <p>b. multidrug-resistant non-typhoidal <i>Salmonella</i> bacteraemia Due to (or as a consequence of):</p> <p>c. Community-acquired diarrhoea Due to (or as a consequence of):</p> <p>d. HIV/AIDS Due to (or as a consequence of):</p>			
<p>Part II. Enter other <u>significant conditions contributing to death</u> but not resulting in the underlying cause given in PART I</p>				

Figure 2. Diagram showing how to calculate mortality attributable to drug-resistant infection

