Harnessing alternative sources of antimicrobial resistance data to support surveillance in low-resource settings

Running title: Alternative sources of antimicrobial resistance data

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Abstract

One of the most pressing challenges to the global surveillance of antimicrobial resistance is the generation, sharing, systematic analysis and dissemination of data in low-resource settings. Numerous agencies and initiatives are working to support the development of globally distributed microbiology capacity, but the routine generation of a sustainable flow of reliable data will take time to establish and deliver clinical and public health impact. By contrast, there are a large number of pharma and academia-led initiatives that generate a wealth of data on antimicrobial resistance and drug-resistant infections in low-resource settings, together with high volume data generation by private laboratories. Here, we explore how untapped sources of data could provide a short-term solution that bridges the gap between now and the time when routine surveillance capacity has been established, and how this could continue to support surveillance efforts in the future. We discuss the benefits and limitations of data generated by these sources, the mechanisms and barriers to making this accessible, and how academia and pharma might support the development of laboratory and analytical capacity. We provide key actions that will be required to harness these data, including a mapping exercise; creating mechanisms for data sharing; use of data to support National Action Plans; facilitating access to, and use of data by the WHO Global Antimicrobial Resistance Surveillance System; and innovation in data capture, analysis and sharing.

Introduction

Surveillance is central to understanding the global burden of antimicrobial resistance (AMR). The generation of surveillance data begins with appropriate sampling of patients with a suspected infectious disease (diagnostic stewardship). Surveillance of sepsis is one example of this, although other specimen types will be required for more comprehensive surveillance. Culture and antimicrobial susceptibility testing of pathogens can improve individual patient management through optimisation of drug therapy, and supports their appropriate use (antibiotic stewardship). These data are commonly collated to inform local empiric prescribing policies for patients presenting with infectious disease syndromes. National data may then be collected by Ministries of Health for the purposes of surveillance, evidence-based guidelines, programmes of prevention and resource planning. Finally, national data may be submitted to global surveillance initiatives that are used to document and track rates of resistance over time, signal where and when interventions are needed, and identify countries that require support to build capacity. The most prominent global initiative for the surveillance of bacterial pathogens (excluding TB) is the WHO Global Antimicrobial Resistance Surveillance System (GLASS),[1] which collects and reports data on resistance rates aggregated by country.

This description of the generation, flow and analysis of AMR data represents an ideal situation in which locally generated microbiological results move from a patient care setting to a national or supranational network, but the reality is that these data are fragmented and dispersed. A recent review commissioned by the Fleming Fund created an inventory of supranational antimicrobial resistance surveillance networks in low- and middle-income countries (LMIC) between January 2000 and August 2017.[2,3] This identified 72 supranational networks for AMR surveillance of bacteria, fungi, HIV,

74 tuberculosis and malaria, of which 34 are on-going.[2,3] Their median duration was 6
75 years (range 1 to 70 years) and the median number of LMICs included in each network
76 was 8 (range 1 to 67). This scenario is not limited to the lowest resource settings. A
77 review of European AMR surveillance found similar fragmentation and heterogeneity,
78 with numerous local and national systems that lacked coordination, harmonization and
79 information sharing with international networks.[4] There was also inadequate
80 standardization of epidemiological definitions, samples and data collected,
81 microbiological testing methods and data sharing policies.[4]

82 Categorization of the 72 LMIC networks identified in the review revealed that
83 the minority (n=26) were led by governments or the WHO, with the remainder being
84 associated with academia (n=24) or pharma (n=22).[2,3] The number of networks that
85 provided unrestricted access to the data was low (n=3); the remainder were closed (no
86 access) (n=38), or categorised as 'shared or unclear' (n=38, shared meaning that data
87 sharing is restricted to specific groups or consortium members). The proportion of
88 networks identified for bacteria (excluding TB) and network provider is reproduced in
89 Figure 1. Although this does not equate to the proportion of data generated by each
90 network, it is notable that for bacterial pathogens the majority of networks are led by
91 researchers and pharma, none of which have the capability to upload their data to
92 GLASS. This represents a substantial untapped source of data from settings where the
93 need for surveillance data is greatest, and could provide a short-term solution that
94 bridges the gap between now and the time when routine surveillance capacity has been
95 established.

96 The purpose of this Personal View is to explore how such information
97 generated in countries with weak AMR surveillance systems could be harnessed for
98 patient and public health, including consideration of the strengths and weaknesses of

these data, mechanisms to increase their standardization, harmonization and sharing, and the benefits that could be derived by investing in innovation.

Alternative sources of AMR data generated in LMIC

Pharma

Pharmaceutical companies generate a large volume of high quality bacterial susceptibility data before and after new agents are marketed to fulfil regulatory requirements. These data are largely undisclosed, but some companies are now providing aggregated data, including Pfizer who have developed ATLAS (Antimicrobial Testing Leadership and Surveillance), a searchable database on resistance to Pfizer anti-infective agents.[5] The SENTRY Antimicrobial Surveillance Program is a notable commercial surveillance programme run by JMI Laboratories since 1997 that collects data from more than 200 sites worldwide,[6] largely from the US and Europe. Findings based on aggregated data of specific species or genera are published, but the dataset is proprietary and not available for wider use. GSK began the Survey of Antibiotic Resistance (SOAR) study in 2002. This focuses on the effectiveness of antibiotics in the treatment of community-acquired respiratory tract infections.[7] This concentrates in particular on countries and regions for which little other susceptibility data is available, findings from which are regularly reported in the published literature.[8,9]

Pharma data have several strengths. Isolates are obtained from a global distribution. Organism identification and susceptibility testing procedures are strictly standardised and quality controlled according to international standards. Isolates are transported and re-tested in a central accredited laboratory, ensuring reliability and reproducibility of results. However, there are several notable disadvantages. There are

often no meta-data (clinical presentation and outcomes or demographic information) associated with the isolates. Organism sampling fulfils the requirements of the particular pharma project rather than being representative or generalizable to the local population, and centralised testing means that quality controlled test data are not available to guide individual patient care, nor do local laboratories benefit from improved quality management as a result of participation. Locations perceived to represent small markets are typically under-represented. Furthermore, there is no information on denominator data and so the results may be biased and may not reflect the true burden of resistance in the area tested.

Academia

Researchers generate a wealth of data on antimicrobial resistance in numerous LMIC. The reasons for data generation include the study of infectious disease aetiology and associated antimicrobial susceptibility, therapeutic drug trials, and studies on disease pathogenesis and the molecular biology of bacteria. Some research laboratories have become embedded within district hospitals or other healthcare facilities in LMIC where they provide the only source of ongoing diagnostic microbiology, adopting a model in which research and the provision of microbiological services work in partnership. Compared with pharma data, these often provide greater depth of information for specific populations (e.g. all patients treated in a particular hospital) and many have been operating for several years or even decades.

Research data has several potential strengths. Laboratories may be subject to good laboratory practice (GLP) when the information generated is performed to specific standards, supported by laboratories and methods that are rigorously evaluated through robust Quality Assurance and Quality Control programmes. The methods used to

generate bacterial susceptibility data are notoriously error prone and data generated outside of quality controlled laboratories may be of sub-optimal quality,[10,11] and the inclusion of quality-assured research data in national and global databases could increase the proportion of accurate data points. Patient information may also be collected on clinical presentation, duration of hospital stay, antibiotic treatment, complications and outcome. Furthermore, understanding the trajectory for resistance often requires evaluation of susceptibility data over long time-scales, and newer national surveillance programmes may not yet have sufficient retrospective information to make the most of new data.

Researcher-defined infectious disease aetiology and common susceptibility patterns, even if performed intermittently, supports empiric prescribing in settings where the treatment of febrile illness is based on clinical features and there is no funding to offer routine testing to patients. Empiric prescribing may result in over use of antibiotics and increased rates of resistance. In the longer term the ideal would be to have a global surveillance programme that promotes laboratory testing for better patient care and directed antibiotic therapy associated with antibiotic stewardship. In the short term, however, empiric prescribing is an essential approach that saves lives, provided that data are sufficiently contemporaneous. Although not always the case, research-driven AMR data may not be generated with sufficient speed to provide information that guides individual patient treatment.

When research laboratories are embedded in district hospitals in rural areas (as they often are), inclusion of their data in global databases could also go some way to balancing selection bias that can arise. For example, WHO GLASS requires participating countries to establish at least one surveillance site and then extend the number over time. In LMIC where diagnostic microbiology laboratories are scarce,

these are most likely to be situated in tertiary hospitals. Bacteria isolated at tertiary hospitals in any part of the world are more likely to be associated with patients with more severe or complex disease, patients who have received numerous courses of antibiotics, patients with prolonged hospitalisation, and those transferred from other hospitals with hospital acquired infection, all of which will lead to over-representation of bacterial resistance compared with patients at district hospitals or the wider community.

Research-generated data also has several potential limitations. Data may be biased, including ascertainment and sampling biases.[12] For example, the study design may target patient sub-sets that do not reflect the wider population with infectious diseases, such as sampling of patients within cohorts that have better access to care, or patients with the most severe infection syndromes. Since a proportion of bloodstream infection will be hospital-acquired, studies of severe invasive disease may inflate rates of resistance and may not capture milder forms of community-associated infection in patients treated as out-patients, which may be caused by organisms with lower antimicrobial resistance. Research data may also include duplicate samples. Six main types of potential bias that may influence the validity or interpretation of surveillance data have been identified, which provides a framework for reviewing the use of research data in AMR surveillance (use of inadequate or inappropriate denominator data; case definitions; case ascertainment; sampling bias; failure to deal with multiple occurrences; and biases related to laboratory practice and procedures).[13]

Private laboratories

A source of susceptibility data that may remain unseen by national surveillance systems, particularly in many LMIC settings, is laboratories in private hospitals that

generate data for patient care.[14-16] The quality of data generated by private laboratories varies considerably, but those that are accredited and perform quality assured services produce data of similar or better quality than public laboratories. In India, almost all medical laboratories accredited by the National Accreditation Board for Testing and Calibration Laboratories (NABL) are in the private sector, and in South Africa more than 80% of SANAS (South African National Accreditation System)-accredited medical laboratories are in the private sector.[15] This has led to calls to utilise these data, and the inclusion of such data by initiatives such as ResistanceMap.[17] This displays antimicrobial resistance data on twelve bacterial species isolated in 49 countries, collected between 1999 to 2015 (depending on the country), together with antibiotic consumption data from 75 countries between 2000 and 2014. The primary sources of data are public and private laboratory networks that routinely collect susceptibility results, but data from India comes exclusively from the private sector.

Private laboratories can provide extensive datasets for populations for whom there is a very limited supply of reliable AMR data from alternative sources, but again can suffer from the types of bias already described for research data. Furthermore, these laboratories often serve a sub-set of more affluent people, including medical tourists and members of the expatriate community, which may not provide an accurate representation of rates of resistance for similar types of infection in the wider population.

Barriers to using alternative sources of AMR data from LMIC

Despite the obvious utility of placing AMR surveillance data generated by academia, pharma or private laboratories into the public domain, very little of these data generated in LMIC is utilised by organisations involved in regional or global surveillance. There

are several barriers that prevent this from happening. Data are held in numerous silos with highly restricted access. Academics generate data that usually remains private until published in peer-review journals, when individual patient-level data may not be released and may be delayed by several years from the point of collection because of the time taken to analyse, write and publish. Pharma companies have to jump through several legal hoops before they release their data into the public domain. Even if researchers and pharma companies are keen to deposit data towards global analyses, its aggregation is hampered by a lack of harmonisation in data collection, a lack of tools that allow easy data deposition, and a framework that prevents publication of their data by unscrupulous competitors. Furthermore, GLASS collects and reports data on resistance rates aggregated at national level by Ministries of Health, and cannot currently accept information generated by research activities or pharma. In general, national programmes take ownership of surveillance activities in-country, and agreement may not be reached for direct data deposition to WHO GLASS by non-governmental groups. Furthermore, AMR surveillance data can represent potentially sensitive data, particularly when these describe high rates of resistance or the emergence of a novel resistance mechanism to a key antibiotic.

Mechanisms to unlock AMR data

Incentivising access to data from academia and pharma

'Bottom-up' research and pharma activity that generates AMR data is not public health surveillance in the strict sense. Furthermore, the majority of researchers and pharma-employed scientists would be quick to highlight that public health surveillance is neither their responsibility nor area of interest. Agreeing on the principle that researchers and pharma companies could make a major contribution to global

surveillance should be aligned with the recognition that this is not their primary purpose, and will be associated with a financial cost. Debate is required about incentives to support the additional workload associated with sharing data to national programmes or other repositories and who should coordinate this. This could draw on experience gained on academic incentives during the development of WWARN (the WorldWide Antimalarial Resistance Network platform).[18] Any investment should not detract from funding that provides improved data sources for patient care, surveillance and prevention of antimicrobial resistance.

The flow of research-generated data to global initiatives could be facilitated by funders, who could develop guidelines on sharing of specific data sets, which could become an integral component of a successful funding award. This is already the case for some forms of data, examples being the submission of all sequence data generated by the Wellcome Trust Sanger Institute into public databases, and funding by the Wellcome Trust linked to an open access publication policy. Such changes would require a clear plan for formatting and destination of data deposition. Journals and publishers could also develop guidelines on data deposition for publications on drug-resistant infection, and could make this a necessary part of submission. Data released into public databases by researchers would need to be protected by data access committees or through other mechanisms, but this is not insurmountable since solutions are already in place for numerous types of data. There are also examples of training and data sharing/open access agreements having been developed that are contextualised and locally acceptable.[19, 20]

The Wellcome Trust have begun to address access to untapped sources of global surveillance data held by pharma through a recently funded project conducted by the Open Data Institute. This has created a mechanism to bring together leaders from public

health and the pharmaceutical industry, who are collaborating to explore how value could be added by the re-use of available data. An evaluation of the mechanisms and barriers to making this open access has been completed and detailed in a post-project report.[21] One proposal is to create a public-private partnership to improve local laboratory capacity. Another is to suggest that relevant metadata and denominator data are also collected, fulfilling the objectives of the pharma project whilst also informing local AMR prevalence, which while not informing individual patient care could inform empiric prescribing protocols.

Supporting Ministries of Health to access data

Ministries of Health could collaborate with research institutions where this is not the case, or a public–private partnership could be forged so that data generated by research, pharma or private laboratories efforts can be submitted to GLASS as national data. There are examples of research units in Asia and Africa that have already developed close and sustainable working relationships with the relevant Ministry of Health, who use the information provided to shape national prescribing policies. In this way, countries can be empowered to utilize data generated in their own country, with local researchers undertaking in-depth analyses using a range of sources, encouraging comparisons of incidence and prevalence rates of drug-resistant infection between different areas in the country to monitor disease burden and impact of action plans in each area. This also represents an important training opportunity for government staff, who can develop the technical capability to analyse data that is ultimately generated through country-led capacity building.

The need for specialist networks

Having argued that the development of new initiatives that effectively replicate WHO GLASS and that fragment data are generally to be discouraged, there are some circumstances when additional networks add vital new information. A notable example is the Institute for Health Metrics and Evaluation, which has recently been funded by a joint award from the Wellcome, the UK Fleming Fund and the Bill and Melinda Gates Foundation to gather, map and analyse disease and death caused by drug-resistant infections. This will be used to quantify the global burden of disease (GBD) from drug-resistant infections compared with other diseases and causes of death, and so inform policy and decision-making. Estimating GBD for AMR faces numerous challenges, including difficulties in linking surveillance data with clinical or outcome data and causal attribution, and cannot be regarded as a routine surveillance activity at present.

Investing in innovation

Investment is needed to promote innovation in AMR surveillance. For example, harnessing emerging technologies relating to Big Data and Artificial Intelligence could lead to more effective mechanisms of AMR data capture, sharing and analysis tools. An innovative system to support automatic data harmonisation between different laboratories and institutions could achieve numerous objectives, including an inbuilt system to standardise data analysis and quality tests for data from multiple sources; capture of patient outcome data to underpin calculations of GBD; and rapid relay of information to treating clinicians e.g. via electronic decision support algorithms. Data could be automatically linked to national agencies and international data repositories. Innovation in data capture would benefit from early involvement of experts in the social sciences so that the behaviour change required to support buy-in is an integral part of planning and development. Mapping of data sources may also require consideration of

the regulatory environment in some settings. New innovation needs to be linked to effective translation, scale up and integration, and assessed in terms of impact on policy.[22] Any alternative system developed will need to be either fully inter-operable with WHO GLASS, or able to generate data in a format that can be uploaded.

Conclusions and next steps

Our understanding of the global burden of disease from drug-resistant infection in LMICs is rudimentary, and data from academia, pharma and private laboratories could make an important and rapid contribution. A dialogue is required to determine how data generated in LMICs might flow from these bodies to national and global AMR surveillance networks, and how they might support the development of laboratory and analytical capacity, including robust quality management systems, for prospective data collection. This should build on current initiatives such as the Fleming Fund, which is providing regional grants to collect existing AMR and antimicrobial use data from all possible sources. Table 1 summarises proposed changes that could help to bring this into effect.

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Transparency declaration

Nothing to declare

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FIGURE LEGENDS

Figure 1. AMR surveillance networks since 2000

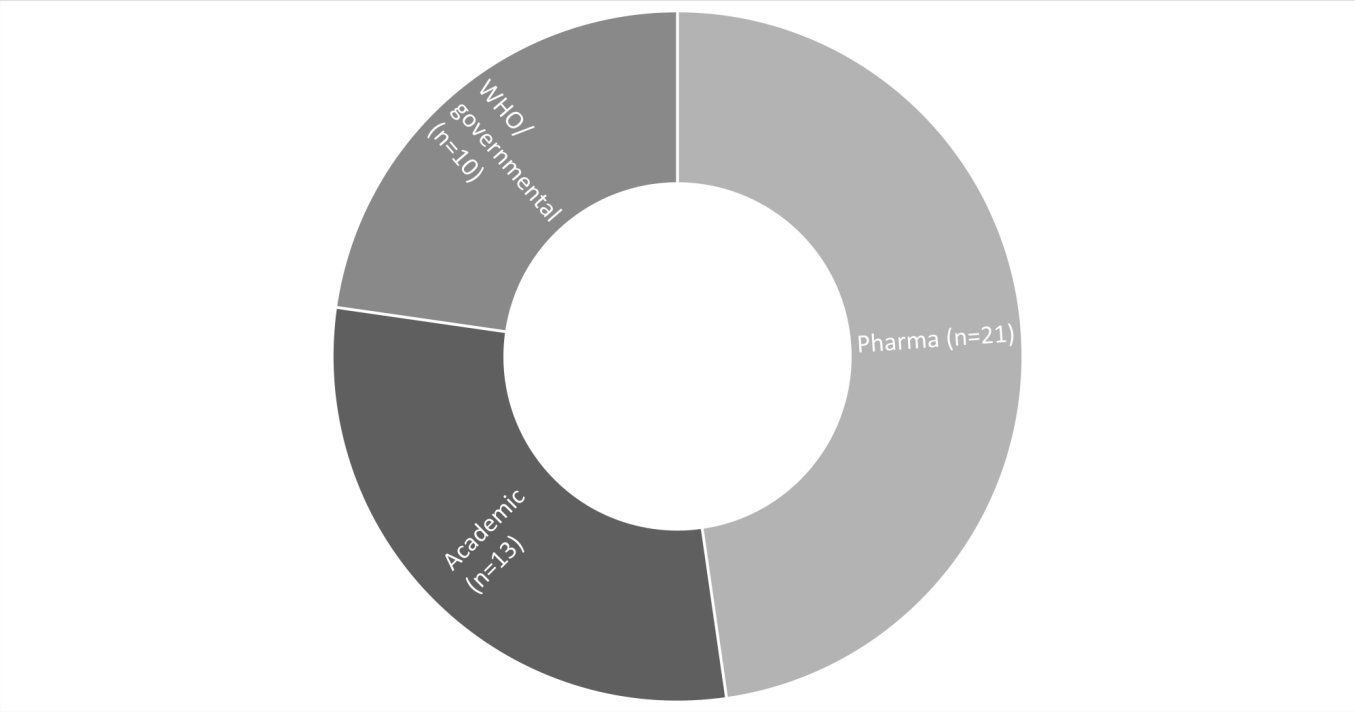
Sunburst chart representing 44 supranational networks performing AMR surveillance in bacteria (not including TB) categorised according to their lead organisation type (Pharma, academia, WHO/governmental). Adapted from reference 1.

409 **Table 1. Key actions to harness AMR data from alternatives sources in LMIC**
410

Objectives	Actions
Map data	• Map and evaluate quality/utility of data held and generated • Determine how to enhance these resources, i.e. through the addition of patient outcome data • Determine how data can contribute to the global burden of disease due to AMR
Create mechanisms for data sharing and capacity building	• Identify incentives that promote the contribution of data from academic, pharma and private laboratories • Agree the basis for data sharing, including ownership, ethical and legal considerations • Develop mechanisms for data harmonisation, collation and analysis • Promote private – public partnerships to build capacity in local laboratories for patient care and surveillance
Facilitate update of data nationally and internationally	• Use data to support National Action Plans • Seek mechanisms and create funding opportunities to support uptake of academia/pharma/private lab data by WHO GLASS and other data sharing initiatives
Innovation in data capture, analysis and sharing	Create a data collection interface that supports: • Case-based surveillance • Quality assurance and control and a universal reporting standard for patient data • Automated linkage to national agencies and international data repositories

411

412 **Figure 1**



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