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REVIEW ARTICLE

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A history of antimicrobial drugs in animals: Evolution and revolution

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Abstract

The evolutionary process of antimicrobial drug (AMD) uses in animals over a mere eight decades (1940–2020) has led to a revolutionary outcome, and both evolution and revolution are ongoing, with reports on a range of uses, misuses and abuses escalating logarithmically. As well as veterinary therapeutic perspectives (efficacy, safety, host toxicity, residues, selection of drug, determination of dose and measurement of outcome in treating animal diseases), there are also broader, nontherapeutic uses, some of which have been abandoned, whilst others hopefully will soon be discontinued, at least in more developed countries. Although AMD uses for treatment of animal diseases will continue, it must: (a) be sustainable within the One Health paradigm; and (b) devolve into more prudent, rationally based therapeutic uses. As this review on AMDs is published in a Journal of Pharmacology and Therapeutics, its scope has been made broader than most recent reviews in this field. Many reviews have focused on negative aspects of AMD actions and uses, especially on the question of antimicrobial resistance. This review recognizes these concerns but also emphasizes the many positive aspects deriving from the use of AMDs, including the major research-based advances underlying both the prudent and rational use of AMDs. It is structured in seven sections: (1) Introduction; (2) Sulfonamide history; (3) Nontherapeutic and empirical uses of AMDs (roles of agronomists and veterinarians); (4) Rational uses of AMDs (roles of pharmacologists, clinicians, industry and regulatory controls); (5) Prudent use (residue monitoring, antimicrobial resistance); (6) International and inter-disciplinary actions; and (7) Conclusions.

KEYWORDS

antimicrobials, history, veterinary medicine

1 | INTRODUCTION

The historiography (the writing of history based on a critical examination of sources) of the actions, fate and uses of antimicrobial drugs (AMDs) in animals, and the science, welfare and economics underlying these uses, have been the subject of many thousands of articles and many millions of words. This review seeks to summarize key aspects of this history. This inevitably involves both selection from and compression of the voluminous literature. The review does not aim to prosecute past uses in the court of the present, but rather seeks to report and analyse "the what, when and why" of the history, as a basis for comprehending current uses and enabling better uses

for the future. The review is supported by Supplementary files on biographies of individuals contributing to the AMD story. A recently published Chapter on AMDs in veterinary medicine has outlined the main historical timelines of important events and trends in the use of AMDs in animals but with limited discussion of pharmacological aspects (Prescott, 2017).

2 | THE BIRTH AND INFANCY OF VETERINARY CHEMOTHERAPY; SULFONAMIDES

A comprehensive review of the sulfonamide–diaminopyrimidine story was authored in this Journal by Adelbert van Miert in 1994 (van Miert, 1994). The first sulfonamide, sulfanilamide, the active metabolite of the pro-drug Prontosil from Bayer, was first prepared in 1908 by the Austrian chemist Paul Josef Jakob Gelmo (1879–1961) but its antimicrobial properties were not recognized (Anonymous, 2019e). At the time of the discovery of its anti-infectious properties, it was not covered by patent restrictions and it therefore became available at low cost in veterinary medicine.

The first veterinary use of sulfanilamide was for bovine mastitis therapy in 1937 (Allott, 1937). Its pharmacodynamic (PD) properties were reported in ruminants in 1939 by Stableforth (1939)—cited by Roach and Hignett in their review on treatment of mastitis (Roach & Hignett, 1945). A classical early publication was the review of L. Meyer Jones on penicillin and sulfonamides, including three sulfonamides in combination, for treatment of calf pneumonia (Jones, 1946). The first epidemiological survey on the efficacy of sulfonamides, in 1948, compared percentage recovery in 1,729 cases of pneumonia in cattle in New York between 1937 and 1947. Prior to the introduction of sulfonamides, the recovery rate was 67.3%; it increased to 81% in cattle treated with sulfanilamide and to 94.6% with sulfamerazine/sulfamethazine, whilst for other treatments, the recovery rate was 77.2% (Roberts & Kiesel, 1948). Another sulfonamide innovation was the advent of the routine use of AMD incorporation in poultry feeds to prevent coccidiosis with the marketing of sulfoquinoxaline in 1948 by Merck (Campbell, 2008). The development of sensitive analytical methods for sulfonamides demonstrated the correlation between blood concentration and clinical efficacy (Stowe, 1976; Figure 1). This was notable as the first veterinary expression of the pivotal pharmacokinetic (PK)/PD paradigm.

Sensitive analytical methods also provided considerable impetus to comparative veterinary pharmacology, by highlighting major differences between domestic species in sulfonamide metabolism, distribution and excretion, illustrated by Francis' comparison of seven sulfonamides in four domestic species (Francis, 1947). At that time, PK data were presented on a categorical scale (crosses) to indicate blood concentrations as either relatively high or low and relatively long or short persistency of drugs in vivo. Less than 20 years later, Gary Koritz, of the University of Illinois, at Urbana, USA, modelled the disposition of several sulfonamides in several species, using the most advanced nonlinear regression compartmental modelling approach (Koritz, Bourne, Dittert, & Bevill, 1977; Koritz et al., 1977).

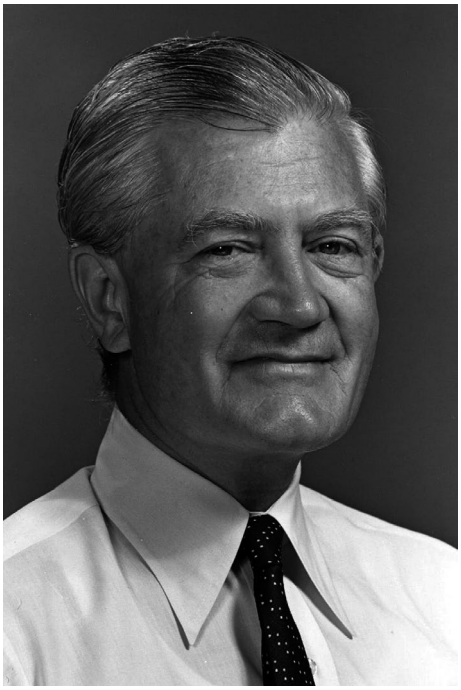

FIGURE 1 Clarence M. Stowe (1922–1995) authored more than 100 publications, especially on sulfonamides (Stowe, 1965) and antibiotics. His paper, co-authored with Sisodia, on the mechanisms of drug secretion in milk (Sisodia & Stowe, 1964) is a classic

FIGURE 2 Folke Rasmussen (1930–) published many early studies on sulfonamides in cattle. His scientific contributions include the mammary, renal and salivary excretion of drugs, bioavailability, residues and tissue tolerance of drug formulations at injection sites, focusing predominantly on antimicrobial drugs

Folke Rasmussen at the University of Copenhagen reported, in cattle and goats, that sulfonamides, penicillin, erythromycin and penethamate (penicillin) crossed the blood–milk barrier through passive diffusion, down the concentration gradient of the unionized moiety of weak organic acids and bases (Rasmussen, 1958, 1959; Figure 2). Further evidence of the applicability of the pH partition theory and the Henderson–Hasselbalch equation for veterinary drugs, including eight sulfonamides, was provided by Sisodia and Stowe of the University of Minnesota, USA (Sisodia & Stowe, 1964).

Franco Faustini, a veterinary pharmacologist at Milano University, developed several sulfonamides (on which he held many patents), specifically for use in veterinary therapeutics (Faustini & Vaghi, 1962a, 1962b). In the Netherlands, Jacques Nouws (Figure 3) published a series of papers on the comparative PK of sulfonamides in domestic species and humans, with emphasis on: acetylation-deacetylation mechanisms (Nouws, Vree, Tijhuis, & Baakman, 1983); nonlinearity of drug disposition (Nouws et al., 1985); and effect of age on PK (Nouws et al., 1986). Nouws was affiliated to a meat inspection service and he also published landmark papers on sulfonamide residues in meat and milk (Nouws, 1981). Also in the Netherlands, van Miert's group at Utrecht (see Figure 4) published a series of classical papers on comparative aspects and sex differentiation of sulfonamide disposition and metabolism (Witkamp et al., 1992). This group documented the influence of fever on sulfonamide PK (van Gogh, van Deurzen, van Duin, & van Miert, 1984) and reported correlations between structure-activity relationships of antibacterial activities and physico-chemical properties of sulfonamides (Mengelers, Hougee, Hougee, Janssen, & Van Miert, 1997).

With hindsight, it is clear from the history of sulfonamides that they established milestones and standards for the pharmacology of all veterinary drugs.

The American chemist George Hitchings (1905–1988, Nobel Laureate in 1988) was the discoverer of sulfonamide–diaminopyrimidine combinations. Trimethoprim (TMP) was the first-in-class diaminopyrimidine compound. TMP-sulfonamide combinations proved to be synergistic. Sulfamethoxazole was selected for commercial development because it has, in humans, the same elimination half-life as TMP. To achieve optimal synergy, the sulfamethoxazole:TMP in vivo blood concentration ratio should be 20:1. This value was obtained with co-trimoxazole (Bactrim©), a fixed combination product having a formulation ratio of 5:1, first available in 1969. In veterinary medicine, the formulation was copied directly, ignoring species PK differences. For example, TMP for pigs has been formulated with either sulfadimethoxine (SDM) or sulfamethoxazole (SMX). The elimination half-lives of SMX and TMP were similar (2–3 hr) but SDM had a relatively long half-life of 13 hr (Mengelers et al., 2001). The SDM:TMP combination thus transgressed the objective of sustained synergism by failing to maintain, over the duration of treatment, the optimal blood ratio of 20:1. Additionally, large inter-species PD differences exist. Using a tissue cage model in calves infected with *E. coli*, it was shown that several concentrations of TMP had no effect on the action of sulfadoxine (Greko et al., 2002). This unexpected finding was attributed to a high level of thymidine in calf serum, thymidine being a known antagonist of the action of TMP on some pathogens, including *E. coli*. These findings additionally illustrate the problem of extrapolating data between species. In this case, thymidine serum concentration is high in

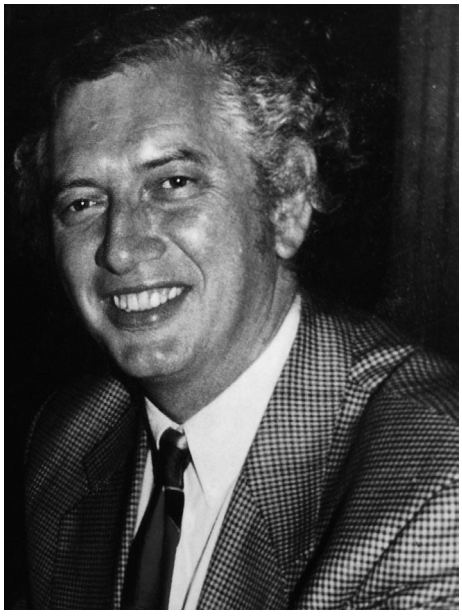

FIGURE 3 Jacobus F.M. Nouws (1944–2001) had a lifelong interest in drug residues, notably of antibiotics and their detection under meat inspection conditions. His most cited paper was on the comparative local tolerance and residue aspects of five oxytetracycline formulations in calves, pigs and sheep (Nouws, Smulders, & Rappalini, 1990)

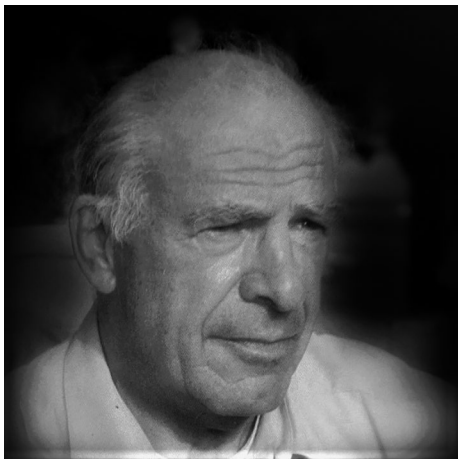

FIGURE 4 Adelbert van Miert (1937–) authored many articles in several fields: acute phase responses to infections, comparative pharmacokinetics, drug metabolism in large animal species with particular reference to antimicrobial drugs and pharmacological aspects of feed intake in small ruminants

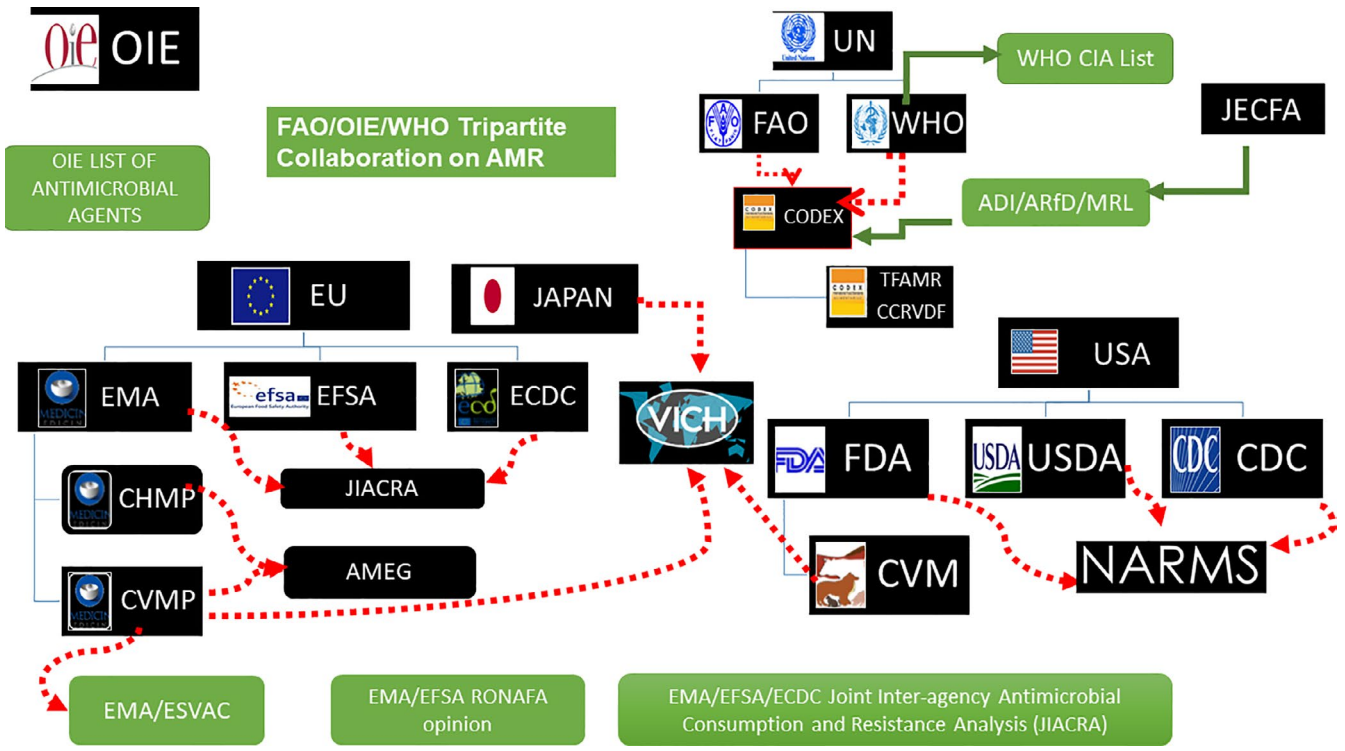

FIGURE 5 International organizations concerned with antimicrobial drugs and their inter-connectivity. The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) are International organizations of the United Nations (UN). Codex Alimentarius Commission (CAC) develops harmonized international food standards to protect consumer health. It established a first Task Force on AMR (TFAMR) and Code of Practice to Minimize and Contain Antimicrobial Resistance. The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) determines Maximal Residue Limits (MRL), together with the FAO/WHO Joint Expert Committee on Food Additives (JECFA). WHO developed a list of antimicrobial drugs critically important for human medicine (CIA List). Originally the Office International des Epizooties, OIE became the World Organisation for Animal Health in 2003 but retained its acronym. From 2010, OIE became increasingly focussed on the "One Health" paradigm including AMR and created an OIE List of antimicrobial agents of veterinary importance, in parallel to the WHO list. OIE collaborates with FAO and WHO in a "tripartite Partnership" to combat the rise in AMR. In the USA, the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) monitors AMR, with contributions from the Center for Disease Control and Prevention (CDC, link too sick people) and in particular with the Food and Drug Administration (FDA, link to retail meat) and the US Department of Agriculture (USDA, link to food animals). The Center for Veterinary Medicine (CVM) is the FDA body involved with regulation of veterinary AMDs. In Europe, the European Medicines Agency (EMA) includes the Committees for Medicinal Products for Human (CHMP) and Veterinary (CVMP) Use. Both CHMP and CVMP have links to the European Food Safety Authority (EFSA) and Centre for Disease Prevention and Control (CDC) in an antimicrobials Expert Group (AMEG). The EMA is involved in: (a) the ESVAC project (European Surveillance of Veterinary Antimicrobial Consumption) to collect information on how antimicrobial medicines are used in animals across the European Union; (b) "RONAFA" opinion or joint opinion with EMA/EFSA on measures to reduce the need to use antimicrobial agents in animal husbandry; and (c) the JIACRA Report or the Joint Interagency (ECDC/EFSA/EMA) Antimicrobial Consumption and Resistance Analysis Report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. VICH: is the trilateral (EU CVMP-Japan-USA CVM) programme aimed at harmonizing technical requirements for veterinary product registration—Its full title is the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

cattle, rats and mice but low in dogs and man (Nottebrock & Then, 1977).

Currently in veterinary medicine, sulfonamides and their combination with dihydrofolate reductase inhibitors have been placed in category D of the Antimicrobial Advice ad hoc Expert Group (AMEG) (see Figure 5

) classification. This is the class of lowest risk in terms of public health (Anonymous, 2019a). Hence, there are now opportunities for re-visiting and optimizing this class of AMD combination by rational selection of both the sulfonamide and the diaminopyrimidine.

3 | NONTHERAPEUTIC USES OF ANTIMICROBIAL DRUGS

3.1 | Agronomists' roles: antimicrobial use as growth promoters

The early history of AMDs in animals was dominated by agronomical applications in animal husbandry, with only limited contributions from veterinary clinicians and no input of veterinary pharmacologists. It must be stressed that the use of AMDs in animals is not synonymous with AMD applications in veterinary medicine. Moreover, early

agricultural AMD uses were not limited to animal husbandry. They encompassed also crop and fruit production (Stockwell & Duffy, 2012) and other practices, such as the preservation of meat (Deatherage, 1957). Antibiotics were licensed in the UK for the preservation of fish and, according to Britain's *Times* newspaper, antibiotic preservative usage comprised the greatest advance in the field of processing perishable foods since the advent of refrigeration (Kirchhelle, 2018b). The Swann Committee, a joint committee on the use of antibiotics in animal husbandry and veterinary medicine (*vide infra*), clearly acknowledged this separation between veterinary (therapeutic) and nonveterinary (nontherapeutic) uses of AMDs (Randall, 1969).

Early AMD incorporation in animal feed had the objective of enhancing growth through improved feed conversion efficiency. The mechanism of this effect on growth rate remains uncertain (Chattopadhyay, 2014). In the period 1950–1960, the published literature in animals suggests that growth promotion was the main use of AMDs and most AMD publications from 1950 to 1969 were in animal and dairy science, not veterinary, journals.

The benefit of feed additives as growth promoters was a serendipitous discovery. It commenced with the search for an inexpensive source of vitamin B12 in high-value protein fermentation cake. As a by-product of the fermentation process, the cake given to poultry was intended to improve weight gain and enhance the food conversion ratio. In fact, the weight gain was not attributable to vitamin B12 but to small amounts of chlortetracycline in the cake (Gustafson, 1991; Jones & Ricke, 2003).

In 1951, the United States Food and Drug Administration (FDA) approved the use of antibiotics in animal feeds without a veterinary prescription. Although more recently questioned, the justification at that time was to reduce food prices in a period of postwar austerity (Kirchhelle, 2018b). This is mirrored today with the wish to satisfy the demand for inexpensive protein of animal origin in middle- and low-income countries (Hao et al., 2014).

Historically, the use of feed additives was accompanied by new farming systems, with large groups of animals confined together in restricted spaces. This integrated model of production (feed-lots and Concentrated Animal Feeding Operations [CAFOs]) originated in the USA in the late 1930s (Graham, Boland, & Silbergeld, 2007). Confined animal populations are unavoidably exposed to excreta, and the price paid was new pathogen risks to both animal and human health. Nevertheless, such systems were made possible by mass AMD dosing, with the dual goals of high productivity and the requirement to control infectious diseases. As quoted by Kirchhelle, antibiotics' "role was that of an universal lubricant" to control disease pressures (Kirchhelle, 2018b).

There were early expressions of concerns for human health, arising from the widespread use of AMDs in intensive farming practices (Manten, 1963) but at that time plasmid-borne resistance and its horizontal transfer between bacteria were unknown. Resistance to chlortetracycline was believed to be solely chromosomal and its spread solely vertical (hereditary). The dominant opinion was that development of resistance to antibiotics at hospitals and in farms was separate and unrelated issues. Dangers of hypersensitivity reactions to drug residues in meat and fungal overgrowth in animals were believed to be of greater concern than resistance (Kirchhelle, 2018b).

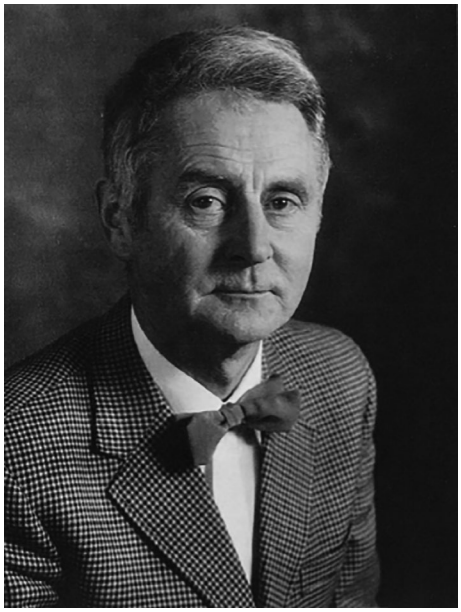

FIGURE 6 Herbert Williams Smith (1918–1987) undertook detailed studies of the bacteriology of the intestinal tract in health and disease. He was prescient in expressing early concern on the use of antibiotics in livestock, both as food additives to promote growth and as prophylactics against infection

3.2 | The growing concern on antimicrobial resistance in the UK

It was the scientific contribution of Herbert W. Smith (Figure 6) and Ephraim Saul Anderson in the UK to challenge the paradigm of two separate medicines with watertight barriers. This led to the first regulation of AMDs following publication of the Swann report.

Up to the 1960s, considering the then only known vertical transfer of resistance, recommendations were based on the belief that resistance selection in farm animals was only a local problem. In addition, it was believed that resistance would spontaneously disappear after discontinuing AMD administration, due to the natural competition between bacteria that would presumably favour susceptible bacteria in the absence of antibiotic selective pressure (fitness cost). Introduction of a new technique, phage typing, was destined to radically change this erroneous assumption. As some bacteriophages can only infect one or a few bacterial strains, phage typing can be used to identify and distinguish different bacterial strains of the same species, and thus to trace the source of an outbreak of infection. In 1958–1960, as veterinary researchers, H. W. Smith and his co-worker W.E. Crabb started to employ the phage-typing method. They showed that AMD used for growth promotion exerted major effects on antibiotic resistance in *E. coli* isolated from pig and chicken faeces. They warned that resistance

selection on farms could also harm humans indirectly by transfer of resistant bacteria between animals and humans (Smith, 1968, 1969, 1970, 1971).

In 1965, an influential paper by Anderson (a vocal whistle-blower) and Naomi Datta was published in the Lancet (Anderson & Datta, 1965). They directly challenged the dominant paradigm of the sole vertical transmission of resistance. They demonstrated the possibility of inter-bacterial horizontal transfer of resistance to ampicillin to previously sensitive strains of *S. typhimurium* and *E. coli* by exchange of extra-chromosomal DNA fragments (now known as plasmids). More importantly, they showed for the first time that horizontal resistance transfer can occur between bacteria present in animal populations and human-associated bacteria, confounding the dogma of an impenetrable barrier between humans and animals. These findings were revolutionary with respect to risk assessment of AMD use for growth promotion. Thus, after 1965, scientific evidence established that resistance can no longer be considered solely as a phenomenon confined to those farms using AMDs. Rather, it indicated the potential global environmental risks of antibiotic resistance, which has since been confirmed. This saga, leading to the establishment of the Swann committee, is well documented by Kirchhelle from both sociological and historical perspectives (Kirchhelle, 2018a).

In this new scientific framework, including the possibility of horizontal transfer of resistance, the human health concerns were mainly focussed on AMD use for growth promotion, this being the largest use of these drugs globally. It was recognized that human populations were exposed to antimicrobial-resistant pathogens and their resistance genes, both via the food chain and through widespread release into the environment (Silbergeld, Graham, & Price, 2008).

Between 1963 and 1965, Anderson and Lewis (Anderson & Lewis, 1965) described in the UK a spectacular rise, in both humans and calves, of isolates of *S. typhimurium* phage type 29 that were multi-resistant. Moreover, there were clear geographical and epidemiological links between humans and bovines, with emergence of resistance to furazolidone, an AMD that, due to its sole use in agriculture and veterinary medicine, exerted the role of a tag, signing the direction of exchanges from veterinary to human medicine cases. Beyond scientific concepts and laboratory findings, several food-borne dramatic events occurred in the UK with the deaths of dozens of children that could not be cured by antibiotic therapy (Kirchhelle, 2018a). This sounded the death knell for the concept that growth promoters posed no dangers to humans. Arising from both public and scientific concerns on this nontherapeutic use of AMDs in animals, a committee was established in 1968, under the chairmanship of Michael Meredith Swann (Figure 7) and eponymously named after him. Its terms of reference were as follows: "To obtain information about the present and prospective use of antibiotics in animal husbandry and veterinary medicine with the particular reference to the phenomenon of infective drug resistance, to consider the implication for animal husbandry and also for human and animal health, and to make recommendations."

FIGURE 7 Michael Meredith Swann (1920–1990) was nominated as Chairman, in July 1968, of the Joint Committee on the use of Antibiotics in Animal Husbandry and Veterinary Medicine in the UK, based on his a priori neutral opinion on this increasingly controversial topic and his contributions to cell biology

3.3 | The Swann Committee And the long journey to ban antimicrobials as growth promoters in Europe, USA and China

The Swann Report, published in 1969, listed 35 recommendations. It concluded that outbreaks of infection due to *S. typhimurium* included cases in which human disease and death resulted from multi-resistant isolates, which had acquired their resistance through the use of antibiotics in animals. The Committee proposed a ban on growth promotional use of penicillin, chlortetracycline and oxytetracycline and revocation of legislation permitting their use without prescription. In addition, for three AMDs used therapeutically, sulfonamides as a group, tylosin and nitrofuran, it was recommended that they should no longer be supplied without prescription (Randall, 1969). In fact, the Swann report failed to fully acknowledge the consequences of horizontal resistance transfer. Not all its recommendations were implemented, and AMD consumption continued to rise as did AMR in the UK in the 1970s. However, the regulation of feed additives in the European Union dates to 1970 (Council Directive 70/524/EEC of 23 November 1970). The Directive concerns the use of tetracyclines, penicillins, a mixture of penicillin/streptomycin and oleandomycin; these were regulated for phasing-out in June 1976 (tetracyclines and penicillins) and September 1979 (oleandomycin). The Swann report therefore marked an important milestone in the history of precautionary substance regulation and it was one of the first examples of precautionary European risk regulation (Kirchhelle, 2018a).

Shortly after publication of the Swann report, in 1972, a Food and Drug Administration (FDA) task force report on antibiotics raised the question of possible dangers to public health from the

use of AMDs in livestock. It was acknowledged that the use of AMDs, especially in growth promotion and when used in sub-therapeutic amounts, favoured the selection and development of AMR and "R-factor" bearing bacteria, with animals serving as a reservoir of AMD resistant pathogens present in meat (Lehmann, 1972). The task force recommended that restrictions be placed on the use of AMDs as growth promoters and, in February 1972, a proposed policy statement appeared in the Federal Register. The feed industry reaction was that this was conjecture (Williamson & Cravens, 1972) and called for proof of harm. Industrial feed companies employed, successfully, counter science and pharmaceutical lobbyists (Kirchhelle, 2018b). Subsequently, Gustafson, from American Cyanamid, continued the debate on implications of the use of AMD in livestock, in relation to human health concerns (Gustafson, 1991) and any negative connotations on this use were denied.

In the mid-late 1990s, concerns were expressed on AMD use in farm animals, centring on avoparcin, a glycopeptide used extensively in the EU and Australia as a food additive growth promoter in chickens, pigs and cattle but not in the USA, due to its carcinogenic effect (Barton, 2000; Wegener, 1998; Wegener, Aarestrup, Jensen, Hammerum, & Bager, 1999). Avoparcin is structurally related to vancomycin and teicoplanin, two AMDs critical, in human medicine, for treatment of serious gram-positive bacterial infections, especially when resistance or allergy to beta-lactams prevent their use. In the 1980s, avoparcin use was claimed to have generated vancomycin-resistant enterococci (VRE). It is because its addition to animal feeds was associated with the widespread distribution of VRE, not only in livestock but also in pets, uncooked chicken meat and sewage; glycopeptide resistance of *Enterococcus faecium* occurred on farms where avoparcin had been used (Aarestrup, 1995; Aarestrup et al., 1996; Bager, Madsen, Christensen, & Aarestrup, 1997). Reports in medical journals speculated on resistance passage from animals to humans (van den Bogaard, Jensen, & Stobberingh, 1997; Das, Fraise, & Wise, 1997), based on the fact that VRE harbouring the same *vanA* and *vanB* genes as those found in animals were present in the faeces of nonhospitalized patients in Europe. This was not the case in the USA, supporting the view that, in Europe, people were exposed to VRE from animal or environmental sources (Barton, 2000). This led to challenge on the use of avoparcin in animals (Mudd, 1996a, 1996b) then to a ban on its use in Europe in 1997. However, there was major controversy. Notwithstanding the fact that avoparcin was not licensed for food-producing animals in the USA, VRE was at this time a serious clinical issue for human medicine in the USA, but paradoxically not in Europe. The apparent paradox reflects the difference between risk and hazard. In the USA, the risk of VRE for hospitalized patients was explained by the over-consumption of glycopeptides and other AMDs in hospitalized patients. In Europe, where the resistance in clinical bacteria was considerably lower than in USA, it was primarily a hazard for the general population, arising from use of avoparcin as a growth promotor. This led some to challenge any "evangelical call for action," as there was no robust evidence to support the spread of AMR gram-positive bacteria from livestock to humans (Acar, Casewell, Freeman, Friis, & Goossens, 2000).

Many calls were made for a total ban on the use of all AMDs as growth promoters in animals (van den Bogaard & Stobberingh, 1996, 1999; Mudd, 1996b). In 1986, Sweden pioneered prohibition of incorporation of antibiotics in animal feeding-stuffs, including the use of all antibiotic-containing additives. Sweden retained this restrictive regulation, when it applied for membership of the EU (Castanon, 2007). Subsequently, there followed the ban in Denmark on avoparcin and virginiamycin in 1995 and 1998, respectively. There followed the EU ban on avoparcin in 1997 and the four remaining antibiotics used for growth promotion in 1999. An EU-wide ban was placed on animal feed additives containing antibiotics in the EU and this became effective from 1 January 2006 (Anonymous, 2005). From this date, food derived from livestock using AMD for growth promotion could not be marketed or used. In parallel, the European Antibiotic Resistance Surveillance System (EARSS) was established in 1998. Some authors challenged the ban (Phillips, 2007) but they, in turn, were challenged on grounds of misinterpretation of data (Hammerum et al., 2007).

It was predicted that the ban on the use of antibiotics as growth promoters in animals would be associated with an increased incidence of food-borne diseases in humans and more frequent use of antibiotics for therapeutic purposes in animals (Casewell, Friis, Marco, McMullin, & Phillips, 2003). However, an epidemiological study (Grave, Kaldhusdal, Kruse, Harr, & Flatlandsmo, 2004) found no compensatory increase in the level of therapeutic use of AMDs (Arnold, Gassner, Giger, & Zwahlen, 2004). Moreover, improvement in productivity following the ban indicated no long-term impact on swine productivity (Aarestrup, Jensen, Emborg, Jacobsen, & Wegener, 2010; Jensen & Hayes, 2014).

For the United States, a Guideline for Industry, issued in 2012 by the Center for Veterinary Medicine (CVM) of the FDA (Anonymous, 2019c) recommended "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals," that is sanctioning use for the prevention, control and treatment of infections in animals but not for growth promotion, increased performance and improved food conversion efficiency. Additionally, the Guideline restricts the use in animal agriculture of some AMDs of critical importance (e.g. third-generation cephalosporins). These drugs are now reserved for use in humans.

After a transitional period, based on the voluntary decision of companies to cease selling AMDs for this use, a new FDA regulation, effective from 1 January 2017, banned the use in USA of antibiotics as feed supplements for livestock and poultry. It also prohibits over-the-counter sale to farmers of AMDs medically important for humans, and farmers are required to obtain prescriptions for all AMDs (Drouillard, 2018). In 2019, China decided to ban the use of AMDs as growth promoters, which will take effect in 2020. Currently, China is more concerned with domestic policy and resource competition than with addressing the existential health threat from AMR (Thomas & Lo, 2020). The concern is that implementation of welcome decisions might suffer the same fate as those of the Swann report recommendations.

3.4 | The current use of antimicrobials as growth promoters in low- and middle-income countries

Using Bayesian statistical models, which take account of livestock densities and projections of demand for meat products and current estimates of AMD consumption in high-income countries, the global trend in AMD use in food animals was predicted to increase significantly (Van Boeckel et al., 2015). It was estimated that, between 2010 and 2030, overall consumption of AMDs would increase, if no action was taken, by 67%. This is largely attributable to changing production practices in middle-income countries, where extensive farming systems will be replaced by intensive farming operations that routinely use AMDs in sub-therapeutic doses (Van Boeckel et al., 2015). To mitigate potentially consequential ecological disasters, several scenarios to reduce AMD consumption were simulated. One of the most efficient would be worldwide promotion of low-animal–protein diets, that is to drastically reduce meat consumption by humans in Western countries and to encourage those countries having currently a low meat consumption per capita to adopt a plant-based diet, in preference to animal-based food. As the world's largest consumer of veterinary AMDs, both in relative (per animal body weight) and in absolute terms, China is well placed to exert an important leadership role on future AMD use (Van Boeckel et al., 2017).

FIGURE 8 Gideon Ziv (1930–1997) was recognized internationally for his research on bovine mastitis. He conducted pioneering researches in several aspects, embracing pharmacokinetics, residues and clinical efficacy of intramammary infusions of antimicrobial drugs

4 | RATIONAL USES OF ANTIMICROBIAL DRUGS IN VETERINARY MEDICINE

4.1 | The avant-garde role of mastitis treatment

In the decade 1950–1960, the predominant therapeutic indication for AMDs in food-producing animals was mastitis in dairy cattle. This arose because mastitis is an infectious condition of global reach. After 1960, many publications on udder conditions continued to dominate the cattle infectious disease literature, with research reports on the pathophysiology of mastitis, as well as many clinical trials on AMD-containing products administered by intramammary infusion. Mastitis was and is a condition at the interface of veterinary medicine and animal husbandry. The earliest mastitis control programmes and treatment recommendations were implemented in the 1960s. Mastitis prevention was never regarded as the sole domain of veterinarians (LeBlanc, Lissemore, Kelton, Duffield, & Leslie, 2006). Rather, the therapeutic uses of AMDs, from initial diagnosis, to selection of drug of choice, to administration strategy have involved integrated decision-making management options, as outlined in national Mastitis Control Programmes in many countries. Even systemic therapy is feasible in sub-clinical conditions, through availability of efficacious AMDs such as ceftiofur, having a milk discard time of 0 to 2 days, depending on the country (Kausche & Robb, 2003).

Whereas clinical mastitis is readily detected and treated, this is not the case for the most prevalent form, sub-clinical mastitis. Whilst signs of the sub-clinical condition are not readily apparent to the veterinarian, detection by the farmer becomes apparent through lower yield and altered quality of milk, together with his acute awareness of economic losses. Progressive lowering of regulatory limits for bulk milk somatic cell counts (SCC) encouraged the use of AMDs by farmers. This led to promotion of blanket strategic AMD therapy at drying-off to cure ongoing chronic conditions and prevent future infection at calving (Dodd, Westgarth, Neave, & Kingwill, 1969). For many years, it was claimed that the local AMD use for mastitis control in dairy cows had minimal impact on the emergence of AMR (Oliver, Murinda, & Jayarao, 2011). However, this limited view failed to recognize the consequences of such routine practices as the re-cycling of wasted and unsaleable milk as feed for calves (Brunton, Duncan, Coldham, Snow, & Jones, 2012; Duse et al., 2013). This practice is responsible for the emergence of AMR in the gastrointestinal tract (g.i.t.) microbiota of preweaned calves (Pereira et al., 2018). Some reduction of AMD use for mastitis therapy is clearly now appropriate, in conjunction with implementation of alternative approaches. These include nonantimicrobial therapy with new compounds, such as those that are assumed to improve the immune status of the udder at the time of calving and the peri-partum period (Van Schyndel, Carrier, Bogado Pascottini, & LeBlanc, 2018) and selective dry cow treatments (Krömker & Leimbach, 2017).

From a pharmacological perspective, it is with the treatment of mastitis that clinical veterinary pharmacology really began to be the subject of focused research. In a series of classical papers in

1980, Gideon Ziv of the Kimron Veterinary Institute, Bet-Dagan, in Israel (Figure 8), outlined the state-of-the-art of mastitis treatment (Ziv, 1980a, 1980b, 1980c). Subsequently, the role of Antimicrobial Susceptibility Testing (AST) in rational mastitis treatment was reviewed by Constable and Morin (Constable & Morin, 2003) and also challenged. A classical overview of advances affecting the health and welfare of dairy cows has been presented (Barkema et al., 2015). Automated milking systems and the adoption of new technologies, together with possibilities of using milk for disease diagnostics and monitoring, will ineluctably impact on mastitis control and the place of AMDs in therapy (Jacobs & Siegford, 2012).

The early unique approach to mastitis, evaluating its causes and management, was not matched by comparable research programmes on the pathophysiology and therapeutic innovations for other major microbial-based infections, such a bovine respiratory disease (BRD) as explained in Section 4.3.

4.2 | Pharmacologists' roles: from pharmacokinetics to PK/PD and population pharmacokinetics

Contributions made by several pharmacologists (notably Rasmussen, Van Miert, Nouws and Ziv) are outlined in Section 2 of this review. It was in the mid- to late-1990s that other pharmacologists became involved in quantifying AMD concentrations in a range of biological fluids (serum, inflammatory exudate, interstitial fluid) at the Royal Veterinary College, London (Aliabadi, Landoni, & Lees, 2003; Aliabadi & Lees, 2001, 2002) and at Uppsala, Sweden (Greko, 2003; Greko, Finn, Ohagen, Franklin, & Bengtsson, 2003). These researchers derived PK parameters and variables and applied them in PK/PD integration and modelling methods. The correlated PK and PD data were used to characterize types of bacterial kill (concentration-dependent, time-dependent or co-dependent) and to predict dose schedules for a given Probability of Target Attainment (PTA) also termed Target Attainment Rate (TAR) (see review by Toutain et al. in this issue). As early as 2002, it was advocated in the veterinary field that dosage regimens should be optimized using the PK/PD paradigm, in preference to the classical dose–effect relationship (Aliabadi & Lees, 2002; Toutain, del Castillo, & Bousquet-Mélou, 2002).

In earlier decades, the focus of pharmacologists had been on factors (species, breed, age, sex, disease, feeding schedule, dose, route of administration etc.) influencing variability of AMD PK profiles. Of note were the classical studies of Stowe and Rasmussen on sulfonamides (see Section 1 on sulfonamides) and Ziv for milk PK profiles and mastitis (see Section 4.1). Particular note also should be made of the roles of Desmond J. Baggot and Lloyd E. Davies. In the 1970s, Baggot co-authored with Davis of Illinois University at Urbana a series of papers on the comparative PK of several drugs, including chloramphenicol (Davis, Neff, Baggot, & Powers, 1972), and on inter-species differences in protein binding (Baggot & Davis, 1973; Baggot, Davis, & Neff, 1972). Baggot (Figure 9) authored the first book dedicated to veterinary clinical pharmacology (*Principles of Drug Disposition in Domestic Animals: the Basis of Veterinary Clinical Pharmacology*; Baggot, 1977).

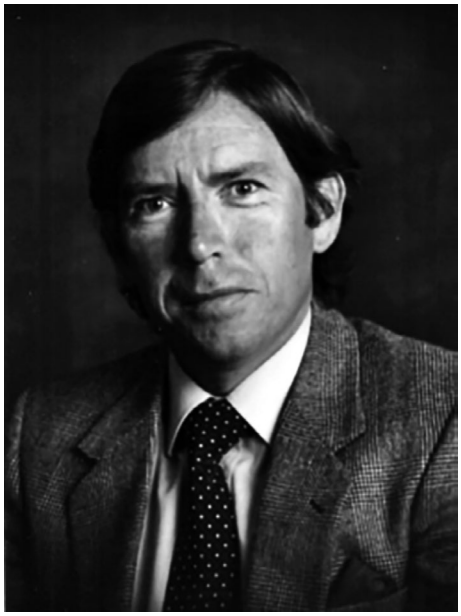

FIGURE 9 Desmond Baggot (1940–2016) authored many articles and reviews, including some classical papers, including "Distribution of anti-microbial agents in normal and diseased animals" (Baggot, 1980). He also authored the first book dedicated to veterinary clinical pharmacology (Principles of Drug Disposition in Domestic Animals: the Basis of Veterinary Clinical Pharmacology (Baggot, 1977))

This text retained its status as the most influential for our discipline for several decades. Baggot also wrote the first review on the comparative disposition of AMDs in healthy and diseased animals (Baggot, 1980). With John F. Prescott, Baggot was the first editor of the classical book "Antimicrobial Therapy in Veterinary Medicine," (Prescott & Baggot, 1988). Important recent reviews in this field on the effect of sex, heritable traits, age, body composition, circadian rhythms and disease are those of Martinez and Modric (Martinez & Modric, 2010; Modric & Martinez, 2011).

In the 1960s, Van Miert of Utrecht University (Figure 4) made early contributions on the pathophysiology of fever (Van Miert & Frens, 1968; Van Miert & Atmakusuma, 1970). He documented the influence of fever on the bioavailability of sulfonamides (Van Gogh & Van Miert, 1977) and highlighted the influence of hormonal status on sulfonamide metabolism (Witkamp, Nijmeijer, Yun, Noordhoek, & van Miert, 1993). He further authored a classical review on the influence of fever on drug disposition (van Miert, 1990). Van Miert pioneered the introduction into veterinary medicine of hepatocyte cultures to investigate AMD metabolism (Mengelers, Kleter, Hoogenboom, Kuiper, & Van Miert, 1997; Witkamp, Nijmeijer, Monshouwer, & Van Miert, 1995). More recently, Papich has pioneered tissue PK distribution studies of AMDs (see review by Toutain et al, in this issue) and played a major role in interfacing with clinicians (see Section 4.4).

TABLE 1 Sequential introduction of AMDs for respiratory disease in cattle[a]

Antibiotic	Class	Drug sponsor	Commercial name	Year of approval
Enrofloxacin	Fluoroquinolone	Bayer	Baytril	1987
Ceftiofur	Third-generation cephalosporin	Pfizer	Excenel	1988
Tilmicosin	Macrolide	Elanco	Micotil	1990
Florfenicol	Phenicol	Schering-Plough	Nuflor	1990
Danofloxacin	Fluoroquinolone	Pfizer	Advocin	1991
Cefquinome	Fourth-generation cephalosporin	Intervet	Cobactan	1995
Marbofloxacin	Fluoroquinolone	Vetoquinol	Marbocyl	1995
Tulathromycin	Macrolide	Pfizer	Draxxin	2003
Gamithromycin	Macrolide	Merial	Zactran	2008
Tildipirosin	Macrolide	Intervet	Zuprevo	2011

[a]Adapted and updated from Shryock (2004).

Most recently, PK/PD modelling with Monte Carlo simulation has enabled pharmacologists to establish or confirm rational dosage regimens. A recent example is tulathromycin (Toutain, Potter, et al., 2017) (see also the review on PK/PD by Toutain et al in this issue). Also contributing to these pioneering advances in pharmacology are population PK methods (Bon et al., 2018; Lin, Gehring, Mochel, Lavé, & Riviere, 2016; Martín-Jiménez & Riviere, 1998; Riviere, Gabrielsson, Fink, & Mochel, 2016), especially for establishing PK/PD cut-offs (Cagnardi et al., 2018; Toutain, Sidhu, Lees, Rassouli, & Pelligand, 2019). PK/PD cut-offs are one of the three MICs required to establish a clinical break point for antimicrobial sensitivity testing (AST) by Vast/CLSI (Papich, 2014) and VetCAST, a sub-committee of EUCAST (Toutain, Bousquet-Mélou, et al., 2017). Novel approaches to the design of dose schedules which optimize bacteriological cure and minimize opportunities for the emergence of resistance are promoted (for a recent review see Guardabassi, Apley, Olsen, Toutain, & Weese, 2018). In silico approaches, as veterinary alternatives to in vivo dose fractionation studies (traditionally conducted using rodent models) to identify the best PK/PD index predictive of AMD efficacy, have recently been introduced (Pelligand, Lees, Sidhu, & Toutain, 2019). The role of biofilms, notably in recurrent mastitis infections was investigated (Melchior, Fink-Gremmels, & Gaastra, 2007) and reviewed in 2006 (Melchior, Vaarkamp, & Fink-Gremmels, 2006).

Whilst the scientific basis of veterinary therapeutics began to emerge in the nineteenth century, the transition from *Materia Medica* to pharmacology occurred as late as the 1950s with publication of the classical textbook *Veterinary Pharmacology and Therapeutics* in 1954, authored by L. Meyer Jones. This *magnum opus* continues to be the veterinary pharmacologists' bible, now in its 10th edition (2017) under the editorship of Riviere and Papich. It includes the most comprehensive pharmacological review available on AMDs in use, on a class-by-class basis. A milestone development for the veterinary pharmacology community was the launching of an international journal in 1978, *The Journal of Veterinary Pharmacology and Therapeutics*, under the editorship of Charles Short and Andrew Yoxall.

Finally, the bi-annual "International Conference on Antimicrobial Agents in Veterinary Medicine" (AAVM) inaugurated, nurtured and chaired by Stefan Soback has provided an international forum, where microbiologists, pharmacologists and other specialists meet to disseminate the latest knowledge on AMD actions and usage. From its first inception in 2000 in Helsinki to the 9th Conference held in Rome in 2018, it has provided a platform for debate across a range of disciplines between scientists based in academia, regulatory authorities, industry and veterinary clinical practice.

4.3 | Clinicians' roles: drug efficacy in food producing animals

As discussed in Section 4.1, mastitis treatment pioneered clinical research on the use of AMDs in veterinary medicine. It was only later that bovine respiratory disease (BRD), historically termed pneumonia or shipping fever, was investigated by clinicians. In the 1965, Third Edition of the standard reference textbook "Veterinary Pharmacology and Therapeutics" (Meyer Jones, 1965), the chemotherapy chapter reported that there was no prophylactic medication to protect cattle against respiratory infection, although tranquillisers had been claimed to prevent shipping fever (Huber, 1965). A factor accounting for the lag between AMD treatment of mastitis and that of lung conditions is that dairy cattle are under daily scrutiny of the farmer at milking (Huber, 1965). In due course, the use of AMDs to treat BRD, the most economically important disease of feed-lot animals, was related to the rapid development of feed-lots in the 1960s, encompassing hybrid grain and irrigation techniques (O'Connor et al., 2016).

For the treatment of respiratory diseases, the tetracycline group (oxytetracycline, chlortetracycline, doxycycline…) remains in widespread use in farm animal species. Its attractions to the clinician

are low cost, convenience of oral administration and availability in long-acting formulations, enabling single-dose therapy. However, several negative issues were revealed for these products, including low and erratic oral bioavailability, typically of 10% or less in pigs (Little, Crabb, Woodward, Browning, & Billman-Jacobe, 2019), and for systemic administration, of a poor local tolerance. The latter with a significant tissue irritation is an animal welfare issue and also a possible human safety concern due to residues at the injection site. Nouws expressed early concerns on the advantage/risk balance of these long-acting oxytetracycline formulations (Nouws, 1984). As for all antimicrobials, the development of resistance and efficacy issues were increasingly reported for tetracyclines. This led to the introduction, commencing in the late 1980s, of the "modern" range of AMDs, notably enrofloxacin in 1987 (Table 1).

The relative efficacy of these AMDs has recently been assessed using a mixed-treatment comparison meta-analysis and Ranking Forest plots (O'Connor et al., 2016), suggesting that the historical treatment with oxytetracycline (the main reference drug for several decades) does not differ significantly from nonactive control therapy.

One Health concerns, arising from the contribution of veterinary medicine to global AMR issues, have triggered new regulatory guidance, which includes restriction on the prophylactic use of AMDs (see Section 6). Now, an objective for clinicians involved in food-producing animal medicine should be to re-visit the practice of metaphylaxis (*sensu stricto* of very early AMD treatment). As a therapeutic option, metaphylaxis is soundly based, given the greater efficacy of AMDs when administered during the prepatent period of an infection (Ferran, Toutain, & Bousquet-Mélou, 2011; Vasseur, Lacroix, Toutain, Bousquet-Melou, & Ferran, 2017; Vasseur et al., 2014). The challenge, however, is to replace, as a management option, the mass medication with which metaphylaxis is almost always implemented (Baptiste & Kyvsgaard, 2017), by more selective treatments, that is by application of precision medicine. Rapid progress in precision medicine is envisaged and, with the technical feasibility of individual animal treatment, monitoring disease onset will become practicable, even at flock and herd levels (Bousquet-Mélou, 2018; Lhermie, Toutain, El Garch, Bousquet-Mélou, & Assié, 2017). The components of evolving precision medicine are as follows: the conduct of in-depth researches on diagnosis (Jackson, Carstens, Tedeschi, & Pinchak, 2016); and the use of diagnostic tools with sensors (Rutten, Velthuis, Steeneveld, & Hogeveen, 2013) to provide selective clinical treatments as an alternative to mass medication.

4.4 | Clinicians' roles: drug efficacy for companion animals

In the 1950s–1960s, there were relatively few clinician-authored' papers addressing small animal infectious disease. The consequence was failure to document important issues requiring clinical expertise, including decisions on: when to commence; how long to maintain treatment and what dose to select. Nevertheless, from the early 1950s, the PK basis for rational dosing of penicillin was known; Scheidy (1951) reported that penicillin, being very rapidly eliminated by the kidney, made necessary the selection of an appropriate salt or formulation. David Watson of Sydney University was one of the first veterinary pharmacologists to document the PK of AMDs in dogs and cats (Watson, 1972, 1991). According to Shryock, it was only in the 1990s that the research focus of animal health companies shifted from products for use in food animals to products targeting companion animals (Shryock, 2004).

In developing AMDs for companion animal diseases, clinical trials were pivotal. Drug companies largely copied and pasted the drugs and dosage regimens established in human medicine onto companion animals. This explains why some historically set dosage regimens have recently been debated and updated. For example, amoxicillin with clavulanic acid was marketed in the late 1970s in cats by Beecham Laboratories as Clamoxyl®. In a clinical trial conducted by the sponsor in 224 cats, it was reported that 94% excellent-to-good results were obtained with a fixed oral dose of 50mg administered once or twice daily. A second trial employing 193 cats was conducted to determine the frequency of dosage of this tablet. The results indicated that the efficacy of 50-mg amoxicillin given once daily was equal to that of two 50-mg doses per day for a range of conditions (respiratory, urinary, skin…) (Keefe, 1978). This regimen is still marketed but consensus guidelines now indicate for amoxicillin a dosage per kg body weight and not a per animal dose. Moreover, dosage regimens vary for differing conditions; 22 mg/kg twice daily for respiratory conditions (Lappin et al., 2017), 11–15 mg/kg every 8h for urinary tract infections (Weese et al., 2011) and 12–25 mg/kg in association with clavulanic acid for treatment of superficial bacterial folliculitis in the dog (Hillier et al., 2014).

In earlier decades, clinical trial method and design were not well consolidated in veterinary medicine and, to support its product, Beecham Laboratories published a "clinical trial" on 615 cases of dogs and cats from which it was stated "Those taking part were asked to use amoxicillin in the treatment of all conditions that they considered required an antibiotic and to report their results in terms of success or failure according to criteria laid down" (Francis, Marshall, & Turner, 1978).

In the present century, veterinary pharmacology and therapeutics have become a more active and sophisticated field. Now many guidelines for the rational use of AMDs and dose design (Lappin et al., 2017; Weese et al., 2015, 2019); flows of publications dedicated to specific AMD classes, for example quinolones (Walker, 2000) or to named species, both dogs (Papich, 2012, 2013) and cats (Albarellos & Landoni, 2009), have set new standards.

4.5 | Industry's role in developing new drugs

The pharmaceutical industry has been a major and beneficial innovative force in the discovery, development and marketing of AMDs, formulated in a wide range of products for the seven major species of veterinary interest.

Many AMDs developed for veterinary use arose secondarily to their introduction into human medicine, including for example the early, narrow spectrum penicillins, sulfonamides and amoxicillin (Palmer, Buswell, Dowrick, & Yeoman, 1976). The "modern era" of veterinary antimicrobial therapy was initiated with the regulatory approval of the first veterinary fluoroquinolone (enrofloxacin) in 1987, and the first third-generation cephalosporin (ceftiofur) in 1988 (Table 1). These two AMD classes are currently the most challenged in terms of public health, emphasizing that veterinary medicine must constantly review its AMD armamentarium, if it is to meet public health expectations in the 21st century and optimize outcome in treating animal diseases. Therefore, there is now a need to develop new compounds with minimal impact on g.i.t. flora and on environmental bacterial ecosystems (Toutain, Ferran, Bousquet-Melou, Pelligand, & Lees, 2016).

Many of the AMDs used in veterinary, but not in human, medicine were drugs that did not proceed to licensing for human use for safety or other reasons. Others are second-in-class drugs or drugs not showing sufficient promise at some stage of development. Veterinary licensing thus gave some "payback" to companies on research development costs. For example, tiamulin was considered too toxic for human use. Enrofloxacin is an example of a second-in-class veterinary quinolone. In several species, it is a pro-drug of ciprofloxacin and both parent compound and metabolite account for the antimicrobial activity. The same may also be true for pradofloxacin (Lees, 2013) versus moxifloxacin.

A few drugs in the veterinary AMD armamentarium were innovatory. For example, the replacement of chloramphenicol by florfenicol was dictated by the need to resolve a tissue residue issue in food-producing species, as reviewed by Page (Page, 1991). A second example is those macrolides of the azalide sub-group, such as tulathromycin (Arsic et al., 2018; Evans, 2005; Kilgore et al., 2005; Villarino, Brown, & Martín-Jiménez, 2013), which were developed for sole veterinary use. The therapeutic advantage of azalides is their long elimination half-life, single-dose therapy providing a long duration of action. Following the successful introduction of tulathromycin, pharmaceutical companies were motivated to introduce other azalides, gamithromycin (Huang, Letendre, Banav, Fischer, & Somerville, 2009) and tildipirosin, with similar properties and benefits for sole veterinary use (Menge et al., 2012).

Few AMDs were developed specifically for veterinary medicine. An example of specific and extensive veterinary use is the ionophore group of coccidiostats; monensin has been used for the control of coccidiosis in poultry for almost 50 years (Chapman, Jeffers, & Williams, 2010). However, there is no clear sanctuary for veterinary AMDs. Tiamulin, a pleuromutilin derivative, was originally proposed for use in humans, but not developed for safety reasons. It was then approved for veterinary use in 1971 and was initially regarded as a noncritical AMD for human medicine. However, pleuromutilins have been re-considered for use in human medicine (Novak, 2011). An example is lefamulin (Perry & Golan, 2019). It could not have been foreseen, but it is the case, that this veterinary AMD class has later become, in 2011, a human AMD class (Paukner & Riedl, 2017). In the process, and from the perspective of development of resistance and impact on humans, pleuromutilin class drug usage in food-producing animals in the EU has been challenged (van Duijkeren et al., 2014). Colistin has long been used in veterinary medicine, but it has now become a drug of last recourse in human medicine, for infections where the organism is resistant to a wide range of alternative drugs.

An example of therapeutic re-purposing, that is switching to an alternative or additional therapeutic use, is provided by the salicylanilide class of anthelmintic drugs to treat infections caused by drug-resistant *Staphylococcus aureus*. Niclosamide and oxyclozanide were shown to possess strong activity in vivo and in vitro against MRSA (Rajamuthiah et al., 2015). The re-positioning of veterinary drugs, such as rafoxanide and closantel, to provide a synergistic combination with colistin has been proposed to target multidrug-resistant colistin-resistant gram-negative bacilli (Domalaon, Okunnu, Zhanel, & Schweizer, 2019).

4.6 | The role of industry in developing new formulations

Over many years, industry has made great strides in developing new modalities of AMD administration and new formulations. Terminologies describing dosage forms and release characteristics can be confusing; they have has been reviewed in a veterinary context (Martinez, Lindquist, & Modric, 2010).

Administration of AMDs in feed or drinking water required specific pharmaceutical development. This is essential to ensure stability (e.g. at varying water pHs, in soft and hard waters), good mixing properties, animal acceptance and compatibility with feed. These factors have been reviewed for poultry (Vermeulen, 2002). For companion animals, good appetence is required to ensure usage compliance, especially for AMDs in cats, as exemplified by pradofloxacin (Litster et al., 2007).

The principal example of a specifically veterinary administration route is intramammary infusion of AMDs. An overview of factors affecting the disposition of intramammary preparations used to treat bovine mastitis was published in this journal (Gehring & Smith, 2006).

The development of long-acting (LA) formulations of AMDs has been especially beneficial to food-producing animals for parenteral (intramuscular or subcutaneous) dosing. Challenges and issues in developing LA formulations of AMDs have been reviewed (Sun, Scruggs, Peng, Johnson, & Shukla, 2004). Martinez has addressed how species-specific physiological variables are of importance for parenteral dosage (Martinez, 2011). A significant challenge for formulators is to ensure AMD stability, not only over product shelf-life but also in animal tissues over several days postadministration. This may explain companies' preference for developing for small animals long-acting compounds, for example cefovecin for dogs (Stegemann, Sherington, & Blanchflower, 2006) and cats (Stegemann, Sherington, Coati, Sherington, Coati, Brown, & Blanchflower, 2006) rather than

long-acting formulations, as for first and second cephalosporin generation drugs.

4.7 | Industry's role in developing generics

In human medicine, the extensive use of generic products has been reported to increase the overall consumption of AMDs and associated with the emergence and spread of bacterial resistance (Jensen et al., 2010; Monnet, Ferech, Frimodt-Møller, & Goossens, 2005). Similarly in veterinary medicine, the use of generics has been questioned (Toutain & Bousquet-Melou, 2013) and debated (Toutain & Bousquet-Melou, 2014; Vecino, 2014). A further issue arising in veterinary medicine from the use of generics has been to encourage the use of older drug products, by the promotion of economic incentives. Some of these drugs, for example tetracyclines, have low oral bioavailability, are marketed with historically derived dosage regimens e.g. doxycycline in pigs and are excreted into and spread widely within the environment. They provide a disincentive to the development of new and innovative products, required to meet the therapeutic needs of the veterinary community, whilst being consistent with One Health issues. The development of novel eco-friendly agents, with minimal impact on commensal gut flora and biodegradability in the environment, is discouraged by the widespread use of generic drug products of some classes. These issues have been further discussed in considering the desirable properties of "green" AMDs (Toutain et al., 2016).

4.8 | Industry's role in developing alternatives to antimicrobials

The global concerns on AMR, its incidence and spread, have stimulated extensive searches for alternative means of disease control. Industry has responded by embarking on searches for credible, efficacious alternatives to or supplementary approaches to AMDs. These include probiotics, prebiotics, symbiotics, organic acids, enzymes, phytogenics, antimicrobial peptides, hyper-immune egg antibodies, bacteriophages, clay and metals (Gadde, Kim, Oh, & Lillehoj, 2017), (Gaggìa, Mattarelli, & Biavati, 2010), (Ly-Chatain, 2014). Exploring the potential contribution of bacteriophages to AMR control (Lekunberri, Subirats, Borrego, & Balcázar, 2017) is not new (Wagenaar, Bergen, Mueller, Wassenaar, & Carlton, 2005) but may now succeed under the stimulus of new researches deriving from global pressures.

For bovine mastitis, vaccines have been proposed by some (Midtlyng, Grave, & Horsberg, 2011) and discounted by others (Hojberg, Canibe, Poulsen, Hedemann, & Jensen, 2005; Middleton, Luby, & Adams, 2009; Roselli et al., 2005). Alternative therapies can bring their own problems; they are not necessarily total panaceas, including probiotics (Hummel, Hertel, Holzapfel, & Franz, 2007) and essential oils (Brenes & Roura, 2010; Franz, Baser, & Windisch, 2010), proposed for broilers (Huyghebaert, Ducatelle, & Immerseel, 2011), and pigs (Thacker, 2013). Alternatives can even be counter-productive, as exemplified by zinc and copper (Yazdankhah, Rudi, & Bernhoft, 2014); zinc increased the proportion of multi-resistant *E. coli* in vivo in piglets (Bednorz et al., 2013). A similar effect was observed with heavy metals in liquid pig manure (Hölzel et al., 2012).

Future innovations in AMD therapy will be based on the knowledge base created by past successes, failures and misuses. For example, the use of drug combinations was proposed to retard the emergence of resistance (Chait, Craney, & Kishony, 2007; Fischbach, 2011), through reduction of mutation rate.

5 | THE PRUDENT USE OF ANTIMICROBIALS: RESIDUES IN FOOD, ANTIMICROBIAL RESISTANCE AND REGULATORY CONTROL AND MONITORING

5.1 | The analyst's (chemist's) roles: the risks of residues in food and their quantification

An early concern arising from AMD use was the issue of residues in milk, in consequence of their extensive use in mastitis therapy. Penicillin is highly antigenic and, in 1956, it was estimated by FDA that some 10 % of the US population had a "proneness" to become sensitive during their lifetime to some food, drug, cosmetic or other substances (Welch, 1957). This was especially significant for penicillin, because of the high frequency of penicillin residues, in up to 10% of milk samples in some surveys. In addition, penicillin was actually added (illegally) to milk to lower bacterial counts, a practice declared as an adulteration in 1953 (Welch, 1957). However, in November 1955 the FDA, under the Miller Amendment, approved the use of chlortetracycline in the processing of poultry, as a preservative, extending the shelf-life of meat and for fish preservation. According to Deartherage, the great promise of using antibiotics to prolong the useful life of perishable food items stimulated intensive work in both Academia and Industry (Deatherage, 1957). In 1955, at the invitation of the FDA, a Medical Advisory panel concluded that antibiotics, including tetracycline, polymyxin and neomycin, all of which were contained in marketed mastitis products, did not pose public health concerns, even though they may be detected in marketed milk (Welch, 1957). This extraordinary judgement (by current values) was challenged when the Wall Street Journal reported on 29 December 1989 that a substantial number of off-the-shelf milk samples contained antimicrobial residues as determined by the CHARM II assay (Erskine, Tyler, Riddell, & Wilson, 1991). Thereafter, the focus on residues became a priority for public health reasons and in light of its impact on the dairy industry's production of milk derivatives (cheese, yogurt…).

From the 1950s onwards, many publications appeared on both microbiological/biological and chemical analytical methods for detection of residues in edible tissues. These publications quantified

rates of decline in AMD concentrations in edible tissues and also described control, rapid screening and confirmatory methods. Deriving from these researches, the concepts of "Method Validation" and "Good Laboratory Practice" became mandatory for product licensing, introducing into veterinary medicine the concept of the "quality approach". In addition, rapid advances in analytical methods were accompanied by a steady flow of publications describing improvements in drug extraction and quantification and introducing such indices as Lower Limit of Quantification (LLOQ) of analytes.

The aminoglycoside group of AMDs illustrate the requirement for analytical methods which are selective, representative and have appropriate LLOQs. Some aminoglycosides are drug mixtures with two or more components, each with its own disposition profile (Steinman, Isoherranen, Ashoach, & Soback, 2002). Disposition profiles where 2 compartments could be identified can now be described by 3-compartment models, with improved analytical sensitivity. It is the second (beta) phase of approximately 2–4 hr, in all species, that is clinically relevant. However, for residues, it is the so-called very late-terminal (gamma) phase which accounts for the long withdrawal period. In farm animal species, the late-terminal half-life for gentamicin ranges from 11 hr in rabbits to 167 hr in sheep with intermediate values of 20 hr (pig), 45 hr (cattle) and 142 hr (horse) (Brown & Riviere, 1991). This prolonged late-terminal phase corresponds to the final slow release of drug sequestered in tissues, particularly in the renal cortex. Accumulation and persistence at this renal site also accounts for aminoglycoside nephrotoxicity and withdrawal periods for kidney tissue, which may be several weeks (Gehring et al., 2005). This persistency of aminoglycosides in tissues led to the progressive abandonment of aminoglycosides for use in food-producing animals.

The problems of penalties associated with residues of AMDs in milk and dairy products have given rise to several generations of rapid screening tests for monitoring noncompliant residues of AMDs in milk. One of the most popular was the Delvotest, developed 40 years ago in the Netherlands and still used extensively (Bion et al., 2015). The several generations of the CHARM tests were developed in 1978 and later and are extensively used in United States to test raw milk of different species (Salter et al., 2011).

For residues analyses, sophisticated, specific and sensitive methods are now used routinely, as well as multi-residue methods for simultaneous determination of different members of an AMD class such as quinolones (Gaugain-Juhel et al., 2009; Verdon, Couedor, Roudaut, & Sandérs, 2005). The analysis of AMD residues in food has been reviewed in a textbook devoted exclusively to the subject (Wang, MacNeil, & Kay, 2012).

5.2 | The toxicologist's roles: residue risk assessment and prediction of withholding periods

Residues of AMDs must conform to the general rules applying to drugs of all classes for setting Maximum Residues Limits (MRLs) (EU) or tolerances (United States) and calculating withholding periods (WPs). For the EU, Directive 2377/90, defining procedures for establishing MRLs, and Directive 96/23/EC, describing requirements for monitoring residues, were important steps in building EU regulations. The specific hazards of residues of AMDs in milk and other edible products are immunotoxicity (allergenicity), emergence of resistance in human g.i.t. microbiota and industrial hazards, through impacting on the manufacture of fermented products, such as cheese and yoghourt. In addition, there were drug-specific issues for some AMDs, for example chloramphenicol (see Section 5.3). Allergenicity is not a significant issue for most AMDs, the main exception being benzylpenicillin. For a review of risks to humans of residues in edible tissues, see (Dayan, 1993).

For AMD residues' impact on the human intestinal flora, regulatory authorities require establishment of a microbiological Acceptable Daily Intake (ADI), if microbiologically active residues reach the human colon. At a conference held at the Royal College of Physicians in London on 2-3 December 1991 entitled "Antimicrobials in Veterinary Medicine: Public Health and Good Veterinary Practices," a session was devoted to evaluation of risk relating to residues of veterinary AMDs. This provides the basis for evaluating residues' risks for the g.i.t. flora (Boisseau, 1993; Corpet, 1993; Nord, 1993) and promoting the concept of microbiological ADIs. At that time, Industry expressed some dissenting views and concluded that there was no scientific evidence, which might lead to the conclusion that residues have effects on human intestinal flora (Kidd, 1995). In the United States, in 1993, the Center for Veterinary Medicine (CVM) and Animal Health Institute (AHI) sponsored a symposium on the microbiological significance of drug residues in food. A transcript of symposium papers and ensuing discussion was published in a special issue of the journal, Veterinary and Human Toxicology (Teske, 1993). The consensus of the Congress was that the very low levels of AMDs, present as residues in food, will probably not produce deleterious effects on the human intestinal flora. The use of microbiological end points in the safety evaluation and elaboration of MRLs for veterinary drugs intended for use in food-producing animals was subsequently reviewed in this Journal by Woodward (Woodward, 1998) and later by Cerniglia and Kotarski (Cerniglia & Kotarski, 2005). In due course, most regulatory agencies and international committees followed an harmonized process, as described in VICH GL(36) document (Cerniglia, Pineiro, & Kotarski, 2016).

The influence of health status on residue levels and WPs was appreciated by the late 1970s. Nouws considered that disease state is the main factor affecting the WP. He determined tissue residue concentrations and persistence of AMDs of several classes, including beta-lactams, aminoglycosides, tetracyclines, macrolides, chloramphenicol and sulfonamides in normal (healthy) and emergency-slaughtered ruminants after parenteral and intramammary administration (Nouws & Ziv, 1978). At that time, analytical assay methods (microbiological) were relatively crude and MRLs were not established. Nevertheless, comparing depletion rates with the same PK model in healthy and emergency-slaughtered cattle, he concluded that, in order to predict WPs for muscle and kidney in emergency-slaughtered ruminants, it was necessary to multiply by

a factor of 2–3 or 4–5, respectively, the values obtained in healthy animals.

Riviere promoted Physiologically Based Pharmacokinetic (PBPK) modelling, incorporating species- and chemical-specific parameters, to better predict the multiple factors impacting on residues, with the possibility of violation of WPs and therefore extrapolating WPs across species and doses (including extra-label use). In 1998, the conceptual framework of population PK was introduced into veterinary medicine (Martín-Jiménez & Riviere, 1998) to enable prediction of tissue residues depletion profiles and determine WPs for penicillin in cattle and swine (Li et al., 2014) using pooled data from published PK studies (Wu et al., 2013). PBPK approaches are now used extensively for AMDs (Henri, Carrez, Méda, Laurentie, & Sanders, 2017).

Riviere was an early promotor of the Food Animal Residue Avoidance Databank (FARAD) (Sundlof, Craigmill, & Riviere, 1986), a comprehensive computerized data-bank of invaluable regulatory and pharmacological information. FARAD was applied to mitigation of drug and chemical residue problems in food-producing animals and to facilitate trades between countries having varying standards (Riviere, Craigmill, & Sundlof, 1986). In 1998, in Europe, Anadon of the University of Madrid reported extensively on both PK and regulatory aspects of AMD residues in food species (Anadón & Martínez-Larrañaga, 1999) especially in poultry (Anadón et al., 1995).

Regulations designed to manage residues risks were established in the framework concept of Risk Analysis (Food and Agriculture Organization of the United Nations & World Health Organization, 2009). This involved international cooperation between the principal organizations (JECFA, EMA, FDA...) concerned and was harmonized within the Codex Alimentarius (see Section 6 and Figure 5 for relationships between these organizations).

5.3 | The regulator's role: example of the ban on chloramphenicol and the development of florfenicol

Chloramphenicol (CAP), formerly approved for use in cattle in the EU but not in the US, provides an emblematic example of public health issues arising from veterinary drug residues. In 1969, an incidence of 1:30,000 patients treated with CAP suffered blood dyscrasias (Wallerstein, Condit, Kasper, Brown, & Morrison, 1969; Wallerstein et al., 1969) with fatal aplastic anaemia occurring in some subjects, whilst leukaemia ensued in some recovery cases. CAP has been evaluated by the European Commission (1994) and the US Food and Drug Administration (1985) (see Berendsen et al., 2010). It is classified as a suspected carcinogen and, for this reason, was banned in 1994 in the EU for use in food-producing animals (Commission Regulation (EC) 1994) and in many other countries, including the USA, Canada, Australia, Japan and China. In 2005, JECFA (FAO) (see Section 6) at its 62nd meeting concluded that determination of an ADI for human consumers of residues was not possible, because no threshold could be predicted for the aplastic anaemia. Because CAP is regarded as probably carcinogenic, the zero-tolerance approach was first enforced to comply with the use of the linear nonthreshold model (for a review of models used before the 1990s for residues assessment, see Lu & Sielken, 1991). However, progress in analytical methodology, together with the unexpected and poorly understood ubiquitous presence of CAP in food products (Hanekamp & Calabrese, 2006), albeit at very low levels, together also with evidence of the natural occurrence of CAP in herbs and grasses (Berendsen et al., 2010), account for nonfeasibility of the zero-tolerance requirement. In 2005, a Minimum Residues Performance Limit (MRPL) of 0.3 μg/kg was assigned by the European Commission for analytical methods testing for CAP in products of animal origin. In consequence, the concept of a Toxicological Insignificant Exposure Level (TIEL) (Kroes et al., 2004) was implicitly accepted. Therefore, CAP was no longer regulated at zero level but at the MRPL. With this decision, MRPLs have now been granted legal status in terms of explicit levels of toxicological concern and have been applied to other substances including nonveterinary residues.

FIGURE 10 Thomas E. Powers (1925–2010) had many research interests in veterinary medicine. He specialized in the pharmacology of antimicrobial drugs especially florfenicol, developing an ethically acceptable tissue cage model to facilitate his studies on drug actions in vivo and ex vivo

The ban on CAP in food-producing species facilitated the introduction florfenicol, a similar drug to CAP but lacking blood dyscrasia toxicity, for sole veterinary use. The in vitro activity of florfenicol was first reported in 1982 (Syriopoulou, Harding, Goldmann, & Smith, 1981). The first veterinary publication appeared in this Journal in 1986 (Varma, Adams, Powers, Powers, & Lamendola, 1986). It was based on cooperation between Schering Plough Corporation (now MSD) and the Department of Veterinary Physiology and Pharmacology of Ohio State University, headed by Tom Powers, one of the fathers of veterinary pharmacology in the United States (Figure 10). To date, more than 2,000 publications have been published on this major veterinary AMD.

5.4 | Ecotoxicology: the roles of analysts (chemists), microbiologists and epidemiologists

Chemists' contributions to the field of ecotoxicology, relating to the concept of One Health, are now highly significant. Matrices of interest are no longer confined to meat and milk but encompass

all components of the environment, air, water and soil. In the present decade, ecotoxicology, underwritten by increasingly sensitive analytical methods, has become a major consideration, one major element of which comprises AMD use in veterinary medicine. Of increasing interest to chemists and others are as follows: the elimination of AMDs in urine from treated animals, driving the selection of resistant bacteria and of resistance genes in the environment (Subbiah, Shah, Besser, Ullman, & Call, 2012); the presence of AMDs in soil (Thiele-Bruhn, 2003); the uptake of veterinary medicines from soils into plants (Boxall et al., 2006); environmental selective pressure of AMDs on bacteria of importance to public health (Tello, Austin, & Telfer, 2012); and the relevance of these issues for regulators (Singer, Shaw, Rhodes, & Hart, 2016).

Ecotoxicology is not limited to the measurement of environmental contamination by AMDs. It involves also the environmental presence of bacteria and genes of resistance. The spread of resistance genes in manure was early documented (Heuer, Schmitt, & Smalla, 2011). Urban wastewater treatment plants are both a major source of release of AMDs into the environment (Rizzo et al., 2013) and "hotspots" for the admixing of resistant bacteria and genes of resistance from human and veterinary sources. In many locations, wastewater from slaughterhouses is simply collected with human waste in municipal treatment plants, thereby favouring genetic exchanges between bacteria of differing sources. Class 1 integrons, genetic elements which acquire foreign genes from the environment and play a central role in spreading antibiotic resistance, can be used as a proxy for anthropogenic pollution (Gillings et al., 2015). It was estimated that, depending on the host (food-animal species, human) up to 10^{23} copies of class 1 integrons are shed every day into the environment with the following ranking: pigs > poultry > cattle > man (Zhu et al., 2017). It can be noted that this ranking order correlates well with the biomass of domestic species and supports the One Health paradigm to manage AMR.

5.5 | Antimicrobial resistance risks and the roles of microbiologists and epidemiologists

5.5.1 | The scientific basis for understanding, detecting and monitoring antimicrobial resistance

Microbiologists' contributions to AMDs evolved with time and now relate to all aspects of AMR and public health issues, as indicated in previous sections of this review. In early developments, microbiologists were the first to report PK data for a range of drugs, because assay methods were initially microbiological. The most emblematic microbiological growth medium used to measure plasma concentration of AMDs, but also used for antibiotic susceptibility testing and MIC determination, is the Mueller-Hinton Broth (MHB), which was co-developed by the microbiologist John Howard Mueller and the veterinary scientist Jane Hinton at Harvard University (Figure 11).

FIGURE 11 Jane Hinton (1919–2003) was a US veterinarian who co-developed a protein-free medium for the isolation of gonococcus and meningococcus, now known as the Mueller-Hinton agar/broth (Mueller & Hinton, 1941). This culture medium continues to be widely used to test bacterial susceptibility to antimicrobial drugs

The discovery in Japan in the late 1950s that resistance to a set of four or more antibiotics could be transferred by cell-to-cell contact, that is by conjugation, between Enterobacteriaceae of the same or of different species, marked a major advance in the understanding of AMR and its implications (Watanabe & Fukasawa, 1961). These early studies showed that "infective" resistance determinants, initially called R-factors, were episomal, and could therefore exist and replicate independently of the bacterial chromosome. Later, it transpired that these R-factors were circular pieces of DNA, which were then referred to as R-plasmids, according to the term introduced by Lederberg in 1952 (Lederberg, 1952). In the 1960s, the impact of transferable antibiotic resistance on public health was increasingly recognized, and many authors suggested that the use of antibiotics in livestock, for example tetracyclines in pig and fowl diets, could contribute to the emergence and dissemination of resistant bacteria (Anderson & Datta, 1965), (see Section 2.1).

The contribution of microbiologists has passed through stages of technical and methodological innovations, notably in the rapid identification of bacteria and their sensitivity to AMDs. The state-of-the-art methodologies for identification and susceptibility testing of veterinary pathogens has recently been reviewed (Guardabassi et al., 2017). MALDI-TOF (matrix-assisted laser desorption/ionization-time of flight) mass spectrometry (MS) is now used routinely to identify species of bacteria within minutes. Phenotypic Antimicrobial Susceptibility Testing (AST) was and remains the cornerstone for individual diagnostic tests for AMR. The conventional approach, using disk diffusion or broth dilution, involves a delay of some 48–72 hr to obtain a result. This

has prompted, currently, the development of so-called rapid AST (result obtained within 8 hr) (van Belkum et al., 2020). In parallel, several nonphenotypic new technologies, including those based on molecular and genome sequencing, are being developed (Vandenberg et al., 2020).

Molecular AMR detection methods specify resistance genes and resistance-conferring mutations (van Belkum et al., 2020). Whole-genome sequencing (WGS) provides global information on the presence of all resistance genes in a given sample (resistomes analysis). WSG also enables characterization and comparison of isolates from several animal species, including humans, and hence documentation of phylogenetic similarities and epidemiological relationships among isolates. By these means, WGS can be predicted to improve AMR surveillance and interpretation on the transmission of resistant bacteria and AMR genes throughout the food chain. The potential is for WGS to replace traditional phenotypic methods for routine surveillance of AMR (Collineau et al., 2019).

Using these new and older methodologies, a multitude of data has been generated over the last four decades, leading to the current state of AMR knowledge. For the period 1975–2015, Schwarz, Enne, and van Duijkeren (2016) in a review entitled "40 years of veterinary papers in Journal of Antimicrobial Chemotherapy—what have we learnt?" summarized the contributions of microbiologists. Among others, contributions of major impact were those of Holmberg, Osterholm, Senger, and Cohen (1984), Engberg (2001), McEwen and Fedorka-Cray (2002), Guardabassi, Schwarz, and Lloyd (2004), Hasman, Mevius, Veldman, Olesen, and Aarestrup (2005), Cabello (2006), Juhász-Kaszanyitzky et al. (2007), Kemper (2008), van Belkum (2008), Hendriksen, Mevius, Schroeter, Teale, Meunier, et al. (2008)), Perreten et al. (2010), Weese and van Duijkeren (2010), Leverstein-van Hall et al. (2011), Catry et al. (2010), Graveland et al. (2010), van Hoek et al. (2011), Dierikx et al. (2012), Zhu et al. (2013), Catry et al. (2015), Kempf et al. (2013), Wu et al. (2013)), Pomba et al. (2016) and Liu et al. (2016). These contributions have been made to all aspects of AMD discovery, development, use and regulation, but most particularly to epidemiology (*vide infra*). Microbiologists have also been whistle-blowers, challenging certain practices and thereby leading veterinary medicine to define more prudent uses of AMDs. Among others contributing in this manner are Smith (1969), Piddock (1996), Van den Bogaard and Stobberingh (1999), Aarestrup et al. (1998), Mevius, Sprenger, and Wegener (1999), Aarestrup (1999), Barton (2000), Levy and Marshall (2004), Marshall and Levy (2011) and Liu et al. (2016).

5.5.2 | Proof of the link between antimicrobial drug use in animals and antimicrobial resistance in humans

In the 1970s, scientific tools were available to understand and unequivocally prove the relationship between AMD uses in animals and the emergence of AMD resistance in humans, as discussed in Section 2.1. A direct epidemiological relationship between animal and farmer bacterial isolates, that is a professional risk (Gustafson & Bowen, 1997) was confirmed early for MRSA in pigs and cattle (Manten, 1963) and also in poultry (Mulders et al., 2010). The possibility of a more global (community) risk was clearly demonstrated by two emblematic events: first, the use of nourseothricin as a feed additive and, second, the misuse of ceftiofur in Canadian hatcheries.

Nourseothricin is a member of the streptothricin class of aminoglycoside AMDs that was used only in East Germany, as a growth promoter in pigs. Between 1983 and 1990, microbiologists were in a position to trace a transposon-encoded streptothricin gene of resistance (Kirchhelle, 2018b). After two years' use, plasmid-borne resistance to streptothricin occurred in *E. coli* from nourseothricin fed pigs. More importantly, there was evidence of widespread dissemination of resistance in manure, river water, food and the g.i.t. flora of farm employees, their family members, healthy outpatients not related to animal husbandry and in urinary tract infections (Hummel, Tschäpe, & Witte, 1986). In addition, the resistance determinant was detected in *Salmonella* and *Shigella* strains isolated from human diarrhoea cases (Tschape, 1994). As *Shigella* is a pathogen of primates, but does not occur in the g.i.t. of swine, it was deduced that the horizontal transfer of streptothricin resistance had occurred in the intestinal tract of humans.

A second emblematic case of quasi-experimental epidemiology of AMR is that of ceftiofur resistance in *Salmonella enterica* Serovar Heidelberg, harvested from chicken meat and humans in Canada (Dutil et al., 2010). In Québec, changes in ceftiofur resistance in chicken *Salmonella* Heidelberg and *E. coli* isolates were clearly associated with changing levels of ceftiofur use in hatcheries (an illegal practice in the EU). Moreover, this change mirrored the incidence of human infections from ceftiofur-resistant *Salmonella* Heidelberg. When ceftiofur was used, the prevalence of ceftiofur resistance isolates from retail chicken was up to 62% for *Salmonella*, decreasing to 7% after the voluntary withdrawal of ceftiofur, then increasing again to 20% after its re-introduction. Also during this period, the incidence of ceftiofur-resistant *Salmonella* Heidelberg in human infections in Quebec was 36%, when ceftiofur was in use, decreasing to 6% after its withdrawal and increasing again to 12% after a partial re-introduction of ceftiofur in hatching.

These case studies were related either to a now banned EU practice (use of AMDs as growth promoters) or to the misuse of an AMD (ceftiofur use in hatcheries). It was not until the 1990s that more global threats, associated with approved therapeutic uses of veterinary AMDs, were better appreciated. In 1987, an oral formulation of enrofloxacin for the treatment of respiratory poultry infections due to *Mycoplasma* spp. and *Pasteurella multocida* was launched in the Netherlands. Almost 10 years later, in 1996, enrofloxacin was approved by US FDA for the reduction of mortality associated with *E. coli* in poultry. This had rapidly led, both in the EU and United States, to the emergence of resistance in food-borne pathogens (*Campylobacter* spp. and *Salmonella* spp.). Enrofloxacin is closely related to ciprofloxacin, an extensively prescribed fluoroquinolone in human medicine. In several domestic species, enrofloxacin is a prodrug metabolized to ciprofloxacin. This invalidates the marketing concept for the species specificity of a veterinary quinolone. When

administered in feed or water, enrofloxacin rapidly induces (24–48 hr) the emergence of fluoroquinolone resistance in *Campylobacter jejuni*, a commensal bacterial species present in the g.i.t. of poultry (van Boven, Veldman, de Jong, & Mevius, 2003). Moreover, in flock treatment, nearly 100% of *Campylobacter* become resistant with a persistency of up 4 weeks after cessation of treatment (Humphrey et al., 2005). As early as 1990, it was reported in the Netherlands that the recorded increase of quinolone resistance in human *Campylobacter* spp. was temporally related with the large-scale use of enrofloxacin in veterinary medicine (Endtz et al., 1990). Considering the almost exclusive transmission route of *Campylobacter* from chicken to man, by the food chain, it was concluded that the resistance recorded in humans was due principally to the use of enrofloxacin in the poultry industry (Endtz et al., 1991). In human medicine, campylobacteriosis is generally a self-limiting condition, not requiring treatment. In some critical circumstances, however, for example in the elderly, in immunocompromised patients and in cases of co-morbidity, fluoroquinolones and macrolides are the drugs of choice (Yang et al., 2019). Even if correlation is not synonymous with causation, this should have led at that time to the hypothesis that therapeutic failures in human medicine to treat zoonotic infections might have been due to the use of AMDs in veterinary medicine, including treatment for campylobacteriosis (Piddock, 1996).

In the USA, similar events were reported in the years immediately following the introduction of enrofloxacin to treat poultry diseases. This led the US FDA to decide, in 2000, to withdraw the use of enrofloxacin in poultry, this being a first such occasion in the US regulatory history for an AMD. However, in a commercial setting of widespread use food additives, the Agency's decision was legally challenged, and it was not until 5 years later, in 2005, that the ban took effect (Kirchhelle, 2018b). After withdrawal of enrofloxacin from use in poultry in the United States, the prevalence of fluoroquinolone resistance in *Campylobacter jejuni* in poultry decreased. As predicted, this was also the case for human medicine and, at that time, it was thought that this regulatory FDA decision was a major success in public health terms (Nelson, Chiller, Powers, & Angulo, 2007). In subsequent years (2008–2011), however, a new surge of ciprofloxacin-resistant *Campylobacter jejuni* from retail chicken was reported. Similarly in the EU, despite withdrawal of fluoroquinolones as growth-promoting agents, the incidence of fluoroquinolone-resistant *Campylobacter jejuni* in broilers increased from 5.3% in 2001 to 26% in 2013, indicating that the banning of fluoroquinolones as growth promoters per se may not suffice to reduce or eliminate reservoirs of resistant bacteria. However, and in contrast with the situation in the United States, the ECDC/EFSA/EMA JIACARA recorded no association between the consumption of fluoroquinolones in food-producing animals and the occurrence of resistance in *Campylobacter* spp. from cases of human infection (Anonymous, 2015). A similar conclusion was reached for *Salmonella* (Helke et al., 2017).

Now, even with 30 years hindsight on the above case, and several others recently reviewed (Hao et al., 2016), the link between veterinary and human clinical isolates of *Campylobacter* remains controversial. Recent studies confirm that on farms AMD selection pressure can increase colonization of animals with drug-resistant *Campylobacter* spp., whilst it is not possible to establish a clear causal relationship between AMD use in animals and prevalence of drug-resistant food-borne campylobacteriosis in humans (McCrackin et al., 2016). It is known that pressure from AMD use is not the sole factor for the selection and dissemination of resistance. Recently, the detection in Australia of a sub-population of *Campylobacter* isolates, exclusively resistant to fluoroquinolones, was unexpected, because fluoroquinolones were never used in that country (Abraham et al., 2020).

5.5.3 | Polemics and uncertainty: from militant opinions to source attribution on the risk of antimicrobial resistance

Today, the possibility of transfer of AMR from animals to human is no longer debated, but the question remains as to the magnitude of the contribution to the overall level of AMR in humans deriving from animal uses of AMDs. Many authors have expressed strong, even strident, opinions on the implication, or not, of veterinary uses of AMDs on AMR prevalence in humans. Moreover, the opinions have generally been highly polarized. For example, it was suggested that "the contribution of animals to the overall problem of human resistance is likely to be very small" (Bywater, 2004). Others were likewise doubtful (Richez & Burch, 2016; Wallinga & Burch, 2013), whilst one eminent microbiologist (Phillips, 2003, 2007) directly challenged the suggestion that veterinary medicine, rather than human medicine, was the primary factor responsible for AMR in humans. He further suggested that restrictions on animal use would actually be ineffective. The opposing view has been to criticize the veterinary use of AMDs, impressing on the debate their interpretation of literature data. An example relating to AMR is the estimate of 1,518 additional deaths per year resulting from cephalosporin and other AMD usage in poultry, with the wholly unsubstantiated claim that *the number of avoidable deaths and the costs of healthcare potentially caused by third-generation cephalosporin use in food animals is staggering* (Collignon, Aarestrup, Irwin, & McEwen, 2013).

In addressing this debate, with its opposing factions, the crucial role of epidemiologists is now to describe and quantify the relationships between AMD field use, including amounts consumed and conditions of field use and AMR emergence (Chantziaras, Boyen, Callens, & Dewulf, 2014). Indeed, this AMR animal–human debate was not and is not merely a speculative ethereal exercise. Many jurisdictions have implemented restrictions on the use of AMDs in agriculture, and they have been influential in promoting the concept of AMDs critical to human medicine, for example by the WHO (Anonymous, 2018e).

If these polarized debates are to progress to satisfactory conclusions, more nuanced approaches, based on advances in epidemiological methodologies will be used when available. The application of WGS is expected to support more objective and accurate risk assessments of food-borne AMR, based on quantitative microbial

risk evaluation, adopting Codex Alimentarius principles for conducting microbiological risk analysis (Collineau et al., 2019). Indeed, the high discriminatory power offered by WGS analysis has the potential to attribute cases of food-borne disease to putative sources of infection (Fegan & Jenson, 2018) as do Source Attribution methods (Pires, Duarte, & Hald, 2018). The latter are statistically based methods, which estimate the probability that a sample from a given case is the source (donor) of infection for another case (recipient). As an example, these mechanistic oriented investigations aim to quantify molecular similarities between a multiplicity of reservoirs, as a first step towards Source Attribution, as reported recently for the epidemiology of ESBL- and AmpC-producing *E. coli* (ESBL/AmpC-EC) (Dorado-García et al., 2018). Comparison across 22 reservoirs (human, animals, food, environment) of the molecular relatedness of ESBL/AmpC-EC indicated distinguishable ESBL/AmpC-EC transmission cycles in different hosts but failed to demonstrate a close epidemiological linkage of ESBL/AmpC genes and plasmid replicon types between livestock farms and people in the general population (Dorado-García et al., 2018). The authors suggested that livestock reservoirs, including poultry and poultry meat, are not major contributors to ESBL/AmpC occurrence in humans. This large data set was analysed quantitatively using Source Attribution methodology. It was shown that most community-acquired carriage of ESBL producing and plasmid-encoded AmpC (pAmpC)-producing *E. coli* were attributable to human-to-human transmission (approximately two-thirds), followed by food, animal and environmental sources (Mughini-Gras et al., 2019). This finding challenges the alarming and unsubstantiated opinions expressed earlier by others (Collignon et al., 2013).

For the future, this methodology for attribution of sources should become essential for the development of rational and effective public health interventions. In the previous example, although direct contributions of animals were estimated to be smaller than human-to-human exchanges, infection, contamination and dissemination of ESBLs and pAmpCs from nonhuman reservoirs (animal, meat, seafood, raw vegetables…) were considered to be sufficiently large to justify their specific monitoring and to enforce mitigation policy (Mughini-Gras et al., 2019).

5.6 | The one health initiative

In 2020, AMR must be regarded as a global ecological problem with an animal contribution. Factors determining AMR prevalence and its dissemination are numerous. They include both medical and veterinary use, overuse, misuse and abuse of AMDs, as well as nonmedical AMD uses (e.g. use of streptomycin in agriculture); and use of other, nonantibiotic antimicrobials, such as triclosan and heavy metals, that can select for antibiotic resistance mechanisms.

One Health concepts, and their relationship to broad aspects of ecology, are now the AMD and AMR paradigms dominating scientific research and public debate, deriving from recognition that AMR is a global ecological issue of over-riding significance (Gelband & Laxminarayan, 2015).

Acknowledging the inextricably inter-connected three health (animal, human and environmental) issues, Roger K. Mahr, when President of the American Veterinary Medical Association (AVMA) in 2007, invited his counterpart in human medicine, Ronald Davis, then President of the American Medical Association (AMA), to open discussions on subjects of common concern. The goal was to find common cause between animal and human medical communities. The AMA unanimously adopted a "One Health" resolution in June 2007. The initiative task force defined One Health as "the collaborative efforts of multiple disciplines working locally, nationally, and globally, to attain optimal health for people, animals and our environment." The document entitled "One Health: A New Professional Imperative" (Anonymous, 2008) describes the goals and approaches of the One Health initiative. Since 2008, the EU has also promoted the One Health approach, with concept integration into EU documents, such as that entitled "One Health: Addressing health risks at the interface between animals, humans and their environments" (Anonymous, 2013).

In the conceptual framework of One Health, politicians seek scientific expertise, including answers to complex, multi-factorial problems. The longer term response from the scientific community therefore demands a multi-factorial approach and, in particular, global solutions to global problems. This is required to address predictions/scenarios, such as those of the WHO (Shallcross & Davies, 2014). Their doomsday scenario of the world in 2050 was based on predictive models, which assumed no alteration of course for the global AMD ship. The predicted consequence of inaction was as follows: "Armageddon" for the effective treatment of infectious diseases; consequential "losses of life and increased suffering"; and associated "astronomical financial costs." The necessary response, initially and encouragingly, has been the requisitioning of, reflections on, and now urgent actions addressing official reports, of which the O'Neill Report (O'Neill, 2014) is one of many.

6 | REGULATORY CONTROL AND INTERNATIONAL ORGANIZATIONS

6.1 | Awareness of the danger of antimicrobial resistance and implementation of surveillance programmes

In the EU, awareness of the dangers of AMR was clearly expressed and the principles underlying solutions were described following a conference entitled "The Microbial Threat." This invitation conference, held in Copenhagen in 1998, made AMR an official EU concern for the first time. The initiative yielded a set of conclusions which, together with a summary of the conference, were published as Copenhagen recommendations (Anonymous, 1998). Recommendations included the surveillance of AMR and monitoring the use of AMDs in both animals and humans. In animals, it was proposed that surveillance should be focussed on potential transfer

of resistant, zoonotic, food-borne pathogens and resistance genes to humans (Mevius et al., 1999). This initiative was shortly followed by a recommendation from the Council of the EU in 2001 urging member states to follow and adopt the recommendations of the Copenhagen meeting. Funding from EU research funds was then provided for projects to monitor resistance and the use of AMDs, which, until then, had been lacking in most EU countries. This initiative is a good example of a major health problem raised by concerted and official EU action (Frimodt-Møller, 2004).

Two EU concerted actions (EU 4th and 5th Framework programmes) were established to create a network of national veterinary reference laboratories in Europe and establish a surveillance system for monitoring AMR of animal origin. The first action, named "Antibiotic Resistance in Bacteria of Animal Origin" (ARBAO I), aimed to establish the state-of-the-art and promote standardization and harmonization of methodologies and of reporting AMR. Co-ordinated by Pascal Sanders, its conclusions were published in a special issue of "The International Journal of Antimicrobial Agents" in 2000 (Sanders, 2000). The second initiative (ARBAO II) for the period 2003-2005 was co-ordinated by Frank Aarestrup; its objective was to create a stable EU network for generating comparable and representative data on AMR (Hendriksen, Mevius, Schroeter, Teale, Jouy, et al., 2008).

Industry has also been involved in surveillance. VetPath is an ongoing Pan-European resistance monitoring programme, encompassing food-borne bacteria and target pathogens of food-producing and companion animals (El Garch et al., 2016; de Jong et al., 2013). In addition, there are national, not harmonized, surveillance schemes for monitoring AMR for pathogenic bacteria (Schrijver et al., 2018).

These initiatives have been followed by a multitude of others, emanating from a range of professional, national and international organizations; these bodies have developed, within the framework of their missions and strategic axes, guidelines aimed at limiting the development of AMR and/or promoting good therapeutic practices. Moreover, many organizations, representing veterinary clinical groups, for example on species' bases, have issued guidelines to their members on prudent and rational use of AMDs in clinical veterinary medicine—see (Whitehead, Chambers, Lees, & Toutain, 2019) as one example.

6.2 | The Food and Agriculture Organization (FAO) and Codex Alimentarius

The United Nations involvement with AMD and AMR is channelled through two organizations, namely the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) each served by several committees.

The FAO was established in 1945; its headquarters is in Rome, Italy. For FAO, the Codex Alimentarius Commission (CAC) is the committee charged with developing harmonized international food standards to protect consumer health, and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) is specifically concerned with establishing Maximal Residue Limits (MRL) including those for AMDs.

In 2006, Codex established a first Task Force on AMR (TFAMR). In the period 2007–2011, they developed guidance, using principles of risk analysis, to assess and manage risks to human health associated with the presence in food and feed (including aquaculture) of antimicrobial-resistant microorganisms and their onward transmission through food and feed. A second Task Force, established in 2017, has the remit of developing guidance for the management of AMR in the food chain.

The FAO/WHO Joint Expert Committee on Food Additives (JECFA) was established in 1956. It enunciates principles and develops tools (Sanders, Henri, & Laurentie, 2016) for evaluating safety and quantifying risks of residues of veterinary drugs in food. JEFCA also recommends MRLs for target tissues and determines criteria for, and evaluates methods of, analysis for detecting and/or quantifying residues in food. It provides independent scientific advice to Codex on residues of veterinary drugs, facilitating recommended MRLs by CCRVDF. More specifically for AMDs, it establishes microbiological ADIs, to be considered alongside conventional "toxicological ADI." The lower of the two ADIs is selected as the final ADI (Boobis et al., 2017). Codex issued Codes of Practice to Minimize and Contain Antimicrobial Resistance in 2005 and Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance in 2011 ("Antimicrobial Resistance | CODEXALIMENTARIUS FAO-WHO" 2019).

6.3 | The World Health Organization (WHO)

WHO was established in 1948; its headquarters are in Geneva, Switzerland. WHO has exerted a decisive influence on AMD veterinary uses, overuse and misuse practices. The WHO document "Optimal use of antimicrobial medicines in human and animal health" declares in Objective 4: *Optimize the use of antimicrobial medicines in human and animal health* ("WHO | Global action plan on AMR"). A clear goal is to adopt measures which preserve the effectiveness of AMDs of importance for human medicine by reducing their usage in animals. WHO launched its updated guidelines on use of medically important AMDs in food-producing animals on 7 November 2017. These recommend first, that farmers and the food industry cease routine usage of drugs to promote growth (as required in the EU from 2006) and second, that veterinarians cease usage in disease prevention in healthy animals (i.e. prophylaxis).

Commencing in 2005, WHO has released lists of AMDs critically important for human medicine (WHO CIA List) (Anonymous, 2019h). The WHO classifies currently used AMDs in humans and animals in three categories, based on their relative importance in human medicine—"important," "highly important" and "critically important" (see the fifth revision published in 2017 of "Critically important antimicrobials for human medicine" (WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance & World Health Organization, 2017).

A recent controversial topic for WHO concerns the use and regulation of colistin. Colistin has been used in pig medicine for many years, and colistin resistance in bacteria from animals has been described (Kempf et al., 2013). Rhouma et al. have reviewed the role of colistin in pig production, outlining its chemistry, mechanisms of action and resistance emergence, as a contribution to One Health perspectives (Rhouma, Beaudry, Thériault, & Letellier, 2016). In 2016, Liu et al. (2016) reported the emergence of the first plasmid-mediated colistin resistance gene, Mcr-1 in Enterobacteriacea isolated from animals and humans in China. Olaitan, Morand, and Rolain (2016) reported the emergence of colistin-resistant bacteria in humans with no colistin usage, describing this as "a new worry and cause for vigilance". However, in 2016, the AMEG final recommendation was to uphold the veterinary use of colistin with an objective of reducing its use by 65% over 4 years (Anonymous, 2016b).

The WHO seeks to preserve the long-term effectiveness of those AMDs critically important in human medicine. However, the effectiveness of the accompanying proposed restrictions is unclear. Recently, the WHO commissioned two systematic reviews to directly address these questions, that is does limiting the use of AMDs in food animals reduce either the presence of AMR genetic determinants or AMR bacteria first in food animals and then in humans. In the first review (Tang et al., 2017), a meta-analysis was conducted. It was concluded: that restriction of AMD use in food-producing animals led to a reduction of AMR in these animals; that a smaller body of evidence indicated a similar association in human populations, particularly those with direct contact with food-producing animals; that the implications for the general human population are unclear, given the small number of studies. The second review (Scott et al., 2018) included 104 articles, but the quality of the data did not suffice to enable a meta-analysis. It was concluded that limiting AMD use in food animals not unexpectedly reduces AMR in food animals and probably reduces resistance in humans also but the magnitude of the latter effect could not be quantified.

6.4 | The World Organisation for Animal Health (OIE)

Emmanuel Leclainche, (Figure 12), established the World Organisation for Animal Health, based in Paris, in 1924 under the French name of, Office International des Epizooties (OIE).

In 2003, the Office became the World Organisation for Animal Health but retained its historical OIE acronym. From 2010, OIE became increasingly focussed on the "One Health" paradigm including AMR. OIE developed a strategy to support Member Countries (currently numbering 182) in assessing and managing AMR. OIE promotes surveillance and supports good governance, for enforcing the prudent use of AMDs in developing countries. A OIE guideline on the harmonization of national AMR monitoring and surveillance programmes in animals and animal-derived foods has been developed by the Ad hoc Group of experts on antimicrobial resistance (Franklin et al., 2001). OIE also manages a database to establish global

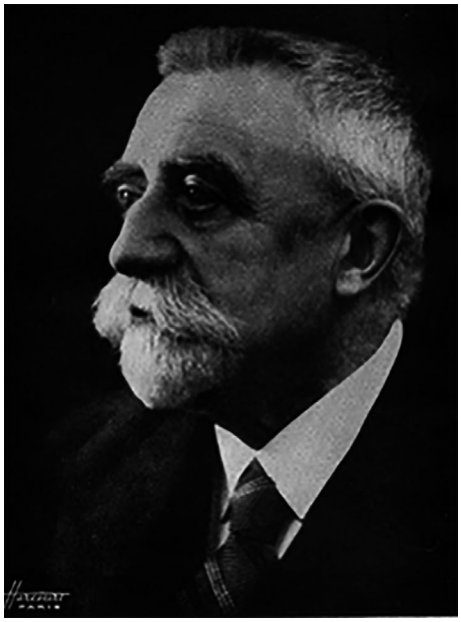

FIGURE 12 Emmanuel Leclainche (1861–1953) was a French veterinarian and microbiologist. He was the founder and first General Director of the Office International des Epizooties (OIE), the counterpart of the WHO for human medicine

surveillance of AMD usage in animals, monitoring both drug type and specific uses of AMDs. According to OIE, in 2015, 64 countries had regulations in place banning the use of AMDs for use in growth promotion. OIE has claimed an international consensus that such use should be phased out globally, with immediate universal revocation of use for growth promotion purposes of those AMDs listed by the WHO as Highest Priority Critically Important drugs for human medicine. In October 2018, at Marrakesh (Morocco), OIE convened a meeting of worldwide leaders in animal health, with the remit of addressing the global rise of AMR in the animal farming sector.

OIE, in association with FAO and WHO—the so-called tripartite Partnership—illustrates the co-operative effort underlying the One Health concept (Figure 5). The Partnership drives the development of policies and tools to support measures within Member Countries to combat the rise in AMR. On 21 September 2016, the United Nations General Assembly adopted a political declaration, aimed at combating the global threat posed by AMR and confirming the One Health approach, in line with the Global Action Plan.

6.5 | The European Medicines Agency (EMA), the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC)

The European Medicines Agency (EMA) was created in 1995. Previously, regulations had been nationally based.

In 2020, combatting the threat of AMR is a high priority for EMA and its Committee for Medicinal Products for Veterinary Use (CVMP). CVMP is serviced by a Scientific Advisory Group

on Antimicrobials of the Committee for Medicinal Products for Veterinary Use (SAGAM) (Anonymous, 2009). CVMP promotes the prudent use of AMDs in animals, collecting data on their veterinary use in the EU and providing scientifically based recommendations on the animal' use of specific drugs. In October 2016, CVMP published the Agency's strategy on AMDs for the period 2016–2020 (Anonymous, 2018c). In line with this strategy, the Agency has published a revised CVMP guideline on demonstration of efficacy for veterinary medicines containing AMD substances (Anonymous, 2016a). This second revision of the EU guideline provides further information on the use of AMDs in animals that are at risk of being infected (metaphylactic use).

Developing and monitoring policies on the responsible use of AMDs in EU Member States depends on collecting accurate data on usage. At the request of the EU Commission, a harmonized approach for collecting and reporting data on AMD use in animals from EU and European Economic Area (EEA) Member States is in place. EMA started monitoring AMD use in 2010 by enforcing the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project to identify possible risk factors that might lead to the development and spread of AMR in animals (Anonymous, 2018d). The quantities of veterinary AMDs sold are linked to animal demographics in each country. To normalize the sales data for the animal population subjected to treatment with AMDs, a population correction unit (PCU) is used by ESVAC as a proxy for animal population size.

The implementation of resistance monitoring in bacteria responsible for food-borne zoonoses commenced in the 1980s by national initiative. Following Directive 2003/99/EC on the monitoring of zoonoses and zoonotic agents, Member States (MSs) are now obliged to monitor and report AMR in *Salmonella* and *Campylobacter* isolates from animals and food. In contrast, the monitoring and reporting of AMR data from the indicator organisms *E. coli* and enterococci is voluntary. These data are now stored centrally by the European Food Safety Authority (EFSA). EFSA, located in Parma, Italy, was established as an independent EU agency in 2002. Its mission is to provide objective scientific advice on any matters having impact on food and feed safety. Its remit includes AMR. To execute its mission, EFSA aggregates and analyses annually the data on AMR. Its annual survey encompasses: zoonotic *Salmonella* and *Campylobacter* isolates from humans, food and animals and; indicator *E. coli* and enterococci isolates from animals and food. Data on methicillin-resistant *Staphylococcus aureus* in animals and food are also included. For this task, EFSA collaborates with the European Centre for Disease Prevention and Control (ECDC). ECDC is an EU agency based in Stockholm, Sweden. It was established in 2005, and its mission is to strengthen Europe's defences against infectious diseases.

EMA, EFSA and ECDC have responsibility for analysing the potential relationship between the consumption of AMDs by humans and animals and the occurrence and incidence of AMR. They deliver their findings in joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) reports (Anonymous, 2018b).

EMA supports the EU Commission's action plan against the rising threats from AMR by providing scientific input and advice on impacts of using AMDs in animals in partnership with other relevant EU bodies. This includes a joint opinion with EFSA on measures to reduce the use of AMDs in animal husbandry (also known as the "RONAFA" opinion, Figure 5) (Anonymous, 2017). In July 2017, the European Commission requested EMA to update the Antimicrobial Advice Ad Hoc Expert Group (AMEG) categorization of AMDs. AMEG is an ad hoc group established jointly under the CVMP and the corresponding EU human committee, that is the Committee for Medicinal Products for Human Use (CHMP). CVMP issued a discussion document on the categorization of AMDs, to be followed by final guidelines. It includes new drug classes, additional categorization criteria and the availability of alternatives to AMDs in veterinary medicine (Anonymous, 2018a).

For all novel AMDs, there are necessary regulatory hurdles (Martinez, Watts, & Gilbert, 2019; Shryock, 2004). For existing AMDs, EMA/CVMP has issued a discussion document on proposed categories of use in veterinary medicine (EMA/CVMP/CHMP/682198/2017) (Anonymous, 2019a). These or modified classes of use (after completion of consultations) will form the basis of AMDs in veterinary use in the next decades, at least in EU countries.

6.6 | The US Food and Drug Administration (FDA) and the Center for Disease Control and Prevention (CDC)

In the USA, the Food and Drug Administration (FDA) and its Center for Veterinary Medicine (CVM) are the principal bodies involved in regulation of AMDs. The FDA mission statement is "Protecting Human and Animal Health." FDA is responsible for the Marketing Authorisation of AMDs and establishing MRLs/tolerances in food products. FDA also conducts research in the areas of its remit. Whilst in many fields FDA plays a leadership role and is at the forefront of regulatory science and policy, this is not the case for AMR in veterinary medicine. This is due, first, to the difficulty of regulating the use of AMDs as growth promoters and, second, to the fact that the FDA cannot, by its constitution, formally require the submission of PK data for food animal drug applications. In consequence, FDA cannot (in contrast to EMA) issue specific guidance, for example to promote PK/PD integration and modelling approaches for the design of rational AMD dose schedules, unless data from applicants are supplied.

In 2018, FDA released its Five-Year Plan for Supporting Antimicrobial Stewardship in Veterinary Medicine. A plan objective is to eliminate production uses of medically important antimicrobials and to encompass all remaining therapeutic uses under the oversight of licensed veterinarians. The FDA approach was based on the belief that a collaborative approach involving all stakeholders would be the quickest way to implement the required changes in USA, as outlined in its Guidance #213 (Anonymous, 2019c). This approach to initiating regulatory action was preferred to the alternative of proceeding laboriously on a product-by-product basis, requiring not only additional resources but also delays to implementation. FDA recognizes

that diseased animals require AMD treatment and therefore that drug availability must continue for this purpose. In addition, FDA will continue to authorize AMDs for controlling disease (prophylaxis) being at variance with the EU in this regard. In 2017, AMD production indications (e.g. growth promotion) were withdrawn from all applications that included such indications for use in USA (Anonymous, 2019d).

CVM has issued several generic guidance documents relevant to AMD and AMR, including CVM Guidance for Industry (GFI) #144 (VICH GL27) entitled "Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food-Producing Animals with Respect to Antimicrobial Resistance" (Anonymous, 2019b). The body, International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products, acronym VICH, provides harmonized technical guidance between the EU, Japan and the United States for registration of antimicrobial veterinary medicinal products intended for use in food-producing animals, with regard to characterization of the potential for each AMD to select for resistant bacteria of human health concern. An important US document is GFI #209 entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" (Anonymous, 2019c). This FDA document provides the framework for the voluntary adoption of practices to ensure appropriate and judicious use of medically important AMDs in food-producing animals.

The US Center for Disease Control and Prevention (CDC) monitors AMR through a tracking platform, comprising multiple networks, including the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) with contributions from the FDA and the US Department of Agriculture (USDA). NARMS was established in 1996. It is the USA national public health surveillance system for tracking changes in antimicrobial susceptibility of enteric (intestinal) bacteria in sick people (CDC), retail meats (FDA) and food animals (USDA) in the United States (Anonymous, 2019f).

6.7 | Other jurisdictions

Many other jurisdictions have addressed issues of AMD use and AMR emergence in veterinary medicine. An example is the ban on fluoroquinolones for food-producing animals in Australia (Cheng et al., 2012). Japan has a "National Action Plan on Antimicrobial Resistance (AMR) 2016-2020," which incorporates integrated one health surveillance of antimicrobial-resistant bacteria isolated from humans, animals, food and the environment. Co-operative links have been established between Japan, United States and EU (Gerbin, 2014).

7 | CONCLUSIONS

Writing in The Edinburgh Review in 1835, the historian Thomas Babington Macaulay, who had no scientific training, described a series of epochal events in medicine (Macaulay, 1878):

> Sydenham first discovered that the cool regimen succeeded best in cases of small-pox. By this discovery he saved the lives of hundreds of thousands and we venerate his memory for it, though he never heard of inoculation… Montague brought inoculation into use; and we respect her for it, though she never heard of vaccination. Jenner introduced vaccination; we admire him for it, although some still safer preservative should be discovered. It is thus that we ought to judge of the events and the men of other times. They were behind us… but the question with respect to them is not where they were but which way they were going… were their faces set in the right or the wrong direction?… It is the fundamental law of the world in which we live that truth shall grow, first the blade, then the ear, after that the full corn in the ear.
>
> [Bible, Mark, 4,28]

These stirring words, outlined almost 200 years ago, have been matched by the rapidly evolving uses of AMDs in animals over the last 80 years, 1940–2020. Further, possibly seismic, changes can be expected over the next 80 years. The series of articles in this issue of the Journal provides insights into recent advances and speculation on future developments.

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CONFLICT OF INTEREST

All authors declare that they have no competing interests.

AUTHOR CONTRIBUTION

P. Lees and P-L. Toutain drafted this article. E. Giraud and L. Pelligand edited several draft versions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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