

Impact assessment of risk management interventions

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Summary

Much effort has been invested in the development and implementation of international recommendations to manage the risk of foodborne antimicrobial resistance, and monitoring programmes to measure bacterial antimicrobial resistance and antimicrobial product volumes. A variety of approaches have been recommended for various stakeholders in the food animal and food production sectors. Interestingly, much less consideration has been given to the establishment of success criteria for the individual interventions and even less for the cumulative effects, when all interventions are considered together as consecutive 'hurdles' along the food chain. The author explores the outcome and unforeseen consequences of these various interventions and appropriate methods that could provide data to assess their impact, as well as key learning experiences that should lead to refinements of such interventions in the future.

Keywords

Animal – Antibiotic – Food – Human – Monitoring – Resistance – Risk – Usage.

Goals of responsible use guidelines

The Codex Alimentarius Code of Practice for the responsible use of antimicrobials and the World Organisation for Animal Health (OIE) *Terrestrial Animal Health Code (Terrestrial Code)* (Chapter 6.9.) contain guidelines for the responsible use of antimicrobial drugs in food-producing animals that include recommendations intended to prevent or reduce the selection of antimicrobial-resistant microorganisms in animals and humans, in order to:

- protect consumer health by ensuring the safety of food of animal origin intended for human consumption
- prevent or reduce, as far as possible, the direct and indirect transfer of resistant microorganisms or resistance determinants within animal populations and from food-producing animals to humans
- prevent the contamination of animal-derived food with antimicrobial residues which exceed the established maximum residue limits
- comply with the ethical obligation and economic need to maintain animal health (6, 27).

These global objectives are to be achieved by various stakeholder organisations and authorities implementing risk management interventions at the national or regional level. To assess the impact of these interventions, we must carefully define the specific actions for a stakeholder group, the criteria for success and the means to measure impact, as well as noting unintended consequences. It is appropriate to consider the outcome of a particular intervention but, more importantly, it is necessary to evaluate the totality of risk management interventions to achieve the global objectives. It is also worthwhile considering refinements to the fundamental risk management interventions, at the global level, to make better use of the lessons learned and experience obtained with national or regional interventions.

Risk management options

Overview

Table I provides a high-level overview of the antimicrobial resistance (AMR) risk management recommendations made by a World Health Organization (WHO) consultation (25), by the OIE within the *Terrestrial Code* (27), and by a Codex Alimentarius committee (4, 6). There is much

similarity among these recommendations, which are directed to various stakeholders within the food chain for action within their own organisations. The responsible use guidelines encompass regulatory authorities, veterinary pharmaceutical companies, distributors, veterinarians and producers.

Regulatory authorities

Regulatory authorities are directed to develop regulatory risk assessment guidelines that match approval conditions and product-label directions for use to the proportionate

level of risk for a particular antimicrobial product. To accomplish this, the OIE *Terrestrial Code* provides a general risk assessment pathway, as further clarified by Vose *et al.* (24). So far, only a few countries have implemented this intervention. Within the 'consequence' component of the regulatory risk assessment, national authorities have categorised antimicrobial classes on the basis of perceived importance to human disease treatment within their countries. A joint Food and Agriculture Organization/OIE/WHO (FAO/OIE/WHO) consultation has generated a comparison of antimicrobials that were ranked for importance to both human and veterinary

Table I

General recommendations from the World Health Organization, the World Organisation for Animal Health (the OIE) and Codex Alimentarius to minimise and contain antimicrobial resistance (4, 6, 25, 27)

Intervention	Stakeholder/description	Outcome of intervention	Unforeseen consequence of intervention
Responsible use guidelines – direct stakeholders to take actions within their organisations	Regulatory authority	National regulatory guidance for antibiotic approvals based on OIE approach (24, 27) in only a few countries Ranking of antibiotic importance (11)	Injectable antibiotics viewed as preferable to orally delivered products, thereby limiting commercialisation approaches Ranking connotation now employed beyond original purpose and is applied to formularies, regulatory evaluations and public debate, resulting in bias against use for certain antibiotic classes Interpreted differently by regulatory authorities in each region
	Veterinary pharmaceutical industry	Codex guidelines for antibiotic approvals applied (22,23) Compliance with new guidance requires additional investment Limitation of label indications and restrictions on use Alternatives to antibiotics emphasised	Negative business incentive for novel antimicrobial commercialisation likely to shift industry towards other product opportunities, which means no or few new antibiotic classes (18)
	Distributors	Unknown, but likely to vary within each country due to national situation	Complicated by financial and market access considerations with supplier veterinarian, producer, and pharmacy or feedmill; as well as prescription or over-the-counter status
	Veterinarians	Clinical practice guidelines, regional and national (1, 9, 28), written and in implementation phase Veterinarians need to dedicate more time to implementation in their practices	Additional veterinarians needed Regulatory restrictions on antibiotic use limit veterinarians' ability to meet animal health and welfare needs
	Producers	Antibiotic use guidelines and good production practice documents, written and in implementation phase (AVMA-CVM)	Producers selling to food companies that have strict corporate antibiotic use policies drives production practices
Food hygiene	Codex Food Hygiene documents as listed in (7)	Reduced contamination of foods, including the subset of antimicrobial-resistant (AMR) microorganisms	Focus on AMR microorganisms may divert attention from susceptible population
Legislative	National or regional legislative approaches	Elimination in Europe of performance indications for antibiotics in feed Some countries are working on prescription legislation or restrictive measures for antibiotic indications	Minimal decrease in human foodborne AMR bacterial disease (10) Conflict between legislative and regulatory agencies

medicine at the global level, to assist in prioritising the work to be undertaken within Codex 'Guidelines for risk analysis of foodborne antimicrobial resistance' (GL77) (7, 11). The effectiveness of regulatory risk assessment for product approval and label directions is difficult to assess. While products have been approved, with specific label indications and directions for use (or restrictions) to guide the veterinarian in clinical practice, and thus provide for animal health and welfare needs, the outcome, in terms of AMR containment, remains unclear. One unforeseen consequence is that injectable antimicrobial products are now viewed as preferable to orally administered products, which may limit commercialisation opportunities for the veterinary pharmaceutical industry, as well as deprive veterinarians of new tools to meet animal health and welfare needs. Another unforeseen consequence of categorising antimicrobial classes is that there is a negative connotation for human health implications associated with the 'critically important' status, which has now been applied to formulary listings, regulatory evaluations and public debate, resulting in bias against the use of antimicrobials from this group. Other regulatory approaches are embodied in Veterinary International Cooperation on Harmonization (VICH) Guideline 27, which is a general evaluation (not a risk assessment) of the potential for antimicrobial resistance to be selected by a particular product (22). This has been the main approach taken in Europe by the Committee on Veterinary Medicinal Products (CVMP) for new antimicrobial regulatory reviews. In addition, VICH Guideline 36 provides an outline of studies that enable authorities to establish a microbiological average daily intake (ADI) value, which supports food safety by limiting residue ingestion by consumers (23). Although harmonisation of these VICH guidelines has been achieved, there are sometimes differences in the regulatory authorities' interpretation of the data.

Veterinary pharmaceutical industry

The veterinary pharmaceutical industry has a responsibility to provide the regulatory authorities with appropriate data to enable them to make their decisions. This requires additional investment to generate the necessary data. The approved label frequently has limitations on its use, especially for antimicrobial agents that are ranked for higher importance to human medical use. While research on alternatives to antibiotics is recommended, commercialisation challenges have surfaced with new technologies that may require new regulatory guidance to be developed. Thus, the net outcome for companies is that it is possible to obtain approvals for new indications within existing antimicrobial classes, but there may be a longer-term shift of research investment into non-antibiotic product opportunities and away from infectious diseases (18).

Distributors of antimicrobial products

Distributors of antimicrobial products have a role to play as regards supply to veterinarians or other authorised users. The issue of over-the-counter access *versus* prescription access complicates the matter, as does the relationship between the manufacturer and veterinarian, producer, pharmacy or feedmill. This remains a complicated area, still in need of attention.

Veterinarians were asked to develop clinical practice guidelines and this has largely been accomplished. At the global level, the World Veterinary Association has written such guidelines, with regional guidelines available in Europe, and a variety of national veterinary organisations are doing the same (1, 9, 28). Implementation is ongoing in many countries. While these clinical practice guidelines have been said to increase awareness of the appropriate use of antibiotics, specific measures of compliance or other objective data are difficult to obtain at a national level. One unforeseen outcome has been to identify the need for additional food animal veterinarians, particularly in remote areas. Moreover, as antimicrobial product labels become more restrictive, veterinarians are likely to become more limited in their ability to meet animal health and welfare needs.

Food animal producers

Producers, specifically those who raise food animals, were given responsibility for minimising disease outbreaks on their premises and for abiding by appropriate production practices that ensure the health and welfare of their animals. As this objective is closely related to veterinarian clinical practice guidelines, one national programme directed at producers specifies that some actions should be conducted in close association with animal health specialists (21). Implementation by local producers is dependent on many factors, making compliance a matter of strategic priorities on a case-by-case basis. In general, there has always been a desire to minimise disease on the farm because it reduces profitability and compromises animal health and welfare. However, the paradigm has now shifted to employing alternatives to antibiotics to prevent disease and using antimicrobial products only in at-risk or clinically ill animals. One unforeseen consequence for producers has arisen from food companies or retailers that have developed strict corporate antibiotic use (or non-use) policies that now dictate production practices.

Food hygiene sector

Codex has recently approved guidelines for risk analysis of foodborne antimicrobial resistance. These contain many risk management interventions which should be chosen and implemented on the basis of a risk assessment estimation of their potential effectiveness (7). All of the

interventions mentioned above are included as options. It is necessary to highlight the many food hygiene codes and recommended practices that can be applied, which contribute to minimising foodborne contamination by microorganisms, without regard to their antimicrobial resistance status. An overemphasis on minimising AMR foodborne contamination of food products may divert attention from minimising the pan-susceptible populations of pathogens which also cause foodborne illness.

National veterinary medicine legislation

Although not specifically mentioned as a stakeholder in the Codex, WHO or OIE documents, governments possess law-making authority to mandate specific actions. To this end, some countries are drafting veterinary prescription legislation to enable future responsible use of antimicrobials whereas, in other countries, legislation is proposed that will restrict the use of certain antimicrobial products or indications. An unforeseen effect of the legislative approach to antimicrobial-use restrictions in particular food animal species has been an increase in therapeutic antimicrobial use, due to increased disease, with only an equivocal impact on human AMR foodborne disease. Moreover, in some countries, a certain amount of overlap is seen between regulatory agencies that work within their own procedures and proposed legislative approaches that mandate a particular action.

Evaluation of risk management measures

Approaches

The effectiveness of AMR interventions can be evaluated, in part, by AMR monitoring and antibiotic use sales data or foodborne disease surveillance, as outlined in Table II

(10, 13, 26, 27). These have generally been considered as risk management interventions; however, this type of survey data is most appropriately applied to evaluating the effectiveness of specific activities (6). This can range from trends in AMR over time to changes in antimicrobial usage or sales. Foodborne disease surveillance trends are becoming available but attribution to specific commodities and practices remains a challenge. In reviewing the many AMR risk management interventions that have been described, surprisingly there are no specific success criteria attached to them before implementation (e.g. a reduction in resistance to a particular antibiotic in a specific bacterial type associated with a given animal species or a decrease in human cases of AMR bacterial foodborne disease associated with consumption of a particular food). Perhaps this is due to an incomplete cause and effect association between the action and the measured result, which becomes more difficult as the epidemiologic distance between the farm and patient increases? Thus far, an outcome determination has been generally left to national authorities as a retrospective exercise. This has led to declarations of success being shifted from the original objective of reducing the prevalence of human foodborne bacterial resistance to a reduction in the prevalence of such bacteria in food animals. The key lesson here is that it is necessary to define both the specific actions to be taken by a stakeholder as well as the agreed criteria for success and the means to measure the effect.

Although not mentioned as components of the evaluation approach, other measurements appropriate to the interventions should also be described. For example, veterinarian education on clinical practice guidelines could be documented or records of antibiotic use on the farm could be summarised.

Impact assessment of risk management action

The best known risk management action taken to date is the 1999 discontinuation of performance uses of

Table II
General methods to assess effectiveness of antimicrobial resistance interventions

Method to assess effectiveness	Description	Output data expected	Reference
Antimicrobial resistance monitoring	National bacterial isolate acquisition, susceptibility testing and reporting programmes	National or regional reports on cumulative susceptibility testing results, preferably with minimum inhibitory concentrations and context data Microorganism categories include animal pathogens, zoonotic and commensal (indicator) bacteria with connection to particular animal classes of origin	27
Antibiotic sales/use data reporting	National data on antibiotic classes sold or used in a country	Amount of bulk drug sold or estimated use as calculated by various means (e.g. defined daily dose) Generally presented on antibiotic class basis	13
Foodborne disease surveillance	National data on reportable diseases	Primarily salmonellosis and campylobacteriosis are of interest Typically not connected to susceptibility testing	10, 26

antimicrobial agents in feed in Europe, beginning with tylosin, virginiamycin, bacitracin, spiramycin and avoparcin. The basis for the legislative mandate was the precautionary principle, not risk assessment (12). Of the four remaining antimicrobial products that were in use from 1999 to 2006, none was medically important or used in human medicine (avilamycin, flavomycin, narasin or monensin) and no evidence has been presented that there was a risk to human health. A review by Phillips in 2007 raised questions as to why removing performance uses in food animal production did not, as expected, decrease the prevalence in the EU of antibiotic-resistant human enterococcal infections, which were already of low prevalence, even in 1997 (17), yet did result in an unforeseen increase in animal disease and subsequent therapeutic antibiotic use (2).

In contrast, a successful example of reducing the need for antimicrobial use by decreasing disease outbreaks in Norwegian aquaculture illustrates an alternative approach

(14). Through a combination of innovative vaccine production, vaccination strategy and changes in production systems and management, made possible by the collaborative approach of key stakeholders, a significant reduction in antimicrobial use and increase in production was achieved in a short period of time. The downside is that the minimal use of antimicrobial agents has also limited the attractiveness of introducing new products into the marketplace.

A vision for the future

Finally, it is valuable to consider refinements to fundamental risk management interventions at the global level, to make fuller use of the learning and experience obtained to date with national or regional interventions. Table III proposes several approaches and their potential impacts. The One Health initiative is intended to foster

Table III
Proposals for a global approach to antimicrobial resistance interventions

Global approach	Description	Potential impact	Reference
One Health	Initiative to increase communication and exchange key learning across veterinary and human medical sectors	Recognition by veterinarians and physicians that their common One Health goals can be achieved more effectively by improved communication and collaboration. This could extend to research on novel antibiotics or other interventions, clinical practice guidelines, etc.	15
Codex Alimentarius	Implementation of Codex GL77 (7)	Reductions in foodborne AMR microorganism contamination of food products resulting from selected risk management interventions	7
Consensus on AMR-monitoring data	Harmonisation of AMR-monitoring methods, reporting and interpretation	Harmonised susceptibility testing methodology applied to representatively collected isolates will provide a common basis for reporting MIC data for comparison across time and geography. A common basis for interpreting the data, appropriate to the objective, will facilitate risk communication	3, 27
Consensus on monitoring of sales/use data	Harmonisation of monitoring methods for antibiotic sales and/or use data, reporting and interpretation	An agreed methodology for data collection and reporting will provide a common basis for comparison across time and geography, with other possible parameters included. A common basis for interpreting the data, appropriate to the objective, will facilitate risk communication	27
Clinical practice guidelines	Extend EPRUMA or adapt WVA guidelines to other regions and nations	May increase awareness and practice of appropriate antibiotic use guidelines by veterinarians in as many geographic regions as possible. Would provide a basis for veterinary school and continued education programmes	9, 28
Clearer clinical outcome data for AMR foodborne disease impact	Develop medical consensus on public health significance of antibiotic use and effectiveness in patients with campylobacteriosis or salmonellosis caused by susceptible compared to resistant isolates; intestinal illness compared to systemic illness	Would provide evidence-based information to guide antibiotic importance rankings for certain antibiotic classes, with application to regulatory risk assessments and to improve physician diagnosis and antibiotic use in patients	8, 20, 19
Regulatory harmonisation on AMR risk assessment for product approval	Explore potential for a global antibiotic regulatory risk assessment methodology and interpretation	Consensus approach could lead to increased efficiency of data submission, review and speed of marketing in multiple regions	

AMR: antimicrobial resistance

MIC: minimum inhibitory concentration

EPRUMA: European Platform for the Responsible Use of Medicines in Animals

WVA: World Veterinary Association

common ground for veterinarians and physicians, particularly with regard to zoonotic disease (15). Increased communication and shared learning between the sectors might result in more effective implementation of risk management interventions or disease prevention, to name but two areas. The implementation of Codex GL77 is only beginning. However, it is recognised that not all countries currently have the infrastructure necessary to undertake all aspects; thus, capacity building may initially be required. This document has the potential to guide appropriate risk management interventions with clearly established success criteria and measurement tools. Antimicrobial resistance monitoring remains an important tool; however, the potential for harmonising antimicrobial susceptibility testing methodology applied to representatively collected isolates to allow data to be compared across time and geography will greatly facilitate reporting and communication (3).

Similarly, a consensus on or harmonisation of methods to obtain, analyse and report antimicrobial product use or sales data is proposed, perhaps along the lines of the OIE *Terrestrial Code* or other means (13, 27). Successful development of clinical practice guidelines has generated interest in extending such guidelines to other countries or regions, with the goal of increasing veterinarian awareness and the implementation of appropriate practices for antibiotic use, as well as providing a basis for veterinary school or continuing education programmes. Although there is a perception that certain antibiotics are less effective against AMR bacterial foodborne disease, the literature sometimes suggests otherwise (19, 20). Since the consequence component of regulatory risk assessments and antibiotic importance-ranking criteria assume this to be the case, it would be a valuable contribution to develop medical consensus on the public health significance of antibiotic use and clinical effectiveness in patients with campylobacteriosis or salmonellosis (especially intestinal *versus* systemic disease). A variety of comparisons might be explored, depending on the data available, such as outcomes for susceptible *versus* resistant isolates, since being categorised as resistant does not always result in clinical failure (8). A global consensus approach to

regulatory risk assessment methodology and interpretation might be explored. If achieved, such a guideline could lead to increased efficiency of data submission by veterinary pharmaceutical companies, more predictable regulatory reviews and increased speed for marketing in multiple regions. It could also offer a means for assuring capacity-limited nations that the product has been appropriately evaluated.

Given the multiple risk management interventions that are either ongoing or planned, one of the most important measures we can take for the future is to ensure that, early on, risk managers ask the question, 'what does success look like?' Actions taken only against a particular antibiotic or route of use may result in collateral effects that increase problems in other sectors or for other antibiotics, as seen with the performance indication prohibitions in Europe. If the goal of risk managers is to 'restore' foodborne pathogens' susceptibility to antimicrobials by restricting on-farm antimicrobial use, then they need to consider the possibility that the prevalence of foodborne pathogens will not necessarily be reduced nor human disease decreased. Perhaps a better way to proceed is to take a holistic view of how each of several proposed interventions will contribute to the overall objective or 'success', rather than conducting an evaluation of each intervention as a stand-alone action. If the goal is to reduce foodborne disease, including that associated with AMR pathogens, then implementing responsible-use programmes on-farm and simultaneously improving food hygiene practices in food processing would make it more attainable. To accomplish such an evaluation, appropriate and harmonised measurement tools are needed, in conjunction with a spirit of collaboration and improved communication among all stakeholders along the food chain. ■

Évaluation de l'impact des interventions en matière de gestion du risque

T.R. Shryock

Résumé

De grands efforts ont été déployés pour concevoir et mettre en œuvre au plan international des recommandations visant à gérer le risque d'antibiorésistance d'origine alimentaire et pour mettre en place des programmes de suivi destinés à évaluer la résistance des bactéries aux agents antimicrobiens et les quantités d'antimicrobiens utilisées. Plusieurs types d'approche ont été recommandés, s'adressant aux différents acteurs du secteur de la production d'animaux destinés à l'alimentation humaine et aux intervenants de la chaîne de production agro-alimentaire. Fait intéressant, on accorde beaucoup moins d'importance à la mise en place de critères de réussite qualifiant les interventions individuelles, et encore moins aux effets cumulés de celles-ci, lorsque l'ensemble des interventions est considéré comme une série d'« obstacles » consécutifs tout au long de la chaîne alimentaire. Après avoir examiné les résultats et les conséquences imprévues de ces différentes interventions, ainsi que les méthodes appropriées permettant de réunir les données nécessaires à l'évaluation de leur impact, l'auteur tire les leçons fondamentales qui doivent en être tirées afin d'améliorer ces interventions à l'avenir.

Mots-clés

Animal – Antibiotique – Denrée alimentaire – Être humain – Résistance – Risque – Suivi – Utilisation



Evaluación de los efectos de las intervenciones de gestión del riesgo

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Resumen

Se han dedicado grandes esfuerzos a elaborar y aplicar recomendaciones internacionales de gestión del riesgo de antibiorresistencias transmitidas por vía alimentaria, así como programas de control para cuantificar la resistencia a los agentes antimicrobianos y los volúmenes de esos productos. Se han recomendado distintos métodos a las diferentes partes que intervienen en los sectores de la cría de animales de consumo humano y la producción alimentaria. Resulta interesante que se haya prestado mucha menos atención a definir criterios para evaluar el éxito de intervenciones concretas, y todavía menos los efectos acumulativos cuando se considera el conjunto de intervenciones como una serie de 'obstáculos' sucesivos que jalonan la cadena alimentaria. El autor examina los resultados y las consecuencias imprevistas de esas diversas intervenciones, los métodos adecuados para obtener datos que sirvan para evaluar su repercusión y las principales experiencias de las que cabría extraer enseñanzas para perfeccionar tales intervenciones en el futuro.

Palabras clave

Alimento – Animal – Antibiótico – Control – Humano – Resistencia – Riesgo – Utilización.



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