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Advances in addressing antimicrobial resistance

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Summary

Antimicrobial resistance (AMR) has been described as a silent pandemic – one that is ever-present, ubiquitous and growing but often insidious and overlooked. A true One Health issue, AMR affects people, animals, plants/crops and the environment in complex and interconnected but poorly understood ways, and the impact will continue to increase. In animals, AMR affects animal health, welfare and production and is also considered a food safety, food security and substantial economic issue. This article describes recent advances in addressing AMR in bacteria from animals, focusing on surveillance, applied stewardship, new drug development and alternatives to antimicrobials, strengthening animal health systems, changes in global awareness, and obstacles to effective surveillance and stewardship.

Keywords

Antimicrobial resistance – Antimicrobial stewardship – Antimicrobial use – Surveillance – Veterinary.

Surveillance of antimicrobial resistance and antimicrobial use

There is an often-used phrase: 'If you can't measure it, you can't manage it'. While it originates in the business management field, this expression is highly applicable to surveillance of antimicrobial resistance (AMR) and antimicrobial use (AMU). AMR can affect all host species, is found in both pathogenic and non-pathogenic bacteria and can be caused by thousands of different genes and mutations, and determinants of resistance can sometimes be found on mobile elements that move between bacterial species. This makes conducting surveillance difficult in terms of decisions to be made and the resources and infrastructure required. Logistical and political barriers also exist, such as difficulties in global reporting of country-level data when there are fears of trade repercussions.

Since AMU is the primary driver of AMR, AMU surveillance has undergone some of the most significant development over recent years, yet it remains challenging because of the multiple types of data available (e.g. sales, purchase, import, prescription or farm records), which originate from multiple sources, such as wholesalers, retailers, customs officials, marketing authorisation holders/pharmaceutical manufacturers, veterinarians, pharmacists and farmers [1]. The types and sources of data contain varying levels of detail, enabling different types of analyses and conclusions. Collection of end-user information requires more resources [2] but has the benefit of encompassing information on dose, duration and reason for use, which can allow for better assessment of appropriateness of use and where refined interventions could be implemented.

For analysing and reporting AMU data, units of measurement (i.e. the numerator) tend to fall into either count-based (e.g. number of farms reporting use of an antimicrobial), weight-based (e.g. kg active ingredients) or dose-based metrics (e.g. number of defined daily doses for animals) [3]. When a denominator is applied, the result is an ‘indicator’ (e.g. number of defined daily doses for animals/1,000 animal-days at risk) [3]. One disadvantage of weight-based metrics is that if a farm switches to an antimicrobial with a lower daily dose (e.g. from a tetracycline to a fluoroquinolone), the trend will appear to be decreasing with a weight-based metric, often substantially, whereas animal exposure may not have actually changed [3]. However, weight-based metrics have the advantage of being easier to generate with more readily available information than dose-based metrics [4]. With good surveillance data, and if dose-based standards are available, the conversion between metrics is possible and relatively simple. One essential factor in choosing the metric(s) to report AMU data is end-user preference, as the information needs to be communicated in a manner that allows the target audience to act on it.

Surveillance development: global and multinational

World Organisation for Animal Health

The World Organisation for Animal Health (WOAH) regularly updates its health codes for terrestrial and aquatic animals and for both AMU and AMR, including guidance on surveillance. The *Terrestrial Animal Health Code* contains AMR surveillance guidance on sampling strategies, sample sizes, sample sources and sample types [5]. There are also recommendations for target bacterial species to include (e.g. animal pathogens, zoonotic bacteria and commensal bacteria) [5]. In addition, there is guidance on the sources and types of AMU data to collect, including information for both numerator and denominator, and an indication that dose and duration are important considerations [6]. There is similar guidance for aquatic animals in the *Aquatic Animal Health Code* [7,8]. WOAH's standards and codes are adopted by approval of the World Assembly of Delegates and represent the perspectives of countries from all economies [9].

WOAH's ANIMUSE system is a substantial achievement in capturing information on antimicrobials intended for use in animals at a global level. Launched in 2022, ANIMUSE is a digital platform designed to capture national quantities of antimicrobials intended for use in animals [10]. The precursor to the digital platform has been in place for many years, with the first annual report on the subject having been released in 2016 [11]. These reports have evolved over time, reflecting advancements both in global surveillance capacity and in addressing AMR/AMU. The first WOAH report included information from 130 of 180 Members [1]. Of the responding Members, 96 (74%) reported no authorisation of antimicrobials as growth promotants (AGPs). Of the Members that did report AGPs, some reported use of colistin (ten Members) or fluoroquinolones (four Members) as AGPs [1]. Eighty-nine Members reported quantitative information [1]. The subsequent report introduced an animal biomass denominator based on number of animals and their live weight at time of slaughter (a weight-based indicator) [12]. The latest WOAH report included information from 157 of WOAH's 182 Members as well as 11 non-Members [13]. In total, 41 respondents indicated they used antimicrobials as growth promotants (26%), with continued reported uses of colistin (4 respondents) and fluoroquinolones (1 respondent) [13]. Out of the 157 Members, 121 (77%) reported quantitative information [13].

As part of the same report, WOAH conducted an analysis of the quantitative trends between 2017 and 2019 and found an overall decrease of 13% in the mg/kg for AMU reported at the global level (for 80 participants with data applicable for this analysis; from 111 mg/kg in 2017 to 97 mg/kg in 2019) [13]. This decrease was primarily due to a decrease in tetracyclines and polypeptides, whereas fluoroquinolones increased [13], highlighting concerns about relying solely on mass-based metrics given the higher-tier nature of fluoroquinolones *versus* tetracyclines and polypeptides. The report also found substantial increases in participants reporting quantitative information by animal category and route of administration [13].

Food and Agriculture Organization of the United Nations (FAO): International FAO Antimicrobial Resistance Monitoring system

The Food and Agriculture Organization of the United Nations (FAO) recently launched the International FAO Antimicrobial Resistance Monitoring (InFARM) system, an initiative aimed at collecting information on AMR in animals, plants/crops and food [14]. FAO pre-tested its data collection platform in 2022. The scope of bacterial species considered for inclusion reflects those recommended by both Codex and WOAH, evaluating bacterial species of interest for animal health, public health and indicator bacteria from both food and animals [15]. InFARM has the potential to address a gap in knowledge about AMR, as while several integrated surveillance programmes conduct surveillance on food-borne pathogens and commensals, there is relatively little information collated and reported on AMR in animal pathogens.

World Health Organization: Advisory Group on Integrated Surveillance of Antimicrobial Resistance

In 2017, the World Health Organization's Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) developed a document on integrated surveillance of food-borne bacteria that provided guidance on surveillance of AMR, AMU, combined analysis and reporting, as well as recommendations for harmonisation of reporting within and across countries [2]. For AMR, AGISAR's document focuses on zoonotic and commensal bacterial species (e.g. from humans, animals and food), and for AMU the document describes activities regarding the quantity of antimicrobials sold, prescriptions and the intake of antimicrobials [2].

Codex Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance

The Codex Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance provide a framework for surveillance and monitoring of food-borne AMR and includes guidance on setting surveillance objectives, prioritising activities, resource considerations, sampling plans, sample sources, target bacterial species (food-borne pathogens and commensal bacteria) and resistance determinants, laboratory considerations and methods, sources of AMU data, data collection and reporting, and data management [16]. For AMU in animals, high-level guidance is provided for what to include as a numerator and a denominator in data collection and reporting [16].

Quadripartite Technical Group on Antimicrobial Resistance and Use Integrated Surveillance

WOAH, FAO, the World Health Organization and the United Nations Environment Programme have formed a Quadripartite Joint Secretariat on AMR. In 2022, the secretariat created a working group, the Quadripartite Technical Group on Antimicrobial Resistance and Use Integrated Surveillance, to provide advice to the Quadripartite and the Global Leaders Group on Antimicrobial Resistance regarding integrated surveillance using a One Health approach, including recommendations for surveillance of AMU and AMR in animals [17].

European Medicines Agency's European Surveillance of Veterinary Antimicrobial Consumption

The European Medicines Agency's European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) was an early developer of standardised reporting across countries. ESVAC uses the indicator mg active ingredient per population correction unit (PCU) [18]. The PCU is a reflection of the animal biomass in each country, calculated by multiplying the number of animals in specific species/categories by the average weight at time of treatment [18]. The European Medicines Agency has also developed standards for reporting dose-based metrics. These standards address differences in formulation, dosing and route of administration for cattle, pigs and broiler chickens [19]. From a global perspective, it is important to recognise that these standards were developed from products and information from nine countries [20]. Not all countries have the same antimicrobials or products licensed, the same livestock populations or the same disease conditions; hence, other countries have started to develop their own dose standards using a similar methodology [21,22]. Development of these standards is considered a resource-intensive process [21].

AACTING network and project

Another multi-country activity is the AACTING network, short for 'Network on quantification of veterinary Antimicrobial usage at herd level and Analysis, CommunicaTion and benchmarkING to improve responsible usage' [23]. The ACTING project developed guidelines for surveillance of AMU at the farm level to inform stewardship of antimicrobials in animals [23]. The AACTING website is a valuable resource that provides information on all participating countries (European countries and Canada) concerning their farm-level AMU surveillance activities and benchmarking capacities, by animal species, and how each country is measuring AMU [23]. An annual AACTING conference brings together experts working in the field to share the latest AMU method developments [24].

European Union Regulation 2019/6

New legislation came into effect in January 2022 in the European Union (EU) with respect to AMU and AMR. In terms of surveillance, Regulation (EU) 2019/6 on Veterinary Medicinal Products describes the requirement for EU members to collect both sales and AMU data in animals [25,26]. Article 57 describes a phased approach to meet this requirement, starting with select animal species in the first two years, then collecting information for all food animals within five years, followed by other animals [26].

Antimicrobial stewardship

While surveillance activities provide critical information to describe the problems of AMU and AMR, there is a need to act on such data. Effective surveillance programmes underpin stewardship activities that aim to reduce the prevalence and impact of both AMU and AMR. While applied stewardship has tended to lag behind surveillance efforts, there has been an accelerating pace in research evaluating implementation and impact of antimicrobial stewardship practices. Some examples are presented in Table I. Still, there is a substantial need for broader studies evaluating implementation strategies and, critically, the impact on AMU in animals on AMR.

Implementation of interventions can be challenging, and interpretation of them can be complicated. Often, a bundle of strategies (e.g. education, feedback, guidelines) is used in an intervention, and if an effect is noted, it is often impossible to determine what component drove that effect. It is also challenging to determine optimal but practical outcome measures. AMU is a typical outcome measure, which is reasonable as that is what interventions typically aim to address. However, the impacts of reduction in AMU or changes in the relative use of different drugs on AMR are often not studied. While it is reasonable to infer that decreased AMU will have positive effects on AMR, this is not guaranteed, and effects may differ by bacterial species. Other impacts, such as impacts on animal health, welfare and production, need to be considered in parallel. Impacts may also vary greatly between animal species, production systems or regions, and differences in management, vaccination and other health system components may impact the ability to extrapolate results. Ultimately, the impact of changes in AMU on AMR in diseased humans or animals would be the ideal outcome measure, but there are few situations in which this can be clearly assessed. Perhaps the best description is a study from 2010 that showed elimination of prophylactic administration of ceftiofur in eggs was associated with a reduction in third-generation cephalosporin resistance in *Salmonella* from people with salmonellosis [40]. This provides support for the assumption that reduced AMU will result in reduced AMR, but significant evidence gaps and inconsistencies remain.

Drug development and antimicrobial alternatives

Development of new drugs is a focus in human medicine, with substantial outlays in both push and pull incentives. While new drugs have been licensed in animals in the past decade, no new drug classes have been developed for use in animals, and it is unlikely that this will change in the near future, as new drug classes should be prioritised for use in humans. New formulations that provide more effective, safer or more convenient treatment could still be developed and could facilitate optimal AMU, but since new drug classes are unlikely, alternative approaches to innovation must be the focus.

Vaccination is a highly effective disease prevention tool that is widely used in domestic animals. Since optimisation of animal health (reducing disease) is the foundation of reducing and improving AMU, continued vaccine development will continue to be a cornerstone of antimicrobial stewardship efforts. While beyond the scope of this article, development of vaccines remains a key priority for both research and intervention. New vaccines continue to be developed, both ones against new diseases and ones with superior properties compared to existing vaccines (e.g. efficacy, duration of immunity, storage requirements, ability to differentiate antibodies from vaccination from those from natural infection).

Alternative approaches to prevent and treat disease are also of increasing interest. While efficacy data are variable, there have been promising data for probiotics in some species for prevention of disease [41,42], and with lesser data, as a replacement for antimicrobials for treatment of disease. Immunomodulators and monoclonal antibodies to control underlying diseases have also shown promise for reduction of disease and a need for AMU, particularly in companion animals [43,44].

The use of lytic bacteriophages, viruses that predate bacteria, continues to be an area of interest, but one that is removed from direct clinical application. Bacteriophages have potential for replacement of antimicrobials, prevention of disease, reduction of shedding of zoonotic pathogens such as *Salmonella* and *Campylobacter* [45-47] and enhancement of production [48,49], but high-quality data tend to be lacking, *in vitro* data do not always correlate with *in vivo* efficacy [50] and there are practical and logistical barriers to routine field use that have yet to be overcome.

Any antimicrobial alternatives must be scrutinised like any other therapeutic to avoid unintended negative consequences, as was seen with the use of high oral doses of zinc in pigs. Zinc has antibacterial properties and is used as an alternative to antimicrobials for prevention of post-weaning diarrhoea. However, it was subsequently found that zinc applied the same selection pressure for methicillin-resistant *Staphylococcus aureus* (MRSA) as antimicrobials [51,52], with an added downside of environmental persistence. This has led to regulation or prohibition of the use of high levels of dietary zinc in some regions, such as the European Commission’s 2017 prohibition of pharmacological doses of zinc oxide in pig feed, restricting its use to 150 ppm or less.

Other approaches, such as phytochemicals, are being explored as antimicrobial alternatives for treatment or prevention of disease, or reduction in pathogen shedding [53-58]. However, studies have predominantly been *in vitro* and properly designed clinical trials are lacking. Some compounds have potent antimicrobial effects, but these products require similar study to conventional antimicrobials for proper assessment of efficacy and AMR selection pressure, something that can be overlooked when they are marketed as nutritional supplements rather than therapeutics.

Animal health systems: improving animal care and building resilience

While there is a focus on AMR as ‘the problem’, the inciting cause is AMU, which itself is caused by disease (or concerns about development of disease). Improving animal health systems to improve animal health and resilience is a core component of antimicrobial stewardship efforts. Animal health system improvements are core requirements for such stewardship, particularly in regions where food animal production is anticipated to increase dramatically. These improvements need to be made simultaneously with the phasing out of antimicrobials for growth promotion [13]. Unfortunately, basic aspects of animal management tend to receive little attention and funding and are not often considered part of innovation and research needs. Similarly, improvement in access to veterinary care and pharmaceuticals is a core need for optimising animal health, reducing disease and improving treatment of disease, yet this is typically overlooked from a research standpoint.

Changes in global awareness, governance and advocacy

Recent years have seen a marked increase in national and international initiatives to address AMR in animals. This has included accelerated development and implementation of national action plans. As of a February 2023 report, 122 of 192 countries assessed (64%) had a national action plan, including 84% of high-income countries, 61% of low- and middle-income countries and 43% of least-developed countries [59]. Other advancements include development of clinical practice guidelines at the species, sector or national level, continued development of guidance by quadripartite agencies (Table II) and development of new initiatives, such as the high-level Global Leaders Group on AMR (https://www.amrleaders.org) and the AMR Multistakeholder Partnership Platform (https://www.fao.org/antimicrobial-resistance/quadripartite/the-platform/en). Many of these activities have incorporated a One Health approach, in recognition of the complexity of the problem, the need for integrated multisector activities and the cross-cutting influence of AMU in humans, animals and plants.

Obstacles to meeting strategic surveillance and stewardship goals

Various challenges exist for enacting surveillance and stewardship strategies and achieving relevant goals. Good surveillance data come at a cost, in terms of both human and financial resources. In a 2023 report by WOAH, the main barriers reported by participants were: i) lack of IT tools and resources, ii) lack of regulatory framework, iii) lack of coordination and cooperation between national authorities and private sector and iv) insufficient regulatory enforcement [13]. For AMR, modern molecular techniques to characterise AMR data may not be available in all countries.

Harmonisation in surveillance reporting across countries and reporting of country-level data remains an obstacle, and not all countries have an objective to ensure international harmonisation because of trade concerns. For example, currently the EU has regulations in place to restrict importation of animals or their products from non-EU countries that are still using antimicrobials as growth promotants [60].

Most strategic goals involve reduction in AMU, often at fairly crude levels, such as the total mass (kg or tonne) of antimicrobials that are administered to animals. While this is an easy-to-understand metric and often the most readily obtainable, more refined metrics or targets are needed for optimal stewardship practices. It is important to ensure that changes do not reduce tonnage of use but instead lead to increased use of higher-potency (lower mg/kg/day doses), higher-tier drugs in lieu of larger masses of older, narrower-spectrum, lower-tier drugs. There is also a need to ensure that changes do not compromise animal welfare and the safe, economic production of food.

Regardless of the metric used, robust and reliable data are required to be able to describe AMU and to benchmark and evaluate the impact of interventions. However, it is not currently possible to collect accurate data in many countries, particularly data of adequate granularity to delineate AMU at the species or sector (e.g. dairy *versus* beef cattle) level.

While it is reasonable to assume that a significant reduction in AMU could be achieved with no negative impact on animal health, welfare or production, enhancement in animal health and animal health systems will be needed. It is presumably well understood that raising healthier animals results in less AMU and that management, preventive medicine, ventilation, nutrition, stress reduction and other factors are core components of that. Yet these tend to receive limited attention in terms of both research support and implementation. There is a need to expand research activities and producer supports to optimise animal management. Similarly, efforts to bring all AMU under the control of a veterinary prescriber and to improve animal health through universal veterinary access are dependent on increased access to veterinary care, particularly in low- and middle-middle countries.

There are substantial surveillance, knowledge and innovation gaps. Yet it is clear that many of the barriers to antimicrobial stewardship relate to human behaviour, with reluctance to change and defensive medicine likely important drivers of unnecessary AMU and challenges with implementation of stewardship strategies. There has been limited involvement of social scientists in antimicrobial stewardship research in animals, which impacts the ability to understand and modify AMU behaviours.

Despite the efforts that are under way to address AMU and AMR in animals, there is limited information about the impact of AMR in animals and the impact of that on humans. AMR surveillance often focuses on testing of healthy animals and food, which provides important information for human health risk but limited context about animal health. The impact of AMR in animals on human health is also poorly understood. While an estimated 4.95 million human deaths were associated with AMR in 2019 [61], only a subset of the most important resistant pathogens are potentially zoonotic, and the fraction of infections that can be attributed to animal sources is completely unknown. There is almost no information on the impact of AMR in animals on the environment and subsequent risks to humans or animal populations. These gaps hamper proper risk and cost–benefit analysis and are reflective of both limited truly integrated research and the challenges of source attribution.

Surveillance of AMU and AMR typically focuses on (or solely involves) food animals, a logical approach given that the vast majority of AMU in animals is in food production. However, there are relevant AMU and AMR concerns in non-food species, particularly companion animals, where AMU can be extensive, and where higher-tier drugs (e.g. fluoroquinolones, third-generation cephalosporins) are commonly used, including drugs that are rarely or never used in food animals (e.g. carbapenems, fourth-generation cephalosporins, oxazolidinones). Yet companion animals are rarely incorporated into national surveillance programmes, so data tend to be sporadic and based on individual research projects that are not coordinated into broader surveillance. Despite these limitations, an increasing number of reports describe AMU in companion animals in various countries and situations [62-69]. Surveillance underpins antimicrobial stewardship through identifying issues, enabling target setting, allowing for monitoring of the impact of interventions and facilitating various activities. However, surveillance usually outpaces applied stewardship efforts because the latter tend to be more complicated to develop and implement and are more often applied as projects, not broad national efforts.

Conclusions

Despite the substantial gains in activities to address AMR and AMU in animals over the past five years, significant obstacles remain. There have been major advancements in data collection systems for antimicrobials intended for use in animals (WOAH's ANIMUSE), more sector-specific and integrated surveillance on AMR and AMU, increasing development of actions based on surveillance and somewhat limited but important successes in the reduction of AMU through targeted interventions. Critical next steps will include a greater understanding of how reporting of surveillance data affects interpretation of findings, how action-oriented surveillance and applied stewardship activities can broadly impact AMU and, importantly, the impact of AMR across the human, animal and environment triad.

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Table I

Examples of antimicrobial stewardship intervention studies

Animal population	Intervention	Outcome	Reference
Dairy calves with diarrhoea	Antimicrobial prescribing algorithm	Decreased antimicrobial use with no impact on calf mortality or morbidity	[27]
Dairy cattle	Selective dry cow treatment for mastitis	24% reduction in antimicrobial use	[28]
Dogs	Online antimicrobial stewardship resources/decision support	Decreased prescriptions, increased compliance with guidelines	[29]
Calves	Online antimicrobial stewardship resources/decision support	Decreased use of highest-priority critically important antimicrobials, increased use of first-line treatments	[30]
Pigs	Antimicrobial stewardship programme targeting voluntary restriction of third- and fourth-generation cephalosporins	>90% decrease in third-generation cephalosporin use	[31]
Dogs and cats	Formal antimicrobial stewardship discussion	Reduction in use of cefovecin in cats and metronidazole in dogs, and increased use of amoxicillin-clavulanic acid	[32]
Dogs and cats	Antimicrobial stewardship programme interventions of different intensities	Reduced prescribing, particularly in high-prescribing clinics	[33]
Veal calves	Antimicrobial stewardship training for producers	50% reduction in antimicrobial use	[34]
Dairy cattle	Meta-analysis of selective dry cow treatment *versus* blanket treatment	Selective treatment reduced antimicrobial use and was non-inferior for microbiological and clinical cure	[35]

Animal population	**Intervention**	**Outcome**	**Reference**
Dogs and cats	Antimicrobial stewardship programme education	Reduced use of second-line antimicrobials and antimicrobials for skin disease	[36]
Food animals	National veterinary feed rule change	Reduction in antimicrobial resistance in certain bacteria from certain food items	[37]
Turkeys	National producer-implemented antimicrobial stewardship strategy	Significant reduction in antimicrobial use and reduction in resistance in *Escherichia coli*	[38]
Food animals	Sector-specific target setting and yellow card system	Sustained reduction in antimicrobial use, particularly on high-user farms	[39]

Table II

Recently developed or updated international guidelines, policies or recommendations pertaining to antimicrobial use and antimicrobial resistance in animals

Item	Source
World Health Organization Medically Important Antimicrobial List	https://cdn.who.int/media/docs/default-source/gcp/who-mia-list-2024-lv.pdf?sfvrsn=3320dd3d_2
World Organisation for Animal Health List of Antimicrobial Agents of Veterinary Importance	https://www.woah.org/app/uploads/2021/06/a-oie-list-antimicrobials-june2021.pdf
Codex Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance	https://www.fao.org/fao-who-codexalimentarius/thematic-areas/antimicrobial-resistance
Codex Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance	https://www.fao.org/fao-who-codexalimentarius/thematic-areas/antimicrobial-resistance
Codex Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance	https://www.fao.org/fao-who-codexalimentarius/thematic-areas/antimicrobial-resistance
Regulation 2019/6 of the European Parliament on veterinary medicinal products and repealing Directive 2001/82/EC	https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006