

Quantitative human health risk assessments of antimicrobial use in animals and selection of resistance: a review of publicly available reports

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Summary

Quantitative risk assessments have been conducted to estimate the probability and magnitude of adverse human health effects from antimicrobial use in food animals through selection for antimicrobial resistance in bacteria. The majority focused on licensed antimicrobials under regulatory scrutiny, including growth promoters and agents of critical importance to human health. Most used models to attribute fractions of surveillance-derived estimates of antimicrobial-resistant infections in humans to antimicrobial use in animals. Risk estimates ranged from a few additional illnesses per million at risk, to many thousands. Although useful, published quantitative risk assessments have been unable to comprehensively address important aspects of antimicrobial resistance, including multiple exposure pathways, interrelationships among bacteria, co-selection, and cumulative effects of antimicrobial use in multiple species and countries. However, quantitative risk assessment shows promise for synthesis and analysis of scientific data. Work is required to develop methodology and train more risk analysts. An international forum is needed to pool expertise, review existing risk assessments and disseminate the results to risk managers throughout the world.

Keywords

Antibiotic – Antimicrobial agent – Resistance – Risk analysis – Risk assessment – Risk characterisation.

Introduction

Antimicrobial resistance can adversely affect the health of humans and animals and many steps have been proposed to prevent its further emergence and spread (35). Among these are measures that seek to reduce the selection pressure for resistance by limiting or restricting antimicrobial use in animals, particularly those raised for food. Some actions are voluntary for veterinarians or farmers (e.g. prudent use programmes), while others are regulatory in nature and therefore are imposed on entire countries or regions. Examples of regulatory measures available to national authorities include pre-licensing review of the human safety aspects of antimicrobials intended for use in animals, restrictions on extra-label use of drugs, and bans on the use of drugs previously approved

for certain species or conditions. Given that these actions may in some cases limit the continued availability of certain antimicrobials for use in animals, they are often controversial and frequently met with stiff opposition by some stakeholders, particularly the pharmaceutical industry, practising veterinarians and farmers, while at the same time being vigorously advocated by public health authorities. Despite the controversy, national authorities must make timely and informed decisions concerning the availability of antimicrobials for use in animals, and increasingly there is an expectation that these decisions will be informed, as completely and transparently as possible, by the best available scientific evidence.

Synthesis, analysis, interpretation and reporting of important and relevant scientific data concerning the very complex (and in many ways poorly understood) biology of

antimicrobial use and resistance in bacteria has been challenging. These subjects are addressed in detail in other articles in this volume and elsewhere (15, 24), but it is important to point out that the complex pathways of human exposure (e.g. through food or water) to antimicrobial-resistant bacteria from animals involve many factors and stages, from animal production through transportation, food processing, distribution, national and international trade, and others. The complexity of the farm-to-fork continuum is such that it has been difficult to measure, with certainty, the extent to which antimicrobial use on farms selects for resistance in commensal and zoonotic pathogens in animals, and their subsequent impacts on human health. Traditional approaches to addressing questions of human safety involving hazardous environmental compounds or contaminants (e.g. laboratory animal studies, epidemiological studies of occupational exposure in humans) do not adequately reflect the complex ecosystem of antimicrobial resistance.

Risk assessment emerged several years ago as an approach or framework for providing scientific support to regulatory decision-making in the field of environmental health and protection, where issues of scientific complexity, uncertainty and conflicting interests are common (25). It is one of the three pillars of risk analysis, along with risk management and risk communication (34). In the context of antimicrobial resistance, risk analysis is discussed further elsewhere (6, 33). Essentially, risk managers (the decision-makers; in this context often national veterinary drug licensing authorities) should identify the specific scientific risk questions to which they need answers, and the risk assessors should bring the best science to bear in providing answers, along with expressions of scientific uncertainty.

The purpose of this paper is to review the publicly available quantitative human health risk assessments pertaining to antimicrobial use in animals and antimicrobial resistance, with a view to increasing understanding of their possible role in the development of policy relating to veterinary antimicrobial use, nationally and internationally. Qualitative risk assessments and risk/benefit assessments have also been conducted, but due to space limitations they are not addressed here.

Methodological considerations

The general principles and methodologies of risk assessment (25) and applications to antimicrobial resistance (28, 29, 32, 33) are widely discussed and reported elsewhere. In this context, risk is the probability and magnitude of an adverse health outcome consequent on exposure to a hazard. Typically, hazards are identified and described, exposure of humans is assessed with

respect to routes, frequency, concentration and other factors, and the relationship between exposure to the hazard(s) and adverse health consequences is characterised. There is no universal approach to human health risk assessment. For example, different approaches and methods have been developed for risks associated with chemical hazards found in the environment, for microbiological hazards found in food and water, and for communicable diseases in humans. Risks pertaining to antimicrobial resistance share elements in common with all three of these scenarios. Antimicrobials are of course chemicals, and have long been assessed for risks as chemical residues in foods from animals (30). Moreover, food is considered to be a major exposure route for humans to resistant pathogens and commensals, and resistant bacteria may spread from person to person after acquiring resistance determinants during animal production. Consequently, approaches to risk assessment of antimicrobial resistance involving veterinary drugs have evolved and been influenced by scientists, methods and data from all of these fields.

In environmental public health and food safety, the predominant general risk assessment model was first described in detail by the National Research Council in the United States (USA) (25) and it is widely used by the Codex Alimentarius Commission (Codex) for food safety risk analysis (12, 13). The basic steps are hazard identification, exposure assessment, hazard characterisation and risk characterisation (Fig. 1a, 'Codex model'). The World Organisation for Animal Health (OIE) has developed (33) a modified model that includes hazard identification, release assessment, exposure assessment, consequence assessment and risk estimation (Fig. 1b, 'OIE model'). Further explanations of these steps and comparisons between approaches are provided elsewhere (26, 29). Recently, a Codex *ad hoc* Task Force has proposed guidelines for risk analysis of antimicrobial resistance derived from antimicrobial use in food animals, including risk assessment (14), and this is also described in more detail elsewhere in this volume (6).

The hazards of interest with respect to antimicrobial resistance have been identified variously as:

- bacteria of significance to human health (e.g. foodborne pathogens, zoonotic pathogens, human pathogens, commensals) that are resistant to antimicrobials used in animals
- genetic determinants of resistance (2, 7, 26).

The adverse human health outcomes of interest include:

- infection with resistant bacteria
- complications of infection
- reduced treatment options
- various conditions associated with increased frequency,

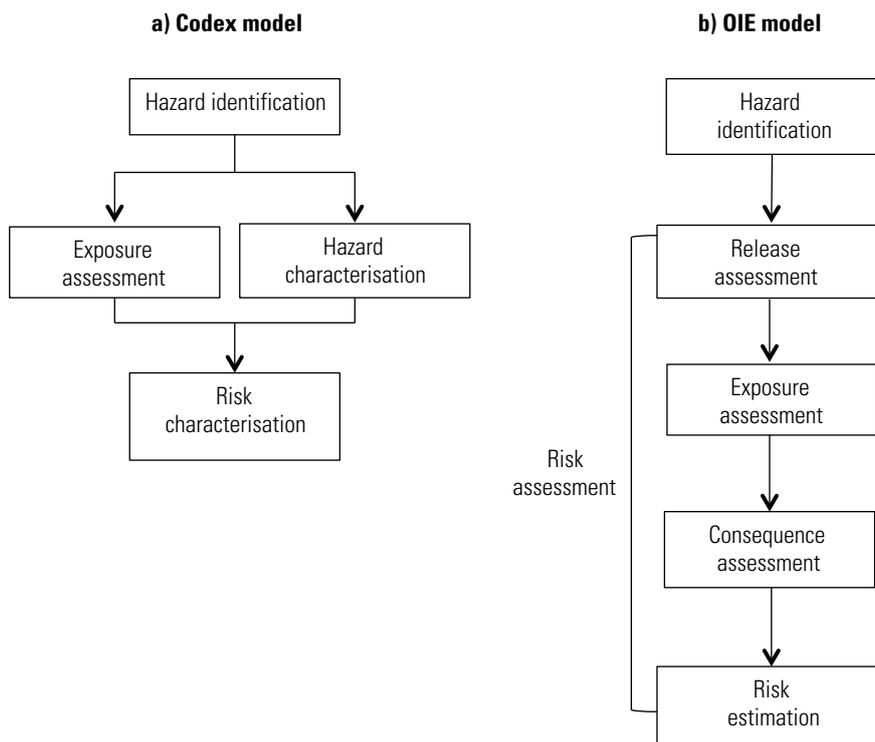


Fig. 1
Main steps in risk assessment approaches used by Codex Alimentarius and the World Organisation for Animal Health (OIE)

Table I
Potential adverse human health consequences based on hazard identification*

Endpoint	Endpoint class
Infection from an antimicrobial-resistant pathogen or commensal organism	Morbidity
Long-term complications from infections	Morbidity
Antimicrobial-resistant infection from pathogens or commensals leading to death	Morbidity
Transfer of resistance genes to secondary pathogens or commensals	Quality of life ^(a)
Increased prevalence of antimicrobial resistance genes in the population	Quality of life ^(a)
Limited choice of drugs for treatment of infections	Quality of life ^(a)

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a) Leads to a second risk assessment process focusing on a hazard presented by the resistant bacterial strain other than the one initially identified, considered a hazard transfer

duration and severity of illness attributable to antimicrobial resistance (7, 35; Table I).

These outcomes may occur through a variety of proposed mechanisms, for example, failure of prescribed antimicrobial treatment, alteration of resistance to

colonisation, and genetic linkage of resistance and virulence determinants in pathogens (4). Although there is some debate and uncertainty concerning the nature of the hazards and potential outcomes, exposure assessment and hazard characterisation/consequence assessment are especially challenging aspects of resistance risk assessment. Figure 2 shows the major foodborne exposure assessment and hazard characterisation (dose–response assessment) components of a so-called ‘farm-to-fork’ risk assessment approach. These are depicted as boxes connected by solid arrows demonstrating the best-described and arguably most important direction of flow within the model. Within each of these components are many substeps and factors (not shown) that may be further characterised and, when possible, quantified when attempting to model the acquisition, spread and dynamics of antimicrobial resistance. Figure 2 also contains several boxes linked by dashed arrows that depict other factors that can contribute to risk and ideally should also be included in risk models. This approach offers many potential advantages in risk assessment, including its conceptual similarity to proposed mechanisms of resistance selection and spread, and the potential capacity to test hypotheses concerning the effects of proposed risk management actions at various points along the continuum from treatment of animals to illness in humans. There are also some disadvantages, however, most notably numerous gaps in existing knowledge/data that are needed

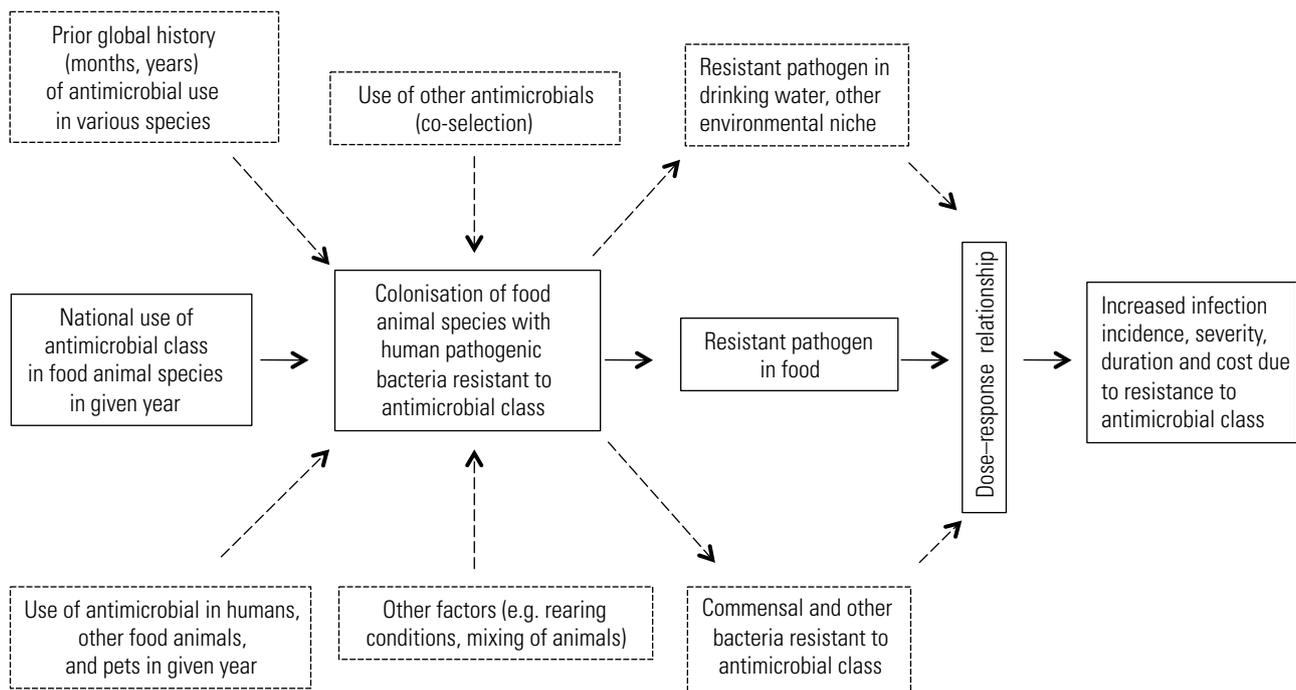


Fig. 2

General structure of an exposure-based model for estimating the national human health risk (burden of disease) from antimicrobial resistance arising from the use of a member of a given antimicrobial class in a particular food animal species

to populate the various steps along the chain (29, 32). A few quantitative farm-to-fork risk assessments using this general model have been conducted for microbial pathogens in foods, for example *Salmonella enteritidis* in eggs, *Campylobacter jejuni* in broilers and *Escherichia coli* O157:H7 in beef (13). There has also been some application of the farm-to-fork approach in antimicrobial resistance risk assessment (e.g. fluoroquinolone resistance in *Campylobacter* in beef – discussed below) (1), but this is limited, largely due to these important data gaps.

Other approaches to assessing risk have been devised. For example, the World Health Organization (WHO) has for several years been conducting a wide variety of studies and consultations on the global burden of disease (the quantity of disease in the population), for individual diseases and injuries, that is attributable to a wide variety of outcomes and associated risk factors (22). These efforts include a number of environmental health initiatives on issues such as sanitation, water safety, and recently the global burden of foodborne diseases (36).

Conceptually, two main approaches have been used to estimate the disease burden from environmental risk factors: exposure-based and outcome-based approaches. In this field, outcomes are typically expressed in terms of death (mortality) and one or more other standardised metrics, such as disability-adjusted life years (DALYs), which express the number of healthy years lost in the

population due to premature death or disability (22). Standardised metrics enable comparisons of impact across diseases or risk factors.

For the exposure-based approach the various disease outcomes associated with the hazard or risk factor of interest (e.g. antimicrobial use in animals) are identified, and an assessment of exposure of the study population (population at risk) to the risk factor is made, based on data from available studies or surveillance programmes. A dose-response relationship for the given hazard is defined for the study population. Exposure and dose-response distributions are combined to produce estimates of outcome (disease/health impact), typically expressed as incidence of mortality or converted to DALYs. This approach is analogous to the risk assessment models described previously, and is sometimes called a 'bottom-up' approach, because it builds through the various steps of the exposure pathway (e.g. farm-to-fork) up to an estimation of disease impact (22, 29).

In contrast, the outcome-based approach starts with estimates of disease incidence, hence it is sometimes described to as 'top-down'. In this approach, various disease outcomes associated with the factor are identified, disease outcome data (incidence, prevalence) are obtained, and the fraction of the burden attributable to the risk factor of interest (e.g. antimicrobial use in animals) is estimated (22, 29). It is well recognised that notifiable diseases are

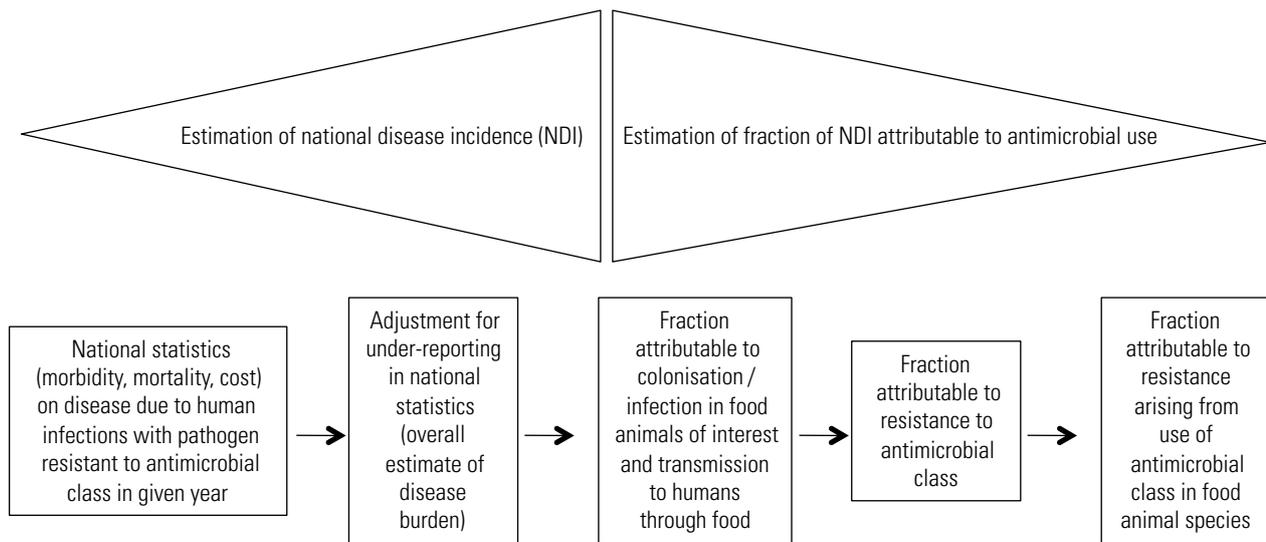


Fig. 3

General structure of an outcome-attribution-based model for estimating the national human health risk (burden of disease) from antimicrobial resistance arising from the use of a member of a given antimicrobial class in a given food animal species

frequently under-reported in surveillance programmes, therefore attempts are often made to adjust incidence estimates at various levels of the reporting chain. A schematic of the outcome-based approach is shown in Figure 3. As will be seen, this is the general approach that has most commonly been used for quantitative antimicrobial resistance risk assessment.

Examples of publicly available risk assessments

Table II lists publicly available quantitative human health risk assessments relating to antimicrobial resistance. It also includes basic information on each, such as the antimicrobials and bacteria of interest, the outcome parameters used, and the risk estimates obtained. The following is a summary of each assessment and major findings, followed by a general discussion and conclusion.

Penicillins and tetracyclines

A pioneering quantitative risk assessment pertaining to antimicrobial resistance of farm origin was performed by an expert committee of the United States Institute of Medicine (21). Most subsequent assessments have used modifications of the basic approach adopted by this committee, which was based on the outcome-attribution concept. The government of the USA had been concerned for several years about potential public health effects of in-feed use of antimicrobials in livestock. To support policy development in this area, it

requested that the Institute of Medicine carry out an independent review of the human health consequences of the use of penicillin and tetracycline at subtherapeutic concentrations in livestock feed. The Institute assembled an expert committee and charged them to perform a quantitative risk assessment in order to address several specific risk-related questions. After review of the published literature and other available data, the committee determined that there were only sufficient data to estimate mortality in the population of the USA from antimicrobial-resistant *Salmonella* infections of farm origin. The risk model was based on outcome attribution, composed of five steps and populated with data from epidemiological surveillance reports and published literature, and, where data were lacking, the committee's best judgement. The five steps were:

- the annual number of reported cases of human salmonellosis in the USA
- the fraction of human cases attributable to antimicrobial resistance
- the case fatality rate
- the fraction of deaths due to infection of farm origin
- the fraction of the above deaths attributable to subtherapeutic use of penicillin and tetracycline in feed.

'Low', 'mid-range' and 'high' values for the outcomes, derived by simple multiplication of the various steps, were estimated. The model estimated that the annual number of fatal salmonellosis cases in the USA caused by subtherapeutic use of penicillin and tetracycline was most likely about 40, but ranged from 1 to 400. The most likely estimate of the number of attributable excess deaths (i.e.

Table II
Main attributes of publicly available antimicrobial resistance quantitative risk assessments, in chronological order

Purpose	Funding source	Type of model	Antimicrobial drug/class of interest		Food animal species of interest	Bacterium of interest	Country /region	Human health outcome modelled and metric used	Risk estimates obtained
			Human	Food animal					
Quantitative estimate of the annual number of salmonellosis deaths in the USA from use of subtherapeutic concentrations of penicillin and tetracycline in animal feed IOM (1989) (21)	IOM, NAS, FDA	OA-based	Penicillin/tetracycline	Penicillin/tetracycline	n/s	<i>Salmonella</i>	USA	– Annual number of deaths associated with infection by <i>Salmonella</i> strains of farm origin resistant to penicillins or tetracyclines due to subtherapeutic uses in feed – Number of excess deaths attributable to subtherapeutic use of penicillins or tetracyclines in feed	– Most likely estimate 40 deaths per year – Most likely estimate 6 per year
Analyse the potential public health risk from fluoroquinolone-resistant <i>Campylobacter jejuni</i> because of fresh beef and ground beef consumption Anderson <i>et al.</i> (2001) (1)	AHI	Exposure-based (Codex approach)	Fluoro-quinolones	Fluoro-quinolones	Cattle	<i>Campylobacter jejuni</i>	USA	Proportion of individuals with fluoroquinolone-resistant <i>C. jejuni</i> infections from beef who are treated with a fluoroquinolone and treatment fails (may require a different treatment strategy, protracted illness, mortality)	After one year of fluoroquinolone use in cattle, 12 cases of failure of fluoroquinolone treatment in humans from fluoroquinolone-resistant <i>Campylobacter</i> in ground beef, 44 cases after 10 years, one associated death after 10 years
Estimate excess morbidity that occurred as a result of the unrelated use of an antimicrobial to which the pathogen was resistant Barza and Travers (2002) (5)	n/d	OA-based	n/s	n/s	n/s	<i>Campylobacter</i> and non-typhoid <i>Salmonella</i>	USA	Excess infections that occurred as a result of the unrelated use of an antimicrobial to which the pathogen was resistant	Each year, antimicrobial resistance results in an additional 29,379 infections with non-typhoid <i>Salmonella</i> , with 342 hospitalisations and 12 deaths, and an additional 17,668 <i>C. jejuni</i> infections, with 95 hospitalisations
Estimate excess morbidity due to increased virulence (prolonged or more severe illness) of antimicrobial-resistant <i>Campylobacter</i> and non-typhoid <i>Salmonella</i> infections Travers and Barza (2002) (31)	n/d	OA-based	Fluoro-quinolones	Fluoro-quinolones	Food animals	<i>Campylobacter</i> and non-typhoid <i>Salmonella</i>	USA	Excess days of illness related to fluoroquinolone resistance of <i>C. jejuni</i> ; excess morbidity attributable to antimicrobial resistance of non-typhoid <i>Salmonella</i>	> 400,000 excess days of diarrhoea per year in the USA due to fluoroquinolone-resistant <i>Campylobacter</i> from chicken; 8,677 days of hospitalisation for non-typhoid salmonellosis

Table II (cont.)

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Purpose	Funding source	Type of model	Antimicrobial drug/class of interest		Food animal species of interest	Bacterium of interest	Country /region	Human health outcome modelled and metric used	Risk estimates obtained
			Human	Food animal					
Estimate the public health impact of fluoroquinolone resistance in <i>Campylobacter</i> that was attributed to the use of fluoroquinolones in chickens Bartholomew <i>et al.</i> (2003) (3)	USDA	OA-based	Fluoro-quinolones	Fluoro-quinolones	Broiler chickens	<i>Campylobacter</i>	USA	Number of patients with campylobacteriosis that seek care and are treated with fluoroquinolones who have fluoroquinolone-resistant <i>Campylobacter</i> attributed to chicken in 1998 and 1999	1998 cases: 4,760 (5th percentile), 14,370 (95th percentile) 1999 cases: 5,230 (5th percentile), 15,330 (95th percentile)
Describe the qualitative dynamics of virginiamycin use and SREF emergence. Make qualitative comparisons of quantitative results of various model scenarios Smith <i>et al.</i> (2003) (27)	Grant from Pfizer Corp.	Compartmental model using differential equations; coupled community exposure and colonisation by SREF to nosocomial transmission	Quinupristin–dalfopristin/streptogramin	Virginiamycin/streptogramin	Chicken	<i>Enterococcus faecium</i>	n/a	Effects of a ban on virginiamycin use on in-hospital prevalence of colonisation of humans with SREF, under various scenarios of SREF transmission. Scenario comparison largely qualitative	The potential effects of a virginiamycin ban were highest in the quasi-epidemic scenario of transmission, moderate under the non-epidemic scenario, and lowest under the epidemic transmission scenario
Estimate bounds of risks and benefits from banning virginiamycin use in Australia and the USA Cox <i>et al.</i> (2004) (9)	n/d	OA-based	Quinupristin–dalfopristin/streptogramin	Virginiamycin/streptogramin	Chicken	<i>Enterococcus faecium</i>	Australia and the USA	Expected reduction by a ban of virginiamycin use in poultry in the number of quinupristin–dalfopristin treatment failures, mortalities and years of life lost in humans in each country over a five-year period	A ban of virginiamycin in 2002 was predicted to: Australia – reduce attributable treatment failures at most by 0.35×10^{-3} , mortality by 0.058×10^{-3} cases and life years lost by 1.3×10^{-3} ; USA – reduce attributable treatment failures by at most 1.85 cases, mortality by at most 0.29 cases and life years lost by at most 6.3 over five years for the US population
Estimate quantitative bounds on the future human health risks to patients treated with quinupristin–dalfopristin from continued use of virginiamycin in food animals Cox and Popken (2004) (10)	n/d	Stochastic discrete event simulation model of transitions among SREF states	Quinupristin–dalfopristin/streptogramin	Virginiamycin/streptogramin	Food animals	<i>Enterococcus faecium</i>	USA	From continued use of virginiamycin, SREF cases per ICU patient–year, individual mortality risk from SREF per hospitalisation, total number of mortalities in USA per year	For prescription rate of 3×10^{-5} , the model predicted the risk of SREF cases per ICU patient–year was 1×10^{-5} , the individual mortality risk from SREF per hospitalisation for ICU patients was 4×10^{-7} , and there would be <1 excess death in the US population per year

Table II (cont.)

Main attributes of publicly available antimicrobial resistance quantitative risk assessments, in chronological order

Purpose	Funding source	Type of model	Antimicrobial drug/class of interest		Food animal species of interest	Bacterium of interest	Country /region	Human health outcome modelled and metric used	Risk estimates obtained
			Human	Food animal					
Assess the risk of failure of quinupristin–dalfopristin (Synercid) therapy for <i>E. faecium</i> infections due to the acquisition of resistance as a result of the ingestion of resistant strains of <i>E. faecium</i> present on food commodities FDA (2004) (18)	n/d	OA-based	Quinupristin–dalfopristin/streptogramin	Virginiamycin/streptogramin	Food animals	<i>Enterococcus faecium</i>	USA	Probability that a susceptible person would become infected with streptogramin-resistant <i>E. faecium</i> infection attributable to food animal use of virginiamycin, and Synercid therapy would be impaired	The estimated risk in the hospitalised population in the USA ranged from 6 to 120 chances in 100 million in one year, and from 0.7 to 14 chances in 100 million in one year for the general population (assuming 10% from food)
Estimate the annual risk for the general US population of failure of treatment of <i>Campylobacter</i> and <i>E. faecium</i> infections that are resistant to macrolides due to the use of tylosin and tilmicosin in food animals Hurd <i>et al.</i> (2004) (19)	Elanco Animal Health	Elements of both exposure- and OA-based models; deterministic	Macrolides	Tylosin, tilmicosin/macrolides	Poultry, pigs, non-dairy beef cattle	<i>Campylobacter</i> , <i>Enterococcus faecium</i>	USA	Yearly probability that an average individual is affected by illness due to macrolide-resistant <i>Campylobacter</i> or <i>E. faecium</i> and adverse therapeutic event (longer duration of diarrhoea, more severe disease, mortality)	The probability of human illness due to macrolide-resistant campylobacteriosis < 1 in 10 million for all meat commodities combined, and due to macrolide-resistant <i>E. faecium</i> < 1 in 3 billion
Conduct a comprehensive microbiological risk assessment to gain insight into the potential effect of a ban on virginiamycin Kelly <i>et al.</i> (2004) (23)	Grant from Pfizer Corp. and Phillips Brothers	Compartmental model utilising differential equations; described in terms of an integration of an EA model and HH model. An adaptation of model of Smith <i>et al.</i> (2003) (27) OA-based	Quinupristin–dalfopristin/streptogramin	Virginiamycin/streptogramin	Chicken	<i>Enterococcus faecium</i>	USA	Effects of a ban on virginiamycin use on in-hospital prevalence of colonisation of humans with SREF, under various scenarios of epidemic potential for SREF transmission. Scenario comparison largely qualitative	The potential effects of a virginiamycin ban were highest in the medium epidemic potential scenario of VREF transmission, moderate under the low epidemic potential scenario, and lowest under the high epidemic transmission scenario
Estimate the potential human health risk due to foodborne <i>Campylobacter</i> spp. infections derived from on-farm macrolide use Hurd and Malladi (2008) (20)	n/d		Erythromycin/macrolide	Various (e.g. tilmicosin, tylosin)/macrolide	Food animals	<i>Campylobacter jejuni</i> , <i>Campylobacter coli</i>	USA	Annual number of adverse outcomes from culture-confirmed resistant infections treated with a macrolide where resistance was due to macrolide use in food animals; annual risk of an adverse outcome due to macrolide use for a person in the USA	Median estimates of annual numbers of adverse outcomes are 3.62 (porcine <i>C. coli</i>), 0.04 (chicken <i>C. coli</i>), 0.11 (chicken <i>C. jejuni</i>), 0.49 (cattle <i>C. jejuni</i>); median annual risk of adverse outcome per person is 1 in 82 million (porcine <i>C. coli</i>), 1 in 6.2 billion (chicken <i>C. coli</i>), 1 in 2.4 billion (chicken <i>C. jejuni</i>) and 1 in 608 million (cattle <i>C. jejuni</i>)

Table II (cont.)

Main attributes of publicly available antimicrobial resistance quantitative risk assessments, in chronological order

Purpose	Funding source	Type of model	Antimicrobial drug/class of interest		Food animal species of interest	Bacterium of interest	Country /region	Human health outcome modelled and metric used	Risk estimates obtained
			Human	Food animal					
Quantify the potential for continued harm from use of penicillin drugs in food animals through increasing the number of ampicillin-resistant non-nosocomial fatal <i>E. faecium</i> infections in human patients	Alpharma	OA-based	Ampicillin/penicillins	Penicillin drugs/penicillins	Food animals	<i>Enterococcus faecium</i>	USA	Mortality; excess mortalities per year	0.04 to 0.14 excess mortalities per year prevented if current uses of penicillin drugs in food animals were discontinued

Cox *et al.* (2009) (11)

AHI: United States Animal Health Institute
 EA: exposure assessment
 FDA: United States Food and Drug Administration
 HH: household to hospital
 ICU: intensive care units
 IOM: Institute of Medicine

n/a: not available (unspecified)
 NAS: National Academy of Sciences
 n/d: not declared
 n/s: not specified
 OA: outcome attribution
 SREF: streptogramin-resistant *Enterococcus faecium*

USDA: United States Food and Drug Administration
 VREF: vancomycin-resistant *Enterococcus faecium*

deaths that would not have occurred if the infections were antimicrobial susceptible) was in the range of six per year.

More recently, Cox and co-workers (11) used a mathematical model to quantify the potential for continued harm to human health (i.e. increasing numbers of ampicillin-resistant enterococcal infections in human patients) resulting from the use of penicillin drugs in food animals in the USA. The hazard of interest was defined as infection of patients in intensive care units (ICU) with ampicillin-resistant *Enterococcus faecium* (AREF). The general approach used was to estimate the fraction of such resistant infections that might be prevented by discontinuing the use of penicillin drugs in food animals. The authors used a version of an outcome-attribution-based model. Potentially preventable mortality was defined to occur under the following conditions: i) ICU patient dies following ii) *E. faecium* infection that iii) is resistant to ampicillin (AREF) that was iv) vancomycin susceptible, v) not known to have been contracted from the hospital environment (i.e. not nosocomial or due to person-to-person spread), vi) could have come from food animals (genotype or resistance determinants of the types found in food animals present), and vii) the patient tolerated penicillin (i.e. was not allergic). The model estimated that 0.04 to 0.14 excess fatalities per year would be prevented if current use of penicillin drugs in food animals was discontinued.

Fluoroquinolones

Fluoroquinolones have been classified by WHO as Critically Important for Human Health (8) and, as such, this class has received considerable attention with respect

to risk assessment. In response to concerns about emerging fluoroquinolone resistance, the United States Food and Drug Administration (FDA) conducted a quantitative assessment of the human health impact of fluoroquinolone-resistant *Campylobacter* associated with consumption of chicken (3, 16). A mathematical model was developed, which was based on an outcome-attribution approach. Data for the model were obtained from surveillance (e.g. the Centers for Disease Control and Prevention FoodNet, the National Antimicrobial Resistance Monitoring System [NARMS]) and published literature. The model was structured to calculate the following for 1998 and 1999:

- the mean number of human *Campylobacter* cases in the USA
- the mean number of fluoroquinolone-resistant *Campylobacter* cases attributable to chicken consumption
- the mean number of these cases in which the patient sought medical care and was treated with a fluoroquinolone.

The model estimated that in 1998 the distribution of cases was between 4,760 (5th percentile) and 14,370 (95th percentile); in 1999 it was between 5,230 (5th percentile) and 15,330 (95th percentile). This risk assessment was subsequently used to support withdrawal of approval for the use of fluoroquinolones in poultry in the USA.

Also in the USA, Anderson *et al.* (1) conducted a risk assessment of fluoroquinolone resistance in *Campylobacter jejuni* derived from use of the drugs in beef cattle, using data from the published literature, surveillance and expert opinion. This was one of the few quantitative assessments that used a farm-to-fork approach

in the general Codex risk assessment model structure. The exposure assessment component began at the retail level and estimated the probability of contamination of cooked ground beef or fresh beef, the concentration of *C. jejuni* in contaminated beef, the effects of cooking, and the probability of illness following consumption of contaminated meat. The potential human health impact of fluoroquinolone resistance in *C. jejuni* was estimated by modelling the number of humans infected with fluoroquinolone-resistant *C. jejuni* from beef cattle that had been treated with fluoroquinolones. The output was expressed in terms of years following the licensing of fluoroquinolones in beef cattle. The model predicted that after one year of fluoroquinolone use in cattle, there would be 12 cases of failure of fluoroquinolone treatment in humans resulting from fluoroquinolone-resistant *C. jejuni* in ground beef, 44 cases after 10 years, and one associated death after 10 years.

Using an outcome-attribution approach, Travers and Barza (31) estimated the number of excess days of illness due to fluoroquinolone-resistant *Campylobacter* infections in the USA. They assumed that, on average, there would be two additional days of illness in affected patients that were treated with a fluoroquinolone. Their model predicted an excess of 410,926 days of illness in the USA per annum attributable to fluoroquinolone use in animals. They also estimated that there would be 8,677 extra days of hospitalisation due to antimicrobial resistance in cases of non-typhoid salmonellosis, 90% of which they attributed to antimicrobial use in food animals. The same authors (5) also estimated the number of antimicrobial-resistant foodborne infections that occurred as a result of patients taking antimicrobials for other reasons (the aetiological fraction). Using random effects meta-analysis of data from epidemiological studies they estimated that an additional 29,379 non-typhoid *Salmonella* and 17,668 *Campylobacter* infections of food animal origin are attributable annually to antimicrobial resistance.

Streptogramins

Cox and Popken (9) quantified the human health risks from quinupristin–dalfopristin (QD)-resistant *E. faecium* (EF) infections due to virginiamycin (VM) use in chickens in Australia and the USA. They used an approach that was based mostly on outcome attribution, defining a VM-attributable treatment failure in humans using the following steps:

- estimation of the total number of VREF (vancomycin-resistant EF) cases per quarter (separately for Australia and the USA)
- estimation of the proportion of EF that are positive for the *vanA* gene

- estimation of the proportion of exogenous (non-nosocomial) cases
- estimation of the maximum proportion of cases attributable to consumption of chicken
- estimation of the fraction of cases that are resistant to QD
- estimation of the proportion of cases for which QD is effective, and estimation of the prescription rate of QD over time
- estimation of the decline in the risk of resistance in human infections following a ban
- estimation of the human health consequences of treatment failures.

For Australia, the model predicted that a ban of VM in 2002 would probably reduce attributable treatment failures at most by 0.35×10^{-3} over a five-year period (to take into account changes in patterns of QD use over time), mortality by 0.058×10^{-3} cases and life years lost by 1.3×10^{-3} . For the USA, the model predicted that a ban would reduce attributable treatment failures by at most 1.85 cases, mortality by at most 0.29 cases and life years lost by at most 6.3 over five years for the population.

In further work, Cox and Popken (10) developed a stochastic simulation model for QD to obtain quantitative bounds on the future human health risks to patients treated with QD that would result from continued use of VM in food animals. In general terms, the model made transitions among four health states of humans: unexposed, exposed, colonised and amplified, where amplified is the condition of being colonised and highly contagious. They applied Bayesian inference to utilise historical information on rates of QD resistance. They also used Monte Carlo analysis with rejection of samples that were inconsistent with past data to derive posterior distributions consistent with past (observed) data. The model predicted that the effects of VM were sensitive to the prescription rate of QD in humans. For a prescription rate of 3×10^{-5} , the model predicted a risk of 1×10^{-5} streptogramin-resistant *E. faecium* (SREF) cases per patient–year (in ICU patients) and <1 excess death in the population of the USA (based on the total number of deaths in the USA per year). They also measured the individual mortality risk from streptogramin-resistant *E. faecium* per hospitalisation.

In 2004, the FDA Center for Veterinary Medicine published a quantitative assessment of the risk of QD (Synercid) treatment failure in *E. faecium* infections originating from food (18). Scientific information relevant to the assessment was presented using the general OIE risk assessment structure (see Fig. 1). The quantitative risk estimation models were based on outcome attribution, and three different models were developed:

- a model based on data from surveillance of ICU and the nosocomial infection literature
- a model based on Synercid usage rates
- a model based on data concerning cases of septicaemia reported to National Center for Health Statistics (NCHS) databases.

Each model sought to estimate the number of QD-resistant *E. faecium* infections treated with Synercid, and the proportion of these attributable to food. The three models yielded similar estimates. Two scenarios were used to estimate the probability that a susceptible person would become infected with streptogramin-resistant *E. faecium* infection attributable to the use of VM in food animals, and that Synercid therapy would be impaired. The first scenario assumed that 10% of the risk of SREF infection is due to a food pathway. Under this scenario, the estimated risk in the hospitalised population in the USA ranged from 6 to 120 chances in 100 million in one year, and for the general population from 0.7 to 14 chances in 100 million in one year. The second scenario assumed that 100% of the risk of SREF infection is due to a food pathway, and the risk estimates were ten-fold greater than in the first scenario.

Smith *et al.* (27) used a different mathematical approach to assess human health risks from the use of VM. They argued that SREF is a pre-emergent pathogen with a high potential for epidemic spread. They did not specifically assess the numerical risks of infection and treatment failure, but they sought to identify parameters critical for the emergence of SREF. A compartmentalised mathematical model with coupled differential equations was used. Under the conditions of the model:

- humans are exposed, unexposed or colonised
- unexposed people are exposed to new strains of SREF (the rate of exposure and the fraction due to VM use in animals are critical parameters)
- after exposure, the population of SREF in the human gut is transient (a few days) unless the bacteria colonise the gut (persist for a few months)
- SREF that spread from person to person and within hospital populations are well mixed
- antibiotic use disturbs the natural flora of the gut, increasing the probability of colonisation
- patients are discharged at random from the hospital to the community, where antibiotic use and transmission rates are very low.

The model assumes that VM use is the main reason for new SREF strains to arise in humans. To assess the impact, separate cases were considered as follows:

- epidemics where $R_0 > 1$ (i.e. each host exposed to SREF leads to exposure of at least one other infected host, so an epidemic ensues)
- those where $R_0 < 1$ (each infected host tends to infect less than one new host, so the pathogen dies out)
- quasi-epidemics, where $R_0 \sim 1$.

The model showed that for non-epidemic dynamics ($R_0 \sim 0$), new strains died out and the effect of VM was directly related to the fraction of exposures attributable to VM use. In the case of epidemics, transmission was affected by hospital infection control and patterns of antibiotic use within hospitals, but not by VM use. The model showed that the potential effects of VM use were highest for quasi-epidemics ($R_0 \sim 1$), where most new strains are the result of VM use, low-level transmission allows strains to persist for long periods of time in populations, and medical antibiotic use plays a lesser role. The authors concluded that emergence of SREF is likely to be the result of an interaction between QD use in medicine and the long-term use of VM in animals (27).

Kelly *et al.* (23) built upon the previously described work of Smith and co-workers to construct a risk assessment model that integrated some of the features of the exposure assessment and household-to-hospital models in Smith's publication. The exposure assessment model estimated the rate of exposure to chicken strains of SREF, per person per day, which was then used to calculate the community prevalence of SREF under the assumption that chickens are the only source of the organism. The model assumes that community prevalence will decline following a ban on the use of VM in chickens. Community exposure and prevalence in hospitals are linked through the admission to hospital of colonised individuals from the community. The prescription rate and the rate at which exposure declines after a ban were varied to investigate the effects of policy options. The authors considered no regulatory changes on VM use, or regulation leading to an exponential decline (as seen in Denmark), and investigated the effect of antibiotic use in people at three assumed levels, which determine the potential for epidemic spread (R_0). Specifically, they investigated low ($R_0 \sim 0.52$), medium ($R_0 \sim 0.69$) and high ($R_0 \sim 1.03$) potential for epidemic spread. Their results are similar to those of Smith; in the case of low epidemic potential, the rate of person-to-person spread was very low and the majority of colonised people were those colonised prior to admission. With a ban on VM use, the prevalence of colonisation dropped and was maintained by amplification of resistance resulting from antimicrobial use in people. When the potential for epidemic spread was high, the main driver was the use of antimicrobials in hospital and community settings and prevalence had a minor effect – a ban did not result in much difference. With medium epidemic potential, individual strains introduced into the

hospital may become extinct or may form sub-epidemics, amplifying resistance. A ban reduced the prevalence at equilibrium, but the time taken to achieve this was slightly longer than in the case of low epidemic potential. A ban would have the largest potential effect if there were medium potential for spread, reducing the potential for sub-epidemics in hospital.

Macrolides

Hurd *et al.* (19) conducted a risk assessment of macrolide (tylosin and tilmicosin) use in beef cattle, poultry and pigs. The adverse human health outcome of interest was illness caused by macrolide-resistant *Campylobacter* or macrolide-resistant *E. faecium* in people treated with a macrolide. The general approach used was a combination of exposure-based and outcome-attribution methods. Risk was modelled as the yearly probability that an average person in the USA would experience an adverse event (e.g. longer duration of diarrhoea, progression to more severe disease, or mortality) as a result of eating contaminated meat. The probability of the occurrence of the following events was estimated using data from a variety of sources, including surveys of antimicrobial use in animals, surveillance and published research:

- macrolide administration to animals
- a hazardous agent selected above background level
- a hazardous agent escaping from the farm
- the hazardous agent remaining on a carcass after slaughter
- the hazardous agent surviving to contaminate retail meat
- a contaminated product presented to a consumer
- a consumer becomes ill
- the patient is treated with a macrolide
- macrolide treatment failure.

The model estimated the probability of human illness due to macrolide-resistant campylobacteriosis as <1 in 10 million for all meat commodities combined, and <1 in 3 billion due to macrolide-resistant *E. faecium*.

Hurd and Malladi (20) continued this work by conducting a stochastic assessment of the public health risks associated with the use of macrolide antibiotics in food animals. Using a largely outcome-attribution-based approach, as presented in the general structure of US Guidance 152 (17), they sought to estimate the potential human health risk due to macrolide resistance in foodborne infections with *Campylobacter* spp. derived from on-farm macrolide use. Unlike their previous work, this assessment considered uncertainties in parameter estimates, used a more elaborate model of resistance development,

combined approaches to estimate the preventable fractions, and separated *C. coli* and *C. jejuni*. The authors determined the resistance fraction attributable to antimicrobial use on the basis of data from conventional compared to antimicrobial-free farms, and from national resistance surveillance data. Their model estimated the annual number of adverse outcomes as: 3.62 (porcine *C. coli*), 0.04 (chicken *C. coli*), 0.11 (chicken *C. jejuni*) and 0.49 (cattle *C. jejuni*), and the median annual risk of an adverse outcome per person as: one in 82 million (porcine *C. coli*), one in 6.2 billion (chicken *C. coli*), one in 2.4 billion (chicken *C. jejuni*) and one in 608 million (cattle *C. jejuni*).

Discussion

This review focused exclusively on assessments yielding quantitative estimates of human health risks from antimicrobial resistance attributable to antimicrobial use in food animals. Several assessments yielding qualitative estimates of risk, and others that have examined risk/benefit, have also provided useful information, but space limitations preclude their inclusion here. The advantages and disadvantages of quantitative and qualitative approaches have been discussed previously (2, 29, 32). Purely qualitative approaches are applicable when quantitative data pertaining to the emergence and spread of resistance in pathogens and commensals are particularly sparse or entirely unavailable, as may be the case before new antimicrobials are released onto the market. Regulatory authorities should undertake pre-licensure human safety evaluations of veterinary antimicrobials with respect to antimicrobial resistance, and guidelines have been developed for this purpose (17). However, the quantitative assessments reviewed in this paper were conducted in the context of licensed antimicrobials already on the market (in some cases for decades) and under regulatory scrutiny with respect to safety; some because they were used as growth promoters and others because of their critical importance to human health. Given that these drugs were in use in various countries, field data were available on the selection for resistance in various species of bacteria, its spread in animals and through the food chain or environment to humans, and adverse health effects in humans. In all cases, however, there were numerous important data gaps that contributed to various uncertainties in the risk estimation.

Few of these assessments employed detailed mathematical models of exposure assessment or hazard characterisation from the point of individual animal treatment through to human exposure and its consequences (i.e. exposure-based, 'farm-to-fork' assessments), and in this sense few followed formal Codex or OIE models of risk assessment

from a quantitative perspective. Some authors pointed out that this was not possible because of key missing data. Instead, the majority took another approach, and attempted to attribute fractions of surveillance-derived population estimates of antimicrobial resistance-related illness in humans to antimicrobial use in animals. The health outcomes of interest included increased frequency, duration and severity of illness, and mortality. In general, the risk estimates ranged widely from very few additional illnesses per million people at risk, to many thousands. Comparison between studies is difficult because few considered the same drug/bacterium combination or the same risk question, and the methodologies varied considerably. All assessments had to contend with sparse data with which to support key model components, which necessitated numerous assumptions and contributed to considerable uncertainty. Collectively, the published quantitative risk assessments have to date been unable to comprehensively address many important aspects of antimicrobial resistance ecology, including multiple potential exposure pathways, complex interrelationships among bacteria of different species, the phenomenon of co-selection, and the cumulative effect on resistance of antimicrobial use over time in multiple species (including both animals and humans) and multiple countries (2). Nevertheless, these assessments have been very useful in

fostering debate, challenging assumptions, identifying key research and surveillance needs, and improving methodology. In the context of antimicrobial resistance, quantitative risk assessment is showing promise as a useful framework for the synthesis and analysis of scientific data that is needed to answer important risk questions. Much work remains to be done, however, to develop the methodology further and to train a larger cadre of risk analysts. For this to occur, it is important that those organisations that commission antimicrobials-resistance risk assessments encourage their peer review and public dissemination. It is also important to train more scientists who are capable of conducting and reviewing these risk assessments, in order to facilitate their use around the globe, and to improve methodology. Quantitative antimicrobial resistance risk assessment is very demanding with respect to data, expertise and other resources, and it is unlikely that more than a few wealthy countries will have the capacity to undertake their own assessments. Therefore, there is a need for an international forum to pool available expertise, objectively review existing antimicrobial resistance risk assessments, and make the results available to risk managers and other interested parties in countries around the world. ■

Évaluation quantitative des risques pour la santé publique associés à l'utilisation des agents antimicrobiens chez les animaux et à la sélection de la résistance : examen des rapports publiés

S.A. McEwen

Résumé

Un certain nombre d'évaluations quantitatives du risque ont été réalisées afin d'estimer la probabilité d'apparition et l'ordre de grandeur des effets secondaires indésirables pour la santé publique induits par l'utilisation des antibiotiques chez les animaux destinés à la consommation humaine, et par la sélection qui en résulte des traits de résistance chez les bactéries. La plupart de ces travaux étaient axés sur les antibiotiques autorisés faisant l'objet d'une surveillance particulière eu égard à la réglementation, en particulier les promoteurs de croissance et les agents antimicrobiens d'importance cruciale pour la santé humaine. La majorité de ces études ont recouru à des modèles visant à déterminer quelle était la proportion d'infections humaines imputables à l'utilisation des antimicrobiens chez les animaux, parmi les infections bactériennes pour lesquelles la surveillance avait révélé l'existence d'une résistance aux antibiotiques. Les estimations du risque ont fait apparaître une proportion allant de quelques cas supplémentaires pour 1 million d'individus à risque, à plusieurs milliers de cas supplémentaires. Malgré leur utilité, les

évaluations quantitatives du risque qui ont été publiées n'ont pas réussi à élucider complètement certains aspects importants de la résistance aux antimicrobiens, notamment les voies d'exposition multiples, les relations réciproques entre bactéries, la co-sélection et les effets cumulés de l'utilisation d'antimicrobiens chez plusieurs espèces et dans plusieurs pays. Elles ouvrent néanmoins des perspectives prometteuses pour la synthèse et l'analyse des données scientifiques. Des efforts devront être déployés pour affiner les méthodologies et pour former davantage d'analystes du risque. Il conviendra également de mettre en place un forum international afin de fédérer les expertises, de faire le point sur les évaluations du risque disponibles et de diffuser les résultats aux gestionnaires du risque dans le monde entier.

Mots-clés

Agent antimicrobien – Analyse des risques – Antibiotique – Caractérisation du risque – Évaluation du risque – Résistance.



Repaso de los informes publicados sobre la determinación cuantitativa del riesgo para la salud humana del uso de agentes antimicrobianos en los animales y de la selección de resistencias

S.A. McEwen

Resumen

El autor describe procesos de determinación cuantitativa del riesgo destinados a estimar la probabilidad y magnitud de los efectos perjudiciales que para la salud humana se derivan del uso de antimicrobianos en animales de consumo alimentario como resultado de la selección de bacterias resistentes. La mayoría de los estudios se centran en antimicrobianos registrados y sujetos a seguimiento por las autoridades competentes, en especial promotores del crecimiento y agentes de gran importancia para la salud humana. En la mayoría de los casos se utilizaron modelos para atribuir al empleo de antimicrobianos en los animales un determinado porcentaje de las infecciones causadas por bacterias resistentes a partir de cálculos basados en las actividades de vigilancia. Las estimaciones del riesgo iban desde unos pocos casos adicionales de enfermedad hasta muchos miles de casos por millón de personas expuestas. Aunque no dejan de ser útiles, los procesos de determinación cuantitativa del riesgo que se han hecho públicos hasta ahora no han servido para abordar globalmente importantes aspectos de la resistencia a los agentes antimicrobianos como las múltiples vías de exposición, las interrelaciones entre bacterias, la coselección o los efectos acumulativos del uso de antimicrobianos en múltiples especies y países. Con todo, los resultados son prometedores para la síntesis y el análisis de datos científicos. Queda trabajo por delante para perfeccionar la metodología y formar a más analistas de riesgos. Se requiere asimismo un foro internacional para poner en común el saber de los especialistas, examinar los procesos de determinación del riesgo en curso y dar a conocer los resultados a quienes en todo el mundo tienen a su cargo la gestión del riesgo.

Palabras clave

Agente antimicrobiano – Análisis del riesgo – Antibiótico – Caracterización del riesgo – Determinación del riesgo – Resistencia.



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