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Antimicrobial Resistance: a One Health Perspective

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ABSTRACT One Health is the collaborative effort of multiple health science professions to attain optimal health for people, domestic animals, wildlife, plants, and our environment. The drivers of antimicrobial resistance include antimicrobial use and abuse in human, animal, and environmental sectors and the spread of resistant bacteria and resistance determinants within and between these sectors and around the globe. Most of the classes of antimicrobials used to treat bacterial infections in humans are also used in animals. Given the important and interdependent human, animal, and environmental dimensions of antimicrobial resistance, it is logical to take a One Health approach when addressing this problem. This includes taking steps to preserve the continued effectiveness of existing antimicrobials by eliminating their inappropriate use and by limiting the spread of infection. Major concerns in the animal health and agriculture sectors are mass medication of animals with antimicrobials that are critically important for humans, such as third-generation cephalosporins and fluoroquinolones, and the long-term, in-feed use of medically important antimicrobials, such as colistin, tetracyclines, and macrolides, for growth promotion. In the human sector it is essential to prevent infections, reduce over-prescribing of antimicrobials, improve sanitation, and improve hygiene and infection control. Pollution from inadequate treatment of industrial, residential, and farm waste is expanding the resistome in the environment. Numerous countries and several international agencies have included a One Health approach within their action plans to address antimicrobial resistance. Necessary actions include improvements in antimicrobial use regulation and policy, surveillance, stewardship, infection control, sanitation, animal husbandry, and alternatives to antimicrobials. WHO recently has launched new guidelines on the use of medically important antimicrobials in food-producing animals, recommending that farmers and the food industry stop using antimicrobials routinely to promote growth and prevent disease in healthy animals. These guidelines aim to help preserve the effectiveness of antimicrobials that are important for human medicine by reducing their use in animals.

INTRODUCTION

Antimicrobial resistance is a global public health crisis that threatens our ability to successfully treat bacterial infections (1, 2). Microbiologists and infectious disease specialists have long recognized the problem—the discoverer of penicillin Sir Alexander Fleming himself drew attention to the threat of resistance from underdosing (3)—but realization of the vast scale of the resistant threat is only now reaching wider audiences. Many infectious agents that could once be successfully treated with any one of several drug classes have acquired resistance to most, and in some cases, virtually all of these drugs (4, 5). The threat is most acute for antibiotics and synthetic antibacterial antimicrobial agents, the focus of this paper, but also threatened are antifungals, antiparasitics, and antivirals (6). How did we get from the point where antimicrobials were truly "wonder drugs" that could be relied upon to cure a wide range of life-threatening infections to the point today, where resistance to most antimicrobials is widely prevalent and the supply of new classes of drugs has dwindled to a trickle? The complete answer is not simple, nor unfortunately, is

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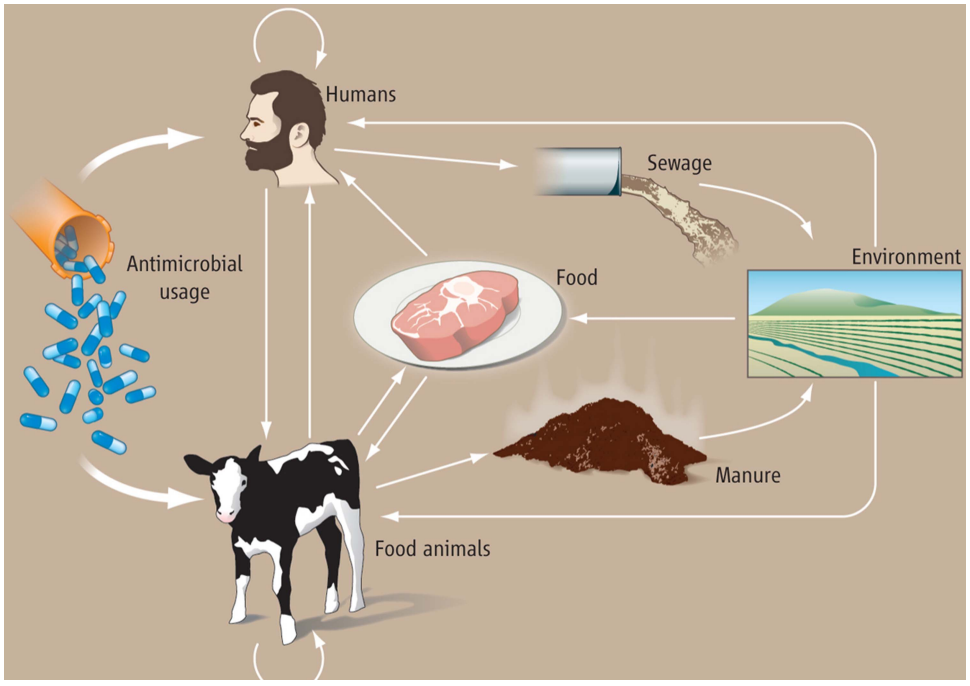
the solution. One thing seems certain: that overuse of these precious drugs in multiple sectors (human, animal, agriculture) is the main problem and one that must be addressed (4, 7).

Through the process of Darwinian selection, microorganisms faced with antimicrobial selection pressure enhance their fitness by acquiring and expressing resistance genes and then share those genes with other bacteria. Thus, antimicrobial use and overuse are important drivers of the resistance phenomenon; the other main drivers are factors that promote the spread of resistant bacteria and their genes locally and globally (8). These include poor infection control, environmental contamination, and geographical movement of infected humans and animals (9, 10). Wherever antimicrobials are used, there are reservoirs of resistance, including within humans and the local environments of hospitals and the community, as well as in animals and the farm and aquaculture environments, but also in water, soil, wildlife, and many other ecological niches, due to pollution by sewage, pharmaceutical industry waste, and manure runoff from farms (Fig. 1) (10, 11). Bacteria and their genes move relatively easily within and between humans, animals, and the environment. Microbial adaptations to antimicrobial use and other selection pressures within any one sector are reflected in any other sector (8, 12). Similarly, actions taken (or not taken) to contain antimicrobial resistance in one sector affect other sectors (13, 14). Antimicrobial resistance is an ecological problem that is characterized by complex interactions involving diverse microbial populations affecting the health of humans, animals, and the environment. It makes sense to address the resistance problem by taking this complexity and ecological nature into account using a coordinated, multisectoral approach, such as One Health (6, 15–19).

One Health is defined as "the collaborative effort of multiple health science professions, together with their related disciplines and institutions—working locally, nationally, and globally—to attain optimal health for people, domestic animals, wildlife, plants, and our environment" (20). The origins of One Health are centuries old and are based on the mutual dependency of humans and animals and the recognition that they share not only the same environment, but also many infectious diseases (19). It has been estimated that as many as 75% of human infectious diseases that have emerged or reemerged in recent decades are zoonotic; that is, they originated in animals (21). Rudolf Virchow and William Osler were medical pioneers that recognized the importance of a comparative approach to medical investigation, and veterinarian Calvin Schwabe coined the term "One Medicine" to denote the many commonalities in

FIGURE 1 Diagrammatic representation of the routes of transmission of antimicrobial resistance between farm animals, the wider environment, and humans. Reprinted from *Science* (12) with permission of the publisher.



human and animal medicine and in recognition that most veterinary activities benefit human health, either directly or indirectly (19, 22). One Health goes further, embracing the health of the environment as well as human and animal health, and promotes the view that with the ever-increasing human population growth that is accompanied by climate change, increasing pollution, and depletion of the earth's resources, health disciplines and others must work together to provide for the future health and well-being of humans, animals, and the environment (19, 20).

In this chapter, we take a One Health perspective on the problem of antimicrobial resistance by showing its multisectoral and interrelated nature, highlighting important risks to the health of humans and animals, and describing One Health approaches to the containment of antimicrobial resistance, particularly at the international level. We then offer some reflections on challenges facing the One Health approach in reconciling the sometimes-conflicting interests that deter some measures to addressing antimicrobial resistance. At the outset, we state our belief that human health and well-being are the most important considerations for preserving the continued effectiveness of antimicrobials, even within a One Health perspective, but that it is also in the greater, long-term interest of humankind to adequately care for animals and the environment.

USE OF ANTIMICROBIALS IN HUMANS, ANIMALS, AND PLANTS

A few antimicrobial classes are reserved more or less exclusively for humans, in particular those used to treat tuberculosis (e.g., isoniazid) or other infections for which animals are typically not treated (e.g., cattle with bovine tuberculosis are usually destroyed rather than treated). A few others are limited to veterinary use (e.g., flavophospholipols, ionophores), mainly because of toxicity to humans. However, the great majority of antimicrobial classes are used in both humans and animals, including domestic mammals, birds, farmed fish and shellfish, honey bees, and others (23–27). In horticulture, tetracyclines, streptomycin, and some other antimicrobials are sometimes used for the treatment and prophylaxis of bacterial infections of fruit, such as apples and pears (e.g., "fire blight" caused by *Erwinia amylovora*) (28). In people, antimicrobials are mostly used for the treatment of clinical infections in individual patients, but there is also limited prophylactic use in individuals (e.g., postsurgery) or in groups (e.g., prevention of meningococcal disease). In veterinary medicine there are notable differences in the ways that antimicrobials are used in companion animals (e.g., dogs, cats, pet birds, horses) compared to food-producing animals. Antimicrobial use practices in companion animals are broadly similar to those in humans; that is, the drugs are mostly administered on an individual animal basis for the treatment of clinical infection, with some use for prophylaxis in individual animals, such as postsurgery (29, 30). In the case of food animals, however, when some animals in a group are clinically infected and in need of antimicrobial therapy, for reasons of practicality and efficiency, the drugs are frequently administered through feed or water to the entire group (e.g., pens of pigs, flocks of broilers), even when the majority of the animals are not displaying signs of infection (in effect, prophylaxis). This is, however, now defined inappropriately by many in the animal health sector as "therapeutic" use. In addition, there is use in food animals similar to what happens in people, when antimicrobials are used to treat individual clinically sick animals (e.g., dairy cows with mastitis) (23). "Metaphylaxis" is a term used variously to describe therapeutic and/or prophylactic treatment at the group level, usually in the context of mass administration of therapeutic doses of an antimicrobial to a group of animals at high risk of infection, e.g., administration of an injectable antimicrobial to groups of calves upon arrival at a feedlot because of a high risk of bovine respiratory disease (23, 31). Antimicrobial prophylaxis in groups of people is uncommon and is usually limited to the management of serious, highly communicable infections such as meningococcal disease. Even in those cases, for example, meningococcal disease in a child at school, antimicrobials are recommended to be limited to those with prolonged and close contact (usually those in the same household) and not to be given to all pupils in same school or classroom (32).

Many in industry justify group-level treatments as therapeutic when clinical infections are observed in at least some of the animals in the pen or flock, or prophylactic when there are no sick animals present, but they are at high risk of clinical bacterial infection due to exposure to infectious agents (e.g., mixing of animals from different sources), unsanitary or crowded conditions, or other factors (e.g., age, stress of transport) (31).

The most controversial type of group treatment in food animals is long-term, low-dose mass medication for purposes of growth promotion. The controversy is rooted partially in the propensity of this practice to select for antimicrobial resistance and partially in its justification on economic grounds, rather than for treatment of clinical infection. Antimicrobial growth promoters

are important contributors to antimicrobial resistance because they are administered to entire groups of animals, usually for prolonged periods of time and often at subtherapeutic doses—conditions which favor the selection and spread of resistant bacteria within and between groups of animals, as well as to humans through food or other environmental pathways (33). The period of exposure is usually greater than 2 weeks and often is for almost the entire life of an animal, e.g., in chickens for 36 days. It is imprudent to extensively use antimicrobials for economic reasons alone when it is clear that such use selects for resistance to antimicrobials of importance to human and animal health (6, 27, 34, 35) and also may have relatively little or no economic benefits (35, 36). Based on experimental studies, mostly conducted decades ago, the purported production benefits of antimicrobial growth promoters range widely (1 to 10%), but surveillance and animal production data from Europe suggest that benefits in animals reared in good conditions are probably quite small and may now be nonexistent. In the past, benefits were derived mainly from the disease prophylaxis properties of the antimicrobials used, rather than enhancement of feed efficiency or other production effect (35). Some large poultry corporations are now marketing chicken raised without antimicrobials administered at the hatchery or farm levels (36).

Concerns are expressed that antimicrobial growth promoters are used to compensate for poor hygiene and housing and as a replacement for proper animal health management (14, 34, 35). For these reasons, the World Health Organization (WHO) advocates for the termination of the use of antimicrobials for growth promotion (6, 34, 37), and the practice has been banned in Europe and elsewhere and phased out in some other countries, such as the United States and Canada (38–40). Recently, the World Organization for Animal Health (OIE) reported that 41% of 146 countries reporting on antimicrobial use in animals allow the use of antimicrobial growth promoters. This represents a reduction from 51% of 151 reporting countries in 2012 (41). Among the drugs allowed are several categorized by WHO as critically important to humans, for example, colistin, fluoroquinolones, and macrolides (42).

ONE HEALTH ANTIMICROBIAL RESISTANCE CASE STUDIES

The following two case studies illustrate some of the antimicrobial resistance problems that arise from the use of the same classes of antimicrobials in humans and animals, as well as the challenges that arise from competing interests and imbalances of risk and benefit in various sectors. The first case, which focuses on the third-generation cephalosporins, illustrates One Health issues concerning an antimicrobial intended mainly for therapeutic purposes in animals, but in some important situations it is also used prophylactically. The second case features colistin, which illustrates One Health considerations arising from an older class of antimicrobial that has long been used in animals for therapeutic, prophylactic, and in some countries, growth promotion purposes, but quite recently has gained importance to human health.

Third-Generation Cephalosporins

Third-generation cephalosporins are broad-spectrum beta-lactam antimicrobials that are widely used in humans and animals. Cefotaxime, ceftriaxone, and several other members of the class are used for a wide variety of frequently serious infections of humans, particularly in hospital settings, e.g., urinary tract, abdominal, lung, and bloodstream infections due to *Escherichia coli*, *Klebsiella pneumoniae*, and other bacteria, but also in community settings, e.g., *Neisseria gonorrhoeae* (42). Because of their important role in the therapy of many bacterial infections where resistance has become a major problem, third-generation cephalosporins have been classified as "critically important" for human health (42).

Ceftiofur is the principal third-generation cephalosporin for veterinary use; others include cefpodoxime, cefoperazone, and cefovecin. Ceftiofur is approved in many countries for the treatment of several bacterial infections, predominantly in food-producing animals. It is limited to parenteral administration, so treatment usually is administered to individual animals, either singly or in groups (43). Depending on the species, it is used to treat pneumonia, arthritis, polyserositis, septicemia, metritis, meningitis, and infections of other body systems (44). However, it is also sometimes used in mass therapy (metaphylaxis or prophylaxis). This can be either under an approved label claim (e.g., injection of feedlot cattle for control of bovine respiratory disease) or off-label (e.g., injection of hatching eggs or day-old chicks for prevention of *E. coli* infections). Factors that favor the use of ceftiofur include its broad-spectrum activity, clinical efficacy, zero withdrawal time of milk from treated lactating dairy animals (due to its high maximum residual level [MRL]), and availability of a long-acting preparation (43, 44).

In Europe, where high-quality data on antimicrobial consumption in animals are available, approximately

14 tonnes of third- and fourth-generation cephalosporins were used in 2014, mainly in food animals (25). This represented about 0.16% of total antimicrobial consumption in animals in Europe. In the United States, total consumption of all cephalosporins (not just third-generation) in animals was approximately 32.3 tonnes in 2015 (45).

In many countries, cephalosporins are commonly used in humans. For example, in Europe, as a percentage of total defined daily dose per 1,000 inhabitants per day for systemic use, cephalosporins accounted for a range of 0.2% (Denmark) to 23.5% (Malta) in 2012; a total of 101 tonnes of third-generation cephalosporins for use in Europe were consumed overall in humans (26). In the United States, approximately 82 tonnes of third-generation cephalosporins for use in humans were consumed in 2011 (46). Among countries that report antimicrobial consumption data, quantities of third-generation cephalosporins used in humans are greater than in animals.

Resistance to the third-generation cephalosporins is mediated by extended-spectrum beta-lactamases (ESBLs) and AmpC beta-lactamases (43). ESBL genes are highly mobile and are transmitted on plasmids, transposons, and other genetic elements. AmpC beta-lactamases were originally reported to be chromosomal but have also been identified on plasmids and shown to have spread horizontally among *Enterobacteriaceae* (43). Unfortunately, in many countries resistance to third-generation cephalosporins is common among *E. coli* and *K. pneumoniae* from severe human infections (47, 48), placing greater reliance on the few remaining classes of available antimicrobials, such as carbapenems. Resistance to these drugs is accompanied by serious public health consequences; a systematic review conducted by the WHO reported that patients with third-generation cephalosporin-resistant *E. coli* infections had a 2-fold increase in all-cause mortality, bacterium-attributable mortality, and 30-day mortality compared with susceptible infections (1). Resistance has also been reported in *Salmonella*, particularly mediated by CMY-2 AmpC beta-lactamase genes, and these are frequently colocated with genes encoding resistance to other classes of antimicrobials, including tetracyclines, aminoglycosides, and sulfonamides. As a consequence, coselection of beta-lactam resistance in *Enterobacteriaceae* (including cephalosporin resistance) by use of other antimicrobials in animals, including tetracyclines administered in feed, has been reported (49).

Much of the spread of *E. coli* with ESBL and other beta-lactamases is thought to be clonal, but there is also horizontal dissemination of the responsible genes in a variety of bacterial species from humans, animals, and the environment (43, 50). Several studies conducted in Europe and the United States have attempted to determine the relatedness of ESBL-bearing *E. coli* from humans, animals (particularly poultry), and food (50–52). In some studies, there was only limited relatedness of ESBL-containing *E. coli* isolates (53), but other studies comparing isolates from animals, food, and human infections have found higher similarity in ESBL genes in plasmids as well as some similar clones (53–55). This includes studies using whole-genome sequencing. One group failed to demonstrate evidence for recent clonal transmission of cephalosporin-resistant *E. coli* strains from poultry to humans but instead found evidence that cephalosporin resistance genes are mainly disseminated in animals and humans via distinct plasmids (50). If one considers the large numbers of different *E. coli* clones likely to be present in food animals, plus the wide distribution of foods and their ingestion by people, it is not surprising that "clonal" transmission is only rarely detected compared to plasmid distribution and exchange. However, it is still unclear to what extent beta-lactamase-bearing *E. coli* strains from animals are directly responsible for human infections. Given the high human disease burden from these organisms, however, even if this was only a small fraction, it is still very important.

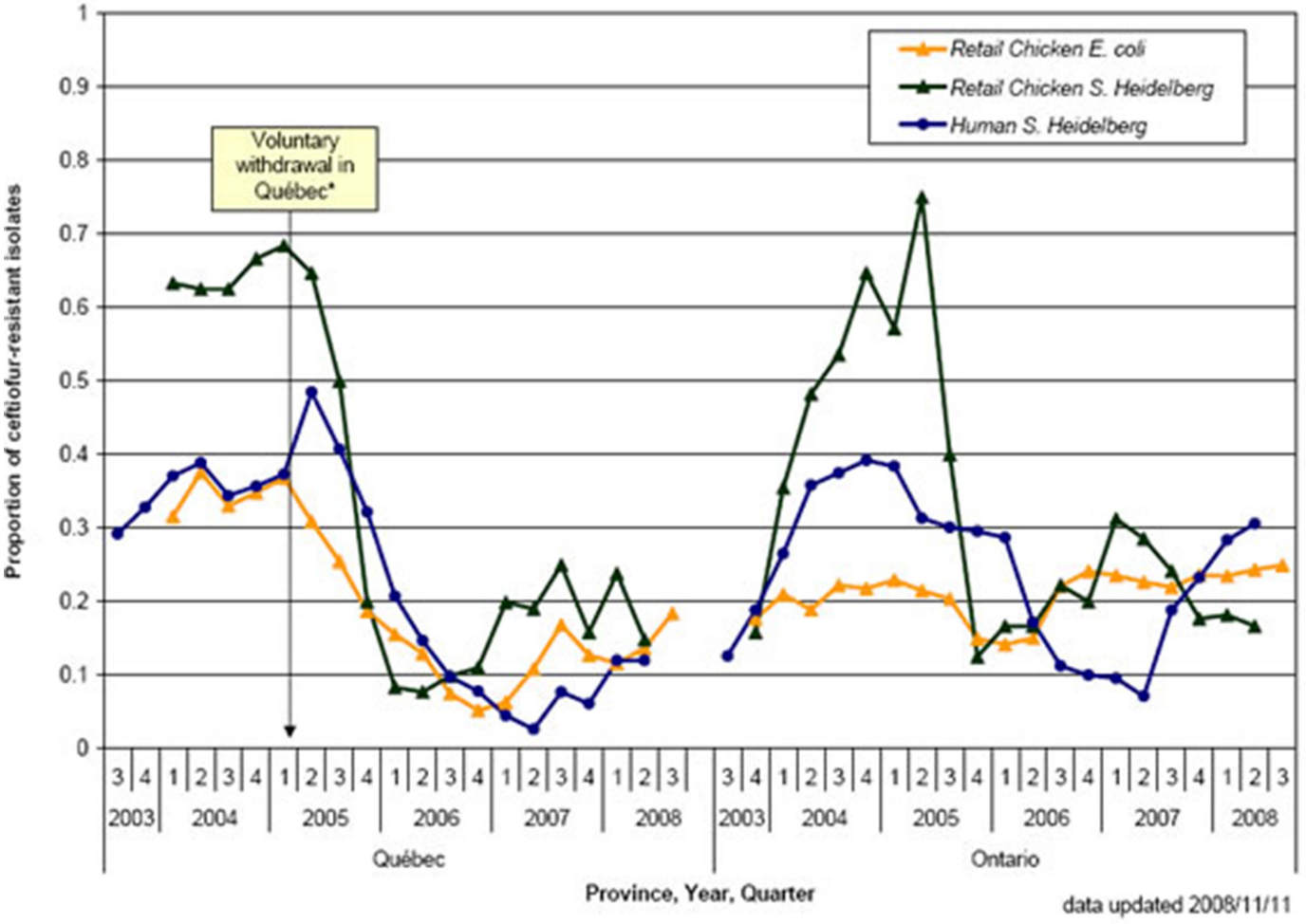
The critical importance of third-generation cephalosporins to human health and serious concerns about the ease with which resistance emerges and spreads, both clonally and horizontally, have focused considerable attention on their use in animals, particularly with regard to mass medication of ceftiofur to groups of animals (26, 33, 43). As mentioned above, the requirement for parenteral administration places practical limits on mass medication to certain situations, such as injection of steers on arrival at the feedlot or routine injection of pigs. However, one such mass exposure application that is now severely restricted in many countries has been convincingly shown to provide powerful selection pressure for resistance in *E. coli* and *Salmonella*. It involves administration of ceftiofur to eggs or day-old chicks at the hatchery using highly automated equipment that injects small quantities of the drug to the many thousands of hatching eggs or chicks intended for treated flocks (56, 57). The main reason for this treatment is prophylaxis against *E. coli* infections and/or yolk sac infections. This practice has been shown to select for cephalosporin resistance in *Salmonella enterica* serovar Heidelberg, an important cause of human illness in many countries that is typically associated with consumption of contami-

nated poultry products (58). Surveillance conducted by the Canadian Integrated Program for Antimicrobial Resistance Surveillance detected a high degree of temporal correlation in trends of resistance to ceftiofur (and ceftriaxone, a drug of choice for the treatment of severe cases of salmonellosis in children and pregnant women) among *Salmonella* Heidelberg from clinical infections in humans, from poultry samples collected at retail stores, and in *E. coli* from poultry samples collected at retail stores (56) (Fig. 2). Voluntary termination of this use of ceftiofur in hatcheries in the province of Quebec was followed by a precipitous drop in the prevalence of resistance to ceftiofur; subsequent reintroduction of its use, apparently in a more limited way, was followed by a return to higher levels of resistance (57).

In recognition of the resultant human health risks, in 2014, the Canadian poultry industry placed a voluntary ban on the use of ceftiofur and other critically important antimicrobials for disease prophylaxis (Chicken Farmers of Canada, http://www.chickenfarmers.ca/what-we-do/antibiotics/faq/). In Japan, voluntary withdrawal of the off-label use of ceftiofur in hatcheries in 2012 was also followed by a significant decrease in broad-spectrum cephalosporin resistance in *E. coli* from broilers (59). Some other countries (e.g., Denmark) have also placed voluntary restrictions on its use (60). The label claim for day-old injection of poultry flocks was withdrawn in Europe, while some countries banned off-label use of third-generation cephalosporins (e.g., the United States) (43, 61), and in other countries there is a requirement that use be restricted to situations where no other effective approved drugs are available for treatment (62).

From the One Health antimicrobial resistance perspective, the third-generation cephalosporins are good

FIGURE 2 Ceftiofur resistance in chicken and human *Salmonella* Heidelberg and chicken *E. coli*. Reprinted from the Public Health Agency of Canada (56) with permission of the publisher.



examples of antimicrobials that are considered critically important for both human and animal health (Table 1) and for which the main concerns for selection and spread of resistance from animals to humans derive from their use as mass medications in large numbers of animals, for either therapy or prophylaxis. In this regard, there are parallels with fluoroquinolones, another class of critically important antimicrobials, to which resistance among *Campylobacter jejuni* isolates emerged following mass medication of poultry flocks (63–65). In Australia, where fluoroquinolones were never approved in food animals, fluoroquinolone-resistant strains in food animals remain very rare (66).

Given the critical importance of these two classes of antimicrobials to human medicine and the clear evidence that treatment of entire groups of animals selects for resistance in important pathogens that spread from animals to humans (57, 65), third- and fourth-generation cephalosporins and fluoroquinolones should be used rarely, if at all, in animals, and only when supporting laboratory data demonstrate that no suitable alternatives of less human health importance are available (37). Their use as mass medications should be restricted.

Colistin

Colistin is a member of the polymixin class of antimicrobials, which have been used in both human and veterinary medicine for over 50 years (67). Polymixins, which cause nephrotoxicity and neurotoxicity in people (68), were until recently mainly limited to topical use in humans and treatment of infections in cystic fibrosis patients (by inhalation as colistimethate sodium). Colistin is gaining importance as a drug of last resort for parenteral use in the treatment of multiresistant Gram-negative infections including carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *K. pneumoniae*, and *E. coli*, mainly in intensive care units in certain

TABLE 1 Classification of importance of antimicrobial classes for human health and animal health

Category	Human health (WHO) (42)	Animal health (OIE) (162)
Critically important	Aminoglycosides Ansamycins Carbapenems and other penems Cephalosporins (3rd and 4th generation) Phosphonic acid derivatives Glycopeptides Glycylcyclines Lipopeptides Macrolides and ketolides Monobactams Oxazolidinones Penicillins (natural, aminopenicillins, and antipseudomonal) Polymyxins Quinolones Drugs used solely to treat tuberculosis or other mycobacterial diseases	Aminoglycosides Amphenicols Cephalosporins (3rd and 4th generation) Macrolides Penicillins (natural, aminopenicillins, aminopenicillins with beta-lactamase inhibitor, antistaphylococcal) Fluoroquinolones Sulfonamides Diaminopyrimidines Tetracyclines
Highly important	Amidinopenicillins Amphenicols Cephalosporins (1st and 2nd generation) and cephamycins Lincosamides Penicillins (antistaphylococcal) Pleuromutilins Pseudomonic acids Riminofenazines Steroid antibacterials Streptogramins Sulfonamides, dihydrofolate reductase inhibitors, and combinations Tetracyclines	Ansamycin—rifamycins Cephalosporins (1st and 2nd generation) Ionophores Lincosamides Phosphonic acid Pleuromutilins Polymyxins (including bacitracin and other polypeptides) 1st-generation quinolones (flumequin, miloxacin, nalidixic acid, oxolinic acid)
Important	Aminocyclitols Cyclic polypeptides Nitrofurantoins Nitroimidazoles	Aminocoumarin Arsenical Bicyclomycin Fusidic acid Orthosomycins Quinoxalines Streptogramins Thiostrepton

countries (69–71). Where approved for use in food animals (e.g., Brazil, Europe, China), most colistin is administered orally to entire groups of pigs, poultry, and in some cases calves, for treatment and prophylaxis of diarrhea due to Gram-negative infections (67, 71, 72). In some countries colistin is also used for growth promotion (41). Other claims for polymixins exist, including mastitis in cows, systemic endotoxemia in horses, and skin and eye infections in companion animals, but the quantities used for these purposes are small (67). In countries where colistin is approved for use in food animals and for which antimicrobial consumption data are available, the quantities consumed for animal production vastly exceed those used in humans. In Europe, for example, colistin use in humans is quite low overall, at 0.012 defined daily doses per 1,000 inhabitants per day in 2014, although there is considerable between-country variation, and there has been an increase in recent years (73). Animal use of colistin in Europe also varies widely, for example, from 0 mg/population correction unit (PCU) (Finland, Iceland, and Norway) to 34 mg/PCU (Spain) in 2013 (67). In 2013, total consumption in animals in Europe was 495 tonnes—99.7% in oral form (e.g., for oral solution, medicated feed premix, and oral powder) (67). Liu et al. reported that in China, with the world's largest production of pigs and poultry, an estimated 12,000 tonnes of colistin was used in food animal production (72).

Until recently, limited data on colistin resistance were available, partly because of technical difficulties in phenotypic susceptibility testing (67, 74), and it was not included in panels for routine resistance surveillance in Gram-negative bacteria from animals, food, the environment, and humans. Mandatory monitoring for colistin resistance in *Salmonella* and *E. coli* from animals and some foods was initiated in Europe in 2014 (75), when it was reported that 0.9% of 4,037 *E. coli* isolates from broilers and 7.4% of 1,663 *E. coli* isolates from fattening turkeys demonstrated phenotypic colistin resistance (>2 mg/liter.) (67). Resistance was also found in 8.3% of isolates from broilers, 4.4% from broiler meat, 2% from turkeys, and 27.7% from turkey meat; a large proportion of resistant isolates were *S. enterica* serovar Enteritidis (but this may represent a type of intrinsic resistance rather than resistance by an acquired chromosomal or plasmid-mediated mechanism [75]). Multidrug resistance was common; among 162 colistin-resistant *E. coli* isolates from poultry or poultry meat, 91.4% were resistant to three or more other antimicrobials; 120 (74.1%) of the isolates were also resistant (using epidemiological cutoff values) to either ciprofloxacin or ceftriaxone. Multidrug resistance was less common among *Salmonella* isolates with phenotypic colistin resistance (67).

Until very recently it was thought that acquired colistin resistance was limited to chromosomal mutation and was essentially nontransferable (67). In November 2015, however, Liu et al. (72) reported a transferable plasmid-mediated colistin resistance gene, *mcr-1*, in *E. coli* isolates obtained from animals, food, and human bloodstream infections from China. Spread of the gene by conjugation has been shown in *K. pneumoniae*, *Enterobacter aerogenes*, other *Enterobacter* spp., and *P. aeruginosa* (72). Aided by the rapid application of whole-genome sequencing techniques to strain collections around the world, retrospective analyses have revealed the *mcr-1* gene in several bacterial species isolated from human, animal, and environmental samples in numerous countries (76–79), and the gene was found in about 5% of healthy travelers (80). The earliest identification of the gene thus far was in *E. coli* from poultry collected in the 1980s in China (81). In Europe, the *mcr-1* gene is still relatively uncommon; for example, Doumith et al. reported that within large United Kingdom databases, *mcr-1* was detected in 15 of 24,000 (0.0625%) isolates of *Salmonella* spp., *E. coli*, *Klebsiella* spp., *Enterobacter* spp., and *Campylobacter* spp., from human and food samples collected between 2012 and 2015 (82). The *mcr-1* gene has also been detected in isolates obtained from wildlife and surface water samples, demonstrating environmental contamination (83). Now even more plasmid-mediated colistin resistance genes have been reported. This started with a novel *mcr-2* gene in *E. coli* from pigs in Belgium (84), and *mcr-3*, *mcr-4*, and *mcr-5* genes have been reported in many other bacterial species and in many countries (85).

Colistin illustrates some important One Health dimensions of antimicrobial resistance that differ from those of the third-generation cephalosporins. These relate, in particular, to the history and patterns of colistin use in humans and animals and to the subsequent emergence of resistance to the polymyxin class of antimicrobials, probably driven by large volumes of colistin used in animals rather than by use in humans. As mentioned above, for many years the toxicity and availability of other safer and more effective antimicrobials limited colistin to mainly topical uses in people. However, with the emergence of multidrug resistance in many Gram-negative bacteria, there has been increasing need for this drug to treat severe, life-threatening infections in humans in some countries. The colistin case demonstrates (once again) that using large quantities of

antimicrobials for group treatments or growth promotion in animals can lead to significant antimicrobial resistance problems for human health, even if the drug class is initially believed to be less important, because the relative importance of antimicrobials to human health changes. The European Medicines Agency (EMA) has recommended an overall reduction of the use of polymixins in animals, with national targets of 5 mg/PCU and 1 or below 1 mg/PCU for countries with previous high and moderate use, respectively (67).

This closely parallels the experience of the 1990s with avoparcin, a glycopeptide antimicrobial growth promoter used widely in pig and poultry production that was initially thought not to be of public health importance. However, another glycopeptide, vancomycin, was critically important in the treatment of life-threatening methicillin resistant *Staphylococcus aureus* (MRSA) and for enterococcal infections of humans (the latter especially in penicillin-allergic patients) (86). Surveillance and research eventually were able to show that avoparcin use in animals contributed to the selection and widespread dissemination of vancomycin-resistant enterococci and glycopeptide resistance genes in enterococci from animals, food, humans, and the environment (87). There should be no need to repeat this lesson; antimicrobials, even if at some times regarded as only of minor importance to human health (e.g., colistin), should not be administered to groups of animals for routine disease prophylaxis or growth promotion.

HISTORY OF ONE HEALTH DIMENSIONS OF ANTIMICROBIAL RESISTANCE

The history of efforts to address the One Health dimensions of antimicrobial use in food animals is in some ways a study of country-by-country variation in the application of the available scientific evidence to antimicrobial policy (for more detail see reference 88). Public health concerns about antimicrobial use in animals have since the 1950s focused on both microbiological and toxicological effects (89, 90). While the latter are largely beyond the scope of this article, it can be argued that the generally successful approaches that quickly evolved to assess and manage the toxicological risks have made it more difficult to address the more challenging microbiological risks from antimicrobial resistance. It is fairly straightforward, using pharmacokinetics and pharmacodynamics, to predict rates of depletion of antimicrobial residues in edible products (meat, milk, eggs) from treated animals and, along with toxicological dose-response data from animal studies, to determine the concentrations of antimicrobial residue in foods (so-called maximum residue levels, or MRLs) that are compatible with acceptable levels of risk in exposed humans (91). This enables the establishment of a "withdrawal time," the time from administration of a drug until residues in foods from animals are reliably below the MRL for that drug. Regulations requiring avoidance of above-MRL (i.e., unsafe) and potentially chemically toxic concentrations of antimicrobial residues were widely established many years ago and are enforced with testing programs and penalties (31). For decades, veterinarians and farmers administering therapeutic antimicrobials to animals have been well aware of the need to adhere to withdrawal times to maintain product quality. This is a simple concept that was straightforward in application, easily communicated and enforced, and did not really interfere with the veterinarian's access to antimicrobials, so long as the withdrawal times and other label requirements were followed. On the other hand, this does not take into account antimicrobial resistance. The dynamics of antimicrobial resistance are not nearly as predictable, and microbiological risks cannot so easily be assessed, managed, and communicated in such a simple, straightforward manner as drug toxicity (33, 92, 93), and this has plagued the timely development and implementation of One Health approaches to address antimicrobial resistance in animals.

Concerns about the human health antimicrobial resistance risks from antimicrobial use in animals initially focused on administration of antimicrobials in animal feeds, particularly those administered without veterinary prescription for growth promotion (88). In 1968, the Swann Committee recommended separate regulation of "feed antibiotics" and "therapeutic antibiotics," such that the latter should be available for use in animals only under veterinary prescription (94). These recommendations were soon adopted in the United Kingdom and elsewhere in Europe, and as a consequence, the use of penicillins, tetracyclines, sulfonamides, and other antimicrobials with therapeutic applications in humans and animals became no longer available over-the-counter in Europe for use as growth promoters (95). However, the United States, Canada, and many other countries did not follow the European example of distinctly separating antimicrobials for food animals into those for veterinary use and those for feed additives.

Concerns about antimicrobial feed additives were not limited to Europe; since 1969, several U.S. organizations (e.g. National Academy of Sciences, Food and Drug Administration ([FDA], Office of Technology Assessment)

have deliberated on the use of antimicrobial drugs in animals, particularly in feeds (96–100), but early attempts to withdraw approval for "subtherapeutic" (growth-promotion) administration of antimicrobials from animal feeds were met with arguments that there was inadequate epidemiological evidence that the resultant antimicrobial-resistant bacteria are commonly transmitted to humans and cause serious illness (98). In 1987, the FDA asked the National Academy of Sciences Institute of Medicine to review the human health consequences and risk associated with including subtherapeutic levels of penicillin and tetracyclines in animal feed (101). The Institute of Medicine committee concluded that there was insufficient direct evidence to establish conclusively the presence of a human health hazard from such use, but the committee found a substantial body of indirect evidence, particularly for *Salmonella*. They developed a quantitative risk assessment model, the first in this field, using data from epidemiological surveillance and published literature, and concluded that the estimated annual number of fatal antimicrobial-resistant salmonellosis cases in the United States due to subtherapeutic use of penicillin and tetracycline was most likely about 40 but ranged from 1 to 400. They went on to use the risk assessment model to identify the fraction of these cases attributable to antimicrobial uses in livestock feed and estimated that these "excess deaths" were in the range of 6 per year in the United States (101). Unfortunately, the assembled indirect evidence and formal quantitative risk assessment findings were apparently insufficient for U.S. regulatory purposes, since the FDA proposal to withdraw "subtherapeutic" (low-dose, long-term administration) use of penicillin and tetracycline from animal feeds was not implemented (98). It is remarkable that the finding of excess deaths could be considered acceptable from a regulatory perspective. After another 3 decades of evidence gathering, and with greater societal and stakeholder acceptance that something must be done about growth promoters, the FDA recently introduced guidance for the voluntary removal of claims for growth promotion and other "production uses" of medically important antimicrobials in the United States (40). The choice of a voluntary approach may at least in part reflect the previous difficulties with forced withdrawals where the burden of proof is placed on the regulator.

The 1990s saw a resurgence in concerns about antimicrobial resistance in the human, agricultural, and veterinary sectors. In particular, growth promoter use of avoparcin and therapeutic use of fluoroquinolones featured prominently in these concerns, along with the emergence and spread of multiple-resistant *S. enterica* serovar Typhimurium DT104 (34, 102). As mentioned previously, avoparcin was a glycopeptide antimicrobial that was used as a feed additive in Europe, Australia, and many other countries and that selected for resistance to vancomycin, another glycopeptide (34, 103). At the same time, increasing concerns about resistance to the fluoroquinolone class among important human pathogens focused attention on the use of these drugs in animals, particularly in poultry, where they were typically administered in water at the flock level (102). Endtz and coworkers demonstrated convincingly that fluoroquinolone resistance among *C. jejuni* isolated from poultry and clinical infections of humans emerged soon after veterinary use of the drugs was introduced (63). In the United States, an application to approve fluoroquinolone use in poultry was met with concern that it would compromise the effectiveness of the drug class for the treatment of human infections. The FDA eventually approved the application, but to address resistance concerns restricted off-label use of the drug in food animals and established the U.S. National Antimicrobial Resistance Monitoring program in 1996 to improve food chain surveillance of antimicrobial resistance of human health concern. Within a short time, surveillance and research confirmed that fluoroquinolone use in poultry did indeed adversely affect human health by selecting for resistance to this class of drugs in *C. jejuni*, and the FDA withdrew its approval of its use in poultry, but this required a prolonged legal process (65).

In 1986, Sweden was the first European country to ban antimicrobial growth promoters in food animals (34). Denmark, through a combination of voluntary industry initiatives and regulatory action, terminated the use of avoparcin in 1995 and then other antimicrobial growth promoters by 1999 (35). Subsequently, the European Union terminated the use of all antimicrobial growth promoters as of January 1, 2006. The European Union has continued to permit therapeutic use of approved antimicrobials in animals, including fluoroquinolones and some other critically important antimicrobials for humans, with some restrictions, for example, that third-generation cephalosporins should not be used in poultry (104).

The history of some of these major attempts to address One Health antimicrobial resistance issues reveals remarkable differences between countries in the speed and efficiency with which they made major regulatory changes to the availability of antimicrobials for use in animals on the basis of concerns about human health. This is especially the case for drugs that had been on the market for years. Globally, Europe and the United States

have been the dominant centers of regulatory activity, with some other countries more or less following suit, particularly with U.S. approaches. Broadly speaking, European countries have been more nimble in moving forward with major regulatory changes to antimicrobial availability (e.g., implementation of the Swann recommendations and, later, the outright ban on antimicrobial growth promoters), and this may reflect a greater willingness in Europe to exercise precaution in favor of public health when making antimicrobial policy. The United States, while quite ready to exercise precaution in some stages of the drug licensing process (e.g., preapproval human safety evaluation), has been hampered by demands for higher levels of proof of adverse effects on human health (by legislatures and industry groups) to justify revoking specific drug authorizations for animals (e.g., subtherapeutic uses of penicillin and tetracycline in livestock feed and fluoroquinolone for the treatment of poultry).

RISKS TO PUBLIC HEALTH AND ANIMAL HEALTH

Antimicrobial resistance is harmful to health because it reduces the effectiveness of antimicrobial therapy and tends to increase the severity, incidence, and cost of infection (4, 105). Antimicrobial use in humans has been associated with resistance in numerous important human pathogens affecting various body systems (2), and there is now considerable evidence that antimicrobial use in animals is an important contributor to antimicrobial resistance among pathogens of humans, in particular, common enteric pathogens such as *Salmonella* spp., *Campylobacter* spp., *Enterococcus* spp., and *E. coli* and in some cases other bacteria that can also be zoonotic, e.g., *S. aureus* (7, 14, 23, 33, 34). There is also increasing concern that exposure of bacteria to heavy metals and biocides (e.g., disinfectants, antiseptics) in animals and environmental niches may coselect for resistance to antimicrobials (106).

Nontyphoidal *Salmonella* is among the most common bacteria isolated from foodborne infections of humans. It has been estimated that globally, there are around 94 million cases, including 155,000 deaths, of nontyphoidal *Salmonella* gastroenteritis each year (1). Animals are the most important reservoirs of nontyphoidal *Salmonella* for humans, and resistance has been associated with antimicrobial use in animals, along with other management factors such as mixing of animals from different sources and transport (33, 94, 101, 107). Fecal shedding by carrier animals is an important source of antimicrobial-resistant *Salmonella* contamination of meat and poultry products (33) and may also be responsible for fruit and vegetable contamination through fecal contamination of the environment (108). *Salmonella* resistance to any medically important antimicrobial is a public health concern, but particularly to those critically important to human health, such as cephalosporins and fluoroquinolones (33, 34, 57), for which therapeutic options can be limited. Therapy in some groups (e.g., children and pregnant women) can be very restricted because of issues of toxicity with many antibiotics. Beta-lactams such as third-generation cephalosporins often may be the only therapy available to treat serious infections.

Concerns have been expressed that fluoroquinolone use in food animals is linked to quinolone resistance in *Salmonella* (34, 102, 109, 110). Surveillance data compiled by WHO indicate that rates of fluoroquinolone resistance in nontyphoidal *Salmonella* vary widely by geographical region. For example, rates are relatively low in Europe (2 to 3%), higher in the Eastern Mediterranean region (up to 40 to 50%), and wide-ranging in the Americas (0 to 96%) (1). Many *Salmonella* strains are also resistant to antimicrobials that have long been used as growth promoters in many countries (e.g., Canada, the United States), including tetracyclines, penicillins, and sulfonamides (34, 107). Antimicrobial resistance in some of the more virulent *Salmonella* serovars (e.g., Heidelberg, Newport, Typhimurium) has been associated with more severe infections in humans (33, 101, 105, 111). Resistance to other critically important antimicrobials continues to emerge in *Salmonella*; for example, a carbapenem-resistant strain of *Salmonella* was identified on a pig farm that routinely administered prophylactic cephalosporin (ceftiofur) to piglets (112).

C. jejuni infections are among the most common food- and waterborne infections in many countries, and while antimicrobial treatment is typically not indicated in uncomplicated cases, because they are usually self-limiting, resistance to some antimicrobials, e.g., fluoroquinolones, has been associated with greater severity, including longer duration of infection (105, 113). As mentioned above, fluoroquinolone resistance is associated with the use of this drug in animals, especially in poultry, where it is typically administered as a mass medication in drinking water (63, 64). In Australia, where fluoroquinolones have never been licensed for use in poultry but are widely used in humans, quinolone resistance among *C. jejuni* isolates from human infections remains very low (66). Macrolides are widely

used in animals, and in many countries they are administered in feed to groups of animals and in some cases as growth promoters, and such uses have been associated with macrolide resistance in *Campylobacter* (33, 40).

E. coli is an important pathogen of both humans and animals. In humans, *E. coli* is a common cause of serious bacterial infections, including enteritis, urinary tract infection, and sepsis. For example, reported rates of bloodstream *E. coli* infections in developed countries ranged between 30 and 50 episodes per 100,000 population annually in the past (114, 115). Currently in England, the rate is about 64 cases per 100,000 per year and rising. A large and increasing proportion is antimicrobial resistant (116). These higher rates are also being seen in countries with good surveillance systems in place, e.g., Denmark (60).

In animals, *E. coli* is responsible for enteritis, various extra-intestinal infections such as mastitis in lactating animals, and septicemia. In poultry, *E. coli* causes cellulitis, salpingitis, synovitis, and omphalitis (yolk sac infections) (117). Some *E. coli* strains appear to be species-specific pathogens, while others are capable of infecting multiple species, including humans. Many *E. coli* strains appear to behave as commensals of the gut of animals and humans but may be opportunistic pathogens as well as donors of resistance genetic elements for pathogenic *E. coli* or other species of bacteria (51, 118). Although antimicrobial resistance is a rapidly increasing problem in *E. coli* infections of both animals and humans, the problem is better documented for isolates from human infections, where resistance is extensive, particularly in developing countries (1, 119). Humans are regularly exposed to antimicrobial-resistant *E. coli* through foods and inadequately treated drinking water (120, 121). Resistance to third-generation cephalosporins, fluoroquinolones, and/or carbapenems is increasing in many regions, particularly in developing countries (1, 119). Travelers from developed countries are at risk of acquiring multiresistant *E. coli* from other people or contaminated food and/or water (114, 121, 122). There are now serious problems with ESBL *E. coli* in both developing and developed countries, and foods from animals, poultry in particular, have been implicated as sources for humans (50, 53, 55), although the magnitude of the contribution from food animals is uncertain. WHO is attempting to improve this situation by the establishment and expansion of integrated surveillance of antimicrobial resistance in foodborne bacteria using the application of a One Health approach, which will help establish links and calculate risks including by using newer methodologies such as whole-genome sequencing (123). WHO has also reported wide-ranging rates of *E. coli* resistance to third-generation cephalosporins, for example, up to 48% in the Americas and 70% in Africa and South-East Asia (1). A systematic review of the health burden from third-generation cephalosporin resistance (including ESBL) in *E. coli* infections relative to susceptible infections revealed a significant 2-fold increase in all-cause mortality, bacterium-attributable mortality, and 30-day mortality. Patients with fluoroquinolone-resistant *E. coli* infections experienced a significant 2-fold increase in all-cause mortality and 30-day mortality (1).

MRSA is an important pathogen of humans in both community and hospital settings, causing skin, wound, bloodstream, and other types of infection (1, 124, 125). Serious staphylococcal infections in people are common: about 10 to 30 per 100,000 inhabitants per year (126). WHO reports that beta-lactam resistance (i.e., MRSA) is a global problem, with rates of resistance of up to 80 to 100% in Africa, up to 90% in the Americas, and up to 60% in Europe (1). Systematic review of the health burden of MRSA relative to methicillin-susceptible *S. aureus* showed that patients with predominantly healthcare-associated MRSA infections experienced a significant increase in all-cause mortality, bacterium-attributable mortality, and intensive care unit mortality and septic shock (1). Community acquired MRSA bacteremia has increased with time, and the disease is associated with more necrotizing pneumonia and cutaneous abscesses, although with less endovascular infection compared to more sensitive strains of *S. aureus*. Unlike healthcare-associated infections, patients with community-acquired MRSA bacteremia did not have higher mortality than did patients with more sensitive strains of *S. aureus* (127).

S. aureus and other staphylococci are also recognized pathogens of animals; for example, they are responsible for cases of mastitis in cattle and skin infections in pigs and companion animals (128, 129). MRSA was until recently relatively rare in animals, but strains pathogenic to humans have emerged in several animal species (129–132). Transmission to humans is currently thought to be mainly through contact with carrier animals (132). The predominant strain isolated from animals, sequence type 398, while pathogenic to humans, is not considered a major epidemic strain (128, 129). Antimicrobial use in livestock, as well as lapses in biosecurity within and between farms and international trade in animals, food, or other products are factors contributing to the spread of this pathogen in animals (129, 133).

ONE HEALTH CONSIDERATIONS FROM THE ENVIRONMENT

Antimicrobial resistance in other pathogens as well as gut commensals and bacteria in other ecological niches can also be driven by antimicrobial use in animals and humans. One Health includes consideration of the environment as well as human and animal health (19, 134). The ecological nature of antimicrobial resistance is a reflection and consequence of the interconnectedness and incredible diversity of life on the planet (18). Many pathogenic bacteria, the antimicrobials that we use to treat them, and genes that confer resistance have environmental origins (e.g., soil) (8, 16, 135). Some important resistance genes, such as beta-lactamases, are millions of years old (135, 136). Soil and other environmental matrices are rich sources of highly diverse populations of bacteria and their genes (135, 137). Antimicrobial resistance to a wide variety of drugs has been demonstrated in environmental bacteria isolated from the preantibiotic era, as well as from various sites (e.g., caves) free of other sources of exposure to modern antimicrobials (8, 134, 136, 138). Despite having ancient origins, there is abundant evidence that human activity has an impact on the resistome, which is the totality of resistance genes in the wider environment (135, 137, 138). Hundreds of thousands of tonnes of antimicrobials are produced annually and find their way into the environment (14, 24). Waste from treatment plants and the pharmaceutical industry, particularly if inadequately treated, has been shown to release high concentrations of antimicrobials into surface water (14, 15, 139, 140). Residues and metabolites of antimicrobials are constituents of human sewage, livestock manure, and aquaculture, along with fecal bacteria and resistance genes (137, 141–143). Sewage treatment and composting of manure reduce concentrations of some but not all antimicrobials and microorganisms, which are introduced to soil upon land application of human and animal biosolids (144).

Various environmental pathways are important routes of human exposure to resistant bacteria and their genes from animal and plant reservoirs (14, 112) and provide opportunities for better regulations to control antimicrobial resistance (Fig. 3). In developed countries with good-quality sewage and drinking water treatment, and where most people have little to no direct contact with food-producing animals, transmission of bacteria and resistance genes from agricultural sources is largely foodborne, either from direct contamination of meat and poultry during slaughter and processing, or indirectly from fruit and vegetables contaminated by manure or irrigation water (33, 65, 108). In countries with poor sewage and water treatment, drinking water is likely to be very important in the transmission of resistant bacteria and/or genes from animals (114, 134, 139). Poor sanitation also facilitates indirect person-person waterborne transmission of enteric bacteria among residents as well as international travelers who return home colonized with resistant bacteria acquired locally (119, 145). Through these and other means, including globalized trade in animals and food and long-distance migratory patterns of wildlife, antimicrobial-resistant bacteria are globally disseminated.

General measures to address antimicrobial resistance in the wider environment include improved controls on pollution from industrial, residential, and agricultural sources. Improved research as well as environmental monitoring and risk assessment are required to better understand the role of the environment in the selection and spread of antimicrobial resistance and to identify more specific measures to address resistance in this sector (11, 14, 116, 119, 135, 146).

ONE HEALTH STRATEGIES TO ADDRESS ANTIMICROBIAL RESISTANCE

WHO and other international agencies (e.g., Food and Agriculture Organization [FAO], OIE), along with many individual countries, have developed comprehensive action plans to address the antimicrobial resistance crisis (6, 147–153). The WHO Global Action Plan seeks to address five major objectives, discussed in the following subsections. The WHO Global Action Plan embraces a One Health approach to address antimicrobial resistance, and it calls on member countries to do the same when developing their own action plans (6).

Improve Awareness and Understanding of Antimicrobial Resistance through Effective Communication, Education, and Training

Antimicrobial resistance is a rapidly evolving, highly complex topic, not least its One Health dimensions, which feature various forms of antimicrobial use within human, animal, and environmental sectors, accompanied by selection of antimicrobial resistance among bacteria in a wide variety of niches and with serious consequences to the health of humans and animals. At the most basic level, everyone should understand the principles of basic hygiene to prevent the spread of infections, understand the need to follow the antimicrobial prescriber's instructions for treatment, and have a basic appreciation of the risks to themselves and others

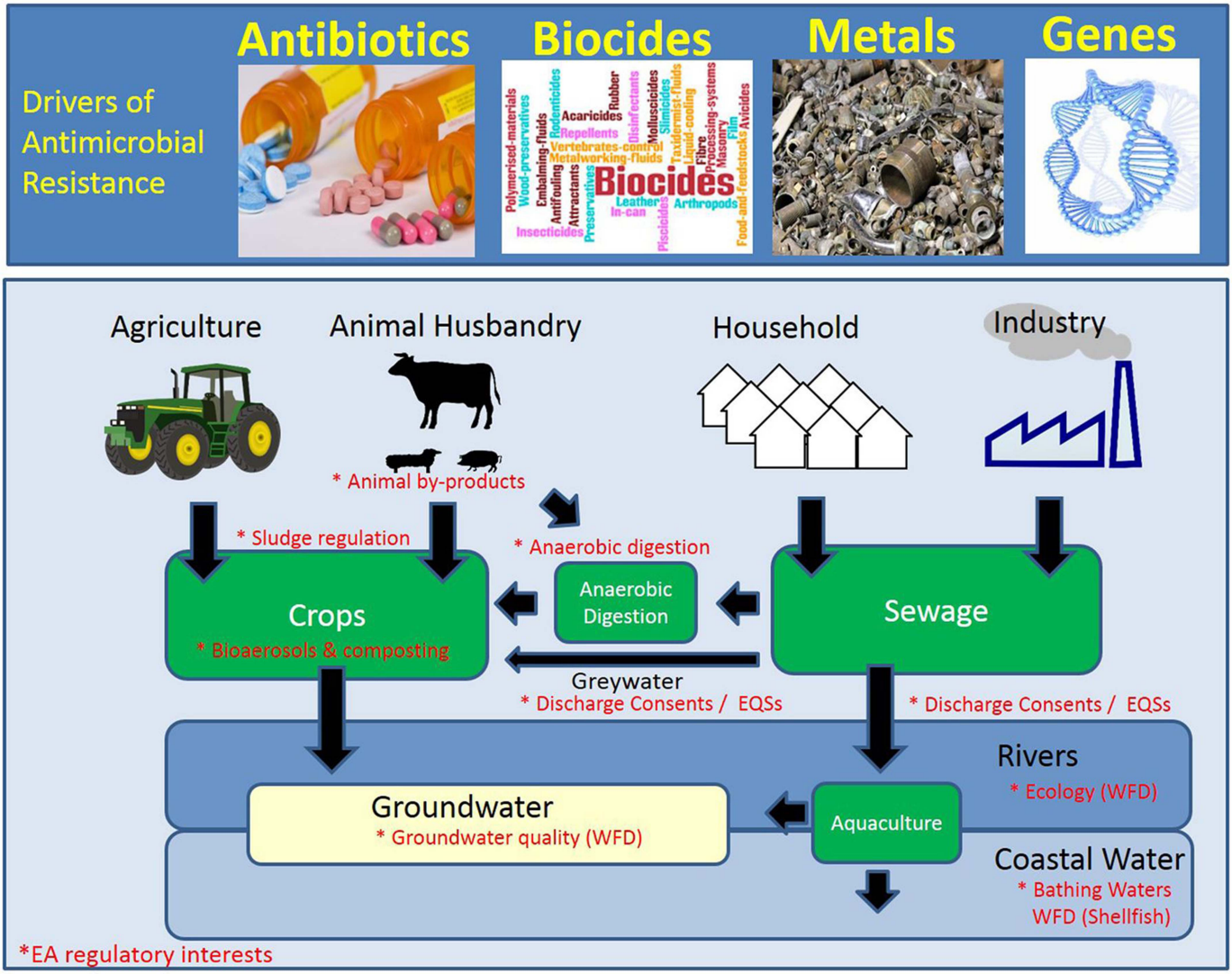


FIGURE 3 Schematics of the hotspots and drivers of antimicrobial resistance. The environmental compartments that are currently monitored or regulated by the Environmental Agency (EA; England) are denoted by an asterisk in red. WDF, Water Framework Directive. Reprinted from *Frontiers in Microbiology* (140) with permission of the publisher.

associated with antimicrobial use, in addition to the benefits (4, 6). This applies to antimicrobial use in humans as well as animals. While all can benefit from a more in-depth understanding of the One Health dimensions of antimicrobial resistance, those with particular need include companion animal owners, farmers, veterinarians, and others involved in food production and the wider food industry. The depth of understanding that these groups require varies. Animal owners should understand that some bacterial infections are shared by animals and humans and that they should follow veterinary advice on antimicrobial use and prevention of disease transmission. Farmers should understand how to raise animals, fruits, and vegetables with no or minimal use of antimicrobials and ideally use them only for the treatment of clinically ill individual animals. They also need to know how to reduce the need for antimicrobial treatment by improving overall levels of husbandry and minimizing overcrowded, unsanitary, and stressful conditions that promote the spread of disease in populations of animals and plants (154, 155). Veterinarians who prescribe antimicrobials and advise farmers on disease prevention obviously require a deeper understanding of the One Health dimensions of antimicrobial resistance. Veterinarians should possess the knowledge, attitudes, and behaviors that characterize good antimicrobial

stewardship, thereby protecting the health and welfare of their patients, the economic interests of their clients, as well as the health of the wider community (147, 153–155). Human health professionals would also benefit from a good understanding of the One Health aspects of antimicrobial resistance and a better understanding and implementation of the mechanisms that help control the spread of pathogens, including resistant bacteria, e.g., by infection control, improved hygiene, improved sanitation, etc. All health professionals should have a good understanding of the modifiable drivers of antimicrobial resistance (Fig. 4) and be motivated to reduce their impact on antimicrobial resistance selection and spread.

Opportunities to enhance awareness and understanding of One Health dimensions of antimicrobial resistance include the health promotion and health protection programs offered by pubic health and animal health organizations, consumer information campaigns (public, animal owners), farmer outreach activities, veterinary consultations, farm industry publications (farmers), veterinary curricula, and professional development programs (veterinarians, physicians).

Strengthen the Knowledge and Evidence Base through Surveillance and Research

Surveillance and research are essential because they identify antimicrobial resistance problems and how to prevent them (1, 6). There are many gaps in our understanding of the complex biology that characterizes the One Health dimensions of resistance, but many advances have been made in recent years that support evidence-based interventions to address antimicrobial resistance (4, 7, 136).

Surveillance of antimicrobial resistance and antimicrobial use in both human and nonhuman sectors is necessary to estimate the extent, patterns, and health burden of resistance at the national, regional, and international levels (123, 156). Such surveillance should be able to detect emerging trends in antimicrobial resistance of clinical significance to humans and animals (1, 26, 56). Surveillance should inform educational efforts to minimize antimicrobial resistance, as well as antimicrobial use policies and antimicrobial stewardship programs (4, 6, 7). Surveillance is also needed to measure the effectiveness of interventions and other measures that are taken to control antimicrobial resistance (17, 157). One Health surveillance of antimicrobial resistance should include sampling of appropriate bacteria from specimens collected in various human, animal, and environmental settings including hospitals, extended-care and community settings, veterinary clinics, farms, food, and the environment (e.g., wildlife, soil, water) (17, 123, 155). Surveillance of antimicrobial use should also be conducted in human, veterinary, and

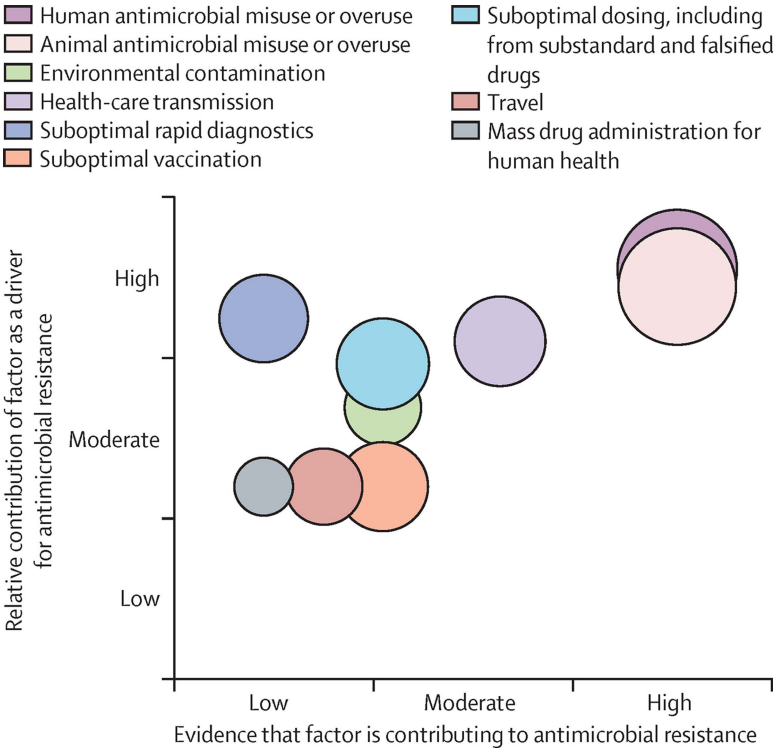


FIGURE 4 Role of modifiable drivers for antimicrobial resistance: a conceptual framework. Reprinted from Lancet (8) with permission of the publisher.

agricultural settings and should provide estimates of antimicrobial consumption in humans and animal species at the national level along with suitable denominators (e.g., population size, numbers of animals, PCUs) to enable comparisons among countries (17, 60, 123). To provide information that is useful for assessing and guiding prescribing practices and antimicrobial use behaviors, antimicrobial use monitoring should also take place at the level of prescribing (e.g., hospitals, community, veterinary clinic, farm) (60, 123, 158). Surveillance data should be analyzed, interpreted, and presented in an integrated fashion across sectors, and reports should be timely in order to be useful to relevant stakeholders (60). WHO has provided guidance on harmonized, integrated surveillance of antimicrobial resistance and antimicrobial use to assist developed and developing countries in implementing their own national surveillance programs and to contribute to improved global surveillance activities which are essential for better coordination of international efforts to contain antimicrobial use (123).

Targeted research is essential to demonstrate how resistance develops and spreads within and between ecological niches and species of bacteria, including pathogens as well as enteric commensals and environmental bacteria (4, 11, 33). To reduce antimicrobial use in animals, additional research is needed for suitable cost-effective alternatives to antimicrobials for disease prevention and enhancement of growth and production efficiency (7, 14, 15). Additional research is also needed to support antimicrobial stewardship such as improved diagnostic tools, ways to improve antimicrobial prescribing and utilization behaviors, and better vaccines (4–6).

Reduce the Incidence of Infection through Effective Sanitation, Hygiene, and Infection Prevention Measures

Infection control in healthcare settings, particularly hospitals, is a well-recognized and important means to limit the spread of antimicrobial resistance in humans (16, 118). In veterinary clinics, however, formal infection control programs are underutilized (159, 160). At the farm level, infection control in the form of biosecurity and other disease control programs is important in most food animal industries, particularly for intensive production in the poultry and swine sectors (7, 23). Some animal disease control programs are applied at the national level, particularly to prevent the introduction of exotic animal pathogens to the national herd, while others are applied at the farm level (147, 154, 155). These programs usually target production-limiting animal pathogens or specific zoonoses, and the extent to which they are effective in limiting the spread of antimicrobial resistance, particularly in nonpathogenic bacteria, is rarely if ever evaluated. Nevertheless, to reduce the need for antimicrobial use in animals, whether for treatment or prophylaxis, it is important to adopt health management measures to prevent disease in animals, particularly those responsible for the largest quantities of medically important antimicrobials (e.g., *Streptococcus suis* infections and diarrhea in pigs, pneumonia in calves, *E. coli* infections in broilers, mastitis in dairy cows) (31, 155).

To reduce human exposure to the spread of antimicrobial resistance from environmental sources and pathways, it is also important to implement measures to improve the safety of food and drinking water, particularly in underdeveloped countries, and to control environmental pollution from the pharmaceutical industry (118, 135, 140). Foodborne pathogen reduction programs at the farm, slaughter, and further processing levels are important for controlling the spread of enteric bacteria such as *Salmonella* and *Campylobacter* to humans (154). Likewise, measures to improve the microbiological quality of drinking water (from source water protection through to disinfection) as well as proper sewage treatment are important to reduce exposure to bacteria from environmental sources, as well as to reduce indirect human-human transmission of enteric bacteria (both susceptible and resistant) (16, 114).

Optimize the Use of Antimicrobial Medicines in Human and Animal Health

A One Health approach to improved antimicrobial stewardship involves a range of regulatory, voluntary, and other means to preserve the effectiveness of antimicrobials in human, animal, and agricultural settings (4). This approach should include interventions to promote judicious use of antimicrobials, as well as monitoring of antimicrobial utilization and mechanisms for continued improvement of prescribing and utilization (7, 147, 160). A One Health approach to stewardship requires some alignment of activities in the various sectors (human, veterinary, agriculture) to achieve the overall goal of preserving antimicrobial effectiveness for both humans and animals (6, 160). This involves finding a way of balancing the sometimes-competing interests that exist in the different sectors, and this can be contentious. Typically, human health interests predominate, but animal health and welfare are also important considerations (37). In our view, economic interests are subordinate to health considerations. From the One Health perspective, antimicrobial stewardship programs

should seek to ensure that antimicrobials are reserved for the treatment of clinical infections in humans and animals that occur despite the existence of good infection control and other programs designed to minimize the need for treatment (147, 155, 160). Overall, there is greater emphasis on national regulatory interventions to control antimicrobial resistance in the veterinary/agricultural sectors than in human medicine (160). This is a reflection of the importance that society places on the health of humans relative to other interests, and with it, a more frequent need in the veterinary/agricultural sectors for mandatory controls and restrictions that are best applied at a systems level, rather than relying on voluntary measures at the prescriber or user level. Regulatory approval of antimicrobials for use in animals normally depends on the demonstration that such use is safe for humans (through exposure to residues in food and selection of antimicrobial resistance) as well as being safe for animals and efficacious (31, 40, 62). Examples of regulatory interventions taken to address antimicrobial resistance include the ban on the use of antimicrobial growth promoters in food-producing animals in the European Union, restriction of the extra-label use of fluoroquinolones and third-generation cephalosporin in animals in the United States, and the prescription-only availability of antimicrobials for veterinary use in many countries (7, 35, 61).

Drug classification is an important tool for addressing antimicrobial resistance. From the One Health perspective, the most important classification schemes are those that categorize antimicrobials with respect to their importance to human and animal health (Table 1). Beginning in 2005 and then updated at regular intervals, WHO has developed a scheme to classify antimicrobials used in humans into three categories: critically important, highly important, and important (42, 161). The purpose of the classification is to guide risk management strategies to prevent and control antimicrobial resistance from food animal production. Two criteria are used for classification, and additional criteria are used to prioritize those antimicrobial classes in the critically important category. Examples of the highest-priority classes are quinolones and third- and fourth-generation cephalosporins (42, 161).

The OIE has developed a system of classification of antimicrobials of importance to animal health (162). The list was first adopted by the OIE in 2007 and then updated in 2013 and 2015. It was based on information obtained from a survey of OIE member countries. There is considerable overlap of the WHO and OIE lists; for example, third- and fourth-generation cephalosporins, fluoroquinolones, and macrolides are found in the critically important category of antimicrobials on both lists (Table 1). Some individual countries (e.g., Canada, United States) and the European Union have developed their own approaches to categorizing antimicrobial classes with respect to importance to human health (62). It would be useful to harmonize the criteria used in these different classifications of antimicrobials with respect to human health and to make progress in reconciling the overlap in the human and animal lists (163).

There are several ways to incorporate this antimicrobial classification into antimicrobial risk management strategies. One example is to eliminate the growth promotion uses of medically important antimicrobials (i.e., classes within the critically important, highly important, and important categories of the WHO list) (34, 37, 155). This strategy has been used in the European Union and Korea and is being implemented in other countries (e.g., Canada, United States) (38, 39). Another way is to completely restrict the use in animals of certain microbials that are critically important in humans. For example, in the European Union carbapenems, glycopeptides, monobactams, and some other classes are not licensed for use in food animal species, nor may they be used off-label in these species, and in companion animals they may be used only in exceptional circumstances (38, 62). It is also possible to utilize categorization in schemes involving treatment cascades or formularies (e.g., first-line, second-line, etc. choices). For example, the European Union stipulates that in consideration of their importance to human health, third- and fourth-generation cephalosporins and fluoroquinolones should be used only when there are no alternative antimicrobials authorized for the target species and indications (38, 62). Another application of antimicrobial classification is the promotion of antimicrobial stewardship by industry. For example, the McDonald's corporation, Perdue, Tyson Foods, and other major food companies have adopted antimicrobial use policies that require suppliers to restrict food animal use of antimicrobials classified by WHO as critically important for human medicine (36, 164, 165).

Develop the Economic Case for Sustainable Investment that Takes Account of the Needs of All Countries and Increase Investment in New Medicines, Diagnostic Tools, Vaccines, and Other Interventions

While this particular objective of the WHO Global Action Plan is aimed largely at the human health sector,

there is also a need for investments in the animal health sector that reduce the need for antimicrobials, such as additional vaccines and other nonantimicrobial disease control strategies.

CURRENT ROLES OF INTERNATIONAL ORGANIZATIONS IN ONE HEALTH ASPECTS OF ANTIMICROBIAL RESISTANCE

Several international organizations have made important One Health contributions to the containment of antimicrobial resistance. Since the early 1990s, WHO has undertaken several expert, multidisciplinary, multisectoral consultations and advisory groups, compiled considerable objective evidence of and scientific opinion about the human health impacts of antimicrobial use in animals, and formulated wide-ranging recommendations applicable to all stakeholders (e.g., regulatory authorities, pharmaceutical industry, animal production industry, veterinarians, farmers, public health, consumers) (155). The first was the 1997 report Medical Impact of the Use of Antimicrobials in Food Animals (34), which was quickly followed by numerous others (6, 35, 102, 155). The need to consider the human health importance of antimicrobials when managing antimicrobial resistance in animals led to the previously mentioned work by WHO to categorize antimicrobial classes according to their relative importance in human medicine (42, 161). Furthermore, since 2008, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance has issued six reports that include scientific information, guidelines for integrated surveillance of antimicrobial resistance and antimicrobial use, and recommendations in support of global efforts to contain antimicrobial resistance, particularly in the developing world (37, 123, 166). WHO recently launched new guidelines on the use of medically important antimicrobials in food-producing animals, recommending that farmers and the food industry stop using antimicrobials routinely to promote growth and prevent disease in healthy animals. The purpose of the guidelines is to preserve the effectiveness of antimicrobials that are important for human health by reducing their excessive use in animals (37).

The OIE has contributed technical guidance on antimicrobial resistance and antimicrobial use monitoring, antimicrobial resistance risk analysis, and the prudent use of antimicrobials in veterinary medicine and aquaculture (167, 168). As mentioned previously, the OIE also developed a list of critically important antimicrobials for animal health (162).

Codex Alimentarius is a set of international food standards administered under the auspices of the FAO and WHO. In 2001, in recognition of the importance of antimicrobials to human health as well as animal health, Codex recommended that the FAO, OIE, and WHO jointly address antimicrobial resistance issues. One outcome was a series of joint FAO/WHO/OIE expert workshops on nonhuman antimicrobial usage and antimicrobial resistance that implicitly took a One Health perspective (33, 154, 163, 169).

The 29th session of the Codex Alimentarius Commission established the Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance with a mandate to propose guidelines for risk analysis of foodborne antimicrobial resistance (170). These guidelines are most applicable to national public health agencies that regulate the nonhuman use of antimicrobials (92). There is a focus on foodborne antimicrobial resistance (to the exclusion of nonhuman sectors, such as companion animals and the environment) because Codex is a food standards organization. This undertaking built on previous work on risk assessment and management of foodborne chemical and microbiological hazards conducted by Codex, as well as the OIE and VICH (International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products). The resulting Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CAC/GL 77-2011) provide a methodology for evidence-based decision-making and policy formation on One Health dimensions of antimicrobial resistance and will be particularly important if antimicrobial resistance control becomes an international trade issue (170).

On the international front, the European Union has been very active in One Health antimicrobial resistance activities, particularly with regard to the regulation of antimicrobials for veterinary use and in the integrated surveillance of antimicrobial resistance and antimicrobial use (17, 25, 26, 38, 43, 67, 104, 110, 124, 171–173). The European action plan to address antimicrobial resistance declared the need for a One Health approach to address antimicrobial resistance, in view of the interconnection between animal health, human health, and ecosystems (147). In many ways, the European approach is a model for other regions/countries to follow because it is relatively proactive, thorough, consistent with international standards, policy oriented, and well communicated through abundant publicly available information on antimicrobial use policies and the scientific information on which they are based. European agencies with important responsibilities in this One Health

approach include the EMA, the European Center for Disease Control (ECDC), and the European Food Standards Agency (EFSA). The Committee for Medicinal Products for Veterinary Use of the EMA regulates veterinary drugs across the European Union and has articulated a strategy to address antimicrobial resistance concerns that includes periodic re-evaluation of marketing authorizations, public release of decisions, promotion of alternatives to antimicrobials, advice, and reflection papers (172). An example of the latter is the recent review of colistin use in human and veterinary medicine in Europe that addresses resistance mechanisms, evidence of the selection and spread of colistin resistance, a profiling of the risks to public health from the use of colistin in animals, and risk management options, including those rejected and those recommended with full discussion of the rationale (67).

Monitoring of veterinary antimicrobial use from countries within the European Union and European Economic Area (EEA) has been conducted since 2009 under the ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) project (17, 25). ESVAC has been instrumental in developing national-level antimicrobial use data collection methodologies for the veterinary sector, technical units of measurement, and approaches for the collection of antimicrobial consumption data by animal species. ESVAC publishes annual reports on sales of veterinary antimicrobial agents in European Union/European Economic Area countries (25). Monitoring of antimicrobial use in the human health sector, conducted by the ECDC through ESAC-Net, has been in place since 2001 and focuses on consumption in the community and hospital sectors. Certain ESAC projects studied antimicrobial consumption in the community and hospital sectors. The ESAC has also conducted point-prevalence surveys of antimicrobial prescribing in hospitals and in long-term care facilities and developed indicators of appropriate antimicrobial prescribing in primary care. The ESAC data were used to explain the variation of antibiotic resistance in Europe and to assess the impact of interventions in the community (72).

Surveillance of antimicrobial resistance in Europe is conducted by the ECDC (bacteria from human infections) and EFSA (bacteria from animals and food). The ECDC and EFSA publish annual summaries of antimicrobial resistance (as well as zoonotic infections and food-borne outbreaks) for individual member states within the European Union (75). The ECDC, EFSA, and EMA have also published Joint Interagency Antimicrobial Consumption and Resistance Analysis integrated reports and analyses of antimicrobial resistance and antimicrobial use data from Europe, including analyses of statistical associations between antimicrobial resistance and antimicrobial use data across sectors (26, 171). While recognizing the limitations in the data, the analyses demonstrated positive ecologic (national level) associations between consumption of antimicrobials and resistance in bacteria to corresponding antimicrobials in both humans and animals. There were also some positive associations between antimicrobial consumption in animals and resistance in bacteria from humans. These findings reinforce the need for many countries to reduce the overall consumption of antimicrobials in both the human and animal sectors (26).

ONGOING ONE HEALTH CHALLENGES IN ADDRESSING ANTIMICROBIAL RESISTANCE

The need for a One Health approach to address antimicrobial resistance is now firmly established at the international level and is included in the action plans of many countries around the world (6, 147–153). This is fostering communication among sectors that for too long operated in isolation and offers the potential for greater coordination and understanding across sectors. Other positive developments include the establishment of integrated antimicrobial resistance and antimicrobial use surveillance systems in many countries, explicit consideration of antimicrobial resistance issues in the regulation of veterinary use of antimicrobials, a trend toward more countries terminating the use of medically important antimicrobials as growth promoters, and actions by some major food industries to use their buying power to limit the use of medically important antimicrobials in food animals. However, despite these positive signs, the available data indicate that globally, antimicrobial use is still far too excessive in both the human and animal sectors and antimicrobial resistance among important pathogens continues to increase at alarming rates (2, 4, 16, 24). Much more progress is needed in addressing these issues in the human and animal sectors on a global basis, in both developed and developing countries.

There are many challenges to improving antimicrobial stewardship in humans and animals (155, 160). These include a lack of adequate motivation for change and awareness of the need for all prescribers and users to be good antimicrobial stewards, a lack of oversight and controls on antimicrobial availability in many countries, and pressures on prescribers from patients and animal owners to use antimicrobials even when they are unnecessary (4, 7, 154). Reflection on the history of

antimicrobial use shows, not surprisingly, that we have been very quick to adopt uses for these drugs but exceedingly slow to cut back on use when it is harmful to the wider community. In the veterinary/agricultural sectors, most antimicrobials were authorized for use before there was any systematic evaluation of the potential adverse effects on antimicrobial resistance. Like pesticides, improved genetics of animals and crops, and advances in animal nutrition, large-scale use of antimicrobials was widely adopted during the post-WWII intensification and scaling-up of agriculture and is still considered in many circles as necessary for efficient food production. In some countries, agricultural interests and veterinary medical organizations have been too slow to accept the scientific evidence of harm to public health from excessive antimicrobial use in animal production and to make the changes needed to raise animals humanely with reduced use of antimicrobials. Notwithstanding the tremendous new insights provided by antimicrobial resistance research and surveillance, and major improvements in antimicrobial resistance risk analysis methodologies, there will always be uncertainties and data gaps in a subject as complex as antimicrobial resistance. Improvements in our ability to analyze bacteria and their genes using whole-genome sequencing and metagenomics in animals, people, and the environment, along with metadata analysis and phylogenetic studies should allow us to make better links and understand with more precision the ways they multiply and spread. More importantly, it will help us better track how antimicrobial resistance genes that have long been in existence spread and recirculate in plants, insects, animals, people, soil, and water. This will help us better understand what is driving the development and the spread of antimicrobial resistance and better manage it.

Nevertheless, given the highly unpredictable nature of antimicrobial resistance, and the propensity of resistance to spread between ecological niches in the human, animal, and environmental sectors, we need to be much more cautious. Antimicrobial stewardship programs should be aggressive in setting their targets to reduce antimicrobial use, and not simply focus on those practices that are most obviously linked to resistance selection, such as growth promotion. All mass medication should be aggressively addressed.

Other antimicrobial stewardship barriers to overcome include the lack of controls on the over-the-counter availability of antimicrobials for use in humans and animals in many countries, particularly in the developing world, the lack of data from most countries on the quantities and types of antimicrobials that are used, and the relatively limited uptake of animal treatment guidelines and formularies in most countries (147, 155, 123, 174). To address antimicrobial resistance on a global scale, it is important that all countries have the basic regulatory, infrastructure, oversight, and enforcement capabilities to control antimicrobial availability and use as laid out by international guidelines, such as those from WHO and OIE (147, 155, 123). Related to this is the need for good antimicrobial consumption data from all countries. Antimicrobial consumption is an essential indicator of resistance selection pressure and, when adjusted for population size, allows for comparison between countries, regions, hospitals, veterinary clinics, farms, etc. This can be a powerful tool for improving antimicrobial stewardship, as has been shown in countries that are using it (60, 158). When collected regularly at the level of prescriber or use (e.g., farm), these data can be used to evaluate and improve stewardship and to set benchmarks and reduction targets.

CONCLUSION

History has shown that it is not feasible to neatly separate antimicrobial classes into those exclusively for use in humans or animals, with the exception of new antimicrobial classes. These should probably be reserved for use in humans as long as few or no alternatives are available. The majority of classes, however, will be available for use in both sectors, and the challenge for One Health is to ensure that the use of these drugs is optimal overall. This is likely to be achieved when antimicrobials used in both sectors are used for therapy, only rarely for prophylaxis, and never for growth promotion and when we better control the types and amounts of antimicrobials plus the numbers of resistant bacteria that we allow to be placed into the environment.

REFERENCES

1. World Health Organization (WHO). 2014. *Antimicrobial Resistance: Global Report on Surveillance*. WHO, Geneva, Switzerland.

2. Centers for Disease Control (CDC). 2013. *Antibiotic Resistance Threats in the United States*. Centers for Disease Control and Prevention, Atlanta, GA.

3. Fleming A. 1945. Penicillin. Nobel lecture.

4. O'Neill J. 2016. Tackling drug-resistant infections globally: final report and recommendations. The review on antimicrobial resistance. https://amr-review.org/.

5. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O. 2013. Antibiotic resistance: the need for global solutions. *Lancet Infect Dis* **13:**1057–1098 http://dx.doi.org/10.1016/S1473-3099(13)70318-9.

6. World Health Organization (WHO). 2015. *Global Action Plan on Antimicrobial Resistance*. WHO, Geneva, Switzerland.

7. Aarestrup FM, Wegener HC, Collignon P. 2008. Resistance in bacteria of the food chain: epidemiology and control strategies. *Expert Rev Anti Infect Ther* **6:**733–750 http://dx.doi.org/10.1586/14787210.6.5.733.

8. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, Guerin PJ, Piddock LJ. 2016. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* **387:**176–187 http://dx.doi.org/10.1016/S0140-6736(15)00473-0.

9. Burow E, Käsbohrer A. 2017. Risk factors for antimicrobial resistance in *Escherichia coli* in pigs receiving oral antimicrobial treatment: a systematic review. *Microb Drug Resist* **23:**194–205 http://dx.doi.org/10.1089/mdr.2015.0318.

10. Marti E, Variatza E, Balcazar JL. 2014. The role of aquatic ecosystems as reservoirs of antibiotic resistance. *Trends Microbiol* **22:**36–41 http://dx.doi.org/10.1016/j.tim.2013.11.001.

11. Huijbers PMC, Blaak H, de Jong MCM, Graat EAM, Vandenbroucke-Grauls CMJE, de Roda Husman AM. 2015. Role of the environment in the transmission of antimicrobial resistance to humans: a review. *Environ Sci Technol* **49:**11993–12004 http://dx.doi.org/10.1021/acs.est.5b02566.

12. Woolhouse MEJ, Ward MJ. 2013. Sources of antimicrobial resistance. *Science* **341:**1460–1461.

13. Heuer OE, Kruse H, Grave K, Collignon P, Karunasagar I, Angulo FJ. 2009. Human health consequences of use of antimicrobial agents in aquaculture. *Clin Infect Dis* **49:**1248–1253 http://dx.doi.org/10.1086/605667.

14. O'Neill J. 2015. Antimicrobials in agriculture and the environment: reducing unnecessary use and waste. The review on antimicrobial resistance. https://amr-review.org/. Accessed January 3, 2018.

15. So AD, Shah TA, Roach S, Ling Chee Y, Nachman KE. 2015. An integrated systems approach is needed to ensure the sustainability of antibiotic effectiveness for both humans and animals. *J Law Med Ethics* **43**(Suppl 3):38–45 http://dx.doi.org/10.1111/jlme.12273.

16. Collignon P. 2013. The importance of a One Health approach to preventing the development and spread of antibiotic resistance, p 19–36. *In* Mackenzie JS, Jeggo M, Daszak P, Richt JA (ed), *One Health: the Human-Animal-Environment Interfaces in Emerging Infectious Diseases*. Springer, Berlin, Germany.

17. Torren-Edo J, Grave K, Mackay D. 2015. "One Health": the regulation and consumption of antimicrobials for animal use in the EU. *IHAJ* **2:**14–16.

18. Robinson TP, Bu DP, Carrique-Mas J, Fèvre EM, Gilbert M, Grace D, Hay SI, Jiwakanon J, Kakkar M, Kariuki S, Laxminarayan R, Lubroth J, Magnusson U, Thi Ngoc P, Van Boeckel TP, Woolhouse MEJ. 2016. Antibiotic resistance is the quintessential One Health issue. *Trans R Soc Trop Med Hyg* **110:**377–380 http://dx.doi.org/10.1093/trstmh/trw048.

19. Zinsstag J, Meisser A, Schelling E, Bonfoh B, Tanner M. 2012. From 'two medicines' to 'One Health' and beyond. *Onderstepoort J Vet Res* **79:**492 http://dx.doi.org/10.4102/ojvr.v79i2.492.

20. One Health Commission. 2018. What is One Health? https://www.onehealthcommission.org/en/why_one_health/what_is_one_health/. Accessed January 3, 2017.

21. Woolhouse MEJ, Gowtage-Sequeria S. 2005. Host range and emerging and reemerging pathogens. *Emerg Infect Dis* **11:**1842–1847 http://dx.doi.org/10.3201/eid1112.050997.

22. Schwabe CW. 1984. *Veterinary Medicine and Human Health*, 3rd ed. Williams & Wilkins, Baltimore, MD.

23. McEwen SA, Fedorka-Cray PJ. 2002. Antimicrobial use and resistance in animals. *Clin Infect Dis* **34**(Suppl 3):S93–S106 http://dx.doi.org/10.1086/340246.

24. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, Teillant A, Laxminarayan R. 2015. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA* **112:**5649–5654 http://dx.doi.org/10.1073/pnas.1503141112.

25. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. 2016. Sales of veterinary antimicrobial agents in 29 European countries in 2014. (EMA/61769/2016).

26. ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority), EMA (European Medicines Agency). 2015. ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. *EFSA J* **13:**4006.

27. Food and Agriculture Organization (FAO). 2016. *Drivers, Dynamics and Epidemiology of Antimicrobial Resistance in Animal Production*. FAO, Rome, Italy. http://www.fao.org/publications/card/en/c/d5f6d40d-ef08-4fcc-866b-5e5a92a12dbf/.

28. Vidaver AK. 2002. Uses of antimicrobials in plant agriculture. *Clin Infect Dis* **34**(Suppl 3):S107–S110 http://dx.doi.org/10.1086/340247.

29. Sykes JE. 2013. Antimicrobial drug use in dogs and cats, p 473–494. *In* Giguère S, Prescott JF, Dowling PM (ed), *Antimicrobial Therapy in Veterinary Medicine*, 5th ed. John Wiley & Sons, Hoboken, NJ. http://dx.doi.org/10.1002/9781118675014.ch28

30. Giguère S, Abrams-Ogg ACG, Kruth SA. 2013. Prophylactic use of antimicrobial agents, and antimicrobial chemotherapy for the neutropenic patient, p 357–378. *In* Giguère S, Prescott JF, Dowling PM (ed), *Antimicrobial Therapy in Veterinary Medicine*, 5th ed. John Wiley & Sons, Hoboken, NJ. http://dx.doi.org/10.1002/9781118675014.ch21

31. National Research Council. 1999. *The Use of Drugs in Food Animals: Benefits and Risks*. The National Academies Press, Washington, DC.

32. Health Protection Agency. 2012. Guidance for public health management of meningococcal disease in the UK. Health Protection Agency. Meningococcus and Haemophilus Forum. Updated March 2012. https://www.gov.uk/government/publications/meningococcal-disease-guidance-on-public-health-management. Accessed 20 December 2017.

33. FAO/OIE/WHO. 2003. Joint FAO/OIE/WHO expert workshop on non-human antimicrobial usage and antimicrobial resistance: scientific assessment. FAO/OIE/WHO, Geneva, Switzerland.

34. World Health Organization (WHO). 1997. *The Medical Impact of the Use of Antimicrobials in Food Animals*. WHO, Berlin, Germany.

35. World Health Organization (WHO). 2003. Impacts of antimicrobial growth promoter termination in Denmark. The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark. WHO, Geneva, Switzerland.

36. Zuraw L. 2014. Perdue announces dramatic reduction in antibiotic use in its chickens. *Food Safety News*. 4 September 2014. http://www.foodsafetynews.com/2014/09/perdue-dramatically-reduces-antibiotic-use-in-chickens/#.VQZbbtKUd8E.

37. World Health Organization (WHO). 2017. *WHO Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals*. WHO, Geneva, Switzerland.

38. European Union (EU). 2015. Guidelines for the prudent use of antimicrobials in veterinary medicine (2015/C 299/04). *Official Journal of the European Union* 11.9.2015. C 299/7-26.

39. Health Canada. 2014. Notice to stakeholders: collaborative efforts to promote the judicious use of medically-important antimicrobial drugs in food animal production. http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr-notice-ram-avis-20140410-eng.php. Accessed 3 January 2017.

40. Food and Drug Administration (FDA). 2013. New animal drugs and new animal drug combination products administered in or on medicated feed or drinking water of food-producing animals: recommendations for drug sponsors for voluntarily aligning product use conditions with GFI #209. U.S. Department of Health and Human Services, Washington, DC.

41. World Organisation for Animal Health (OIE). 2018. OIE annual report on the use of antimicrobial agents in animals. Second report. http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/Annual_Report_AMR_2.pdf.

42. WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). 2016. *Critically Important Antimicrobials for Human Medicine*, 4th revision. WHO, Geneva, Switzerland.

43. European Medicines Agency (EMA). 2009. Revised reflection paper on the use of 3rd and 4th generation cephalosporins in food producing animals in the European Union: development of resistance and impact on human and animal health. EMA, London, United Kingdom. EMEA/CVMP/SAGAM/81730/2006-Rev.1.

44. Prescott JF. 2013. Beta-lactam antibiotics, p 153–173. *In* Giguère S, Prescott JF, Dowling PM (ed), *Antimicrobial Therapy in Veterinary Medicine*, 5th ed. John Wiley & Sons, Hoboken, NJ. http://dx.doi.org/10.1002/9781118675014.ch9

45. Food and Drug Administration (FDA). 2016. Summary report on antimicrobials sold or distributed for use in food-producing animals. FDA, Department of Health and Human Services. Washington, DC. http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM534243.pdf.

46. Food and Drug Administration (FDA). 2012. Drug use review. FDA, Department of Health and Human Services. Washington, DC. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM319435.pdf.

47. de Kraker MEA, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, Icket C, Kalenic S, Horvatic J, Seifert H, Kaasch A, Paniara O, Argyropoulou A, Bompola M, Smyth E, Skally M, Raglio A, Dumpis U, Melbarde Kelmere A, Borg M, Xuereb D, Ghita MC, Noble M, Kolman J, Grabljevec S, Turner D, Lansbury L, Grundmann H. 2011. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. *J Antimicrob Chemother* **66:**398–407 http://dx.doi.org/10.1093/jac/dkq412.

48. Park SH. 2014. Third-generation cephalosporin resistance in Gram-negative bacteria in the community: a growing public health concern. *Korean J Intern Med* **29:**27–30 http://dx.doi.org/10.3904/kjim.2014.29.1.27.

49. Kanwar N, Scott HM, Norby B, Loneragan GH, Vinasco J, McGowan M, Cottell JL, Chengappa MM, Bai J, Boerlin P. 2013. Effects of ceftiofur and chlortetracycline treatment strategies on antimicrobial susceptibility and on *tet*(A), *tet*(B), and *bla* CMY-2 resistance genes among *E. coli* isolated from the feces of feedlot cattle. *PLoS One* **8:**e80575 http://dx.doi.org/10.1371/journal.pone.0080575.

50. de Been M, Lanza VF, de Toro M, Scharringa J, Dohmen W, Du Y, Hu J, Lei Y, Li N, Tooming-Klunderud A, Heederik DJJ, Fluit AC, Bonten MJM, Willems RJL, de la Cruz F, van Schaik W. 2014. Dissemination of cephalosporin resistance genes between *Escherichia coli* strains from farm animals and humans by specific plasmid lineages. *PLoS Genet* **10:**e1004776 http://dx.doi.org/10.1371/journal.pgen.1004776.

51. Hammerum AM, Larsen J, Andersen VD, Lester CH, Skovgaard Skytte TS, Hansen F, Olsen SS, Mordhorst H, Skov RL, Aarestrup FM, Agersø Y. 2014. Characterization of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* obtained from Danish pigs, pig farmers and their families from farms with high or no consumption of third- or fourth-generation cephalosporins. *J Antimicrob Chemother* **69:**2650–2657 http://dx.doi.org/10.1093/jac/dku180.

52. Willemsen I, Oome S, Verhulst C, Pettersson A, Verduin K, Kluytmans J. 2015. Trends in extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* and ESBL genes in a Dutch teaching hospital, measured in 5 yearly point prevalence surveys (2010–2014). *PLoS One* **10:**e0141765 http://dx.doi.org/10.1371/journal.pone.0141765.

53. Lazarus B, Paterson DL, Mollinger JL, Rogers BA. 2015. Do human extraintestinal *Escherichia coli* infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review. *Clin Infect Dis* **60:**439–452 http://dx.doi.org/10.1093/cid/ciu785.

54. Johnson JR, Sannes MR, Croy C, Johnston B, Clabots C, Kuskowski MA, Bender J, Smith KE, Winokur PL, Belongia EA. 2007. Antimicrobial drug-resistant *Escherichia coli* from humans and poultry products, Minnesota and Wisconsin, 2002–2004. *Emerg Infect Dis* **13:**838–846 http://dx.doi.org/10.3201/eid1306.061576.

55. Jakobsen L, Kurbasic A, Skjøt-Rasmussen L, Ejrnaes K, Porsbo LJ, Pedersen K, Jensen LB, Emborg H-D, Agersø Y, Olsen KEP, Aarestrup FM, Frimodt-Møller N, Hammerum AM. 2010. *Escherichia coli* isolates from broiler chicken meat, broiler chickens, pork, and pigs share phylogroups and antimicrobial resistance with community-dwelling humans and patients with urinary tract infection. *Foodborne Pathog Dis* **7:**537–547 http://dx.doi.org/10.1089/fpd.2009.0409.

56. Canadian Integrated Program for Antimicrobial Resistance (CIPARS). 2009. Update: *Salmonella* Heidelberg ceftiofur-related resistance in human and retail chicken isolates—2006 to 2008. Public Health Agency of Canada. http://www.phac-aspc.gc.ca/cipars-picra/heidelberg/heidelberg_090326-eng.php.

57. Dutil L, Irwin R, Finley R, Ng LK, Avery B, Boerlin P, Bourgault AM, Cole L, Daignault D, Desruisseau A, Demczuk W, Hoang L, Horsman GB, Ismail J, Jamieson F, Maki A, Pacagnella A, Pillai DR. 2010. Ceftiofur resistance in *Salmonella enterica* serovar Heidelberg from chicken meat and humans, Canada. *Emerg Infect Dis* **16:**48–54 http://dx.doi.org/10.3201/eid1601.090729.

58. Smith KE, Medus C, Meyer SD, Boxrud DJ, Leano F, Hedberg CW, Elfering K, Braymen C, Bender JB, Danila RN. 2008. Outbreaks of salmonellosis in Minnesota (1998 through 2006) associated with frozen, microwaveable, breaded, stuffed chicken products. *J Food Prot* **71:**2153–2160 http://dx.doi.org/10.4315/0362-028X-71.10.2153.

59. Hiki M, Kawanishi M, Abo H, Kojima A, Koike R, Hamamoto S, Asai T. 2015. Decreased resistance to broad-spectrum cephalosporin in *Escherichia coli* from healthy broilers at farms in Japan after voluntary withdrawal of ceftiofur. *Foodborne Pathog Dis* **12:**639–643 http://dx.doi.org/10.1089/fpd.2015.1960.

60. DANMAP. 2014. *2015. Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark*. DANMAP, Denmark.

61. Food and Drug Administration. New animal drugs; cephalosporin drugs; extralabel animal drug use; order of prohibition. *Fed Reg* **77:**735–745.

62. European Medicines Agency (EMA). 2014. Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170253.pdf.

63. Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van der Reyden T, Mouton RP. 1991. Quinolone resistance in *Campylobacter* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *J Antimicrob Chemother* **27:**199–208 http://dx.doi.org/10.1093/jac/27.2.199.

64. McDermott PF, Bodeis SM, English LL, White DG, Walker RD, Zhao S, Simjee S, Wagner DD. 2002. Ciprofloxacin resistance in *Campylobacter jejuni* evolves rapidly in chickens treated with fluoroquinolones. *J Infect Dis* **185:**837–840 http://dx.doi.org/10.1086/339195.

65. Nelson JM, Chiller TM, Powers JH, Angulo FJ. 2007. Fluoroquinolone-resistant *Campylobacter* species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. *Clin Infect Dis* **44:**977–980 http://dx.doi.org/10.1086/512369.

66. Cheng AC, Turnidge J, Collignon P, Looke D, Barton M, Gottlieb T. 2012. Control of fluoroquinolone resistance through successful regulation, Australia. *Emerg Infect Dis* **18:**1453–1460 http://dx.doi.org/10.3201/eid1809.111515.

67. European Medicines Agency (EMA). 2016. Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health. EMA, London, United Kingdom.

68. Falagas ME, Kasiakou SK. 2006. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* **10:**R27 http://dx.doi.org/10.1186/cc3995.

69. Falagas ME, Kasiakou SK, Saravolatz LD. 2005. Colistin: the revival of polymyxins for the management of multidrug-resistant Gram-negative bacterial infections. *Clin Infect Dis* **40:**1333–1341 http://dx.doi.org/10.1086/429323.

70. Linden PK, Kusne S, Coley K, Fontes P, Kramer DJ, Paterson D. 2003. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*. *Clin Infect Dis* **37:** e154–e160 http://dx.doi.org/10.1086/379611.

71. Fernandes MR, Moura Q, Sartori L, Silva KC, Cunha MPV, Esposito F, Lopes R, Otutumi LK, Gonçalves DD, Dropa M, Matté MH, Monte DFM, Landgraf M, Francisco GR, Bueno MFC, de Oliveira Garcia D, Knöbl T, Moreno AM, Lincopan N. 2016. Silent dissemination of colistin-resistant *Escherichia coli* in South America could contribute to the global spread of the *mcr-1* gene. *Euro Surveill* **21:**30214. http://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2016.21.17.30214. http://dx.doi.org/10.2807/1560-7917.ES.2016.21.17.30214.

72. Liu Y-Y, Wang Y, Walsh TR, Yi L-X, Zhang R, Spencer J, Doi Y, Tian G, Dong B, Huang X, Yu L-F, Gu D, Ren H, Chen X, Lv L, He D, Zhou H, Liang Z, Liu J-H, Shen J. 2016. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings inChina: a microbiological and molecular biological study. *Lancet Infect Dis* **16:**161–168 http://dx.doi.org/10.1016/S1473-3099(15)00424-7.

73. European Center for Disease Prevention and Control (ECDC). 2015. Summary of the latest data on antibiotic consumption in the European Union. https://ecdc.europa.eu/en/publications-data/summary-latest-data-antibiotic-consumption-eu-2015.

74. Landman D, Georgescu C, Martin DA, Quale J. 2008. Polymyxins revisited. *Clin Microbiol Rev* **21:**449–465 http://dx.doi.org/10.1128/CMR.00006-08.

75. European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC). 2016. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014. *EFSA J* **14:**4380.

76. Catry B, Cavaleri M, Baptiste K, Grave K, Grein K, Holm A, Jukes H, Liebana E, Lopez Navas A, Mackay D, Magiorakos A-P, Moreno Romo MA, Moulin G, Muñoz Madero C, Matias Ferreira Pomba MC, Powell M, Pyörälä S, Rantala M, Ružauskas M, Sanders P, Teale C, Threlfall EJ, Törneke K, van Duijkeren E, Torren Edo J. 2015. Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health. *Int J Antimicrob Agents* **46:**297–306 http://dx.doi.org/10.1016/j.ijantimicag.2015.06.005.

77. Prim N, Rivera A, Rodríguez-Navarro J, Español M, Turbau M, Coll P, Mirelis B. 2016. Detection of mcr-1 colistin resistance gene in polyclonal *Escherichia coli* isolates in Barcelona, Spain, 2012 to 2015. *Euro Surveill* **21:**30183 http://dx.doi.org/10.2807/1560-7917.ES.2016.21.13.30183. http://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2016.21.13.30183.

78. Irrgang A, Roschanski N, Tenhagen B-A, Grobbel M, Skladnikiewicz-Ziemer T, Thomas K, Roesler U, Käsbohrer A. 2016. Prevalence of *mcr-1* in *E. coli* from livestock and food in Germany, 2010–2015. *PLoS One* **11:** e0159863 http://dx.doi.org/10.1371/journal.pone.0159863.

79. Hasman H, Hammerum AM, Hansen F, Hendriksen RS, Olesen B, Agersø Y, Zankari E, Leekitcharoenphon P, Stegger M, Kaas RS, Cavaco LM, Hansen DS, Aarestrup FM, Skov RL. 2015. Detection of *mcr-1* encoding plasmid-mediated colistin-resistant *Escherichia coli* isolates from human bloodstream infection and imported chicken meat, Denmark 2015. *Euro Surveill* **20:**30085 http://dx.doi.org/10.2807/1560-7917.ES.2015.20.49.30085. http://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2015.20.49.30085.

80. von Wintersdorff CJH, Wolffs PFG, van Niekerk JM, Beuken E, van Alphen LB, Stobberingh EE, Oude Lashof AML, Hoebe CJPA, Savelkoul PHM, Penders J. 2016. Detection of the plasmid-mediated colistin-resistance gene *mcr-1* in faecal metagenomes of Dutch travellers. *J Antimicrob Chemother* **71:**3416–3419 http://dx.doi.org/10.1093/jac/dkw328.

81. Shen Z, Wang Y, Shen Y, Shen J, Wu C. 2016. Early emergence of *mcr-1* in *Escherichia coli* from food-producing animals. *Lancet Infect Dis* **16:**293 http://dx.doi.org/10.1016/S1473-3099(16)00061-X.

82. Doumith M, Godbole G, Ashton P, Larkin L, Dallman T, Day M, Day M, Muller-Pebody B, Ellington MJ, de Pinna E, Johnson AP, Hopkins KL, Woodford N. 2016. Detection of the plasmid-mediated *mcr-1* gene conferring colistin resistance in human and food isolates of *Salmonella enterica* and *Escherichia coli* in England and Wales. *J Antimicrob Chemother* **71:**2300–2305 http://dx.doi.org/10.1093/jac/dkw093.

83. Zurfuh K, Poirel L, Nordmann P, Nüesch-Inderbinen M, Hächler H, Stephan R. 2016. Occurrence of the plasmid-borne *mcr-1* colistin resistance gene in extended-spectrum-β-lactamase-producing *Enterobacteriaceae* in river water and imported vegetable samples in Switzerland. *Antimicrob Agents Chemother* **60:**2594–2595 http://dx.doi.org/10.1128/AAC.00066-16.

84. Xavier BB, Lammens C, Ruhal R, Kumar-Singh S, Butaye P, Goossens H, Malhotra-Kumar S. 2016. Identification of a novel plasmid-mediated colistin-resistance gene, *mcr-2*, in *Escherichia coli*, Belgium, June 2016. *Eurosurveillance* **21**(27). http://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2016.21.27.30280.

85. Borowiak M, Fischer J, Hammerl JA, Hendriksen RS, Szabo I, Malorny B. 2017. Identification of a novel transposon-associated phosphoethanolamine transferase gene, *mcr-5*, conferring colistin resistance in d-tartrate fermenting *Salmonella enterica* subsp. *enterica* serovar Paratyphi B. *J Antimicrob Chemother* **72:**3317–3324 http://dx.doi.org/10.1093/jac/dkx327.

86. Levine DP. 2006. Vancomycin: a history. *Clin Infect Dis* **42**(Suppl 1)**:** S5–S12 http://dx.doi.org/10.1086/491709.

87. Bager F, Madsen M, Christensen J, Aarestrup FM. 1997. Avoparcin used as a growth promoter is associated with the occurrence of vancomycin-resistant *Enterococcus faecium* on Danish poultry and pig farms. *Prev Vet Med* **31:**95–112 http://dx.doi.org/10.1016/S0167-5877(96)01119-1.

88. Prescott JF. 2017. History and current use of antimicrobial drugs in veterinary medicine. *Microbiol Spectr* **5**(6) http://dx.doi.org/10.1128/microbiolspec.ARBA-0002-2017.

89. National Academy of Sciences – National Research Council (NAS-NRC). 1956. Proceedings, *First International Conference on the Use of Antibiotics in Agriculture*. National Academies Press, Washington, DC.

90. Food and Drug Administration (FDA). Guidance for Industry no. 209. 2012. The judicious use of medically important antimicrobial drugs in food-producing animals. FDA, Washington, DC.

91. Food and Drug Administration (FDA). 2016. Guidance for Industry no. 3. General principles for evaluating the human food safety of new animal drugs used in food-producing animals. FDA Center for Veterinary Medicine, Washington, DC. http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052180.pdf. Accessed 3 January 2017.

92. Codex Alimentarius. 2011. Guidelines for risk analysis of foodborne antimicrobial resistance. Codex Alimentarius. CAC/GL 77- 2011.

93. Food and Drug Administration (FDA). 2003. Guidance for Industry no. 152. Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. FDA, Washington, DC. http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm123614.htm. Accessed 3 January 2017.

94. Swann MM. 1969. *The Use of Antibiotics in Animal Husbandry and Veterinary Medicine*. Her Majesty's Stationery Office, London, United Kingdom.

95. Kirchhelle C. 2016. Toxic confusion: the dilemma of antibiotic regulation in West German food production (1951–1990). *Endeavour* **40:** 114–127 http://dx.doi.org/10.1016/j.endeavour.2016.03.005.

96. Harrison P, Lederberg J. (eds). 1998. "Antimicrobial Resistance: Issues and Options." Workshop Report, Forum on Emerging Infections, Division of Health and Sciences Policy, Institute of Medicine. National Academy Press: Washington, D.C.

97. National Academy of Sciences (NAS). 1980. *The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds*. National Academy Press, Washington, DC.

98. O 'Brien B. 1996. Animal welfare reform and the magic bullet: the use and abuse of subtherapeutic doses of antibiotics in livestock. *Univ Colo Law Rev* **67:**407.

99. National Academy of Sciences (NAS). 1969. *The Use of Drugs in Animal Feeds: Proceedings of a Symposium*. National Academy Press, Washington, DC.

100. U.S. Congress Office of Technology Assessment. 1995. Impacts of antibiotic-resistant bacteria, OTA-H-629. U.S. Government Printing Office, Washington, DC.

101. Institute of Medicine. 1989. *Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed*. National Academy Press, Washington, DC.

102. World Health Organization (WHO). 1998. *Use of Quinolones in Food Animals and Potential Impact on Human Health*. WHO, Geneva, Switzerland.

103. Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR). 1999. The use of antibiotic in food producing animals: antibiotic-resistant bacteria in animals and humans. Commonwealth of Australia.

104. European Medicines Agency (EMA). 2012. Referral procedure on veterinary medicinal products containing 3rd and 4th generation cephalosporins under Article 35 of Directive 2001/82/EC, as amended. EMA/253066/2012.

105. Barza M. 2002. Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. *Clin Infect Dis* **34**(Suppl 3)**:** S123–S125 http://dx.doi.org/10.1086/340249.

106. Wales AD, Davies RH. 2015. Co-selection of resistance to antibiotics, biocides and heavy metals, and its relevance to foodborne pathogens. *Antibiotics (Basel)* **4:**567–604 http://dx.doi.org/10.3390/antibiotics4040567.

107. Anderson ES. 1968. Drug resistance in *Salmonella typhimurium* and its implications. *BMJ* **3:**333–339 http://dx.doi.org/10.1136/bmj.3.5614.333.

108. Hanning IB, Nutt JD, Ricke SC. 2009. Salmonellosis outbreaks in the United States due to fresh produce: sources and potential intervention measures. *Foodborne Pathog Dis* **6:**635–648. http://dx.doi.org/10.1089/fpd.2008.0232.

109. Chiu CH, Wu TL, Su LH, Chu C, Chia JH, Kuo AJ, Chien MS, Lin TY. 2002. The emergence in Taiwan of fluoroquinolone resistance in *Salmonella enterica* serotype Choleraesuis. *N Engl J Med* **346:**413–419.

110. European Medicines Agency (EMA). 2006. Reflection paper on the use of fluoroquinolones in food-producing animals in the European Union: development of resistance and impact on human and animal health. EMA, London, United Kingdom. EMEA/CVMP/SAGAM/184651/2005.

111. Helms M, Simonsen J, Mølbak K. 2004. Quinolone resistance is associated with increased risk of invasive illness or death during infection with *Salmonella* serotype Typhimurium. *J Infect Dis* **190:**1652–1654 http://dx.doi.org/10.1086/424570.

112. Mollenkopf DF, Stull JW, Mathys DA, Bowman AS, Feicht SM, Grooters SV, Daniels JB, Wittum TE. 2017. Carbapenemase-producing *Enterobacteriaceae* recovered from the environment of a swine farrow-to-finish operation in the United States. *Antimicrob Agents Chemother* **61:** e02348-16.

113. Helms M, Simonsen J, Olsen KEP, Mølbak K. 2005. Adverse health events associated with antimicrobial drug resistance in *Campylobacter* species: a registry-based cohort study. *J Infect Dis* **191:**1050–1055 http://dx.doi.org/10.1086/428453.

114. Kennedy K, Collignon P. 2010. Colonisation with *Escherichia coli* resistant to "critically important" antibiotics: a high risk for international travellers. *Eur J Clin Microbiol Infect Dis* **29:**1501–1506 http://dx.doi.org/10.1007/s10096-010-1031-y.

115. Laupland KB, Church DL. 2014. Population-based epidemiology and microbiology of community-onset bloodstream infections. *Clin Microbiol Rev* **27:**647–664 http://dx.doi.org/10.1128/CMR.00002-14.

116. Bou-Antoun S, Davies J, Guy R, Johnson AP, Sheridan EA, Hope RJ. 2016. Descriptive epidemiology of *Escherichia coli* bacteraemia in England, April 2012 to March 2014. *Euro Surveill* **21:**30329 http://dx.doi.org/10.2807/1560-7917.ES.2016.21.35.30329. http://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2016.21.35.30329.

117. Mellata M. 2013. Human and avian extraintestinal pathogenic *Escherichia coli*: infections, zoonotic risks, and antibiotic resistance trends. *Foodborne Pathog Dis* **10:**916–932 http://dx.doi.org/10.1089/fpd.2013.1533.

118. Collignon P. 2015. Antibiotic resistance: are we all doomed? *Intern Med J* **45:**1109–1115 http://dx.doi.org/10.1111/imj.12902.

119. Walsh TR, Weeks J, Livermore DM, Toleman MA. 2011. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis* **11:**355–362 http://dx.doi.org/10.1016/S1473-3099(11)70059-7.

120. Graham DW, Collignon P, Davies J, Larsson DG, Snape J. 2014. Underappreciated role of regionally poor water quality on globally increasing antibiotic resistance. *Environ Sci Technol* **48:**11746–11747 http://dx.doi.org/10.1021/es504206x.

121. Tängdén T, Cars O, Melhus A, Löwdin E. 2010. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. *Antimicrob Agents Chemother* **54:**3564–3568 http://dx.doi.org/10.1128/AAC.00220-10.

122. Vieira AR, Collignon P, Aarestrup FM, McEwen SA, Hendriksen RS, Hald T, Wegener HC. 2011. Association between antimicrobial resistance in *Escherichia coli* isolates from food animals and blood stream isolates from humans in Europe: an ecological study. *Foodborne Pathog Dis* **8:**1295–1301 http://dx.doi.org/10.1089/fpd.2011.0950.

123. World Health Organization (WHO). 2017. *Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria. Application of a One Health Approach*. WHO, Geneva, Switzerland. http://www.who.int/foodsafety/publications/agisar_guidance2017/en/.

124. ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority) and EMA (European Medicines Agency). 2009. Joint scientific report of ECDC, EFSA and EMEA on meticillin resistant *Staphylococcus aureus* (MRSA) in livestock, companion animals and foods. EFSA-Q-2009-00612 (EFSA Scientific Report (2009) 301, 1–10) and EMEA/CVMP/SAGAM/62464/2009.

125. European Centre for Disease Prevention and Control (ECDC). 2015. *Antimicrobial Resistance Surveillance in Europe 2014. Annual Report of the European Antimicrobial Resistance Surveillance Network*. EARS-Net, Stockholm, Sweden.

126. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. 2015. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev* **28:**603–661 http://dx.doi.org/10.1128/CMR.00134-14.

127. Wang JL, Chen SY, Wang JT, Wu GH, Chiang WC, Hsueh PR, Chen YC, Chang SC. 2008. Comparison of both clinical features and mortality risk associated with bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus*. *Clin Infect Dis* **46:**799–806 http://dx.doi.org/10.1086/527389.

128. Price LB, Stegger M, Hasman H, Aziz M, Larsen J, Andersen PS, Pearson T, Waters AE, Foster JT, Schupp J, Gillece J, Driebe E, Liu CM, Springer B, Zdovc I, Battisti A, Franco A, Żmudzki J, Schwarz S, Butaye P, Jouy E, Pomba C, Porrero MC, Ruimy R, Smith TC, Robinson DA, Weese JS, Arriola CS, Yu F, Laurent F, Keim P, Skov R, Aarestrup FM. 2012. *Staphylococcus aureus* CC398: host adaptation and emergence of methicillin resistance in livestock. *MBio* **3:**e00305-11 http://dx.doi.org/10.1128/mBio.00305-11.

129. Weese JS, van Duijkeren E. 2010. Methicillin-resistant *Staphylococcus aureus* and *Staphylococcus pseudintermedius* in veterinary medicine. *Vet Microbiol* **140:**418–429 http://dx.doi.org/10.1016/j.vetmic.2009.01.039.

130. Boost MV, O'Donoghue MM, Siu KHG. 2007. Characterisation of methicillin-resistant *Staphylococcus aureus* isolates from dogs and their owners. *Clin Microbiol Infect* **13:**731–733 http://dx.doi.org/10.1111/j.1469-0691.2007.01737.x.

131. Lewis HC, Mølbak K, Reese C, Aarestrup FM, Selchau M, Sørum M, Skov RL. 2008. Pigs as source of methicillin-resistant *Staphylococcus aureus* CC398 infections in humans, Denmark. *Emerg Infect Dis* **14:**1383–1389 http://dx.doi.org/10.3201/eid1409.071576.

132. Voss A, Loeffen F, Bakker J, Klaassen C, Wulf M. 2005. Methicillin-resistant *Staphylococcus aureus* in pig farming. *Emerg Infect Dis* **11:**1965–1966 http://dx.doi.org/10.3201/eid1112.050428.

133. Dorado-García A, Dohmen W, Bos ME, Verstappen KM, Houben M, Wagenaar JA, Heederik DJ. 2015. Dose-response relationship between antimicrobial drugs and livestock-associated MRSA in pig farming. *Emerg Infect Dis* **21:**950–959 http://dx.doi.org/10.3201/eid2106.140706.

134. Finley RL, Collignon P, Larsson DGJ, McEwen SA, Li X-Z, Gaze WH, Reid-Smith R, Timinouni M, Graham DW, Topp E. 2013. The scourge of antibiotic resistance: the important role of the environment. *Clin Infect Dis* **57:**704–710 http://dx.doi.org/10.1093/cid/cit355.

135. Gaze WH, Krone SM, Larsson DG, Li XZ, Robinson JA, Simonet P, Smalla K, Timinouni M, Topp E, Wellington EM, Wright GD, Zhu YG. 2013. Influence of humans on evolution and mobilization of environmental antibiotic resistome. *Emerg Infect Dis* **19:**e120871 http://dx.doi.org/10.3201/eid1907.120871.

136. Perry JA, Wright GD. 2014. Forces shaping the antibiotic resistome. *BioEssays* **36:**1179–1184 http://dx.doi.org/10.1002/bies.201400128.

137. Ruuskanen M, Muurinen J, Meierjohan A, Pärnänen K, Tamminen M, Lyra C, Kronberg L, Virta M. 2016. Fertilizing with animal manure disseminates antibiotic resistance genes to the farm environment. *J Environ Qual* **45:**488–493 http://dx.doi.org/10.2134/jeq2015.05.0250.

138. Wellington EMH, Boxall AB, Cross P, Feil EJ, Gaze WH, Hawkey PM, Johnson-Rollings AS, Jones DL, Lee NM, Otten W, Thomas CM, Williams AP. 2013. The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria. *Lancet Infect Dis* **13:**155–165 http://dx.doi.org/10.1016/S1473-3099(12)70317-1.

139. Aubertheau E, Stalder T, Mondamert L, Ploy M-C, Dagot C, Labanowski J. 2017. Impact of wastewater treatment plant discharge on the contamination of river biofilms by pharmaceuticals and antibiotic resistance. *Sci Total Environ* **579:**1387–1398 http://dx.doi.org/10.1016/j.scitotenv.2016.11.136.

140. Singer AC, Shaw H, Rhodes V, Hart A. 2016. Review of antimicrobial resistance in the environment and its relevance to environmental regulators. *Front Microbiol* **7:**1728 http://dx.doi.org/10.3389/fmicb.2016.01728.

141. Rizzo L, Manaia C, Merlin C, Schwartz T, Dagot C, Ploy MC, Michael I, Fatta-Kassinos D. 2013. Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review. *Sci Total Environ* **447:**345–360 http://dx.doi.org/10.1016/j.scitotenv.2013.01.032.

142. Zhang QQ, Ying GG, Pan CG, Liu YS, Zhao JL. 2015. Comprehensive evaluation of antibiotics emission and fate in the river basins of China: source analysis, multimedia modeling, and linkage to bacterial resistance. *Environ Sci Technol* **49:**6772–6782 http://dx.doi.org/10.1021/acs.est.5b00729.

143. Cabello FC, Godfrey HP, Buschmann AH, Dölz HJ. 2016. Aquaculture as yet another environmental gateway to the development and globalisation of antimicrobial resistance. *Lancet Infect Dis* **16:**e127–e133 http://dx.doi.org/10.1016/S1473-3099(16)00100-6.

144. Rahube TO, Marti R, Scott A, Tien Y-C, Murray R, Sabourin L, Duenk P, Lapen DR, Topp E. 2016. Persistence of antibiotic resistance and plasmid-associated genes in soil following application of sewage sludge and abundance on vegetables at harvest. *Can J Microbiol* **62:**600–607 http://dx.doi.org/10.1139/cjm-2016-0034.

145. Collignon P, Kennedy KJ. 2015. Long-term persistence of multidrug-resistant *Enterobacteriaceae* after travel. *Clin Infect Dis* **61:**1766–1767.

146. Ashbolt NJ, Amézquita A, Backhaus T, Borriello P, Brandt KK, Collignon P, Coors A, Finley R, Gaze WH, Heberer T, Lawrence JR, Larsson DGJ, McEwen SA, Ryan JJ, Schönfeld J, Silley P, Snape JR, Van den Eede C, Topp E. 2013. Human Health Risk Assessment (HHRA) for environmental development and transfer of antibiotic resistance. *Environ Health Perspect* **121:**993–1001.

147. World Organisation for Animal Health (OIE). 2016. *The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials*. Paris, France.

148. Department of Health and Department for Environment Food & Rural Affairs. 2013. *UK Five Year Antimicrobial Resistance Strategy 2013 to 2018*. Department of Health. London, United Kingdom.

149. Public Health Agency of Canada. 2015. Federal action plan on antimicrobial resistance and use in Canada. http://healthycanadians.gc.ca/alt/pdf/publications/drugs-products-medicaments-produits/antibiotic-resistance-antibiotique/action-plan-daction-eng.pdf.

150. Commonwealth of Australia. 2016. Responding to the threat of antimicrobial resistance. Australia's First National Antimicrobial Resistance Strategy 2015–2019. https://www.health.gov.au/internet/main/publishing.nsf/Content/1803C433C71415CACA257C8400121B1F/$File/amr-strategy-2015-2019.pdf

151. European Commission, Directorate-General for Health and Consumers 2011. *Communication from the Commission to the European Parliament and the Council. Action plan against the rising threats from Antimicrobial Resistance*. COM (2011) 748, November 2011.

152. The White House. 2015. National action plan for combating antibiotic-resistant bacteria. The White House, Washington, DC.

153. Food and Agriculture Organization (FAO). 2016. *The FAO Action Plan on Antimicrobial Resistance 2016–2020*. Food and Agriculture Organization of the United Nations, Rome. Italy.

154. FAO/OIE/WHO. 2004. Second Joint FAO/OIE/WHO expert workshop on non-human antimicrobial usage and antimicrobial resistance: management options, Oslo, Norway. WHO, Geneva, Switzerland.

155. World Health Organization (WHO). 2000. Global principles for the containment of antimicrobial resistance in animals for food. Report of a WHO consultation with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties. WHO, Geneva, Switzerland.

156. Collignon P, Voss A. 2015. China: what antibiotics and what volumes are used in food production animals? *Antimicrob Resist Infect Control* **4:**16 http://dx.doi.org/10.1186/s13756-015-0056-5.

157. Dorado-García A, Mevius DJ, Jacobs JJH, Van Geijlswijk IM, Mouton JW, Wagenaar JA, Heederik DJ. 2016. Quantitative assessment of antimicrobial resistance in livestock during the course of a nationwide antimicrobial use reduction in the Netherlands. *J Antimicrob Chemother* **71:**3607–3619 http://dx.doi.org/10.1093/jac/dkw308.

158. Speksnijder DC, Mevius DJ, Bruschke CJM, Wagenaar JA. 2015. Reduction of veterinary antimicrobial use in the Netherlands. The Dutch success model. *Zoonoses Public Health* **62**(Suppl 1)**:**79–87 http://dx.doi.org/10.1111/zph.12167.

159. Murphy CP, Reid-Smith RJ, Weese JS, McEwen SA. 2010. Evaluation of specific infection control practices used by companion animal veterinarians in community veterinary practices in southern Ontario. *Zoonoses Public Health* **57:**429–438 http://dx.doi.org/10.1111/j.1863-2378.2009.01244.x.

160. Weese JS, Page SW, Prescott JF. 2013. Antimicrobial stewardship in animals, p 117–132. *In* Giguère S, Prescott JF, Dowling PM (ed), *Antimicrobial Therapy in Veterinary Medicine*, 5th ed. John Wiley & Sons, Hoboken, NJ. http://dx.doi.org/10.1002/9781118675014.ch7

161. Collignon PC, Conly JM, Andremont A, McEwen SA, Aidara-Kane A, Agerso Y, Andremont A, Collignon P, Conly J, Dang Ninh T, Donado-Godoy P, Fedorka-Cray P, Fernandez H, Galas M, Irwin R, Karp B, Matar G, McDermott P, McEwen S, Mitema E, Reid-Smith R, Scott HM, Singh R, DeWaal CS, Stelling J, Toleman M, Watanabe H, Woo GJ, World Health Organization Advisory Group, Bogotá Meeting on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR). 2016. World Health Organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies to control antimicrobial resistance from food animal production. *Clin Infect Dis* **63:**1087–1093 http://dx.doi.org/10.1093/cid/ciw475.

162. World Organisation for Animal Health (OIE). 2015. *OIE list of antimicrobial agents of veterinary importance*. OIE, Paris, France.

163. FAO/OIE/WHO. 2007. *Joint FAO/OIE /WHO Expert Meeting on Critically Important Antimicrobials*. FAO, Rome, Italy.

164. McDonald's Corporation. McDonald's global vision for antimicrobial stewardship in food animals. 2017. http://corporate.mcdonalds.com/content/mcd/sustainability/sourcing/animal-health-and-welfare/issues-we-re-focusing-on/vision-for-antimicrobial-stewardship-for-food-animals.html. Accessed 3 January 2018.

165. Tysons Foods. Antibiotic use. https://www.tysonfoods.com/news/viewpoints/antibiotic-use. Accessed 3 January 2018.

166. WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance. 2015. *Report of the 6th Meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance with AGISAR 5-Year Strategic Framework to Support Implementation of the Global Action Plan on Antimicrobial Resistance (2015–2019), Seoul*. WHO, Geneva, Switzerland.

167. World Organisation for Animal Health (OIE). 2016. Terrestrial animal health code, 25th ed. http://www.oie.int/en/international-standard-setting/terrestrial-code/access-online/. Accessed 3 January 2017.

168. World Organisation for Animal Health (OIE). 2016. Aquatic animal health code, 19th ed, 2016. http://www.oie.int/en/international-standard-setting/aquatic-code/access-online/. Accessed 3 January 2017.

169. FAO/OIE/WHO. 2006. *Antimicrobial Use in Aquaculture and Antimicrobial Resistance. Report of a Joint FAO/ OIE /WHO Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance, Seoul*. WHO, Geneva, Switzerland.

170. Codex Alimentarius Commission. 2009. Report of the 3rd session of the Codex ad hoc intergovernmental task force on antimicrobial resistance, Jeju, Republic of Korea. http://www.who.int/foodsafety/publications/thirdsession-codex/en/.

171. ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority), EMA (European Medicines Agency). 2017. ECDC/EFSA/EMA second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals – Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. *EFSA J* **15:**4872.

172. European Medicines Agency (EMA). 2015. *CVMP strategy on antimicrobials 2016–2020. EMA/CVMP/209189/2015*. Draft. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/11/WC500196645.pdf.

173. European Medicines Agency (EMA). 2015. Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals. EMA/CVMP/AWP/706442/2013. Draft. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500183774.pdf.

174. Grace D. 2015. Review of evidence on antimicrobial resistance and animal agriculture in developing countries. International Livestock Research Institute (ILRI). http://www.evidenceondemand.info/review-of-evidence-on-antimicrobial-resistance-and-animal-agriculture-in-developing-countries.