OPEN LETTER

Estimating the global burden of antimicrobial resistance:
Reflections on current methods and data needs [version 1; peer review: 1 approved, 1 not approved]

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Abstract
The prioritisation of policy action, research and the evaluation of progress towards curbing the threat of Antimicrobial Resistance (AMR) is dependent on our knowledge of its burden. The burden of AMR, like that of other causes of death and morbidity, is an important metric that not only provides the opportunity for generating and using data on periodic measures for timely and reliable updates on the prevailing disease situation and its potential to get better or worse, but also guides the development and positioning of interventions, including estimating the costs and benefits of interventions. The urgency with which AMR must be combated as a global public health threat requires the need to determine and apply the most suitable methods, models and metrics for estimating the global burden of AMR to better inform decisions on how to best manage AMR.

Keywords
Antimicrobial resistance, Estimating the burden of AMR

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Introduction
Antimicrobial resistance (AMR) features at the top of the global public health agenda, with a call for action to reduce its threat and the impact on patients suffering from drug-resistant infections. An emerging public health concern with the potential to grow; the full impact of AMR is yet to be fully determined. Initial estimates of its burden\(^1\) indicate that AMR already kills 50,000 people a year in the US and UK and is estimated to lead to the deaths of 700,000 people globally\(^1\). However, the prioritisation of policy action, research and the evaluation of progress towards curbing the threat of AMR is dependent on a greater level of understanding of its burden both globally and at the national level.

Global burden of disease (GBD) estimates\(^2\) for human diseases have been derived for several causes based on established methods. Unlike other diseases and causes of death for which burden estimates have been calculated, AMR is not a disease; rather, it is a phenomenon that occurs across different diseases, arising due to the ability of pathogens to evade antibiotic activity. AMR burden refers to the number of deaths attributable to the failure of antibiotic therapy targeted at a specific pathogen and disease due to antibiotic resistance. Thus, AMR differentially contributes to an increase in the burden of multiple infectious diseases because of prolonged hospital stay due to failed treatments, or mortality where alternative treatments are unavailable or ineffective.

Notwithstanding the complexity, burden estimates are in progress for AMR in an ongoing study\(^3\) conducted by the Institute of Health Metrics and Evaluation (IHME) and the Big Data Institute (BDI), University of Oxford; and in other work by the US Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), European Centres for Disease Control (ECDC) and Centre for Disease Dynamics, Economics and Policy (CDDEP) among others. However, the lack of data, the absence of reliable data capture systems and the capacity to competently curate, analyse and interpret this data means AMR burden estimates are currently unavailable for most countries.

What burden parameters do we need to measure?
Even though data needs for burden estimates are well known, most available data are based on pathogen isolates without a link to the patient. A shift from pathogen or isolate-based data to patient focussed data is required\(^4\) including relevant epidemiological data and patient outcome. Where the outcome is death, AMR is currently not listed in death certification and thus is often not captured as a cause of death leading to incomplete death certification records; and in practice varies widely between countries.

Ideally, the most meaningful AMR data should be captured along the patient care pathway. It should begin at the point of care with clinician records of patient clinical history, capturing important burden parameters that include morbidity or clinical failure from previous medication, recurrent and secondary infections, outcomes based on specific drug- bug combinations and associated economic costs including resource utilization and length of hospital stay. In addition to the epidemiological information, accurate pathogen metadata is important and requires the availability of functional laboratory services.

There are numerous barriers preventing the capture of useful data. Currently, standard laboratory protocols, inadequate laboratory quality control and quality assurance, lack of blood cultures and staffing shortages hinder the efficiency of laboratory services\(^5,6\). Addressing the above has the potential to guide greater focus on improving the quality (not quantity) of AMR data, which in combination with data on patient outcomes, provide data for AMR burden analysis. Current data limitations and associated non-uniform views on how existing AMR data should be analysed are key factors hindering the development and testing of methods for AMR burden analysis.

The harmonisation of data collection
Well established analytical methods require a depth of data that includes relevant pathogen data, clinical data and patient outcome. As a problem that spans global boundaries, AMR data collection should be systematic to allow comparability across countries and regions. However, this is not currently the case. In high-income countries, patient records are most often electronically captured. However, linkage of microbiological, clinical and epidemiological data varies across countries, and sometimes, the two are completely disaggregated. In low- and middle-income countries (LMICs) routine clinical data are almost entirely paper based, with no linkage to epidemiology (except in cases where special research studies are ongoing within a medical facility), with little or no access to an electronic data capture system. Routine microbiological testing is seldom done, with laboratory tests requested only for severely ill patients, a practice which introduces bias in microbiological testing and pathogen detection\(^7\).

There is an urgent need for a high-quality data capture system that supports a unified global analysis of the burden of AMR. This requires the harmonisation of data sets on every bacterial species and all antibiotics from across the world, the clear definition of metadata and the generation of standardised local and national reports which are comparable across countries. This would also streamline country data submission to WHO Global Antimicrobial Resistance Surveillance System (GLASS), the global database on antimicrobial resistance.

One pathway towards achieving this is by developing a basic laboratory information management system (LIMS) that is integrated to health information systems (HIS) and standardising how clinician decisions for a laboratory test are taken, by making blood cultures an integral part of clinical investigations for patients suspected of bacterial infection. In LMICs, there might be a need to change social and cultural norms associated with blood sampling through local and international campaigns for improved and more frequent use of blood cultures as it underpins the estimation of AMR burden.

This will require the provision of support to LMICs to build surveillance systems incorporating microbiological data and antibiotic use in humans and animals. Whilst each country
might require a bespoke AMR LIMS which easily integrates with existing HIS, based on country policies and practices and the variety of challenges they each currently face, it will be important that investments in AMR surveillance systems are designed to produce data that will be accessible in the foreseeable future and can lead to the establishment of a global database on antibiotic resistance and susceptibility.

Improving the methodology for AMR burden analysis

Maintaining current global momentum on the fight against AMR requires consistency in the estimates that are reported, and avoidance of providing different estimates for the same metric. This is achievable only through consistency in methodology and analytical approaches, which calls for the urgent need to determine the most suitable methods, models and metrics for AMR burden estimates.

While heterogeneity in the methodology currently applied is recognised, important barriers to burden estimation still exist beyond modelling. Recently reported estimates have applied either the all-cause mortality, counterfactual approach or the international classification of diseases (ICD) principle. Concerns have been raised over the reliability and accuracy of the approaches in use given the existing data limitations and their suitability, and thus there is no consensus on the best method for estimating the burden of AMR.

In a recent review the scarcity of methods for AMR burden analysis is acknowledged. Three main approaches namely, attributable mortality (or the counterfactual approach), the all-cause mortality and collection of mortality data from the ICD coded death certificates are currently used, often with limitations. Based on the international classification of diseases (ICD) cause of death codes, one person can only die of one cause. This means that based on ICD codes, deaths due to sepsis are not accurately captured or recorded, as sepsis due to AMR is not included in the ICD codes. The ICD approach is therefore unsuitable for country statistics, and most hospital-acquired infections do not appear as causes of death. On the other hand, all-cause mortality includes deaths due to underlying factors while attributable mortality (the counterfactual approach) records total mortality minus all the associated causes. It has been emphasised that the all-cause approach overestimates the burden of AMR, and as such the community should critically discuss which method is best and counterbalance the different approaches to end up with comprehensive estimates. However, while efforts are made to improve analytical methods, it has become important to reliably determine what we are measuring.

Analytically, the interest is in estimating the burden of AMR from all infections. Thus, it becomes important to decompose burden and stratify by drug-bug combinations. However, samples are rarely representative of all infections and are not systematically collected. As a result, routine data sources and laboratory tests are biased to severe cases. In addition to this, obtaining estimates of excess risk per infection depends on access to care, which varies by setting and is often difficult to extrapolate. Thus, longitudinal or special studies are likely to be a good source of data because sample populations are often small, and the value of these data is enhanced because laboratory microbiology results are linked to patient outcome as shown in the data generated by Cassini and colleagues in 2015. Moreover, this approach will provide an opportunity for estimating the joint distribution of AMR in clinical syndromes as opposed to estimates of infection incidence which are often based on the proportion of people who die, because of sepsis\(^2\). In the absence of longitudinal or small studies, electronic patient records are probably the most lasting solution to improve how deaths due to AMR are captured. As efforts are made to improve surveillance and generate good quality AMR data for burden estimation, there is a need to improve the capability of AMR teams to extract and analyse data at country level, and to generate country level AMR reports based on well established analytical approaches.

Data availability

No data are associated with this article.

References

The author highlights an important issue; that of the relationship between the burden of antimicrobial resistance (AMR) and data. There are some key discussion points raised; including data quality issues and feasibility.

In reviewing this work I think the paper would benefit greatly from (i) establishing the scope of the discussion more clearly (what is meant by burden and what is the scope for data sources discussed here) and then (ii) structuring the letter's content accordingly (e.g. across the different data components needed or different issues raised within the defined scope).

In relation to "Is the rationale for the Open Letter provided in sufficient detail?" it is not clear from the abstract or the introduction what specifically is highlighted within this letter. AMR burden is a broad topic in itself; very clearly defining the differences between epidemiological burden, patient outcome and economic burden at the outset may help make this. Additionally, there is no mention of the difference between potential current, direct burden and the wider, secondary and One Health effects. It is definitely reasonable for the author to only focus on primary, human health burden for this Open Letter, but then if this is stated in the introduction/abstract it will make it more clear to the reader what is being discussed here.

The author switches between AMR burden meaning mortality burden and then also incidence/prevalence burden within same sections, which makes it harder to understand as a reader what is meant by 'AMR burden'.

For the question "Does the article adequately reference differing views and opinions?". Though the author touches on a range of important factors and views (like the comparison of different mortality burden estimation processes), these are not discussed in great detail. For example, the paragraph with "Current data limitations and associated non-uniform views on how existing AMR data should be analysed are key factors hindering the development and testing of methods for AMR burden analysis" I'm not sure gives a fair assessment of the AMR burden estimation literature status. A lot of the novel/current methods used in healthcare-associated infection and AMR burden estimation look at associations between AMR and patient outcomes using varying data.
Perhaps these methods are only feasible within settings where patient laboratory, healthcare system administrative and outcome data are available, but then I think this is then the discussion point that should be highlighted - what data do you need for this? is this available?

This section also mentions tightening laboratory protocols etc. for data quality, but then doesn't discuss potential ways of increased data quality across patient outcome data/hospital coding etc. The focus of recommendations seems to be more of harmonisation of laboratory data globally, which is of course an important point, but (if this is the stated focus) the author could then bring in more of previous discussions around this. For example, what then about the use of private data - e.g. ATLAS from the pharmaceutical company (see Wellcome Data Reuse Prize: ATLAS information online).

There is the mention briefly of 'antibiotics data', but this is another large topic not then discussed further (e.g. there is much discussion on antibiotic consumption vs usage data across One Health), and not much discussion of then how this is linked to AMR burden estimation.

The letter includes some bold statements like "Ideally, the most meaningful AMR data should be captured along the patient care pathway." but I think this does depend on "who" the data are intended for, as different stakeholders would focus on different aspects. For example for an outbreak response team, local epidemiological (incidence) burden would be meaningful, for clinicians patient-level data and local-level rates of resistance might be more important, whilst for impact evaluators more average affects on patient outcomes are potentially more useful. Again, I believe the piece would therefore benefit from a clearer clarification at the beginning of what (if a specific) viewpoint the definition of burden is being taken from and/or who the recommendations/discussions are specifically for.

In the paragraph "In a recent review the scarcity of methods for AMR burden analysis is acknowledged. Three main approaches namely...". There are many simplifications (which I agree at some level will be needed for the letter as the author cannot cover everything). However, some of which I believe are oversimplifications (for example that attributable mortality is equivalent to all-cause "minus" underlying factors). The letter does offer some discussion of the potential strengths and limitations of the different methods mentioned, however, there is no reference of previous discussion of these methods in AMR (or in general) given.

For "Are all factual statements correct, and are statements and arguments made adequately supported by citations?" The author highlights some of the key literature in this area, however there are some statements throughout that should be supported with citations such as (non-exclusive):

"It has been emphasised that the all-cause approach overestimates the burden of AMR".

"Concerns have been raised over the reliability and accuracy of the approaches in use given the existing data limitations and their suitability".

There are some references I've added with this report that could be useful.

In reference to "Where applicable, are recommendations and next steps explained clearly for others to follow?"

The author gives a recommendation on "developing a basic laboratory information management system" and states that this "will require the provision of support to LMICs to build surveillance systems incorporating microbiological data and antibiotic use in humans and animals." However, this is not discussed more explicitly, and is in some ways then lost within the more general points raised in following paragraphs (e.g. incorporating patient outcome data).

In conclusion, the author highlights a lot of the problems in AMR burden estimation in terms of direct,
human healthcare impact. However, I think this letter would benefit from either (i) really narrowing the focus and having a more in-depth discussion of a particular problem (such as laboratory data collection and harmonisation), or (ii) more clearly defining and structuring the letter across the different types of AMR burden and data sources and expanding discussion of the points raised currently; being very explicit about how each point relates to AMR burden estimation, and utilising more of the literature available on different methods (for example, there is a wealth of literature on different methods of estimating attributable mortality in the medical statistics community).

In either case it would benefit the reader for the Open Letter to then highlight more explicitly the subsequent key recommendations and/or issues for further discussion.

References

Is the rationale for the Open Letter provided in sufficient detail?
No

Does the article adequately reference differing views and opinions?
No

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Partly

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Health economics and antibiotic resistance burden estimation.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 28 April 2020

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This brief report highlights the key issue in understanding antimicrobial resistance and its impact. O’Neil reported some daunting figures in terms of antimicrobial resistance and its impact. The author describes well the problems of fully assigning the ‘blame’ for mortality on AMR. But as O’Neil pointed there are serious economic consequence to AMR and these are difficult to fully quantitate without good core data. It is this lack of consistent and comprehensive information which is thoroughly assessed by the author.

The are a couple of things worthy of consideration as part of the dialogue. Firstly, susceptibility testing, which is critical to accurately estimating AMR, varies globally. Even though many nations use CLSI, there are differences with EUCAST which could lead to mis-identification of susceptibility. It is important that all labs work from the same set of rules including breakpoints, media etc. Secondly the source of isolates should not be confined to “sterile” sources only. A large proportion of resistant pathogens occur in pneumonia. It does not make sense to ignore this important source of infection. Thirdly there needs to be a consistent list of pathogens considered. For example, Pseudomonas aeruginosa is on the GLASS list but not on others. This is a major AMR pathogen which is a cause of both serious infections and source of resistance mechanisms. I think a comment referring to the lack of consistency is needed.

The author highlights the need for global medical information systems to ensure we understand the situation. It is noteworthy that even in the US there are multiple HER systems, which largely do not “talk” to each other. This should be pointed out.

There have been 2 recent noteworthy publications by Burnham 2018 (Infection Control & Hospital Epidemiology (2018)1 and Wozniak 20192 which discuss different but relevant issues. Burnham pointed out that CDC issue 23,000 as the number of infectious deaths in the US however because there is no code for death related to infection it is likely this number is a major under-estimate. They estimate that infection related deaths in US is in the region of 150,000. Wozniak undertook a literature search of AMR and outcomes resulting in 12 publications making the point that consistency of data is critical to developing AMR policies.

In conclusion this report by Midega raises some key critical issues concerning the gathering of antimicrobial resistance. If the above points could be considered is worthy of publication.

References

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Partly
Are all factual statements correct, and are statements and arguments made adequately supported by citations?  
Yes

Is the Open Letter written in accessible language?  
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?  
Yes

*Competing Interests:* No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.