Improving the estimation of the global burden of antimicrobial resistant infections

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Estimating the global burden of disease from infections caused by pathogens that have acquired antimicrobial resistance (AMR) is essential for resource allocation and to inform AMR action plans at national and global levels. However, the scarcity of robust and accepted methods to determine burden is widely acknowledged. In this Personal View, we discuss the underlying assumptions, characteristics, limitations, and comparability of the approaches used to quantify mortality from AMR bacterial infections. We show that the global burdens of AMR estimated in previous studies are not comparable because of their different methodological approaches, assumptions, and data used to generate the estimates. The analytical frameworks from previous studies are inadequate, and we conclude that a new approach to the estimation of deaths caused by AMR infection is needed. The innovation of a new approach will require the development of mechanisms to systematically collect a clinical dataset of substantial 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 problems.

Introduction

Antimicrobial resistance (AMR) occurs when micro-organisms 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 crucial, 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 effect of actions on AMR, and compare these statistics with those from other countries. It is also crucial for policy makers to be able to compare the effect 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 effect, including heart disease and cancer.

The Review on AMR by Jim O'Neill[4] estimated that 700 000 deaths each year globally might be due to AMR bacterial infections, including multidrug-resistant and extensively drug-resistant tuberculosis. The Global Burden of Disease (GBD) 2016 study[5] estimated that 126 000 deaths are due to multidrug-resistant and extensively drug-resistant tuberculosis in 2016, but the number of deaths due to other drug-resistant bacterial infections, malaria, and HIV were not estimated separately. National estimates of mortality from AMR bacterial infections have been published for places such as the USA,[6] Europe,[7,8] and Thailand.[9,10] 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 scarcity of a robust and accepted 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 use.[1,12] In this Personal View, 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 a review by O'Neill[4] and the GBD study by GBD 2016 Causes of Death Collaborators[5] because of the availability of their estimates of global mortality from AMR and their high effect 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, comorbidities, and acute complications such as a drug-resistant infection that ultimately results in death.[15,16] It is often hard to decipher which of these conditions initiated the series of events that resulted in death. For example, did the patient die because of a drug-resistant infection or did the patient die while being infected by 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, health-care systems document all the 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 and the presence of sepsis[18,19] can be determined from the combination of underlying and non-underlying (ie, immediate or intermediate) causes listed on the death certificate, which are collectively known as multiple causes of death.[17] Sepsis is a life-threatening

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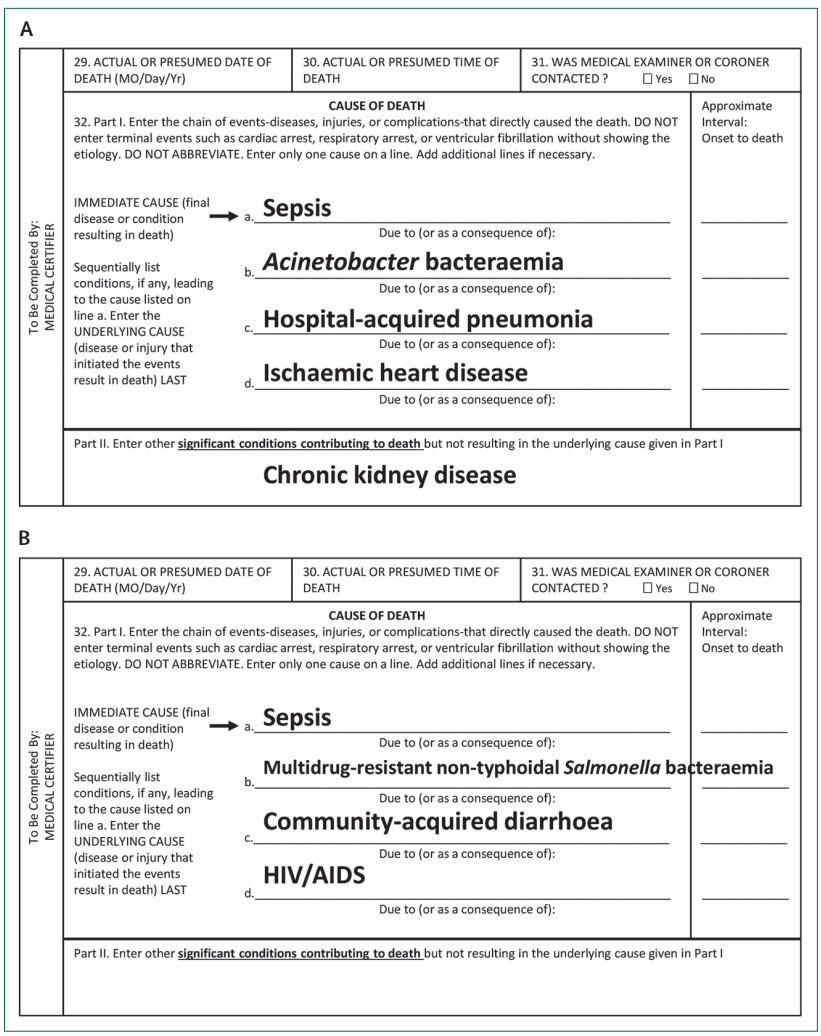

Figure 1: **Hypothetical death certificates**
(A) Hypothetical death certificate for an elderly patient who is admitted to hospital because of ischaemic heart disease and cardiogenic shock. The patient has a history of chronic kidney failure. During hospitalisation, the patient is intubated and develops 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 was infection with a carbapenem-resistant *A baumannii*, whereas another doctor 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. (B) Hypothetical death certificate for a patient with HIV/AIDS and community-acquired multidrug-resistant non-typhoidal salmonella infection; this patient would be recorded in national statistics on causes of death as having died from HIV/AIDS.

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.

Although the ICD principle relies on the assumption that there is only one cause of death,[17] the cause of death, particularly for complex illnesses, is often the interplay between two or more major morbid conditions (figure 1). Assigning a single cause of death according to the ICD principles means that most 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 can also be diagnostically inaccurate because of the subjective nature of ICD certification practices, the limited training and cultural differences that can influence judgement even after 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 often have received little if any formal training on how to correctly fill in a death certificate.[22,23] 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 thoroughly trained physicians or medical coders.

Because 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 meticillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridioides 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 (not only as ICD codes) on the death certificate. The UK Office for National Statistics 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 Office for National Statistics 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 (eg, in-hospital, 30-day, 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. Additionally, all-cause mortality can be categorised according to resistant pathogens and infection type. It is challenging to collect these data from ICD coded death certificates. All-cause mortality is best studied in representative populations to determine mortality and then apply the estimated mortality

to established infection rates.[9] This measure of mortality includes deaths caused or contributed by other underlying and intermediate causes. To account for this potential error, all-cause mortality is noted as deaths involving AMR infection by the UK Office for National Statistics.[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, refers to an artificial distribution of exposure of the population to a certain hazard that would result in the theoretical minimum disease burden from that exposure. For tobacco smoking, the counterfactual approach would assume that 100% of the population had never smoked.

It is probably true that if the first hypothetical patient described in figure 1 did not have ischemic heart disease, they would not have died. However, if 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 1) 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 susceptible to antimicrobial drugs.[6,8,29] 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 comorbidity. Figure 2 shows how mortality attributable to AMR was calculated in the review by O'Neill[4] and the US Centres for Disease Control and Prevention (CDC) Antibiotic Resistant Threats Report based on this assumption.[6,29] An attributable mortality was applied to estimates of the number of bacterial infections to estimate the number of excess deaths due to AMR. The appendix of a publication[8] 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.

Characteristics, limitations, and underlying assumptions of different approaches

Characteristics of the models used for estimating the global burden of AMR by O'Neill[4] and the GBD 2016 study[5] 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 most infectious diseases.[5] The assumptions used by O'Neill,[4] KPMG,[29] and RAND[31] to estimate the future burden of AMR infections with HIV, malaria, tuberculosis, and other bacterial infections are not discussed here.

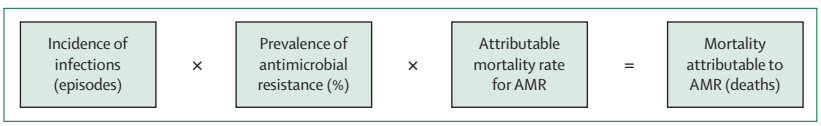

Figure 2: **Diagram showing how to calculate mortality attributable to drug-resistant infection**
AMR=antimicrobial resistance.

	Review on AMR by O'Neill[4]*	GBD study 2016[5]
Main principle	Counterfactual analysis or attributable mortality (ie, estimating the number of avoidable deaths if all causative pathogens were not antimicrobial resistant or if the AMR infection had not occurred)	ICD principle[17] (ie, there can only be a single cause of death for each case)
Main assumptions used in the model estimating the burden of AMR†	Attributable mortality was estimated by comparing case fatality rate of people with infections caused by pathogens with AMR characteristics *vs* those with non-AMR characteristics or *vs* patients without infections; attributable mortality for drug-resistant bacterial infections in the USA and Europe was based on a reports by CDC[6] and ECDC/EMEA[7]; 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 USA,[6] except for tuberculosis, for which global resistance estimates were used	Total number of deaths from each cause in each country was estimated using CODEm;[5] sepsis and unspecified infections were considered as intermediate causes of death and garbage codes 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 <70% were not represented in the model
Source of data	WHO;[30] ECDC/EMEA;[7] CDC[6]	Vital registration (including ICD code data or death certification); national and subnational verbal autopsy; surveillance systems for specific causes
Studied AMR pathogens	Tuberculosis (multidrug-resistant and extensively drug-resistant) and other bacterial infections included in reports by CDC[6] and ECDC/EMEA[7]	Tuberculosis (multidrug-resistant and extensively drug-resistant)

AMR=antimicrobial resistance. GBD=global burden of disease. ICD=International Classification of Diseases. ECDC=European Centre for Disease Prevention and Control. EMEA=European Medicines Agency. CDC=US Centres for Disease Control and Prevention. CODEm=cause of death ensemble model. *The model used for reviews on AMR[4] by KPMG[29] and RAND[31] 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 1: **Characteristics of models used in the review on AMR by O'Neill[4] and the GBD study 2016[5]**

The most important limitation of the review by O'Neill[4] and the GBD 2016 study[5] is the scarcity of data from both high-income countries and low-income and middle-income countries (LMICs). O'Neill[4,32] estimated that 700 000 deaths per year are attributable to AMR infection on the basis of attributable mortality for bacterial infections,[6] European Centre for Disease Prevention and Control, and the European Medicines Agency,[7] and attributable mortality for multi and extensively drug-resistant tuberculosis reported by WHO.[30] These data were used because surveillance data on outcomes of AMR and mortality attributable to AMR were very scarce. The GBD 2016 study[5] estimated mortality from AMR only for multi and extensively drug-resistant tuberculosis, and not for any other pathogen. The quality and availability of

	Advantages	Disadvantages	Example*
ICD code data	A common source of data in high-income countries; can be applied more rigorously with better codes	Requires judgement in applying; medical staff who are not trained often apply ICD codes	GBD study 2016;[5] reports from ONS, UK[26,27]
Death certificate data from vital registration systems	A common source of data worldwide	Difficulties in implementing standardised reporting resulting in variable validity; can be applied by someone without direct care of patients	GBD study 2016[5]
National and international reports (eg WHO, ECDC, and UNAIDS)	Official data from the countries where data is available	Might need to extrapolate data available from high-income countries to LMICs because of data unavailability in LMICs; data available can be biased towards tertiary-care hospitals	Review on AMR by O'Neill;[4] GBD study 2016;[5] report by ECDC/EMEA[7,8]
Research data	Can be done under GLP standard,[33] have pre-defined study design, collect required data, and comply with reporting guidelines[34]	Might need to extrapolate data available from high-income countries to LMICs; data available can be biased towards tertiary-care hospitals	Review on AMR by O'Neill;[4] GBD study 2016;[5] report by CDC;[6] report by ECDC/EMEA;[7,8] two studies from Thailand[9,10]

AMR=antimicrobial resistance. ICD=International Classification of Diseases. ONS=Office for National Statistics. ECDC=European Centre for Disease Prevention and Control. LMICs=low-income and middle-income countries. GLP=Good Laboratory Practice. EMEA=European Medicines Agency. CDC=US Centers for Disease Control and Prevention. *GBD study 2016 used ICD code data, death certificates, and data from international reports and surveillance systems for specific causes.[5]

Table 2: **Advantages and disadvantages of different data sources used to estimate burden of AMR**

	Advantages	Disadvantages	Example*
Estimating a single cause of death using the ICD principle	Can cover all diseases evaluated (eg, 246 causes of death in GBD 2016);[5] consistent methods applied to all diseases evaluated	Most hospital-acquired infections and an unknown proportion of community-acquired bacterial infections might not be counted as cause of death	GBD study 2016[5]
Estimating all-cause mortality (eg, in-hospital, 30-day, and 90-day mortality)	Easy to standardise	Other causes of death can be included	Study from Thailand;[9] reports from ONS, UK[26,27]
Estimating attributable mortality	Specific to AMR; can be used to directly estimate the economic cost of AMR	Hard to accurately measure; hard to understand	Review on AMR by O'Neill;[4] report by CDC;[6] report by ECDC/EMEA;[7,8] study from Thailand[10]

ICD=International Classification of Diseases. ONS=Office for National Statistics. AMR=antimicrobial resistance. CDC=US Centers for Disease Control and Prevention. ECDC=European Centre for Disease Prevention and Control. EMEA=European Medicines Agency. *GBD study 2016 used ICD code data, death certificates, and data from international reports and surveillance systems for specific causes.[5]

Table 3: **Advantages and disadvantages of different approaches used to estimate burden of AMR**

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 so-called 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 visualisation but were not used in the model estimation.[5] The advantages and disadvantages of different data sources are summarised in table 2.

Other major limitations are not separating the burden of community-acquired and hospital-acquired AMR infection (ie, infection origin) and limiting the range of organisms and antibiotics to which they have become resistant. Separating infection origin is important for policy makers because 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 colonisation pressure and cross-transmission of AMR organisms in hospitals.[35,36] Controlling AMR infection in the community is multifaceted and could involve improved community hygiene, care of chronic conditions (eg, ulcers and the presence of long-term urinary catheters), and water and sanitation; reduced overuse and misuse of antibiotics in humans and animals in the community; and control of antibiotic waste in the environment.[37,38]

The advantages and disadvantages of the three different approaches (the underlying cause of death, all-cause mortality, and attributable mortality) to estimate the burden of AMR are summarised in table 3. The reliability of the attributable mortality approach used by O'Neill[4] has been widely debated.[39,40] 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.[39,40] Additionally, the use of complex terminology such as attributable mortality makes the results difficult to understand for health-care providers, stakeholders, and the public. It is unclear whether attributable mortality should be compared with drug-susceptible infection or patients without infection. This ambiguity relates to the debate and ongoing research

about whether or not actions on AMR would result in an overall reduction in burden rather than simply be replaced with antimicrobial-susceptible infections.[41–44]

What would be required to solve the problem?

A more inclusive approach to estimate deaths caused by AMR infection is needed (panel). Although 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 health-care providers for purposes of quantification and monitoring intervention effect. Data on drug-resistant tuberculosis are already included in GBD 2016. To describe the effect of AMR infection accurately and comprehensively, the addition of drug-resistant bacterial infections to GBD should be considered, possibly by using the attributable mortality approach as applied more generally for risk factors such as tobacco smoking[46] or alcohol use[47] in 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 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 to inform the model. This approach will mean boosting both diagnostic and clinical bacteriology capacity globally, particularly in resource-limited settings in which 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 likely be improved over time as more countries enrol and submit data to the WHO Global Antimicrobial Resistance Surveillance System, which is collecting and reporting data on AMR globally.[48] The initial phase of the surveillance system did not include the routine collection of mortality outcomes and other parameters required for modelling 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. Additionally, training for physicians in how to correctly certify causes of death, and a better understanding of how infectious diseases, sepsis[18,19] and AMR infections 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 prioritised 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 (panel) could assist in improving estimations of the burdens of AMR infection.[49]

***Panel*: Key actions to improve the estimation of the global burden of AMR infections**

Strengthen health systems

- Increase country capability and capacity to:
  - Reliably detect the global priority list of AMR bacteria reported by WHO[45]
  - Document clinical outcomes and link to laboratory data
  - Train in correct certification of causes of death using ICD rules
  - 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
  - Systematically use data generated within country
  - Share the data required to estimate the burden of AMR infections with international organisations or make the data open-access
- Consider mandatory notification (similar to statutory notifiable diseases) for AMR infections

Increase confidence in the quality of data used to estimate burden of AMR infections

- Develop and use standardised guidelines for data capture and reporting of AMR infections, together with details on those collecting data (eg, clearly describe population being sampled and laboratory practice being done)
- Improve understanding of how infectious diseases, sepsis,[18,19] and AMR infections are recorded as the main, immediate, or intermediate causes of death in low-income and middle-income countries
- Design and implement prospective studies to generate parameters to inform AMR burden estimation (eg, AMR attributable mortality)

Improve the methodological approaches used to estimate burden

- Develop improved methodological approaches to estimate deaths caused by AMR infections
- New methods need to be robust, reliable, sustainable, and plausible to policy makers and health-care providers
- Include the burden caused by the global priority list of AMR bacteria reported by WHO[45]
- Consider separating the burden of community-acquired infections and hospital-acquired infections

AMR=antimicrobial resistance. ICD=International Classification of Diseases.

Conclusion

The global burden of AMR estimated in the review by O'Neill and colleagues[4] and the GBD 2016 study[5] cannot be compared because of the very different methodological approaches, assumptions, and data used to generate them. In our opinion, neither analytical framework is

adequate. A more inclusive approach to estimate deaths caused by AMR infection is needed. Additionally, 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 approach requires renewed efforts to stimulate innovative thinking and solutions.

Contributors

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

Declaration of interests

We declare no competing of interests.

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