ANNUAL REVIEWS

Annual Review of Animal Biosciences

Beyond Antimicrobial Use: A Framework for Prioritizing Antimicrobial Resistance Interventions

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Annu. Rev. Anim. Biosci. 2021. 9:313–32

The *Annual Review of Animal Biosciences* is online at animal.annualreviews.org

https://doi.org/10.1146/annurev-animal-072020-080638

Keywords

antimicrobial use, antimicrobial resistance, livestock, framework

Abstract

Antimicrobial resistance (AMR) is a threat to animal and human health. Antimicrobial use has been identified as a major driver of AMR, and reductions in use are a focal point of interventions to reduce resistance. Accordingly, stakeholders in human health and livestock production have implemented antimicrobial stewardship programs aimed at reducing use. Thus far, these efforts have yielded variable impacts on AMR. Furthermore, scientific advances are prompting an expansion and more nuanced appreciation of the many nonantibiotic factors that drive AMR, as well as how these factors vary across systems, geographies, and contexts. Given these trends, we propose a framework to prioritize AMR interventions. We use this framework to evaluate the impact of interventions that focus on antimicrobial use. We conclude by suggesting that priorities be expanded to include greater consideration of host–microbial interactions that dictate AMR, as well as anthropogenic and environmental systems that promote dissemination of AMR.

INTRODUCTION

Antimicrobial resistance (AMR) is an extant threat to animal and human health. Initiatives to combat AMR have been launched across sectors locally, nationally, and internationally. At the global level, the World Health Organization (WHO) and the World Organisation for Animal Health have outlined strategies to optimize antimicrobial use (AMU) protocols and to formalize national action plans and surveillance programs for AMR pathogens (1, 2). In the United States, numerous federal agencies have implemented strategic plans and programs for monitoring, reporting, and regulating AMU, many in response to the 2015 National Action Plan for Combating Antibiotic-Resistant Bacteria (3). Most of these national and international initiatives target several key areas: support for the antibiotic development pipeline; development of antibiotic alternatives; and improvements in antimicrobial stewardship (AMS). Efforts within the latter two categories are primarily aimed at reducing AMU as a means for mitigating AMR, and numerous organizations promote these efforts. Although the metrics for defining AMU reductions are often debated, the implicit assumption in all AMU-focused approaches is that AMU is the primary driver for the emergence and spread of AMR, and thus, reductions in AMU will translate to reductions in AMR.

AMR is often considered a quintessential One Health problem, wherein the drivers of AMR involve human, animal, and environmental sectors. Solutions for mitigating the effects of AMR therefore require a collaborative effort across many different disciplines and necessitate a global approach. Multiagency international working groups have developed frameworks for judicious AMU in production animal agriculture and aquaculture systems (4, 5). Multicountry and regional pacts regarding AMU in humans and animals have also been formed (6, 7). Practical AMS tool kits have been developed to extend capacities of low- and middle-income countries (LMICs) to meet AMU global challenges (8). Some of the most consequential recent regulatory actions in the United States have included restrictions on AMU in livestock production, particularly related to growth promotion [80 Fed. Reg. 31707 (2015)].

Many human and veterinary medical organizations have released AMU position statements, guidelines, and resources. Organizations and agencies such as the Centers for Disease Control and Prevention have set forth policies concerning AMS for human practitioners (9). The World Veterinary Association maintains a repository of >150 judicious AMU guidelines and action plans for veterinary medical professionals, according to specific country, clinical disease, and animal species (10). Currently, these documents are a composite of guidelines abstracted from numerous independent and national veterinary medical organizations and regulatory agencies; there is no harmonized AMU stewardship policy across all sectors of veterinary medicine. In the United States, species-specific veterinary organizations and the American Veterinary Medical Association have released judicious AMU guidelines and AMS core principles (11). Recently, a handbook for AMS in companion animals was published in the United States to guide practitioners in the responsible administration of antimicrobials (12). Industry groups and companies have also developed internal guidelines and incentives to encourage judicious AMU and AMS across the food supply chain, and major grocers, restaurants, and suppliers have elaborated varying market-driven strategies for reducing AMU.

The immense attention and resources being devoted to AMU and AMS have led to a somewhat myopic perspective on AMR. For example, in a recent scoping review, researchers found that AMU was the only risk factor evaluated in most studies of AMR in livestock animals (13). This has led to an implicit—and at times explicit—tendency to conflate AMU and AMR. This conflation is especially apparent when reviewing the AMS literature, as studies that evaluate AMS programs often quantify efficacy by measuring changes in AMU over time. Although AMU reductions may signify that a stewardship program has been successfully implemented, these reductions do not

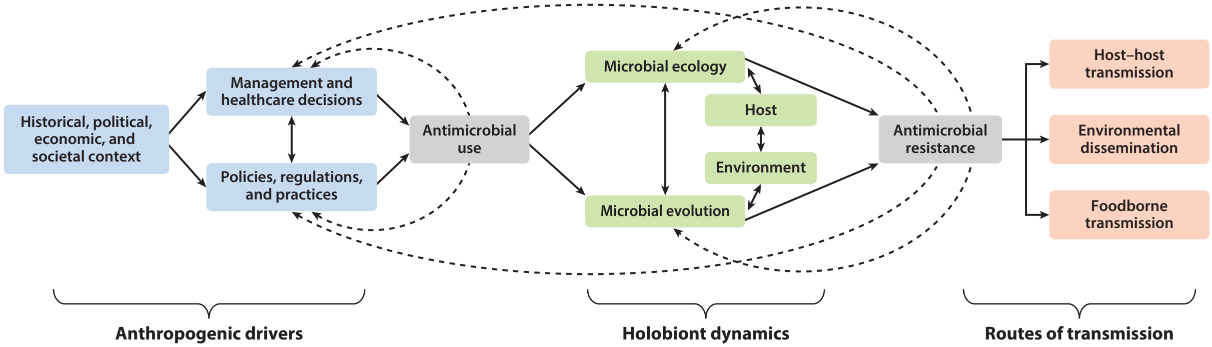

Figure 1

Diagram of direct and indirect connections between antimicrobial use and resistance (AMU and AMR, *gray boxes*) and anthropogenic components (*blue boxes*), host–environment–microbe interactions (*green boxes*), and transmission routes for AMR genes and/or bacteria (*red boxes*). Dashed lines represent potential feedback loops from AMU and AMR to various anthropogenic and holobiont components.

necessarily indicate that the program succeeded in achieving its ultimate goal, i.e., a reduction in AMR. In evaluating progress toward AMR risk reduction, it is important to keep in mind that AMR is the hazard, and AMS programs (and implicitly, AMU reductions) are interventions to control the hazard and improve health outcomes. To truly evaluate the efficacy of these interventions, we must measure AMR and related clinical outcomes.

Scientific advances are prompting a growing recognition of the immensely complex ecological and evolutionary processes that drive AMR within microbes. These processes, in turn, are highly sensitive to the environment and/or host in which microbes exist—including the many anthropogenic activities that influence this environment (**Figure 1**). Therefore, although AMU may be one driver of AMR, it is becoming ever more apparent that other exogenous forces exert equal—if not stronger—pressures on microbial populations, with correspondingly dramatic impacts on AMR (14–16). Additionally, recent ecological and observational studies of AMR dynamics in LMICs have highlighted the importance of contagion and dissemination in maintaining high levels of AMR in human populations and their environs; in some cases, these factors exert larger and more direct impact on AMR than unregulated and widespread AMU (17).

AMR mitigation activities are thus undergoing a period of divergence, with regulatory priorities heading down one path, and scientific discoveries shedding light on a different path. On the one hand, AMU is considered a proxy, or surrogate, for AMR, whereby reductions in AMU are expected to provide corresponding reductions in AMR. On the other hand, AMU is being increasingly recognized as neither a necessary nor a sufficient condition for AMR emergence, dissemination, and persistence. Although this divergence could lead to a decoupling of AMR mitigation efforts, it is also possible to leverage current scientific advances to better inform AMU practices. This approach could reap massive benefits in the fight against AMR, especially because our scientific understanding is advancing rapidly across many fields simultaneously—leading to a more sophisticated understanding of the interactions between anthropogenic, holobiont (i.e., host–microbe–environment), and transmission factors that drive AMR in a mechanistic and causal manner (**Figure 1**).

This more comprehensive approach would support customized prioritization and evidence-driven evaluation of ongoing AMR mitigation efforts that can be tailored for specific geographic areas and temporal periods (18). For example, global improvements in water quality, sanitation, and hygiene (WASH) have been recognized as important components of AMR mitigation, and although guidelines have been released for achieving these improvements, WASH measures are

rarely mentioned in AMR guidelines and action plans (19). An expanded yet customizable approach to AMR mitigation would support the prioritization of WASH measures within such guidelines—perhaps even at the expense of AMU regulations, particularly in some situations (14, 19).

Given the immense effort being devoted to AMR—and increasingly within resource-limited locations—there is a need to develop systematic and ongoing evaluative processes that ensure optimized and strategic allocation of resources (20). Here, we propose a partial framework that may help to rationally prioritize interventional targets given limited resources and inherently messy allocative processes. We use this framework as a vehicle to discuss the growing body of scientific evidence regarding the impact of AMU and AMS programs on AMR mitigation. We focus on research from livestock production systems primarily in North America and the United States, which have amassed the largest body of literature regarding connections between AMU and AMR. Based on this evaluation, we suggest that AMU reductions and AMS programs are insufficient as the primary interventional levers in the fight against AMR, and we discuss promising new avenues of AMR control based on recent advances in microbial, environmental, and social sciences.

A PRIORITIZATION FRAMEWORK

A useful prioritization framework must strike a delicate balance between overly vague evaluative criteria and translatability of the criteria across multiple users and use scenarios. This balance is especially critical for AMR given its transboundary, cross-sectoral, and cross-disciplinary nature. Although the evaluative criteria laid out in this review are not exhaustive, they do cover some of the most critical aspects of a successful AMR mitigation effort (**Table 1**). The first criterion we discuss is biological efficacy; i.e., how likely is the intervention to mitigate AMR given the underlying biological mechanisms? The second criterion is feasibility; i.e., how likely is the intervention to be implemented in a manner that supports efficacy? This is a crucial criterion because even the most biologically efficacious intervention will prove worthless if it cannot be implemented properly. The third criterion we discuss is unintended consequences—both negative and positive. Because most interventions involve alteration of processes within complex systems, they often incur side effects that necessitate careful investigation and potentially mitigation. Although these may be difficult to predict, it is important to gather as much a priori information as possible and to continuously reevaluate the unintended consequences as new information is generated. Finally, we discuss the costs associated with identifying, developing, and properly implementing an intervention. Although some costs may be difficult to estimate, they must be part of a comprehensive prioritization process—particularly in the context of limited resources. We note that, in reality, these four criteria are interrelated and lack clear lines of demarcation. Nevertheless, they provide a useful framework for evaluating AMR interventions.

Biological Efficacy

There are many factors to consider when analyzing associations between AMU and AMR, many of which relate to study design and causal inference (21). In this section, we review recent experimental, observational, ecological, and modeling studies that investigate the efficacy of AMU reductions and AMS programs in mitigating AMR.

Common approaches for evaluating the efficacy of AMU reductions are to analyze AMR dynamics in populations that have experienced reductions in antimicrobial drug exposures and to compare AMR prevalence across populations with varying AMU practices or policies. Although some of these observational or ecological studies report significant associations between AMU and AMR, they are often beset by confounding and ecological fallacies (22, 23), particularly those that

Table 1 List of criteria to evaluate antimicrobial stewardship and use reductions as interventions for antimicrobial resistance

Factor—Description	Relevant questions
Biological efficacy Likelihood that the intervention will suppress antimicrobial resistance (AMR) emergence, persistence, and/or transmission	What is the current strength of evidence for causality? How potent is the AMR suppression? Partial or complete? How generalizable is the suppression; i.e., does it apply to only a single AMR phenotype in a single pathogen? Or would it work across multiple AMR phenotypes/genes and many bacteria?
Feasibility Likelihood that the intervention will be optimally or appropriately implemented	What are the current barriers to adoption? How reliant is adoption on human behavioral change? On policy, legislation, or regulation? On market-driven incentives? How scalable is the intervention? What is the timeframe for implementation and impact? How well does the intervention translate across systems, countries, and/or cultures?
Unintended consequences Likelihood of both positive and negative unintended consequences	Is the interventional target an existing practice, procedure, or tool within an existing system? – If yes, how is the interventional target positioned within the broader system(s)? What roles does the interventional target fulfill within the broader system(s)? Does the interventional target impact outcomes at multiple levels of the system(s)? – If no, how will the new intervention be positioned within existing systems? How will it interface with existing practices and procedures? What activities and resources are needed to develop and implement the intervention, and are they likely to spur new areas of investigation (virtuous cycle) or detract from critical resources?
Cost Foreseeable financial, environmental, societal, and health costs associated with developing and implementing the intervention	What is the estimated range of direct costs to develop and fully implement the intervention? What are the likely indirect costs of developing and implementing the intervention? Will there be any direct or indirect costs associated with mitigating unintended negative consequences (see previous criterion)? Who will bear the brunt of these costs, and will the costs be disproportionately distributed across different sectors, groups, regions, or countries?

investigate correlations using aggregate, national-level AMU and AMR data (24, 25). Hospital- and community-based populations offer more circumscribed geographies for assessing AMU–AMR relationships, and recent analyses have endeavored to evaluate AMR outcomes during implementation of AMS initiatives. Although many of these analyses suffer from the Hawthorne effect and related biases, they can help shed light on whether AMU reductions lead to AMR reductions. The results of such investigations are decidedly mixed, with some suggesting that even large reductions in AMU effect only modest reductions in AMR outcomes (26) and in some cases even increase AMR (27). In some cases, targeted reductions have failed to achieve their intended effects owing to the complexities of microbial dynamics, specifically co-selection of AMR genes that confer resistance to drugs not being used in the relevant host or population (28, 29).

One may hypothesize that these targeted AMU reductions failed to produce consistently positive AMR outcomes because of their relatively limited scope. Whereas it is ethically infeasible to eliminate entire classes of antimicrobial drugs for humans, such dramatic reductions have been undertaken within livestock populations—with similarly mixed results in terms of AMR. These reductions were implemented with the primary goal of mitigating AMR risk in human populations;

thus, the intervention occurred in one host population, with the intended impact in a different host population. The success of this interventional approach therefore rests on the assumption that livestock animals transmit AMR bacteria and/or genes to humans, through either the food chain or environmental routes of exposure. The proportion of human-associated AMR attributable to AMU in livestock has been debated for quite some time (30). Recent systematic reviews and observational studies have concluded that evidence of such transmission exists for humans in close and sustained contact with livestock, i.e., farm workers and veterinarians (31), and less so for people who reside near farming operations (32). However, evidence for sustained, widespread, and indirect (i.e., environmental) transmission from livestock to the general public remains scant (31, 33, 34). Foodborne pathogens, both susceptible and resistant, are obviously able to infect humans through the food chain, but evidence of AMR transmission is only one of the links in the evidentiary chain between livestock antimicrobial drug exposures and clinical AMR in humans. At a high level, this chain involves three discrete causal associations: first, that AMU in livestock increases AMR bacteria and/or genes in the exposed population(s); second, that these AMR bacteria/genes then transmit to humans; and third, that these AMR bacteria then cause clinically resistant illness in the exposed humans. Unsurprisingly, recent systematic reviews have found that the evidence for this causal chain is weak and/or nonexistent (35–37). Models continue to demonstrate only modest effects of livestock AMU on human AMR (38), and quantitative risk assessments consistently conclude that AMU in livestock presents minimal risk to human morbidity and mortality owing to AMR pathogens (39, 40). Indeed, most reviews highlight major evidence gaps (41) and stress the need for well-designed studies to identify specific livestock AMU practices that increase AMR in human populations (42), as well as specific policy interventions that significantly reduce AMR risk in human populations (43).

Whereas the association between livestock AMU and human AMR may be extremely challenging to ascertain owing to the numerous causal links that must be established, a more tractable research question is whether reduced AMU in livestock populations leads to reduced AMR in the same populations, either over time or across different operations. Many studies have posed this question, with mixed results. For example, comparisons of AMR in livestock populations with varying levels of antimicrobial exposures over time or between groups have shown positive (44, 45), negative (46, 47), and mixed (48, 49) correlations. Some studies have compared livestock operations that use antibiotics to operations that do not (such as organic livestock production), with the implicit assumption that any differences in AMR between these two groups are due to differences in AMU. Given the many differences that often exist between these two types of farming practices, this comparison is fallacious, as we have described previously (22). The differences that exist between these two types of farming practices and that could affect AMR emergence and spread are related to the nonantibiotic factors depicted in **Figure 1**.

Temporality is also a critical yet poorly understood factor in the relationship between AMU and AMR. One may argue that AMU-focused interventions should not be expected to produce short-term AMR reductions, given the evolutionary processes that must occur. However, available evidence suggests that even complete bans on specific antibiotics do not necessarily result in significant reductions in AMR, even over a decade's worth of data (50, 51). Furthermore, disappearance of AMR from bacterial populations is often a slow and highly stochastic process (52, 53). Even short-term post-antibiotic AMR temporal dynamics are highly variable (54, 55) and likely depend on a complex combination of specific drug exposure, pathogen, individual health/disease state, percentage of hosts in a group that have been exposed to the antibiotic (i.e., density of treatment), and pre-exposure microbial composition within the host (56, 57). The post-antibiotic recovery of the microbial community is an area of intensive and recent scientific interest, and emerging evidence demonstrates that environment, diet, and host–host interactions

can all significantly impact the likelihood that AMR persists after individual antibiotic exposures (58). Although this postexposure complexity presents challenges in identifying common mechanisms of susceptibility recovery, it also presents numerous opportunities for discovery of novel interventional targets for AMR mitigation.

Feasibility

Feasibility is a crucial component of a successful intervention—even the most biologically efficacious intervention will not achieve success if it cannot be feasibly implemented. From the vantage point of feasibility, one can estimate the likelihood that AMU interventions will be appropriately implemented within a given population, location, or sector. Indeed, context is critical to feasibility, and examples of this are numerous within livestock production. For example, the logistical feasibility of eliminating group-level treatments is much higher for sows than for, e.g., broilers or fish. Similarly, raised-without-antibiotics production is likely more feasible for livestock or aquaculture with shorter life spans compared with long-lived animals.

Country-specific conditions can dictate the feasibility of regulatory actions on AMU. For example, the finishing pig industry in Denmark reacted to changed AMU regulations by implementing tighter biosecurity measures, reducing stock density, and modifying pig production flow (59). In contrast, pig producers in LMICs would face substantial barriers to implementing these types of measures and would likely find alternative routes to respond to such drastic changes in antibiotic access (60, 61). These challenges extend to human medicine as well. For example, in 2012 China passed legislation to restrict nonprescription access to antibiotics, particularly in hospitals (62). However, since that time, illegal access to antibiotics without prescription from pharmacies has actually increased (63). Cases like these emphasize the crucial role that governance plays in supporting the feasibility of interventions that rely on adherence to regulation or societal change (64). The importance of these contextual drivers is especially relevant for AMU, which is itself a human behavior underpinned by complex decision-making at the individual level (65) (**Figure 1**). Human behavioral and societal complexities can greatly complicate the implementation of sustained AMU reductions.

The feasibility of reducing AMU also depends on the clinical diseases for which relevant antibiotics are used, including the type and course of infection, affected tissue(s), pathogenicity, virulence, and availability of diagnostics. For example, a 50% reduction in AMU for clinical mastitis was achieved in dairy cows using rapid on-farm culture diagnostics and targeted treatment, with no sacrifices in treatment efficacy (66). Similar results were achieved in recent randomized controlled trials of culture-driven and algorithmic dry-cow therapies for clinical mastitis, without undue impacts on lactation performance or cow-udder health (67, 68). It should be noted, however, that these large reductions in AMU occurred under a scenario in which both the infection and the treatment route were highly localized, which may explain the lack of major impacts on herd health and welfare. In other contexts, such as when antimicrobials are applied for systemic effects (e.g., respiratory, gastrointestinal, or genitourinary disease), feasibility may be different. For example, a recent modeling effort indicated that fluoroquinolone and macrolide prescribing rates in human hospitals would need to decrease by 85% and 77%, respectively, to decrease local waterborne antibiotic residues to levels that are unlikely to exert significant selective pressure (69). Although some level of hospital-based AMU reductions is likely possible for these classes of antimicrobials without jeopardizing patient care, such drastic reductions are expected to be infeasible in the short- and medium-term, particularly in the absence of appropriate and efficacious substitutes.

The issue of feasibility is also highly relevant to discussions of inappropriate versus appropriate AMU. From an ethical standpoint, inappropriate AMU should be much more feasible to

eliminate than appropriate AMU. However, defining inappropriate versus appropriate use is fraught with imprecision (70), evidence gaps, and moral dilemmas (71). Furthermore, the biological importance of delineating inappropriate from appropriate use is questionable, as microbes react to antibiotic exposures regardless of whether they are inappropriate; therefore, it is equally true that appropriate and inappropriate AMU may cause AMR. Thus, although a focus on reducing inappropriate use may help motivate human behavioral change and increase the feasibility of a given AMU intervention, this focus does not necessarily target the AMU practices that actually promote AMR emergence and persistence from a mechanistic perspective. This distinction between the feasibility and biological efficacy of reducing inappropriate AMU is one example of how different criteria in our proposed framework can intersect, and how the framework can be used to weigh such conflicting considerations.

Negative Unintended Consequences

Modern livestock production and human healthcare systems have been built, developed, and modified over centuries. Since the discovery of antibiotics in the 1930s, these systems have been built on the implicit assumption that antimicrobial drugs will be available to prevent, control, and treat disease. Although the details of this evolution vary by country and by context (72), AMU is a critical and deeply embedded component of comprehensive preventive and therapeutic care across sectors and societies. Therefore, removing or reducing access to these tools is likely to create a ripple effect across the system, with both negative and positive unintended consequences (73).

The poultry industry provides the most recent example of the potential negative consequences of rapid and widespread reductions in AMU. In the span of several years, the vast majority of US broiler production shifted to raised-without-antibiotics programs. This shift was associated with increased incidence and severity of enteric diseases, based on both producer reports (74, 75) and prospective (76) and retrospective (77) analyses. Although these negative health sequelae can be blunted by adjustments in management and production practices, such changes take time and incur their own economic and environmental costs (78). European bans on antimicrobial growth promoters provide a more long-term historical perspective on the impacts of restricted AMU in livestock production (79). Observational studies of these policy changes suggest that negative unintended consequences varied widely by country, livestock species, specific drug banned, and availability of alternative treatments (including other antibiotics) (73). This variability may explain the somewhat dichotomous historical narrative surrounding these bans (80–82). Additionally, societal appetite for such complex risk–benefit trade-offs is highly dependent on historical, political, and cultural context (83, 84), which greatly complicates objective evaluation of country-specific policies.

Unlike livestock, humans have yet to experience such abrupt and widespread cessation of antimicrobial drug access. Instead, human health AMS initiatives tend to focus on tightly controlled, highly monitored, and incremental adjustments to AMU protocols within the context of hospital-based AMS programs. In contrast to more blanket restrictions placed on livestock populations, these human hospital-based initiatives have not generally been linked to adverse mortality and other health outcomes (85, 86), although in some cases AMS strategies did worsen both patient and AMR outcomes (87, 88). Although primary care AMS programs have received less attention in the scientific literature, some results suggest that these programs have either no or limited associations with negative clinical outcomes (89). On the other end of the AMU spectrum, recent trials have demonstrated that mass administration of antimicrobials to humans can significantly

improve morbidity and mortality outcomes in some populations (90–92), although at the expense of increased AMR, at least in the short term (93). Mass antimicrobial administration to cattle has also been shown to significantly reduce incidence of bovine respiratory disease in the early feeding period (94). Studies such as these raise the possibility that population-wide AMU may improve health outcomes even in the absence of contemporaneous clinical indications. Such findings not only complicate judicious AMU definitions but also emphasize the importance of non-AMU interventions in controlling AMR, particularly when AMU reductions will significantly increase morbidity and mortality owing to insidious health challenges within a population.

Taken together, emerging consensus suggests that incremental, stepwise, and targeted AMU reductions can be implemented without negative impacts on morbidity and mortality. However, eliminatory, abrupt, and/or nontargeted AMU reductions are likely to incur substantial damage to morbidity and mortality, particularly in the short term and particularly when implemented in vulnerable populations. This is especially critical given the current global focus on complete restriction of some classes of antibiotic drugs for prevention, control, and treatment of disease in livestock animals (5, 95). Importantly, these restrictions are not often accompanied by sufficient countermeasures to protect animal health, production, and environmental sustainability. For example, producers are rarely provided with funding for increased vaccine coverage, veterinary care, or modifications to facilities and animal management protocols that could help mitigate unintended negative consequences of antimicrobial drug removal. Although some research funding has been allocated toward antibiotic alternatives, it takes years to develop and deploy efficacious alternatives, and this time frame is at odds with the need to deploy these technologies at the same time that antibiotics are being phased out. Furthermore, recent systematic reviews suggest that nonantibiotic interventions long assumed to provide health benefits to livestock actually have little evidence of efficacy (96–99), casting even more doubt on whether viable alternatives to antibiotics exist for livestock producers.

In terms of AMR, the crucial question is whether incremental and narrow AMU reductions will meaningfully reduce AMR and, if so, whether these positive impacts will occur quickly enough to prevent continuing increases in clinical treatment failures from AMR pathogens. Current evidence on this point is mixed, with some modeling suggesting that reduction in extensive, broadly distributed AMU is more effective in controlling AMR than reduction in intensive, repeated-use scenarios (100). If this truly is the case, then targeted AMU reductions may not be very efficacious in combatting AMR, and we may find ourselves in the unfortunate situation of inherent conflict between human health, animal welfare, and AMR mitigation. This open question is particularly important when formulating programs that target inappropriate AMU. Although such use may represent an easy target for AMS efforts (see the section titled Feasibility), it may not effect much change on AMR.

Antibiotic alternatives are another area in which negative unintended consequences could occur. Although innovation around antibiotic alternatives is often considered a positive consequence of AMU-based AMR control efforts, these alternatives could themselves incur negative impacts on AMR. Non-antimicrobial pharmaceuticals, for example, have been shown to promote development of AMR within bacteria (101), and commensal probiotic microbes have been shown to acquire clinically relevant AMR-conferring mutations while circulating within hosts (102). Such findings underline the fact that AMR is a direct function of microbial ecology and evolution, which in turn are driven by continuous fluctuations in the host and environmental milieu (**Figure 1**). Thus, antibiotic alternatives should be evaluated for potential associations with AMR emergence and persistence within microbial populations, and any such associations should be considered as potential negative consequences of AMU reduction strategies that rely on antibiotic alternatives.

Positive Unintended Consequences

The impending loss of antibiotics—whether owing to regulation or AMR—has prompted scientists and clinicians to focus on improvements and innovations in both human healthcare and livestock production. In livestock production particularly, the loss of access to entire antimicrobial drug classes has sharpened interest in potential substitutes, which has led to an explosion of research into antibiotic alternatives (103, 104). One major area of research has centered around concurrent advances in sequencing technologies and our understanding of microbial ecology (105), including use of phages (106). This activity complements efforts to control AMR by elucidating and exploiting the microbial mechanisms that lead to AMR (107, 108). Under this perspective, the microbiome is not only a rich source of antibiotic alternatives but also an AMR control target (109).

By reducing AMU in a quest to reduce AMR, we may also be inadvertently protecting human and animal health via biological mechanisms that remain largely uncharacterized (110). For example, early-life antimicrobial drug exposures may incur lifelong negative impacts that are unrelated to AMR, including increased susceptibility to asthma (111) and allergies (112). Antibiotic exposures may also perturb the normal and protective immune response to pathogens (113) and vaccines (114). In livestock, microbiome diversity and early-life antibiotic administration have been correlated with disease susceptibility and performance in pigs (115, 116), and removal of antibiotics has been associated with increased microbiome diversity (117). It might be inferred, therefore, that removal of antibiotics could modulate disease susceptibility and performance via changes in microbiome diversity, although the host–microbial mechanisms underlying such connections are yet to be fully elucidated. Thus, by reducing early-life antibiotic exposures, human and animal populations may realize long-term health benefits. These emerging connections may bring new considerations into AMS programs, including the need to tailor antibiotic exposures based not only on clinical efficacy and AMR but also on collateral and personalized impacts on the microbiome (118). Although it is difficult to predict and quantify these potential unintended positive consequences of reduced AMU, these are important factors to consider when prioritizing AMU-focused AMR mitigation initiatives.

Cost

In human health, the balance of evidence indicates that AMS programs and AMU reductions result in net financial savings across various local healthcare settings (119–122), as well as nationally (123). Within veterinary medicine, relatively scant data exist with which to assess cost-related outcomes (124–126). Furthermore, antimicrobial drug and direct patient healthcare costs represent only a fraction of the true costs associated with AMU and AMS interventions (127). The removal of antimicrobial drugs from healthcare and livestock production systems necessitates a concerted effort to replace those drugs with other compounds and to modify management and behavioral practices to better prevent and control disease. This more comprehensive definition of cost includes many understudied components that have not typically been incorporated into assessment of AMS and AMU programs.

One major cost of the drastic AMU reductions experienced in animal agriculture has been the imperative to replace antibiotics with other, equally efficacious health management strategies—some of which are believed to exist but then fail to achieve similar levels of performance as the antibiotics they are meant to replace. For instance, there is a solid scientific basis for efficacy of bacterial and viral vaccines in animal populations as alternatives to antimicrobial consumption (128, 129). However, even currently available veterinary vaccines often fail to meet appropriate efficacy, safety, and/or usability expectations (129). Researchers are responding to this need by rapidly developing novel delivery systems, vectors, combinations, and adjuvants (130). The

magnitude of effect of these novel vaccine systems compared with antimicrobials tends to be variable, smaller, and unable to recapture the research and development costs (131). Further, livestock producers and production companies bear the costs of these disease management strategies, including vaccines, and often the cost of the vaccine can exceed the cost of an antimicrobial capable of preventing the same disease. If we wish to supplant antimicrobials with other disease prevention options that could reduce overall AMU, then there has to be a clear return-on-investment benefit for the companies and producers implementing these measures (132). The development of new antimicrobials, vaccines, or other alternatives is slow and costly, and therefore not necessarily a priority for research and development in the private sector. Indeed, many companies have abandoned development of antimicrobial therapies altogether owing to high costs and lack of financial incentives; these failed efforts have their own costs, which are seldom included in the cost calculation associated with AMU reductions. Building a sustained incentivization structure to overcome these market barriers will also come at a cost (132).

An important component of any intervention is the ability to monitor its impact on a continuous basis and make appropriate adjustments. For AMU and AMR, this capability hinges on the existence of quality, standardized, and interconnected surveillance and diagnostic systems. Presently, these systems are best characterized as a vast patchwork of initiatives, only some of which are interconnected. For example, 66 countries self-report data to the Global Antimicrobial Resistance Surveillance System for human samples (133), representing a small number of isolates from limited surveillance sites. There is no comparable global system for livestock-associated AMR and AMU. Europe and North America maintain integrated frameworks to track AMR isolates from humans and/or animals (134, 135), though these efforts do not always include collection of AMU data. Among LMICs, only one nation currently reports surveillance data on animal-related AMR (136). For surveillance in humans and animals, many nations lack effective laboratory infrastructure and the means to curate and share microbiological and clinical data (137). This existing gap is at risk of widening given the rapid shift to genomic-based data in North America and Europe. Therefore, the long-term success of AMS programs hinges on substantial financial investments in global capacity building for monitoring and diagnostic systems. These costs, although critical to implementation, are not always explicitly included in discussions of AMU restrictions and AMS programs.

Similarly, implementing comprehensive AMS programs under the One Health framework necessitates considerable investments in national veterinary medical systems and complementary animal health programs to safeguard animal welfare and food security during the transitionary period. Furthermore, successfully changing AMU practices requires intensive resources for training and retraining of veterinary medical professionals, farmers, and producers and for instituting new clinical AMU protocols across diverse fields of practice and production. These costs are not easily absorbed by the veterinary medicine and animal health fields, which remain immensely underfunded compared with the human healthcare and biomedical research sectors (42, 138). Though there is broad agreement on the need for collaboration between human and veterinary medicine to combat AMR, the imbalance of funding greatly constrains available options within veterinary medicine and livestock production—despite efforts by government, private industry, and academic institutions to maximize available funds through innovative partnerships and initiatives (139, 140).

CONCLUSION

Broadly speaking, AMU interventions have fallen into two categories: first, top-down, blanket restrictions on entire drug classes or use scenarios, and second, participatory, targeted reductions for

specific diseases, host subpopulations, or use scenarios. In general, the former category of interventions has been imposed on the livestock sector, whereas the latter category has been implemented in human healthcare settings. Experience suggests that nontargeted restrictions are the simplest to implement using a top-down and/or market-driven approach. However, it must be noted that these types of interventions are also the most likely to cause unintended damage, the least ethically feasible, and the least likely to translate well across contexts (141). On the flip side, targeted interventions implemented through careful, stepwise, and continuous monitoring programs are the most feasible and the least likely to have negative unintended consequences. Unfortunately, the efficacy of such narrow interventions in reducing AMR risk is questionable based on available evidence, particularly within a short-to-medium timeframe.

Furthermore, it should be clearly stated that AMU-centric interventions are implicitly targeted at AMR dynamics within microbial populations. Because antibiotic drugs exert their effects at the microbial level, there is little inherent biological support for the notion that AMU reductions can directly impact AMR transmission (**Figure 1**). Here, the delineation between intra- versus interhost AMR dynamics is crucial, as the causal and mechanistic processes at play are qualitatively different (142). This point is especially salient given emerging evidence that interhost AMR transmission is a predominant driver of AMR risk in many situations. These emerging threads of evidence have prompted calls for a renewed focus on public health infrastructure, sanitation systems, and governance as potent drivers of AMR (143).

Despite the large uncertainty surrounding the efficacy of feasible AMU reductions, numerous stakeholders continue to place much effort and resources into AMU-focused initiatives (64). Unfortunately, as presented here, mounting evidence suggests that AMU may be acting as a red herring in efforts to combat AMR. This is especially true if AMU continues to be conflated with AMR and if evaluative efforts continue to declare success based on measurement of the intervention (e.g., AMS programs to reduce AMU) instead of the outcome (i.e., AMR). If these trends continue, we will lose a valuable opportunity to fill critical knowledge gaps and to truly advance our understanding of the indirect yet mechanistic connections between AMU and AMR. In a worst-case scenario, we will have exhausted available resources (both monetary and otherwise) without meaningfully reducing AMR risk and without advancing our ability to prioritize interventions using evidence-based weighting of competing and complementary factors. This would be a tragic wasted opportunity given the immense attention currently focused on AMR across sectors.

The need for a systematic prioritization schema is even more urgent given the desire to integrate LMICs into global AMR control efforts. The ultimate efficacy of AMR mitigation efforts is driven largely by national, regional, and contextual circumstances, and such variability is likely to increase as AMR control efforts expand to include LMICs (84). Recent studies of AMR dynamics in LMICs and non-LMICs have already demonstrated that governance, sanitation, and public health infrastructure are more likely to impact AMR than antibiotic consumption rates (17, 64), leading some to suggest that mitigating AMR dissemination and spread will be a more fruitful endeavor than reducing AMU (17). These early observations portend an urgent need to expand and customize AMR mitigation efforts and to support programs that may not even include AMU or AMS initiatives.

The time is ripe for a reframing and expansion of AMR control efforts. Recent advances across the social and life sciences are primed to support a systematic and comprehensive evidence-based reevaluation and reprioritization of AMR mitigation initiatives. Based on a growing body of evidence, we foresee a continuing yet less central role for initiatives that target AMU and, concurrently, a growing and more central role for interventions that target and/or exploit fundamental dynamics of microbial ecology and evolution (142, 144–147).

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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