Burden assessment of antimicrobial use and resistance in livestock data-scarce contexts

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Summary

Misuse and overuse of antimicrobials in livestock production is identified as a driver for antimicrobial resistance (AMR). To improve decision-making concerning livestock health a better understanding of the impact of AMR in livestock and aquaculture, within and beyond farm level, and expenditure on antimicrobial use (AMU), is necessary. It provides grounds for systematic disease prioritisation, establishes a baseline for understanding the value of different strategies to mitigate animal health problems and for the monitoring and evaluation of the impact of those strategies. Limited data availability and quality surrounding AMU and AMR create barriers which prevent this being a straightforward

exercise. These data constraints are also more prevalent in contexts that lack the necessary resources to develop and maintain systematic and centralised data collection and collation systems. Even in regions with robust AMU and AMR monitoring systems in place data limitations remain, so that the expenditure on antimicrobials and impacts of AMR remain unclear. Additionally, the current research funding strategies have been less focused on primary data collection adding further barriers towards filling the data void and reducing the global AMU/AMR knowledge gap. To work around the data scarcity and leverage on previous and ongoing research efforts, a comprehensive knowledge of the people, projects and research consortia dedicated to the topic of AMU/AMR is vital.

Keywords

Animal health expenditure – Antimicrobial resistance – Antimicrobial use – Burden assessment – Data needs – Data scarcity.

The antimicrobial resistance threat

The development of resistance to antimicrobials by pathogens is a natural phenomenon. From an evolutionary standpoint, it is an intrinsic response when a pathogen's survival is threatened, and thus cannot be avoided [1]. Even though this global 'tragedy of the commons' – a situation where a widely accessible common resource is exhausted due to individuals' self-interest [2] (when applied to antimicrobial resistance [AMR], it might be defined as the lack of effectiveness of antimicrobials in managing previously susceptible microbes causing infectious diseases due to the misuse and overuse of antimicrobials by societies) – has gained major attention over the last decade, the issue is not new. Soon after the mass production of Penicillin in 1942, following its discovery by Alexander Fleming in 1928, Penicillin-resistant *Staphylococcus aureus* emerged [3,4]. By late 1960s in the United States of America more than 80% of *S. aureus* isolates that had caused disease, acquired either in hospital or community, were Penicillin resistant [5].

The 'golden era' of antimicrobials, with the constant development of novel drugs from distinct classes and acting upon pathogens via different antimicrobial mechanisms, delayed the expansion of AMR [6]. Over the last decades, however, the drop in pharmaceutical enterprises dedicating resources to new drug development has reduced the array of new active compounds available to manage infections [3]. The lack of novel active compounds resulted in organisms being exposed to antimicrobials with the same type of action, offering repeated opportunities for resistance development. The misuse and overuse of antimicrobials in human health, animal health and agriculture exacerbate the problem.

According to a recent publication using data from 204 countries and territories, in the year 2019 bacterial AMR was associated with 4.95 million deaths, of which 1.27 million were directly attributable to AMR, surpassing the burden of HIV and malaria [7]. In 2017 a report by the World Bank estimated that come 2030, AMR will be costing the global economy US$1 trillion annually as a best-case scenario. The worst-case scenario predicted the yearly loss at $3.4 trillion, a figure higher than the GDP of the United Kingdom, India or France. Additionally, the report suggested that AMR would increase the levels of poverty with a greater impact experienced on the poorest countries [8]. Such projections are largely due to the fact that effective treatment for AMR in many low- and middle-income countries is usually hampered by factors like poor enactment, lack of enforcement of laws and regulations, low awareness on the responsible use of antibiotics and inadequate distribution of treatment guidelines across key One Health sectors (i.e. human, animal, plant and environmental health) [9].

Increasing awareness of the impact of AMR and the evolving global threat it poses led to the planning and adoption of actions meant to foster reduction and prudent use of antimicrobials [10,11]. However, heterogeneity in regulation, infrastructure, health services outreach and/or enforcement capacity between countries and regions, could hamper the success of such measures [12,13]. This is particularly relevant given the evidence on the transfer of genetic elements of AMR between humans, animals and the environment [14], and between regions [15,16]. Antimicrobial resistance is a One Health global threat that can’t be contained regionally, cannot be controlled by a single discipline and must ultimately be addressed through a global and joint One Health approach.

AMU and AMR data in livestock

Challenges surrounding data-scarcity

A key part of addressing the threat of AMR is having a solid understanding of the problem. Baseline knowledge in terms of resistance levels and their epidemiological, microbiological and genetic profile, is a cornerstone in monitoring resistance trends and in the design and implementation of mitigation strategies. Therefore, AMR surveillance is essential.

In recent years, antimicrobial use (AMU) and AMR surveillance efforts have intensified in some sectors and settings, strengthening data collection systems in humans and animals. However, surveillance and monitoring capacities often remain limited. In Africa, for example, a 2020 review on AMU and AMR in animals found that while several countries had national One Health antimicrobial action plans, none had established national surveillance systems for animals [17]. The same study reported high proportions of farms using antimicrobials, including the use of drugs relevant for human health, ranging from 77.6% to 100% depending on the country [17]. Antimicrobials are therefore a widely used health management resource but there is limited information concerning the volume of usage.

The reasons for this data scarcity are manyfold. For the public health sector in low- and middle-income countries (LMICs), Iskandar *et al.* [18] recently identified infrastructure gaps, capacity limitations, constraints in obtaining consumables, and reliance on external funding as factors that contribute to AMU data scarcity. As health care priorities are set by governments, political commitment to improving data collection is key [18]. Conflicts and political instability are especially challenging barriers for governments and organisations to implement and follow through with antimicrobial stewardship programmes [19].

A 2019 study systematically searched for and analysed point-prevalence surveys as an alternative data source for AMR in livestock in LMICs. The authors found that while this approach cannot sufficiently substitute surveillance information, it can be used to highlight data scarce regions and resistance hotspots. They reported a lack of surveys from LMICs in the Americas and large AMR hotspots, which were defined as having high proportions of antimicrobials with over 50% resistance, in Asian countries. Notably, only one major resistance hotspot was identified in Africa in this study [20].

It has been predicted that global AMU in food animals will rise by 8% between 2020 and 2030, with especially rapid increases projected for low- and middle-income countries (LMIC), where demand for animal-based food is growing and fostering the intensification of farming practices [21]. It is against this backdrop that the identified surveillance constraints for AMU and AMR constitute a key capacity gap and are thus a priority area for health systems strengthening.

Challenges surrounding the misuse of antimicrobials

The World Organisation for Animal Health (WOAH) reported in their latest iteration of the voluntary survey for veterinary services on AMU in animals that over a quarter of the 157 participating countries did not have legislations or regulations to control or prevent the use of antimicrobials as growth promoters in animals [13]. This included nine out of ten participating African countries [13]. A scoping review on AMU in Southeast Asia also found frequent use of antimicrobials for growth promotion [22]. The authors identified several drivers to antimicrobial misuse on farms, including individual level factors such as limited knowledge about antimicrobials and alternatives to their usage, as well as easy access to feed containing antimicrobials. They also described contributing factors on the community and policy level, such as lacking animal healthcare access, a paucity of adequate legislation and, in countries that have policies in place, insufficient enforcement [22].

Implications for burden assessments

Understanding disease burden is important in decision making processes concerning health management. When done systematically and accurately, it establishes the grounds for disease prioritisation and creates a baseline for monitoring trends. Additionally, it provides input to different analytical approaches (e.g. cost-benefit analysis, cost-effective analysis) which are key in planning and implementation of different strategies to mitigate disease and monitor their economic effectiveness [23].

Estimating the burden of AMU and AMR in livestock production implies the development of conceptual frameworks and models describing the production system and the relations between animal production, hazard occurrence and human reaction to hazard's presence. Ideally, these tools would provide a close as possible representation of reality, populated with sound data to ensure well-grounded outputs for evidence-based decision making. Robust and repeatable sources of data should be a first resource where available. In clinical decision-making the use of a 'hierarchies of evidence'-based approach is common: Burns *et al.* review a number of hierarchies of evidence which have been developed, for different study designs with different purpose, in the medical literature. All hierarchies have in common that the most reliable evidence comes from well-designed randomised controlled trials or systematic reviews and meta-analysis of such; the evidence pyramid then proceeds through different study designs for which the opportunities to control representativeness and bias are more constrained; finally, where empirical data are lacking other approaches can be considered [24].

Depending on the assessment's scope, epidemiological data on infections and resistance patterns are required along with data on antimicrobial usage, and animal health and production parameters. The wide spectrum of quantitative data required is hence an obstacle for burden assessments in contexts of data-scarcity. Solutions for those obstacles include the careful consideration of any ongoing data capturing systems and flows, and of alternative sources of information. A key first step, particularly considering the complexity of AMR, is to identify stakeholders and appreciate the data ecosystem in which this information is generated. Mapping out these key players and data sources allows understanding of where information can be made available and how, who needs to be involved in the process, and where bottlenecks lie so that solutions to knowledge gaps can be discussed. Additionally, having stakeholders and the current data ecosystem explicitly mapped out helps ensure that data collection efforts are not duplicated if the information required for answering research questions already exists. Behavioural science approaches, drawing insights from social sciences, could be useful in further understanding data collection, sharing and analysis practices of stakeholders', as well as expectations. These insights might identify potential bottlenecks and factors influencing data collection practices. In the field of AMR and AMU, behavioural science approaches have been used in particular to understand AMU and prescription practices [25-27] and frameworks on how to conduct these assessments have been proposed [28].

A conceptual framework will pinpoint data requirements and streamline the mapping exercises outlined above. In the context of the Global Burden of Animal Diseases (GBADs) programme (https://animalhealthmetrics.org), an international research effort to estimate animal disease burden and understand their relative importance, a framework for burden assessment of AMU and AMR in livestock is currently under development (Babo Martins *et al.* upcoming) and could also be a useful starting point.

Once the data ecosystems and data needs are well established, sourcing of data for the estimates is needed. While systematic and standardised surveillance data is still lacking, alternative data sources need to be considered. Empirical data sources such as academic projects and collaboration with the pharmaceutical industry (similar to approaches in human health described by Iskandar *et al.*), can serve as interim or complementary solutions. Moreover, innovative sources of information, such as citizen science initiatives and emerging technologies, could complement traditional surveillance data, particularly in tracking antimicrobial usage.

Private livestock sector data is also a valuable source of information that could be used to address some of the AMU knowledge gaps and shed light on the impact of AMR on animals' productivity. The lack of trust and unperceived benefits of data sharing, however, could prevent farmers from sharing their data with the research community [29,30]. Participatory approaches, with multi-stakeholder platforms such as living labs, meant to involve farmers from the very start of the research proposal can aid the enrolment of farmers and their willingness to share their data. Participatory methods offer a stage to explore farmers' needs and expectations, as well as an opportunity to showcase how research outputs can help to improve their operations, and shed clarity with regards the regulation and code of conduct that ensure the safeguarding of their interests and their data [30-34].

When empirical data is not available other approaches to filling data gaps must be considered. Modelling techniques, and extrapolations have been employed to estimate antimicrobial usage and resistance levels [20,21] and these outputs can be used in burden estimates. Filling in data gaps using documented methods of expert elicitation [35] is also possible, although it is important to conducted these carefully and within a structured framework to minimise the risk of known biases [36]. Ultimately, guess estimates [37] (estimates derived from extrapolations and/or common sense), can be resorted to.

While estimates with imperfect data will inevitably yield imperfect results, understanding burden, even with data caveats, allows understanding of where those caveats are, and in doing so, provides a feedback loop as to what data are missing and how data collection systems can be designed or redesigned to collect the missing elements.

Practical example of stakeholder and data mapping concerning AMU and AMR in Tanzania

As suggested previously, conceptual frameworks and models can help identify data needs, provide opportunity to think of solutions for data gaps and decide on model adjustments depending on the context under which these data and models will be used. Thus, the development of a conceptual framework by Babo Martins *et al.* (publication upcoming) for estimating the burden of AMU/AMR in livestock production laid the founding stone for this work. The framework describes the pathways for losses related to antimicrobial use and resistance, allowing to identify the data required to conduct the burden assessment exercise. After understanding the data needs, identifying reliable sources of data follows, requiring investigators to map out the people and institutional structures that might hold it or can facilitate access to it. As a first step, we explored within our network potential case study candidates. Given the country's strategic plan for tackling AMR [38], the past and ongoing efforts from national and international entities towards AMR mitigation, diverse local contact points and breadth of local expertise, Tanzania was identified as a promising candidate. Contacts were made via email with different people from government bodies, research institutes and inter-agency organisations, presenting the purpose and scope of the project and to assess their willingness to meet with the research team.

A one-week field trip was organised, with four meetings with key stakeholders planned and executed in different cities: one in Arusha with researchers from the Nelson Mandela African Institution of Science and Technology, one in Dodoma with stakeholders from the Ministry of Livestock and Fisheries, and two in Morogoro, one with researchers from Sokoine University and one with stakeholders from an intervention-based international development agency. Unfortunately, it was not possible to meet in person with the colleagues from the Nelson Mandela African Institution of Science and Technology in Arusha.

The results from the field trip are described in Figure 1. It shows the types of data on AMU and AMR in livestock available in Tanzania, the purpose for which it was collected, as well as the stakeholder that holds the data.

Different ongoing or finished research projects have collected production data, in particular COMBAAT, ICARS's funded intervention-based projects and FAO's led Farm Field Schools. Mortality and morbidity data are available via Farm Field Schools and COMBAAT. This type of data can inform estimations of current production losses.

Expenditure in AMU and AMR is also a component of the burden of AMU/AMR. Information on AMR stewardship investments can be made available through the SNAP-AMR project. Governmental data on antimicrobials and vaccines imports, as well as on vaccine production could be useful to capture part of the expenditure.

Looking at the diagram, the main knowledge gap seems to be around diagnostics, which could limit our ability to understand the extent to which AMR affects livestock production. Additionally, little is known about price data. These are existing data gaps that needs to be addressed, either via primary data collection or via other means previously outlined.

In sum, mapping sources of secondary data as observed in Figure 1 allows understanding the overlap of existing data and the data needs for the developed framework, helping us identify opportunities for collaboration and data access and anticipate threats to data sharing. Additionally, it aids in the identification of data gaps that might exists to inform the economic assessment, and to pre-emptively explore ways by which to address them.

The diagram is exploratory in nature, indicating data sharing flows and the types of collaboration that could be created between Tanzanian bodies and; institutes and collaborators from GBADs programme and University of Liverpool. Next, steps can be taken to ensure a common understanding of the scope of the mapping exercise, establish collaborative relationships and ethical agreements concerning data sharing and the generation of practically applicable outputs and publications between the University of Liverpool and international collaborators.

This practical example offers insight about the first steps that can be made towards burden assessment in livestock production.

Discussion

The burden of livestock health problems provides vital information for decision-making at all levels, from livestock keepers to policy makers. In the absence of burden information, it is difficult to define disease priorities, justify interventions to mitigate disease impact, and to monitor the cost-effectiveness and/or cost-benefit of these interventions. Given its complexity, burden assessment of AMU and AMR in livestock production systems is a data intensive exercise, requiring a wide variety of inputs from epidemiology and population, to production and prices. Ideally the AMU/AMR burden assessment would be informed by granular empirical data, consistently and systematically collected by different parties and made openly available for accurate measurements across health sectors.

The current systems for collecting data on AMU and AMR are most developed in high income countries. Yet, with recognised flaws surrounding completeness and granularity that limit our understanding of the true extent of the AMU/AMR problem, in animals, humans and ultimately the environment. In contexts where the lack of resources hampers the development of such systems, the knowledge gap is even wider.

While surveillance systems for AMU and AMR are still under development and research project primary data collection is often carried out at small scale, other data from sources with greater uncertainty currently underpin our understanding of the problem. For example, projections for AMU in livestock production in 2030 were estimated at

105,596 (± 3,605) tons by Van Boeckel *et al.* [39] and at 107,472 tonnes (95% CI: 75,927–202,661 by Mulchandani *et al.* [21]. Even though these point estimates are relatively similar, the uncertainty around them is substantially different so any burden estimates calculated using these data would have substantially different uncertainty intervals and final interpretable results. As another example, data scarcity led to expert elicitation methods being used to facilitate estimations of the burden of foodborne diseases and the authors of this work acknowledged the limitations of such approach which led to large uncertainty intervals [40].

A perfect data ecosystem, providing open access to complete, systematic, current and detailed data is utopic. As the current research funding strategy fosters the sharing of information, empirical data lies in secondary data sources. Therefore, exercises such as the practical example outlined above are an important first step towards understanding which data exist and where, and how data can be made available and by whom. In the absence of complete empirical data, alternative methods must be used to provide information to fill in data gaps. This comes with the caveat that there will be a higher degree of uncertainty around burden estimates calculated using secondary data which must be acknowledged when interpreting results.

The stepwise approach advocated in this position paper is applicable for burden assessment of animal health and production, regardless of the context. Understanding the data needs from the very start allows researchers to have a more informed idea about the feasibility of conducting such an assessment, anticipate limitation and explore solutions to overcome them. Having identified the people and institutions that can facilitate access to the required data, collaboration agreements and data access/sharing paperwork needs to be sorted. Analytical methods will be selected based on the quality and quantity of the data available.

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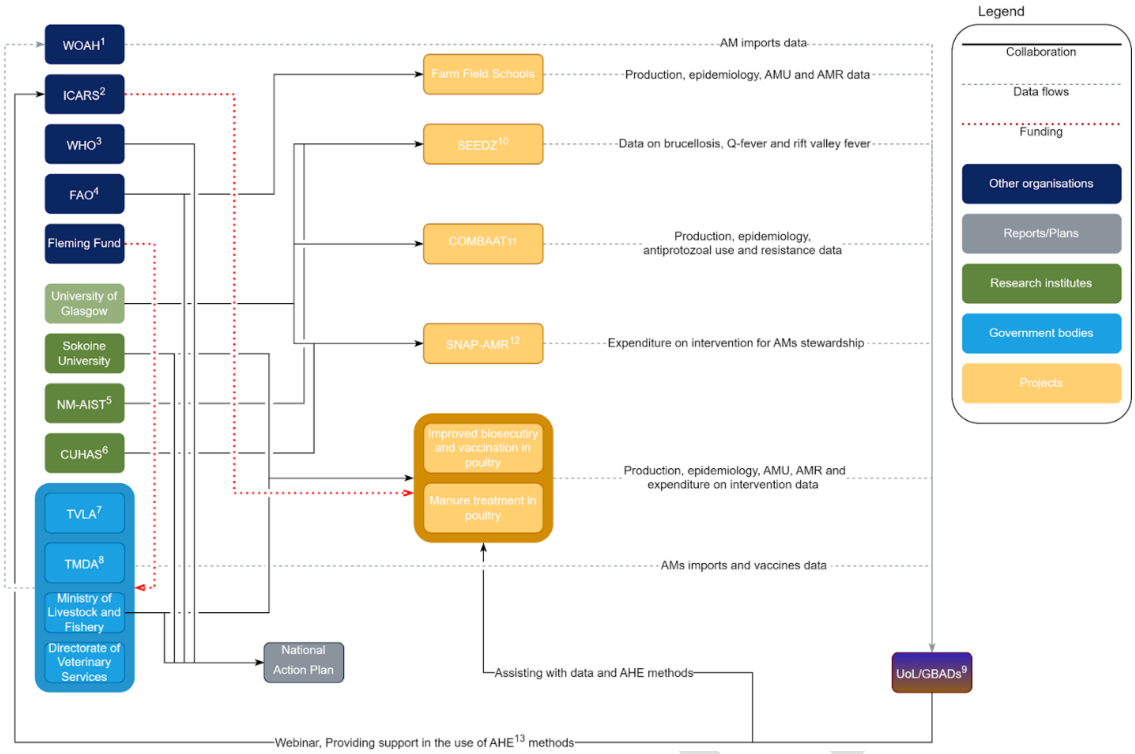

1: World Organisation for Animal Health
2: International Centre for Antimicrobial Resistance Solutions
3: World Health Organization
4: Food and Agriculture Organization of the United Nations
5: The Nelson Mandela African Institution of Science and Technology
6: Catholic University of Health and Allied Sciences
7: Tanzania Veterinary Laboratory Agency
8: Tanzania Medicines and Medical Devices Authority
9: University of Liverpool/Global Burden of Animal Diseases
10: Social, Economic and Environmental Drivers of Zoonoses
11: Combatting Animal African Trypanosomiasis
12: Supporting the National Action Plan for Antimicrobial Resistance
13: Animal Health Economics

Figure 1

Stakeholder and data identification, and links