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Integrating animal health surveillance and food safety: the issue of antimicrobial resistance

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Summary
Surveillance of antimicrobial resistance in commensal, zoonotic and pathogenic bacteria from humans, animals and food is an essential source of information when formulating measures to improve food safety. International organisations (the World Health Organization, the World Organisation for Animal Health, the Food and Agriculture Organization of the United Nations, and the Codex Alimentarius Commission) have developed a complete set of standards related to resistance surveillance programmes and are calling for the establishment of integrated surveillance programmes. The most important task in establishing an integrated surveillance programme for antimicrobial resistance should be the harmonisation of laboratory testing methodology and antimicrobial-use reporting.
Over the last decade, the integration of surveillance of antimicrobial resistance has been an important step toward addressing the global concern with antimicrobial resistance. However, very few systems are in place and there is still a lot to do before harmonised surveillance systems become the norm.

Keywords
Antimicrobial resistance – Integrated human/animal monitoring – Surveillance – Usage.

Introduction

Antimicrobial-resistant populations are present everywhere in all bacterial communities. Their expansion follows complex pathways through environmental systems, people, animals, food and water (15, 28, 29).

Surveillance of antimicrobial resistance (AMR) in commensal, zoonotic and pathogenic bacteria from humans, animals and food is an essential source of information when formulating measures to improve food safety and detect new problems and possible outbreaks. Surveillance data are also necessary to follow policy decisions and to assess and validate their results.

In order to be able to use and interpret these data, an integrated approach is necessary. This type of approach involves several sectors: public health and healthcare organisations, food animal production, food processing and distribution. The integration of their results requires a harmonisation of methodologies and reporting.

Antimicrobial usage/consumption in humans and in animals is considered a driving force in the selection and spread of antimicrobial-resistant bacteria. Data on the consumption of antimicrobials are an important part of an integrated surveillance programme.

Historical perspectives

Interest in monitoring AMR in human pathogens started in the mid-1960s. It was in the 1970s that computers began to facilitate data collection and analysis. A few papers, based on the different systems in place, showed that AMR monitoring in hospitals was helpful. The prescriber, knowing the local rates of resistance, could choose the most appropriate drug for the patient while waiting for laboratory results. Knowing the location of patients with resistant strains was important for those working to control hospital infections. Decisions about empirical treatment and the hospital formulary were more accurate when made using the surveillance data (17, 18).

Over the years, the technical aspects of susceptibility-testing methodologies became more precise and standardised and several systems for analysing the data were developed, but it is not the purpose of this paper to describe them.

The information collected usually concerned: the infecting bacterial isolates (which were sometimes colonising strains), their identity, their susceptibility to each of a set of antimicrobial agents and their resistance pattern (or phenotype). Trends of resistance to each antibiotic tested (i.e. the variation of the resistance pattern, by gain or loss of a resistance marker) were tabulated according to different types of analyses.

In the late 1970s a number of countries started some form of surveillance of resistant bacteria in human infections. Scandinavian countries, the United Kingdom, the United States, France, South Africa, Australia, Thailand and Venezuela were among the earliest.

The need for more useful interpretation for hospitalised patients led to the linking of the quantity of antibiotics used with AMR. Programmes were designed to monitor antibiotic consumption.

The importance of comparing hospitals and expanding the analyses to the community, the city, the country and the region, showed that the harmonisation of the programmes and the data file compatibility across different levels of surveillance were major issues (13, 19). Such integrated and harmonised programmes are in progress in a small number of countries.

Salmonella infections were already being monitored prior to the 1970s. This zoonotic species is responsible for foodborne disease as well as hospital-acquired infections. Its ability to acquire multiple resistance determinants was recognised in the mid-1960s (2). In 1969, the Swann report raised concerns about resistance to antibiotics that were used both as a treatment for human patients and as growth promoters in animals, and stressed the importance of considering the public health consequences of this double usage (14, 15, 26).

No surveillance of animal bacteria was started until the mid-1980s. The study on nourseothricin showed that the mechanism of resistance selected in animal bacteria could be transmitted to human bacteria (10). The studies on vancomycin-resistant enterococci in animals receiving avoparcin were critical to the discussion about the transfer of resistant bacteria and antibiotic usage in animals and in humans (12, 30).

After this, surveillance of antimicrobial-resistant bacteria in food animals, especially bacteria that are transmitted via food and able to cause serious infections, was started in some countries, initially in Scandinavia. Surveillance systems have since been extended in some countries to include animal pathogens and commensal indicator bacteria (15).

Sampling retail foods is part of the integrated monitoring of foodborne antimicrobial-resistant bacteria. The National Antimicrobial Resistance Monitoring System (NARMS) in the United States, which was established in 1996, is a good example of such surveillance (7, 27).

In 1998, the Pan American Health Organization, meeting in Venezuela, recognised the need to monitor AMR and 'to use the information generated for therapeutic, regulatory, and political decision-making' (20). In that same year, the European Antimicrobial Surveillance System (now known as the European Antimicrobial Resistence Surveillance Network) was established to monitor AMR in major pathogens (16).

The European Surveillance of Antimicrobial Consumption project (now known as the European Surveillance of Antimicrobial Consumption Network) was established in 2001 by a group of 32 countries.

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched in 2009 with a first retrospective study concerning nine European countries. In 2012, it published a report giving harmonised sales data for 2010 in 19 countries of the European Union and the European Economic Area (5, 6, 8).

It took almost 40 years for AMR to become the global concern that it is today. At first, only limited local information on bacterial resistance was available and the problem did not receive the attention it deserved. During the last decade, AMR has been recognised as a priority and efforts have been made to bring together those who prescribe antibiotics, and those who study resistant bacteria, to share their practices and their information.

Much is still unknown about how the use of antibiotics is linked to the emergence and spread of resistance.

Contribution of international organisations

In 1997, considering the growing importance of AMR at a worldwide level, the World Organisation for Animal Health (OIE) decided to develop a complete set of standards related to resistance surveillance programmes. These standards are contained in chapters of the OIE *Terrestrial Animal Health Code*:

– Chapter 6.7.: Harmonisation of national antimicrobial resistence surveillance and monitoring programmes

– Chapter 6.8.: Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals

– Chapter 6.9.: Responsible and prudent use of antimicrobial agents in veterinary medicine

– Chapter 6.10.: Risk assessment for antimicrobial resistence arising from the use of antimicrobials in animals.

These standards were adopted in 2003. The idea of integrated systems was present in the chapter on monitoring antimicrobial usage: 'Member Countries may wish to consider, for reasons of cost and administrative efficiency, collecting medical, food animal, agricultural and other antimicrobial use data in a single programme. A consolidated programme would also facilitate comparisons of animal use with human use data for relative risk analysis and help to promote optimal usage of antimicrobials' (38, 39). Around the same time, the World Health Organization (WHO) published the 'WHO Global Strategy for the Containment of Antimicrobial Resistence' (31, 32).

A number of joint WHO/OIE/Food and Agriculture Organization of the United Nations (FAO) expert consultations were organised in the following years. These consultations, which brought together experts working in different fields, contributed to the idea that there was a need to have coordinated approaches. These consultations were the basis for the recognition of critically important antimicrobials for humans and for animals (35, 36, 37).

They also led to the creation of the Codex Alimentarius *Ad Hoc* Intergovernmental Task Force on Antimicrobial Resistence. This task force, created in 2006, produced 'Guidelines for Risk Analysis of Foodborne Antimicrobial Resistence', which were adopted by the Codex Alimentarius Commission in July 2011 (3).

These guidelines recognise the importance of surveillance programmes that monitor the use of antimicrobial agents and the prevalence of foodborne antimicrobial-resistant bacteria. These programmes are essential for exploring potential relationships between the use of antimicrobials and the prevalence of antimicrobial-resistant bacteria in humans, food-producing animals, crops, food, feed, feed ingredients and biosolids, waste water, manure and other waste-based fertilisers.

The guidelines also recommend that surveillance of AMR in microorganisms originating from food-producing animals, crops and food should be harmonised and ideally be integrated with programmes that monitor resistance in humans.

More recently, WHO created the Advisory Group for Integrated Surveillance of Antimicrobial Resistence to develop tools to support countries in their efforts to implement local programmes of integrated surveillance (33, 34).

The use of antibiotics is central to the problem. Improving antibiotic usage is essential. The goal is to find ways of using antibiotics to adequately treat human infections and protect animal health while at the same time minimising selection for antibiotic resistance. International organisations first began working on this ambitious goal in the 1990s, and over the last 15 years extensive work has been carried out to try to tackle the problem. These efforts are also supported by national and regional organisations and have given rise to a large number of publications.

Possible integrated schemes

Integrated surveillance for AMR is a system whereby information and data originating from different sources are joined together. Depending upon the type of data integrated, those systems satisfy different requirements. The aim may be to:

– follow up and evaluate AMR trends in bacterial species

– explore AMR evolution and link it to causal factors, particularly antibiotic use

– compare the prevalence and trend of resistance, to one or more antibiotics, in bacteria originating from humans and animals

– compare the use of antibiotics in animals and humans

– assemble data for the risk analysis process

– use the data to choose management options and evaluate their results

– identify questions which require further research and surveillance.

When protecting food safety and targeting antimicrobial-resistant bacteria, information is obtained from the integration of the following lines of surveillance (Fig. 1):

a) AMR of foodborne bacteria isolated from diseased humans

b) AMR of bacteria isolated from diagnostic samples from sick food animals

c) AMR of zoonotic bacteria isolated from animals

d) AMR of commensal bacteria isolated from healthy animals

e) consumption of antibiotics in humans

f) consumption of antibiotics in animals

g) AMR of bacteria isolated from retail food meat.

Other information on AMR is sometimes added, e.g. AMR in environmental bacteria, bacteria from vegetables and colonising bacteria in humans. Antimicrobial resistence in aquatic animals might be part of integrated programmes.

The presence of resistant pathogens in water is another issue to consider when carrying out surveillance to protect food from resistant pathogens (11). Water can be consumed as a cooking ingredient or directly as a drink, and is used for cleaning in kitchens. Used water spreads in the various environmental ecosystems with their huge load of bacteria. There is no food safety without clean water and this issue is currently neglected (1).

A considerable effort has been made in Europe to obtain and organise information on antibiotic consumption in humans and food animals and to extract from the data useful parameters and ratios to weight the role of antibiotics as a selector of resistant bacteria. These studies have been accepted in most countries and may serve as guidance to begin antibiotic consumption surveillance programmes.

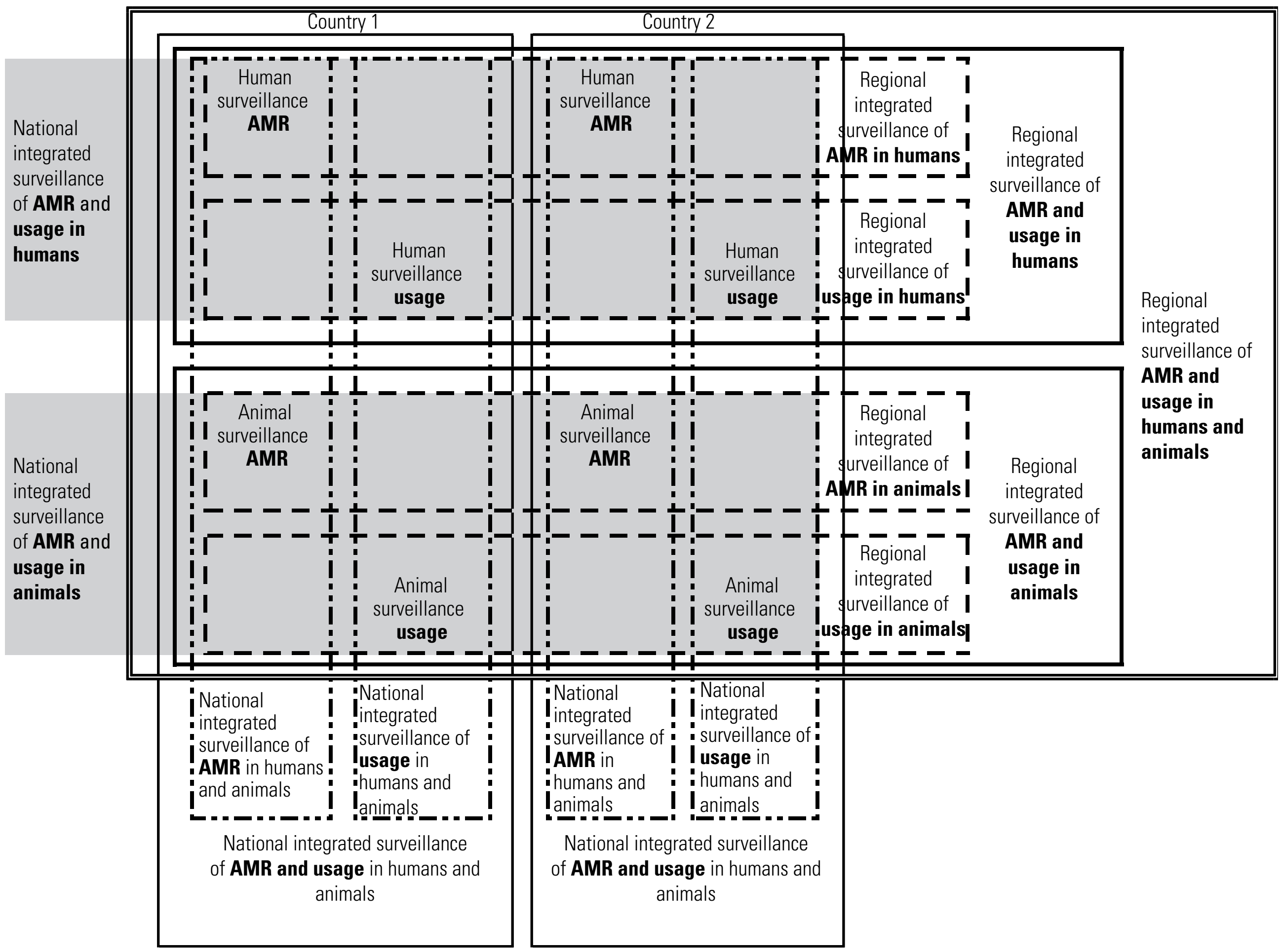

Fig. 1
Possible integrated systems of antimicrobial resistance (AMR)

Technical aspects and challenges

The most important task in establishing an integrated surveillance programme on AMR should be the harmonisation of laboratory testing methodology (23). This will include harmonising:

– the susceptibility method (including quality controls)

– the antimicrobials to be included in the test

– the methods for reading the results, their storage (quantitative data should be preferred: zone size, minimum inhibitory concentrations), their interpretation (break points, cut-off values), the resistance pattern of the strain

– the methods for identification: conventional and molecular for further studies.

The storage of the strains should also be defined and organised.

Harmonising the testing methodology in relation to the standards and the guidance published by the OIE and WHO requires countries to coordinate action between public health infrastructures, competent laboratories, physicians, and veterinarians.

Harmonisation should also be extended to the study population, to the sampling strategy, and to the target microorganisms. The animal samples are taken at different points in the production process. The resistance patterns seen in samples from farms are those that are most directly associated with antimicrobial use. Bacteria isolated from samples collected post slaughter are more representative of those which may survive processing and reach the food supply. Retail meat samples are important in identifying resistant organisms from food animals; however, cross-contamination during handling, processing and packaging is possible.

The target microorganisms include: zoonotic bacteria (salmonellae, *Campylobacter* spp.), commensal bacteria that act as sentinels or indicators (*Escherichia coli*, enterococci) and animal pathogens.

Other bacteria might be included: zoonotic bacteria (e.g. *Staphylococcus aureus*, *Yersinia* spp., *Vibrio* spp.) and animal pathogens. Data on the evolutionary trends of AMR in animal pathogens complete the information given by the surveillance of commensal bacteria. It helps the veterinarian to adjust first-line therapy and use appropriate antibiotics.

The surveillance of antibiotic usage should also be harmonised. This should include, for example, antimicrobial classes reported, the medicinal products covered and the usage indicators used.

Building a sustainable, integrated AMR surveillance programme is extremely challenging. It requires:

– political and financial support

– cooperation between agriculture and public health sectors

– use of the results and risk assessments of hazards

– the creation of alert systems

– a communication policy.

Existing programmes in different countries

Ideally, an integrated surveillance system should include surveillance of AMR and surveillance of antibiotic use in both humans and animals, but few countries have implemented such a system.

Different choices have been made in different countries and regions. Over time, this has resulted in the development of specific systems of surveillance that are designed for a particular country or region at a particular time. When specific surveillance systems are in place, the process of integration requires a lot of effort because the data and results may not be comparable. The process is facilitated if new surveillance programmes are developed with integration in mind and are designed to be compatible with existing systems.

As an example, the ESVAC project for monitoring the use of antimicrobials in animals in Europe was deliberately designed to be compatible with the monitoring of antimicrobial use in humans and surveillance of AMR in commensals and zoonotic bacteria.

When launching an integrated system it is important to bear in mind that the system will have to evolve to face new challenges. Interpretation of the data may need to incorporate elements other than antimicrobial usage, as it is not the only factor involved in the complex phenomenon of the spread of resistant bacteria. The flexibility of the system is important and its compatibility with other systems in the region, essential.

It is difficult to review all existing systems developed in different countries. Most of them lack information on animal bacteria and on antibiotic consumption. In a recent publication, Silley *et al.* reviewed and compared several programmes (24). Some national programmes that are important in the evolving and expanding concept of integrated data and regional comparison are reviewed below.

The earliest programme is the Danish Integrated Antimicrobial Resistence Monitoring and Research Programme. This programme, which was established 18 years ago, inspired a number of the other European programmes which followed (Norway, Sweden, the Netherlands, Germany, France, Italy and Spain). Most European countries now contribute to AMR monitoring organised by the European Food Safety Authority (4).

In the United States, NARMS was established as a partnership between the United States Food and Drug Administration, the Centers for Disease Control and Prevention, and the United States Department of Agriculture. It began in 1995 and is a very large programme.

The Canadian Integrated Program for Antimicrobial Resistence Monitoring Surveillance (CIPARS) is a surveillance programme which was designed very carefully. The creation of CIPARS was based on a 2002 report from the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health that stated that, 'in Canada, as in most countries, the [surveillance] data are fragmentary, often biased, focused on a narrow and variable range of bacterial pathogens, collected in an unsystematic way and not generally compatible between laboratories and/or countries because methods used for testing resistance have not been standardized' (9). This sentence summarises well the challenges that must be faced in creating an integrated system that links data on humans, animals and food.

In Australia, the recommendations of the Joint Expert Technical Advisory Committee on Antibiotic Resistance were implemented in 2000 with a centralised system to integrate the data.

In Asia, the Japanese Veterinary Antimicrobial Resistence Monitoring System started in 1999 and the Korean Nationwide Surveillance of Antimicrobial Resistence was established in South Korea in 1997. The former covered both animals and humans, while the latter was aimed mostly at human pathogens.

Table I lists a number of surveillance programmes that certain countries have implemented. Many countries are following their example and responding to the efforts of the OIE and WHO. They are starting pilot studies or adding other types of surveillance to their existing programmes, or expressing their policy to control AMR in official documents.

Some private-sector programmes developed by the pharmaceutical industry have monitored and compared countries or regions for specific purposes. The European Animal Health Study Centre examines the resistance of animal pathogens. The SENTRY Antimicrobial Surveillance Program examines resistance in human pathogens and has compared results from the United States with results from Europe, Australia and, especially, South America (22).

It is important that global concern for this subject is maintained so as to improve surveillance capacity.

Conclusion

Integrated surveillance of AMR is still not implemented in most countries. It is an ongoing process that extends far beyond food safety to encompass the whole phenomenon of AMR.

It is important to consider some points for the future:

– efforts to harmonise the collection and interpretation of data are essential and must continue (23)

– the surveillance of antibiotic consumption in animals, which is still infrequently considered, deserves to be explored by farmers, producers, veterinarians and pharmaceutical companies to improve the usage of antibiotics for the production of healthy animals and to choose the best practices (8).

Everyone agrees that antibiotics must be used prudently and responsibly, but that improvements still need to be made to optimise treatments in humans and animals and to minimise inappropriate usage. Surveillance of AMR is an invaluable instrument in many areas: epidemiology, therapeutic decision-making, basic research, molecular tracking, animal health and food safety (19, 21).

There is increasing widespread concern about the ever-greater number of resistant pathogens in human infections, the spread of the resistant bacteria within and outside countries, the lack of new antibiotics for humans and animals and the difficulties in treating infectious conditions caused by multidrug-resistant organisms. The practices of the pharmaceutical industry and certain professions (e.g. physicians and veterinarians) are suspected to be partly responsible for the emergence of resistant bacteria. However, the complexity of the resistance phenomenon must be considered to avoid passionate or hasty conclusions. Countries should be prepared to enter into debate and face controversies. The numerous gaps in our knowledge of the evolution of the mechanisms of AMR are the main topic of discussion, as sometimes this lack of understanding can lead us to the wrong conclusions.

Moreover, communications between research disciplines, practitioners and decision-makers should be improved in order to facilitate efficient decisions and actions.

Table I
Examples of programmes for surveillance of antimicrobial resistance in animals, food and humans

Programme	Type of surveillance	Country	Website
National Antimicrobial Resistance Monitoring System (NARMS)	Humans	USA	www.cdc.gov/narms
Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)	Humans, animals and food	Canada	www.phac-aspc.gc.ca/cipars-picra/index-eng.php
Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands (MARAN)	Animals and food	Netherlands	www.cvi.wur.nl/UK/publications/otherpublications/maran/
Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)	Humans, animals and food	Denmark	www.danmap.org
Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM/NORM-VET)	Humans, animals and food	Norway	www.vetinst.no/eng/Research/Publications/Norm-Norm-Vet-Report
European Antimicrobial Resistance Surveillance Network (EARS-Net)	Humans	Multinational [a]	www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx
European Surveillance of Antimicrobial Consumption Network (ESAC-Net)	Humans	Multinational [b]	www.ecdc.europa.eu/en/activities/surveillance/esac-net/pages/index.aspx
Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM)	Animals	Sweden	www.sva.se/upload/Redesign2011/Pdf/Om_SVA/publikationer/Trycksaker/Svarm2011.pdf
Italian Veterinary Antimicrobial Resistance Monitoring (ITAVARM)	Humans and animals	Italy	http://195.45.99.82:800/pdf/itavarm.pdf
The Finnish Veterinary Antimicrobial Resistance Monitoring and Consumption of Antimicrobial Agents report (FINRES-VET)	Animals and food	Finland	www.evira.fi/portal/en/animals/current_issues/?bid=2436
l'Observatoire National de l'Epidémiologie de la Résistance Bactérienne aux Antibiotiques (ONERBA)	Humans and animals	France	www.onerba.org
The Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)	Animals	Japan	www.maff.go.jp/nval/tyosa_kenkyu/taiseiki/monitor/e_index.html
Pilot Surveillance Program for Antimicrobial Resistance in Bacteria of Animal Origin	Animals	Australia	www.daff.gov.au/agriculture-food/food/regulation-safety/antimicrobial-resistance/antimicrobial_resistance_in_bacteria_of_animal_origin

a) 33 European countries
b) 34 European countries

Basic research is needed in a number of areas, and this research should integrate multiple issues. It may lead to new questions. For example, the interpretation of results from integrated antimicrobial surveillance systems may need the development of models. These models may show the importance of other factors that should be taken into account, especially when considering management options.

Research into the integration of genomics and epidemiology would open ways for better local outbreak strategies and more efficient containment (25).

Over the last decade, integrated surveillance of AMR has been an important step toward addressing the global concern with AMR. There is still a lot to do to harmonise surveillance systems and adapt them to the background, social practices and priorities of different countries. Action at the global level and the local level should be complementary.

■

La surveillance intégrée de la santé animale et de la sécurité sanitaire des aliments : le problème de la résistance aux agents antimicrobiens

J.F. Acar & G. Moulin

Résumé

Les informations recueillies lors de la surveillance de la résistance aux agents antimicrobiens des bactéries commensales et zoonotiques pathogènes présentes chez l'homme et les animaux ainsi que dans les denrées alimentaires sont essentielles pour concevoir des mesures visant à améliorer la sécurité sanitaire des aliments. Un ensemble exhaustif de normes couvrant les programmes de surveillance de l'antibiorésistance a été élaboré par les organisations internationales compétentes (l'Organisation mondiale de la santé, l'Organisation mondiale de la santé animale, l'Organisation des Nations unies pour l'alimentation et l'agriculture et la Commission du Codex Alimentarius), qui s'efforcent de promouvoir la mise en place de programmes de surveillance intégrée. La tâche prioritaire lors de l'établissement d'un programme de surveillance intégrée de l'antibiorésistance consiste à harmoniser les méthodes de test appliquées par les laboratoires ainsi que la notification de l'utilisation d'agents antimicrobiens.

Depuis dix ans, la mise en place d'une surveillance intégrée de la résistance aux agents antimicrobiens a constitué une avancée importante dans le traitement du problème lié à l'antibiorésistance au niveau mondial. Néanmoins, les systèmes mis en œuvre sont encore peu nombreux et il reste beaucoup à faire avant que les systèmes harmonisés de surveillance deviennent la norme.

Mots-clés

Résistance aux agents antimicrobiens – Suivi intégré des populations animales et humaines – Surveillance – Utilisation d'agents antimicrobiens.

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Integración de la vigilancia zoosanitaria y la higiene de los alimentos: el problema de la resistencia a los agentes antimicrobianos

J.F. Acar & G. Moulin

Resumen

A la hora de formular medidas para mejorar la inocuidad de los alimentos, la vigilancia de las resistencias a los agentes antimicrobianos en bacterias zoonóticas, comensales o patógenas presentes en personas, animales o alimentos es una fuente básica de información. Varias organizaciones internacionales (Organización Mundial de la Salud, Organización Mundial de Sanidad Animal, Organización de las Naciones Unidas para la Alimentación y la Agricultura y Comisión del Codex Alimentarius) han elaborado un conjunto completo de normas relacionadas con programas de vigilancia de estas resistencias y ahora preconizan la instauración de programas de vigilancia integrada. Al establecer un programa de esta índole, la tarea más importante habría de ser la de armonizar los métodos de prueba en laboratorio y los de notificación de uso de antimicrobianos.

En el último decenio, la integración de la vigilancia de las resistencias a los antimicrobianos ha supuesto un paso importante para responder a la inquietud mundial que suscita la cuestión. Con todo, hay muy pocos sistemas en funcionamiento, y queda mucho por hacer hasta que los sistemas armonizados de vigilancia empiecen a ser la norma.

Palabras clave
Resistencia a los agentes antimicrobianos – Seguimiento sanitario y zoosanitario integrados – Uso de agentes antimicrobianos – Vigilancia.

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