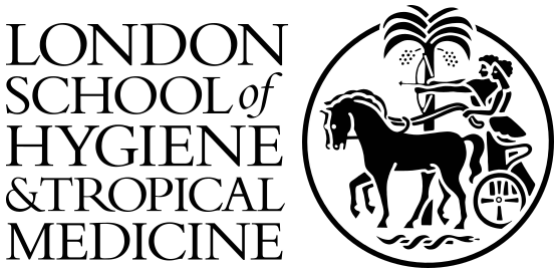

Title: Addressing the unknowns of antimicrobial resistance: quantifying and mapping the drivers of burden

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Keywords: antimicrobial resistance, quantification, mathematical modelling; mapping

Running title: Quantify the drivers of resistance

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Key points: To tackle antimicrobial resistance, we need first to quantify and map its drivers. In this viewpoint, we propose a ~~detail three key action areas that desperately require~~ systems mapping approach to do this, ~~attention: the mapping of sources and transmission routes~~supported by comprehensive~~,~~ data collection and novel quantification analysis.~~ -~~

Abstract

The global threat of antimicrobial resistance (AMR) has arisen through a network of complex interacting factors. Many different sources and transmission pathways contribute to the ever-growing burden of AMR in our clinical settings. The lack of data on these mechanisms and the relative importance of different factors causing the emergence and spread of AMR hampers our global efforts to effectively manage the risks. Importantly, we have little quantitative knowledge on the relative contributions of these sources and are likely to be targeting our interventions suboptimally as a result. Here we propose a systems mapping approach ~~three major actions~~ to address the urgent need for reliable and timely data in order to strengthen the response to AMR.

Introduction

Current situation

Antimicrobial resistance (AMR) "poses a profound threat to human health".[1] Policy makers, researchers and funders have stressed the importance of developing new diagnostics and medicines, improving surveillance and defining appropriate antimicrobial use to counter this global threat.[2, 3] Concerns on AMR are now a regular feature in the popular media, creating an impetus for politicians and policy makers to decisively address the risks. Yet, an important ingredient of an effective response has been largely overlooked: reliable and timely data to map and determine the relative contributions of AMR sources and transmission routes to overall AMR risk. Importantly, for example, we do not know what proportion of patients with infections with resistant pathogens acquired that pathogen from direct person to person transmission versus through the consumption of contaminated meat.

The primary drivers of AMR are thought to include suboptimal use of antimicrobial ~~compounds~~ agents in hospitals, the community and agriculture, as well as background exposure in waste water, soils and other environmental reservoirs.[3-8] However, the extent to which these sources contribute to the development, emergence and spread of AMR is not yet quantified.[9] Without this critical, system-wide knowledge it is impossible to effectively optimise and target interventions.

The selection process that produces AMR occurs through exposure to antimicrobials. However, the relationship between the extent of antimicrobial exposure and the ~~amount~~ rate of AMR selection has not been quantified.[10, 11] The appearance of AMR strains in clinical environments will ~~may [a1]~~ also be dependent on their transmission from source environments. Hence, both the sources and transmission pathways of AMR need to be identified and mapped to understand the flow of AMR to frontline clinical interfaces. For example, high antimicrobial use occurs in the agricultural environment, but we do not know how frequently this use leads to selection of AMR, if there is a dose-response relationship, or the nature and magnitude of AMR transmission from this environment into clinical settings.[12] The overall contribution of agricultural antimicrobial use to clinical AMR risk thus remains unknown. This lack of a quantified risk means that interventions to reduce antibiotic

prescribing in agriculture, whilst logical, will have an ~~undetermined~~undetermined impact on the levels of infection with AMR pathogens in clinical settings. Moreover, the lack of knowledge also hampers advocacy for any intervention in this setting.

Emerging infectious disease outbreaks, such as Ebola, and more recently the Zika virus in Brazil, demonstrate how even rare events can have catastrophic consequences for public health by overwhelming health systems that are typically designed to manage endemic, consistent or predictable health pressures. AMR poses similar risks to health systems.[1] While multiply resistant microbial strains are likely to be rare in comparison to resistant strains that remain treatable by available and alternative compounds, the consequences of an untreatable strain overwhelming our last lines of defence would be great. ~~A key point here is that moving between antibiotic treatments is not as simple as changing oral prescriptions. Susceptibilities are likely to be to older antibiotics or to those less frequently used, but this reduced use is often for a reason. These alternative compounds often have more serious side effects or are more difficult to prescribe (e.g. intravenously).~~ As any new resistance could ultimately be the last one required for a pan-resistant strain, identifying AMR selection hotspots is critical for stemming AMR risks at the most relevant sources, while quantitative knowledge on transmission networks is central to interrupting AMR spread. With ever limited resources, a systems approach to both ~~a~~ rank~~ing~~ ~~of~~ the importance of these hotspots, and the transmission pathways is required for prioritisation of action or control method ~~optimisation~~.

The hotspots and their relative contributions to selection and transmission are likely to vary by setting.[7] For example, countries will have different levels of direct antimicrobial exposure due to varying degrees ~~[13]~~of use of antimicrobials in agriculture [13]. Indirect factors will also vary, such as levels of sanitation, density of antimicrobial-producing pharmaceutical companies and political will to tackle AMR (for example with the formation of national action plans [14, 15]). Until this systems variation (both between and within countries) and then the fundamental information on the relative contribution of each of these factors is known, it will not be~~For example, in Australia high antimicrobial use in both community and hospital settings may select directly for resistance in patients, requiring no importation from external sources to result in healthcare issues,[13] while in India poor sanitation may facilitate the transmission of AMR in communities otherwise unexposed to~~

~~antimicrobials.[3, 14] Hence, improving access to sanitation may have a bigger relative impact on reducing the risk of AMR in India compared to Australia, while targeting antimicrobial prescribing may have a relatively greater effect in Australia than India. In the absence of such data, however, it is not~~ possible to develop policies or efficiently allocate resources to develop targeted and context-specific interventions ~~across~~ for multiple settings.

To date, most AMR research has focused on evaluation of interventions (aimed at infection control for prevention and for ~~reducing~~ antimicrobial ~~use~~stewardship)[16], surveillance, risk factor analysis and strain characterisation (including identification of mechanisms of resistance and genetic determinants of AMR). Research on surveillance of resistance patterns suggest strong spatial variation in AMR ~~[16]~~and in the use of antimicrobials. ~~(e.g., in animal based food production systems).~~[17-19] For instance, the majority of antibiotic prescriptions in the UK are in the community and yet the most clinically serious AMR infections are often hospital acquired.[20] Does this mean that reducing prescr~~i~~iptions in primary care would have a smaller ~~little~~ effect on levels of infection with resistant pathogens than reducing prescriptions in hospitals? Or is it the key that drives colonisation with and selection of AMR, with subsequent ~~opportunites~~opportunities for endogenous infection once a host becomes ~~immunocompromised i.e.~~ hospitalised? Although links have been found across environments, for example between outpatient prescribing and hospital resistance levels [21-23]~~{Vernaz, 201{Hicks, 2011 #32} {Gallini, 2010 #31}1 #33}, f~~Few studies have explored their ~~what the~~ relative contributions ~~contributing environments are to these differences~~ and no studies, to our knowledge, have established which transmission routes contribute the most to the most serious infections with resistant ~~patheogens~~pathogens in clinical settings. For example, although a link between travel and AMR spread has been established [24], and studies have revealed key genetic factors underlying transmission, no studies have quantified the relative contribution of travel to AMR in comparison to other factors.

Future action areas

Based on these observations, we believe that there is a major gap in our understanding of AMR that requires a revolution in the analysis and quantification of the sources and transmission

routes of AMR. To tackle this, we propose that a comprehensive systems mapping approach is needed, with the support of data collection and modelling. The key action points are summarised in Box 1. ~~three interdependent actions.~~

First, there is a need to establish a 'global systems map' of AMR selection sources and transmission routes. Collaborative action by the global public health community is necessary to determine the relative contributions of sources and transmission routes to AMR[25, 26], including the most relevant environments and drivers at local, national and global levels (Figure 1). While there are current efforts to identify drivers of AMR in different environments,[1, 27] a comprehensive approach is lacking.[3] Research is needed to systematically map the complex network of environments and locations of selection, as well as quantifying the interplay of pathways that affect transmission (Figure 1). The formation of a 'global systems map' requires ~~his step requires the~~ international collaboration to: (1) construct a flexible map framework, perhaps within a specifically designed web-based platform, that allows for easy comparison and modification by individual countries, (2) develop a shared language of specific definitions for AMR 'drivers', 'risk factors' and 'transmission pathways', as well as for labelling environments ('sewage' or 'waste water'), (3) use the framework to build consensus around the systems involved in AMR, how they differ by setting and to continually update the systems map through conversations with all stakeholders, from patient groups to international health organisations. ~~community to come together to collate the "map" to provide a comprehensive guide for data collection.~~

~~Second, u~~Using the above map, there is then, secondly, a need to collect and collate data in order to quantify relative contributions to AMR and to populate the 'global systems map' with quantitative information. Currently, there is no global database that collates information on the occurrence of antimicrobial use or AMR.[25] However, building on ~~While~~ the first AMR global surveillance report (~~was~~ published in 2014 [1]) as well as existing national level clinical datasets,[18, 28] the WHO has now launched the Global Antimicrobial Resistance Surveillance System (GLASS) to fulfil one of the 5 strategic objectives of the WHO action plan on AMR.[29] This will collect and then report AMR rates aggregated at the national level, giving information on level of resistance within clinical isolates.

This global endeavour is supported by government and NGO initiatives such as the Fleming Fund in the UK and the Bill and Melinda Gates Foundation.

To populate the 'global systems map' critically requires countries to support these actions, but also requires further resistance data; for example, resistance levels within samples from agriculture, water and soil. For the identification and quantification of transmission pathways, a ~~Similarly~~ comparison of isolates between settings ~~can use~~ using genetic distance ~~to infer~~ can help identify overlapping sources.[19, 30, 31] The map also requires systems level information on the places where antimicrobial are prescribed and transmission pathways; for example, the amount of intensive farming (such as has been mapped globally in [32]) and how much antimicrobials are used where (for some drugs, this has been done globally at the national level [17]). A comparison of the existing resistance environment, using for example composite measures such as the Drug Resistance Index [33], can then be complemented by a comparison of underlying AMR drivers and transmission routes. This stage requires national organisations to (1) collate their new and existing datasets to inform all stages of the 'global systems map' for AMR, (2) compare and contrast between countries to determine data gaps and potential ways for data collection to be effectively performed, perhaps with the inclusion of sentinel sites, (3) use the 'global systems map' as a visualisation tool to identify new potential areas of AMR emergence and areas where effective control has been achieved.

~~a lack of an established surveillance system hampers efforts to systematically gather such data.[29] Collating and analysing existing datasets, such as those on intensive farming areas[30] and existing national level clinical datasets,[18, 31] could help to identify areas of AMR emergence and areas where effective control has been achieved[GK2]. Similarly comparison of isolates between settings can use genetic distance to infer overlapping sources.[19, 32, 33] Building on existing work to collate and analyse data from different selective environments,[13, 17] the next steps are to quantify selection sources and transmission routes, but also to determine data gaps that need addressing.~~

Third, quantification of selection sources and transmission routes will require novel analytic approaches to measure source contributions, to establish relative importance of transmission pathways and to predict the likely impacts of interventions. These analytic approaches will need to combine

cutting edge statistical methods as well as mathematical and systems dynamics modelling, the potential contribution of which to global health is outlined in [34]. For example, mathematical models are needed that capture the movement of AMR pathogens between environments rather than only the dynamics within a single setting (such as a hospital ward). Currently, many mathematical models are only of the transmission of resistant pathogens between individuals within a hospital[35], with some, often fixed, incoming rate of pre-colonisation with resistant pathogens. Only by allowing the latter rate to vary, by including a dynamic modelling of the processes in external settings can our understanding of the relative contribution of selection and transmission in different settings be determined.

Statistical methods, such as multi-level modelling, will need to be adapted to consider the complexities of time-dependent bias in AMR acquisition and different risk factor profiles. The interacting nature of selection and transmission requires adjustment for correlations between statistical hierarchies that may require novel statistical formulations. This is important, as to reveal the relative contributions of different settings, correction for interaction relationships are needed to remove bias from risk profiles.

The resulting models should holistically map and integrate complex pathways and transmission systems, and account for stochastic or random behaviour of AMR spread, such as outbreaks and introductions of AMR strains or genetic determinants. This would enable the models to test for the effects of potential interventions on AMR emergence and control by considering the system as a whole.~~[2]~~ Importantly, this would allow for a "One Health" approach to AMR understanding and intervention optimisation. This stage requires the academic community, supported by the public health and policy community alongside cross-sectoral agencies, to work with the 'global systems map' to develop new quantitative tools that can (1) integrate information from a range of sources, (2) account for multiple environments, complex correlations and stochastic behaviour, (3) predict the impact and hence compare interventions.

With these systems modelling tools, and given sufficient data, the relative contribution of each source and transmission pathway to AMR can then be quantified (Box 1). Only from such

quantification can come the mathematical modelling predictions as to where to optimally target interventions for control.

Conclusion

A systems approach that enables comprehensive mapping of selection sources and transmission pathways in settings at a sub-national, national and global level will enable more holistic exploration and optimisation of policies and interventions designed to control AMR. Collation of data and targeted generation of hypotheses, underpinned by systems modelling approaches will help identify more effective combinations of interventions across multiple settings (e.g., countries, sectors) that could efficiently combat the profound global threat that AMR poses to human health and welfare.

Funding

The work was supported by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London in partnership with Public Health England. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, the Department of Health or Public Health England. The authors also wish to acknowledge support from the NIHR Imperial Biomedical Research Centre provided to AHH.

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Figure

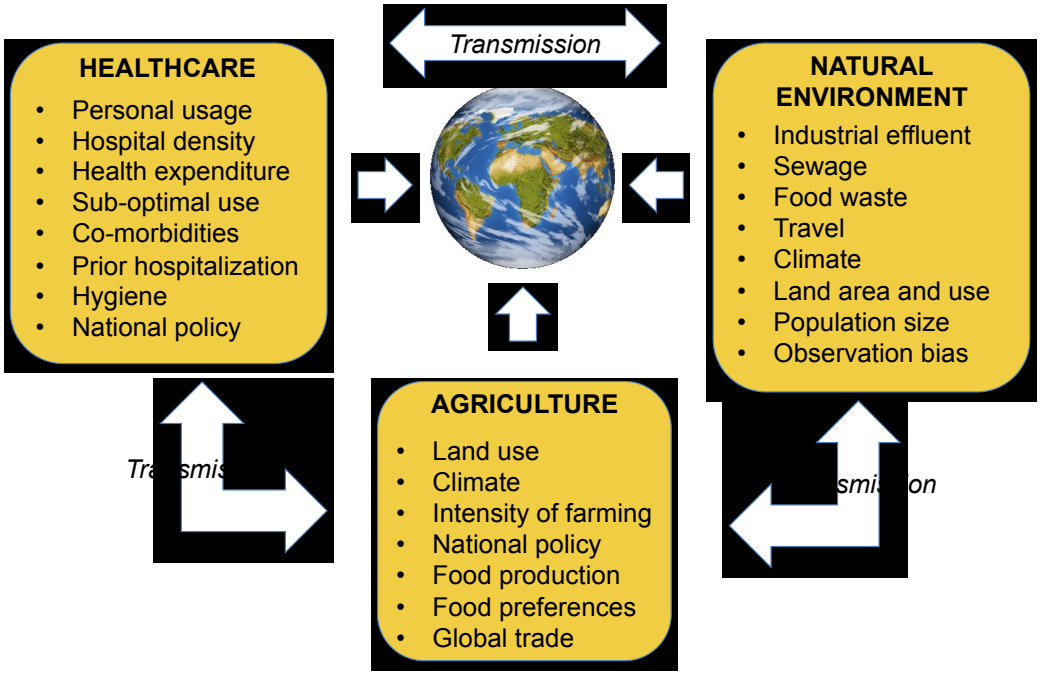

Figure 1: Example factors influencing AMR selection and transmission pathways that require quantification for a more effective and efficient global response.

Box 1: Stages required for determination of the relative contributions of different sources and transmission routes to AMR.

What are the relative contributions of different sources and transmission routes to AMR?

1. Formation of a 'global systems map'

Requires international collaboration to:

- 1.1 construct a flexible map framework
- 1.2 develop a shared language of specific definitions
- 1.3 use the framework to build consensus around the systems involved in AMR

2. Data collation

Requires individual countries to:

- 2.1 collate their new and existing datasets
- 2.2 compare and contrast between countries to determine data gaps
- 2.3 use the 'global systems map' as a visualisation tool for AMR control

3. Modelling analysis

Requires a supported ~~the~~ academic community to develop quantitative tools that can:

- 3.1 integrate information from a range of sources
- 3.2 account for multiple environments and correlations, and stochastic behaviour
- 3.3 make predictions around AMR burden