Amoxicillin and amoxicillin-clavulanic acid resistance in veterinary medicine – the situation in Europe: a review

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ABSTRACT: In the recent past years, important efforts towards the prudent use of antimicrobials have been made in order to optimize antibacterial use, and maximize therapeutic effect while minimizing the development of resistance. Knowledge on the occurrence of resistance in bacteria could help in improving the clinical success of therapeutic decisions. Since the discovery of amoxicillin, this drug has been extensively used throughout the world in veterinary medicine, alone and also in combination with clavulanic acid. This paper provides information regarding the current situation of resistance to amoxicillin (and amoxicillin-clavulanic acid) in animals in Europe. Most data comes from food-animal species, mainly from several national monitoring programmes of antimicrobial resistance, and information on companion animals is also available.

Keywords: amoxicillin; amoxicillin-clavulanic acid; resistance; animal species; monitoring programmes

Contents

1. Introduction

During the last years, the debate on antimicrobial resistance has intensified. Resistance to antimicrobial drugs has increased, becoming a worldwide human and veterinary medicine concern, as resistance genes can be exchanged between animals and humans.

The purpose of the present review is to provide information regarding the current situation of resistance to amoxicillin and amoxicillin-clavulanic acid, drugs commonly used in veterinary clinical practice. Most data comes from food-animal species, although information on companion animals is also available.

Amoxicillin, introduced in 1972, is a semi-synthetic penicillin developed from ampicillin. This compound has the same potent broad-spectrum activity (many Gram-positive and Gram-negative microorganisms) as ampicillin, but much better oral absorption. Amoxicillin is susceptible to be inactivated by bacterial enzymes (β-lactamases; Rolinson, 1979) and is usually combined with clavulanic acid, a β-lactam molecule produced by *Streptomyces clavuligerus*, found to be a potent inhibitor of β-lactamases but with low antibacterial activity (Brown et al., 1976; Rolinson, 1979), resulting in an enhanced antimicrobial activity against many Gram-positive aerobic and anaerobic bacteria and Gram-negative aerobic bacteria (Brogden et al., 1981; Bywater, 1984).

Since its introduction into the market, amoxicillin has been largely used in veterinary medicine. All forms of livestock around the world are treated with it. Alone or in combination with clavulanic acid, amoxicillin is authorized for therapy of food-producing animals in different European countries (for detailed data see Anonymous, 1999). Pet and companion animals are also treated with amoxicillin, alone or in combination with clavulanic acid (Guardabassi et al., 2004).

Amoxicillin can be given on an individual animal basis, orally or parenterally, as in the case of pets, horses or sows. Formulations of amoxicillin can also be administered, in the case of food-producing animals (swine, sheep, cattle or poultry production), as a mass treatment, via feed or drinking water, to all the animals of a group, in order to prevent the further spread of an infectious disease detected in a small number of animals. Of special interest when considering the risk of development of resistance is the usage of antibacterial drugs intended for group medication.

With regard to the consumption of antibacterial drugs, a general reduction in the amount of antimicrobials used in animals has been observed during the last two decades, according to the International Federation for Animal Health (Casewell et al., 2003). In this sense, the ban on growth-promoting agents in food-producing animals (since 1986 in Sweden and then followed by the other countries in the European Union) could have been useful for the reduction of the spread of resistance.

In food production when compared to other antimicrobial agents, the consumption of penicillins in veterinary medicine is relatively high and ranks third in the European Union and Switzerland. It was estimated that, in 1997, the consumption of penicillins reached a volume of 322 tonnes, representing 9% of the total volume of antibacterials, compared with 66% for tetracyclines and 12% for macrolides (Anonymous, 1999). This information was provided to the EMEA by FEDESA in a document dating from 1998. An update of such data is not available. The respective data for 1997 are available on the internet (http://www.fedesa.be/eng/PublicSite/xtra/dossiers/doss9/).

Antimicrobial usage in companion animals is much less studied and has received little attention compared to food-producing animals, although there is also a potential for transfer of resistant bacteria to humans. Some available data regarding this group of antimicrobial drugs show that, in Sweden, more than 50% of the prescribed veterinary antibacterials in dogs and cats, for the period from 1990 to 1998, were β-lactam antibacterials (Odensvik et al., 2001). The situation was similar in Finland. Information on veterinary prescriptions, gathered from 17 University Pharmacies over April 2001, showed that β-lactams were the most commonly used substances in both animal species (Holso et al., 2005). In France, four antimicrobial classes accounted for more than 80% of the antimicrobials sold in veterinary medicine. Tetracyclines alone represented around half of all sales in 2005 (50.4%), followed by sulphonamides/trimethoprim (18.8%), β-lactams (8.3%) and aminoglycosides (5.9%) (Moulin et al., 2008).

2. Status of resistance

In the past years, substantive efforts have been made to acquire data on antimicrobial use and resistance, mainly in food animal production. Thus, Monitoring Programmes of Antimicrobial Resistance have been established in some European countries, particularly in relation to zoonotic organisms. The need for defining a a common European strategy for monitoring is underlined, as such studies use different methods for sampling, selection or testing of isolates, and include data on the occurrence of resistance to different antimicrobial agents among different bacterial species. Nevertheless, the data collected through these programmes can aid in the understanding of the current situation in order to facilitate the optimization of antibacterial use (Caprioli et al., 2000; Monnet, 2000; Wray and Gnanou, 2000; Franklin et al., 2001).

The data collected for amoxicillin/amoxicillin-clavulanic acid, carried out at the national level (in these monitoring programmes) as well as the results of studies conducted by several investigators, are summarised next, listed by country.

In **Denmark**, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) was established in 1995. The objectives of this programme are to monitor the occurrence of resistance in bacteria isolated from animals, food and humans, to monitor the consumption of antimicrobial agents, to determine the association between the consumption and occurrence of resistance and to model the transmission of resistance from animals to humans.

In the DANMAP 2009 report there is no data regarding amoxicillin/amoxicillin-clavulanic acid,

although information dealing with consumption in veterinary medicine is presented. In a previous report (Jensen and Hammerum, 2009), no resistance to amoxicillin-clavulanic acid was found among *Salmonella typhimurium*, neither in samples obtained from food-producing animals (poultry *n* = 18; cattle *n* = 26; pigs *n* = 509), nor in those collected from food (imported turkey meat *n* = 19; Danish pork *n* = 64, imported pork *n* = 37). Resistance was also not detected in the case of *Salmonella enteritidis* (imported broiler meat *n* = 25). Regarding *Escherichia coli*, the situation was similar (0% resistance) in animals (broilers *n* = 123; cattle *n* = 93; pigs *n* = 148), and in Danish food (broiler meat *n* = 534; turkey meat *n* = 9), although percentages of 5.5% and 1.5%, respectively, were found in imported food (broiler meat *n* = 550; turkey meat *n* = 475).

The DANMAP programme also monitors antimicrobial resistance in *E. coli* from diagnostic samples from animals. As most isolates from these samples originate from animals undergoing antimicrobial therapy, a higher frequency of resistance is expected compared to healthy animals sampled at slaughter. Nevertheless, data gathered from pigs (*n* = 118) in 2006 revealed no resistance to *E. coli*.

Apart from this monitoring programme but also in Denmark, the antimicrobial resistance (in 1993) of *S. typhimurium* from human (*n* = 228) and veterinary sources (clinical or subclinical infections in cattle *n* = 48; pigs *n* = 99; poultry *n* = 98) was studied (Seyfarth et al., 1997). No resistance was found to the amoxicillin-clavulanic acid combination, similarly as in another study, also dealing with *Salmonella*, carried out in Danish turkeys between 1995 and 2000, in which the flocks were sampled approximately 14 days before the animals were slaughtered (Pedersen et al., 2002)

Recently, Pedersen et al. (2007) reported on the susceptibility patterns of common bacterial pathogens obtained from clinical samples originating between 2000 to 2005 from Danish dogs (*Staphylococcus intermedius n* = 201; *E. coli n* = 449; *Proteus* spp. *n* = 29; and *Pseudomonas aeruginosa n* = 39; isolates). All *P. aeruginosa* isolates were resistant to amoxicillin-clavulanic acid, while, in contrast to this, resistance was low for the rest of the bacterial species examined. Thus, all *S. intermedius* isolates were susceptible to amoxicillin-clavulanic acid (resistance was detected among the other 11 drugs tested). The absence of resistance to this drug combination is encouraging since for many years it has been one of the most commonly prescribed antimicrobial for dogs, due to the very frequent resistance to penicillin. Among *E. coli* and *Proteus* spp. isolates, low levels of resistance (less than 5% and 6.9%, respectively) were recorded to amoxicillin-clavulanic acid, those values being lower than for most of the other antimicrobial compounds studied.

In **Sweden**, the Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) was started in 2000. Three types of bacteria are sampled: zoonotic (*Salmonella* spp. and *Campylobacter* spp.), indicator (*E. coli* and *Enterococcus* spp.) and specific animal pathogens (Bengtsson et al., 2011).

It should be noted that the surveillance and analysis of resistance to antibacterials in indicator or commensal bacteria isolated from the intestines of randomly selected animals at slaughter provide valuable data on the pool of resistance determinants found in bacteria of animal origin. This phenomenon is the consequence of the selective pressure to which the bacterial species have been subjected as a result of the use of antibacterial drugs both for therapeutic purposes and growth enhancement. In this respect, *E. coli* is generally used as an indicator for Gram-negative and *Enterococcus* spp. for Gram-positive bacteria.

In the latest SVARM 2010 report ((Bengtsson et al., 2011) it is stated that the resistance of *E. coli* from broilers is low. This is in agreement with the rare use of antimicrobials against *E. coli* in broilers in Sweden where only small amounts of amoxicillin and minute amounts of enrofloxacin are used. Notably, the use of amoxicillin in broiler production in the period from 2007 to 2009 due to outbreaks of botulism is not reflected in an increased occurrence of resistance in enterococci. In published reports, there is no specific data for amoxicillin/amoxicillin-clavulanic acid, although information for ampicillin is available. Data on amoxicillin-clavulanic acid was published in the 2003 report and no resistance to amoxicillin-clavulanic acid in was recorded for any of the 101 isolates (zoonotic *Salmonella enterica*) from animals of Swedish origin (the majority from cats, 39%, and pigs, 38%). Resistance was also not found for *S. typhimurium* (*n* = 49). With regard to data obtained for *E. coli* (*n* = 303 isolates from pigs), only a small number of isolates were resistant to amoxicillin-clavulanic acid (lower than 1%). Similar results were reported for chickens (resistant *E. coli* 2%).

On another study, in faecal samples (*n* = 100) obtained from Swedish pigs, Van Den Bogaard et

al. (2000) determined the antibacterial resistance of *E. coli* and *Enterococcus* spp. In *E. coli*, a high prevalence of resistance was observed for amoxicillin (51%) (the same as for oxytetracycline and trimethoprim. In contrast, no amoxicillin-resistant enterococci were found (although resistance was high for oxytetracycline and erythromycin in this bacterial species).

In **Norwey**, the Monitoring Program for Resistance in Microbes – Veterinary Medicine (NORM-VET) was established in the autumn of 2000. In this program, samples from animals, feed and food are being collected and analyzed in a systematic and representative manner. In the latest report (Norstrom and Simonsen, 2010), resistance for amoxicillin was not investigated. In the 2003 report, the resistance to amoxicillin-clavulanic acid was tested for *E. coli* (used as an indicator bacterium) isolated from cattle and sheep. No resistance to the antimicrobial combination was found from cattle samples (meat samples n = 90; faecal samples n = 120), while, in the case of sheep (faecal samples n = 118), resistance was less than 1%. Regarding zoonotic and enteropathogenic bacteria, antimicrobial resistance to amoxicillin-clavulanic acid was determined among *Salmonella* spp. from food-producing animals. Only one of the 14 strains studied (samples from live animals, meat and clinical submissions) was resistant to the antimicrobial combination (that is, approximately a 7% of resistance).

In **Finland**, the Finnish Veterinary Antimicrobial Resistance Monitoring (FINRES-VET) started in 2002. Neither of the reports released thus far describe the evaluation of resistance to amoxicillin/amoxicillin-clavulanic acid. Nevertheless, data for ampicillin is available (Nuotio et al., 2011).

Two antimicrobial resistance monitoring programmes on veterinary pathogens, GERM-Vet and BfT-GermVet, have been conducted during recent years in Germany. GERM-Vet concentrates on the most relevant bacterial pathogens of food-producing animals and has been operating since 2001. Later, in 2003, the Federation for Animal Health, Bundesverband für Tiergesundheit (BfT), decided to start another nationwide monitoring programme (BfT-GermVet) that included mainly bacterial pathogens from horses, dogs and cats (but also bacteria from diseased cattle and pigs not tested in the GERM-Vet programme).

Data from food-producing animals (Wallmann et al., 2003), collected in 2001 gave the following results, as regards amoxicillin-clavulanic acid resistance: in sick fattening pigs (with respiratory diseases), 0% of *Pasteurella multocida* isolates (n = 176), and 4.8% of *Mannheimia haemolytica* isolates (n = 21) were resistant to this drug combination. Meanwhile, isolates of *Staphylococcus aureus*, coagulase negative *Staphylococcus* spp. and *E. coli* from dairy cattle with acute mastitis were 12.7% (n = 212), 0.5% (n = 192) and 1.4% (n = 214), resistant, respectively.

In contrast to the Germ-Vet program, which runs on an annual basis, the BfT-GermVet monitoring programme was designed as a single study with a sampling period of 27 months (from January 2004 to March 2006; Schwarz et al., 2007a).

The results obtained in the BfT-GermVet program have been presented in detail in separate publications. The antimicrobial resistance situation among *E. coli* isolates from horses and small animals was relatively good. In the particular case of amoxicillin-clavulanic acid, low prevalences of resistance were detected (1% to 4%) in a total of 417 isolates collected from five animal species/organ system combinations from swine (urinary/genital tract), horses (genital tract) and dogs/cats (respiratory, urinary/genital and gastrointestinal tract) (Grobbel et al., 2007). On the other hand, Werckenthin et al. (2007) examined *P. aeruginosa* from dogs and cats (n = 99) as well as *Arcanobacterium pyogenes* from cattle and swine (n = 90) for their antimicrobial susceptibility. *P. aeruginosa* was resistant against amoxicillin-clavulanic acid (99% in 71 isolates from the skin, ear and mouth of dogs and cats; 96% in 28 isolates from the urinary/genital tract of dogs and cats), whereas *A. pyogenes* was highly susceptible to this drug combination (0% resistance in all the isolates). On the other hand, a total of 92 canine/feline *P. multocida* strains from respiratory tract infections or infections of skin/ear/mouth, as well as 42 canine/feline *Bordetella bronchiseptica* strains from respiratory tract infections, were investigated for their susceptibility to antimicrobial agents (Schwarz et al., 2007b). All *P. multocida* strains were highly susceptible to amoxicillin-clavulanic acid (0% resistance), while 2% of the *B. bronchiseptica* strains were resistant. Similarly, no resistance was found to this combination of antimicrobial agents among *Streptococcus* spp. (n = 500) isolated from swine (from infections of the urinary/genital tract and the central nervous system and the musculoskeletal system), horses (from respiratory and genital tract infections) and dogs and cats (from infections of the respiratory,

urinary/genital tract, and skin/ear/mouth; Schwarz et al., 2007c). Finally, staphylococcoal strains investigated in the BfT-GermVet programme were isolated from swine (n = 46 from urinary/genital infections; n = 44 from skin infections) and dogs/cats (n = 57 from respiratory tract infections; n = 101 from infections of the skin/ear/mouth). The levels of resistance to amoxicillin-clavulanic acid were low: 2%; 2%; 2% and 0%, respectively (Schwarz et al., 2007d).

The National Institute for Veterinary Research in **Belgium** studies salmonellas isolated from sick and healthy vector animals, animal foods and some food for human consumption (Editorial Committee, 1997). Isolates are tested for their susceptibility to antimicrobial agents and the data obtained is published annually. The report on zoonotic agents in Belgium in 2007, with resistance data for *Salmonella* and *Campylobacter*, has no data in the particular case of amoxicillin-clavulanic acid in animals.

In a trial conducted also in this country, Catry et al. (2007) evaluated the resistance of *E. coli* isolated from the intestinal tract of 19 veal calves, testing several antimicrobial agents. In the case of amoxicillin-clavulanic acid, resistance ranged from 19.3% to 29.1%, depending on the part of the intestine. In general, higher percentages were found for the rest of the antimicrobials evaluated (ampicillin, oxytetracycline, trimethoprim-sulfamethoxazole, gentamicin, nalidixic acid and enrofloxacin).

In **The Netherlands**, the monitoring programme's acronym is MARAN. The latest study, Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in The Netherlands, was launched in 2010 and shows reports data from 2008 (Mevius, 2010). In this report, data on the resistance of foodborne pathogens and commensal indicator organisms are not available for amoxicillin (although data for ampicillin is presented). Regarding animal pathogens, data for amoxicillin-clavulanic acid are presented for both *E. coli* (n = 99) and coliform bacteria (mostly *Klebsiella* and *Enterobacter* species; n = 100) isolated from milk samples from cows with (sub)clinical mastits. The resistance level was low (3%) in *E. coli* strains while 22% of coliform isolates were found to be resistant (this is due to the commonly present β-lactamases in *Klebsiella* and *Enterobacter* spp.). Nevertheless, these percentages were lower than those obtained with ampicillin: 11% and 85%, respectively. The other tested microorganisms were *S. aureus* (n = 101) and coagulase-negative staphylococci (n = 100), also obtained from milk samples, and low resistance values were found (1% and 3%, respectively).

Van Den Bogaard et al. (2000) found a similar trend for the resistance of *E. coli* and *Enterococcus* spp. in Dutch samples to the one reported for the Swedish ones. The authors determined the antibacterial resistance in samples (n = 1321) collected from pigs at slaughterhouses in The Netherlands. For *E. coli*, a high prevalence of resistance was observed for amoxicillin: 70% to 94% (and also for oxytetracycline, trimethoprim and chloramphenicol), while all *Enterococcus* spp. strains tested were susceptible to amoxicillin (and a high prevalence of resistance was found for oxytetracycline and erythromycin).

In the **United Kingdom**, the Veterinary Laboratories Agency monitors antimicrobial resistance in many bacteria of veterinary or public health importance. A summary of the information available from 1999 to 2005 is now provided here (Teale and Martin, 2008). For pigs, data in this report is presented for ampicillin but not for amoxicillin. In *E. coli* from cattle, amoxicillin-clavulanic acid resistance increased in the period from 2003 to 2005 (25% to 29%, in calves less than one month old; 18%, in cattle from one to six months of age) compared to the period from 1999 to 2002 (19% to 22% and 11% to 15%, respectively). In isolates from cattle older than six months, resistance levels were between 4% and 10% (from 1999 to 2005). In general, lower levels of resistance have been consistently observed in *E. coli* isolates from sheep (4% to 9% in sheep less than one month old; 0% to 6% in sheep between one and six months old; 0% to 2% in sheep older than six months). Regarding bovine mastitis organisms, no resistance to amoxicillin-clavulanic acid was confirmed in *Streptococcus agalactiae*, *Streptococcus dysgalactiae* or *Streptococcus uberis*; only 0.7% to 3% of *S. aureus* isolates were resistant in the period from 2003 to 2005 (a marked decline on the values from previous years of 5% to 11%), while, over the monitoring period, the levels of resistance in *E. coli* remained remarkably constant (4% to 6%). Very low levels of resistance were recorded during the whole study in *P. multocida* isolates (bovine: 0% to 4%; ovine: 0% to 8%; the only year that resistance was reported was 2003), similarly to *M. haemolytic*a (bovine: 0% to 3%; ovine: 0% to 1%).

In the case of small animals, data on antibacterial resistance to amoxicillin-clavulanic acid collected in the UK by Lloyd et al. (1996), showed that there was no increase in the resistance to these drugs

used to treat staphylococcal infections in dogs from 1980 to 1996 (*S. aureus; S. intermedius*), despite its widespread use. Later, Speakman et al. (2000) studied 78 isolates of the respiratory pathogen *B. bronchiseptica* from dogs, collected in the UK between 1995 and 2000, and concluded that all isolates were susceptible to amoxicillin-clavulanic acid. In the same year, Normand et al. (2000), also reporting from the UK, found significant rising trends for amoxicillin and amoxicillin-clavulanic acid resistance in *E. coli*, obtained from clinical cases in a small animal hospital between 1989 and 1997.

In **Ireland**, a continuous monitoring programme is run on food animals, especially on pigs, for *S. typhimurium*. A report, entitled "A strategy for the control of antimicrobial resistance in Ireland", was published in 2001 by the Subgroup of the Scientific Advisory Committee of the National Disease Surveillance Centre. This document does not contain data on the consumption of antimicrobials or the prevalence of antibiotic resistance in bacteria from animals and food. But it is stated that projects in resistance monitoring in zoonotic bacteria are being undertaken.

In **France**, surveillance of antimicrobial resistance in bacteria of animal origin is carried out by the French Agency for Food Safety (Agence Française de Sécurité Sanitaire des Aliments, AFSSA) through two types of networks (Martel et al., 2000). The first type (monocentric) is based on gathering non-human zoonotic *Salmonella* isolates in one centre (AFSSA-Paris) where these strains are tested for their antimicrobial susceptibility. The other type of networks, multicentric, managed by AFSSA-Lyon (Réseau d'ÉpidémioSurveillance de l'Antibiorésistance des principales bactéries pathogènes des Bovins: RESABO; Réseau d'ÉpidémioSurveillance des Suspicions cliniques des Salmonelloses bovines: RESSAB), deal with bovine pathogenic isolates and are based on directly collecting antibacterial susceptibility data from the local public veterinary diagnostic laboratories that routinely perform isolation, identification of the bacterial species and test antibacterial susceptibility.

In a report published by FARM (French Antimicrobial Resistance Monitoring in bacteria of animal origin) covering the years 2003 and 2004, the resistance of *Salmonella* spp. Was reported on (AFSSA, 2006). The strains were isolated both in the animal health and production sector (that gathers strains isolated from animal samples and animal production units) and in the food hygiene sector (that gathers strains isolated from food, food processing factories and slaughterhouses). The resistance percentages to amoxicillin-clavulanic acid detected in the animal breeding sector (2003: pigs n = 27, poultry n = 1311, cattle n =124; 2004: pigs n = 17, poultry n = 1230, cattle n = 110) and in the food hygiene sector (2003: pork n = 165, chicken n = 250, beef n = 72; 2004: pork n = 192, chicken n = 299, beef n = 82) were less than 5%. Regarding pathogenic veterinary bacteria, data on *E. coli* showed that in both poultry and pig production, about 50% of strains were resistant to amoxicillin (poultry, 2003 and 2004, respectively, n = 1689 and 1724, with a percentage of resistance of 46.5% and 48%) (pigs, 2003 and 2004, respectively, n = 1260 and 1323, percentage of resistance of 51.5% and 53.2%), while less than 10% were resistant to the combination of amoxicillin-clavulanic acid (poultry, 2003 and 2004, respectively, n = 201 and 243, resistance of 8% and 2.9%) (pigs, 2003 and 2004, respectively, n = 784 and 763, with 9.2% and 2% of resistance). In cattle, during the years 2003 and 2004, 80.7% of the strains isolated from calf diarrhoea were resistant to amoxicillin (n = 352) and 39.9% to amoxicillin-clavulanic acid (n = 923), while 25.2% of the strains isolated from cow mastitis were resistant to amoxicillin (n = 82) and 10.2% to amoxicillin-clavulanic acid (n = 186). No resistance was found for *P. multocida* isolated from pig pathologies for amoxicillin or amoxicillin-clavulanic acid in 2003 (n = 247 and 196, respectively) or in 2004 (n = 175 and 143, respectively). Similarly, no resistance was detected for *Streptococcus suis* isolated from pig pathologies for amoxicillin in 2003 (n = 186) and 2004 (n = 172). Finally, and regarding *Staphylococcus* spp., in poultry, a low percentage of isolates resistant to amoxicillin was detected (0% and 2.6%, respectively, in 2003 and 2004, using n = 95 and 76, respectively, for each year). Similar data were found in swine when assaying amoxicillin (0% and 4.7%, respectively, in 2003 and 2004, using n = 91 and 106, respectively, for each year), while the data on the amoxicillin-clavulanic acid combination was 0% in both years (2003 and 2004, n = 75 and 59, respectively).

In the 2010 report, it is indicated that the percentages of *E. coli* susceptible to amoxicillin were lowest among the frequently tested antimicrobials. For chicken, these percentages decreased between 2003 and 2008. For *E. coli* isolated from turkey, the ratio of susceptible strains decreased for amoxicillin. In pigs, the ratio of strains susceptible to amoxicillin was low (39.7%) and has been stable

since 2003. In cattle, only 14% of the *E. coli* isolates from calves remain susceptible to amoxicillin compared to 72% when isolated from dairy cow mastitis.

The antimicrobial resistance phenotype was determined for 5086 isolates of salmonellae from humans and from 5336 animal salmonellae isolates (60% poultry, 30% cattle, 10% others) in 1994 and 1997, also in France. In *S. enterica* serovar *typhimurium*, one of the two most frequently isolated serovars from humans as well as animals, resistance to amoxicillin-clavulanic was 45% (1997) in animals and 48% to 66% in humans (from 1994 to 1997). In *S. enteritidis*, resistance to amoxicillin-clavulanic was 4% (1997) in animals and 3% to 5% in humans (from 1994 to 1997). Finally, in *Salmonella hadar*, resistance to amoxicillin-clavulanic was 59% (1997) in animals and 70% in humans (1997; Breuil et al., 2000). The results of this study showed similar percentages of resistance in animals and humans.

Regarding small animals, a study conducted by Ganiere et al. (2006) evaluated the degree of *in vitro* activity of different antimicrobial agents (18) against 50 *S. intermedius* strains isolated in France from canine pyodermas in 2002. The coagulase-positive species *S. intermedius*, a common inhabitant of healthy dogs, is also the principal pathogenic bacterial species responsible for canine pyodermas. This organism is increasingly reported to be resistant to many antimicrobials and failures in treatment are a cause of problems in small animal practices. Thirty-one isolates (62%) were β-lactamase producers. However, all the strains were susceptible to clavulanic acid-potentiated amoxicillin (as well as to oxacillin and cephalosporins). This justifies the use of penicillinase-stable drugs when treating *S. intermedius* pyodermas in dogs. Moreover, resistance was found above all for antimicrobials that are not routinely used in canine dermatology. The authors concluded that the most effective compounds include amoxicillin-clavulanic acid, as well as macrolides or lincosamides, cephalexin or cephadroxil, sulphonamide-diaminopyrimidine combinations and some third generation quinolones.

Similar results were obtained previously, in a retrospective study including 131 *S. intermedius* strains isolated from apparently healthy dogs, and 187 *S. aureus* strains isolated from dog pyodermas in France, and covering three successive periods: from 1986 to 1987, from 1992 to 1993 and, finally, from 1995 to 1996. The results indicated that more than 95% of the strains were susceptible to amoxicillin-clavulanic acid (Pellerin et al., 1998).

In **Portugal**, antibiotic resistance is monitored for zoonotic agents (*S. enteritidis*, *S. typhimurium*), sentinel bacteria (*E. coli*, *Enterococcus faecalis: faecium*) and veterinary pathogens (*S. aureus*, *S. hyicus*, coagulase negative staphylococci). Surveillance is carried out on animals and on pig and poultry meat. Samples are collected from sick animals and, in the case of salmonellosis control, on healthy herds. Samples are collected from pork and poultry meat to analyse the occurrence of resistance of *S. enteritidis* and *S. typhimurium*. Results are recorded as resistant, intermediate or sensitive.

In this country, Martins da Costa et al. (2009) studied, under field conditions, the influence of antimicrobial administration (amoxicillin, among others) to growing broilers on the prevalence of antimicrobial resistance among *E. coli* (n = 26 isolates) obtained from cloacal swabs. Four and 11% of resistance resistance to amoxicillin-clavulanic acid in the medicated broilers (n = 16 000), was detected on days 4 and 22, respectively. No resistant isolates were found in this group on the rest of the sampling days.

Hendriksen et al. (2008a) described the occurrence of antimicrobial resistance among pathogenic and indicator bacteria in pigs in different European countries (from 2002 to 2004). In Portugal, the resistance of *E. coli* isolated from diseased pigs to amoxicillin-clavulanic acid was 58%, 31% and 36% respectively in 2002 (n = 33), 2003 (n = 45) and 2004 (n = 44). In other work (Hendriksen et al., 2008b), these authors reported a 0% resistance of isolates of *M. haemolytica* (n = 57) from cattle to this antimicrobial combination (2002).

In **Italy** (Italian Veterinary Antimicrobial Resistance Monitoring, ITAVARM) in the 2003 report presented results obtained regarding the antimicrobial resistance found for *E. coli* isolated from clinical samples of bovine (n = 166), ovine (n = 230) and canine (n = 122) origin; the percentage of resistant isolates was, 10.8%; 2.2% and 15.8%, respectively, for these animal species. The resistance observed in *E. coli* indicators in the different animal species were significantly lower than those of clinical isolates. Regarding respiratory pathogens monitored in ruminants,

the available data demonstrated that *Pasteurella multocida* and *M. haemolytica* did not develop resistance to the combination of these drugs (Battisti et al., 2003).

In a work that investigated the sensitivity of *S. aureus* strains isolated from bovine milk, Carnevali and Nocetti (2001) showed an increasing resistance to β-lactams. For amoxicillin, there was an increase from 56.2% of resistant strains (n = 324), detected in 1996, to 67.7% (n = 232) in 2000. When combined with clavulanic acid, no resistance was detected in the year 2000, while the data for 1999 showed only a 0.4% of resistance.

Since 1996, there has been a veterinary antimicrobial resistance surveillance network in **Spain**, focused on monitoring antibacterial resistance in bacteria of animal origin. This network, named Red de Vigilancia de Resistencias Antibióticas en Bacterias de Origen Veterinario, uses the acronym VAV (Vigilancia Antibiorresistencias Veterinaria: surveillance, antibioresistance, veterinary) (Anonymous, 2005). This network covers the three critical points of veterinary responsibility: bacteria from sick, healthy and food animals. Surveillance of sick animals was first implemented using *E. coli* as the sentinel bacterium. Surveillance of *E. coli* and *E. faecium* from healthy pigs was implemented in 1998. In 1999, data collection on *Salmonella* spp. was initiated in poultry slaughterhouses (Moreno et al., 2000).

The latest report (the twelfth edition of the VAV bulletin), presents data from the 2005 monitoring programme and also summarizes the results obtained previously (from 1999 to 2004). The resistance of *S. enterica* isolates obtained from pigs against amoxicillin was high (47.5%; n = 132). Lower levels were found in healthy broilers (6%; n = 18). When combined with clavulanic acid, the levels were lower: 3% (n = 132) in pigs, and 0% (n = 18) in broilers. Comparative analysis according to animal source shows that the resistance levels were higher in pigs than in broilers. Regarding *Campylobacter coli*, resistance data recorded for amoxicillin were as follows: 58.9% in pigs (n = 141) and 33% in healthy broilers (n = 15), while 44% was found in the case of *C. jejuni* (n = 16) also in pigs. The resistance trend of broiler and pigs isolates during the last five years seemed to become stable, with levels remaining higher in the case of porcine isolates. Resistance data is also available for indicator bacteria. In relation to *E. coli*, broiler isolates had higher values than those of pigs for amoxicillin (64% vs 60.9%; n = 74 and 192, respectively), similar to amoxicillin-clavulanic acid (5% vs 0.5%; n = 74 and 192, respectively, for broiler and pigs). Data obtained through the six broiler monitoring programmes (1999 to 2005) showed a continuous increase in amoxicillin resistance levels among the last years. Nevertheless, this trend was not observed in pigs isolates nor for the combination of amoxicillin-clavulanic acid (in both animal species). Another indicator microorganism studied was *E. faecium*. Very low resistance percentages exist against amoxicillin in both animal populations (6% in 36 broilers and 1% in 83 pigs). Finally, with regard to pathogenic bacteria, for *E. coli*, a 54.5% resistance was determined in 345 isolates obtained from sick animals (all species), which fell to only 4.1% when combined with clavulanic acid. Percentages of resistance for amoxicillin, given alone, were 38.9% in cattle (n = 180), 62% in small ruminants (n = 26) and 76% in pigs (n = 129). For amoxicillin-clavulanic acid: 5.6% in cattle (n = 180), 8% in small ruminants (n = 26) and 1.6% in pigs (n = 129). For the whole group of isolates from sick animals, the pooled data (gathered from 1997 to 2005) show a reversal of the increasing trend detected in the previous years, since 2005 data are lower than those of 2004 and the preceding years. Large ruminants isolates, the biggest group in all the monitoring programmes, clearly show this decreasing trend mentioned above, while the number of small ruminant isolates was insufficient for an in depth analysis. Finally, pig isolates show a similar pattern to that described in the previous years.

Patterns of resistance to antimicrobials were determined for 205 faecal strains isolated from four slaughterhouses in Spain from 220 pigs in 1993 (Teshager et al., 2000). High levels of resistance were seen against amoxicillin (72.2%); and also for tetracycline, sulphonamides and trimethoprim.

Finally, Reviriego-Gordejo et al. (1996) calculated a 83% of resistance to amoxicillin in samples obtained from *E. coli* isolated from sheep (n = 22) and goats (n = 7) with neonatal diarrhoeas in the period from 1994 to 1996 in Spain.

In **Austria**, the Styrian Resistance Monitoring Programme (REMOST) was launched by the Department of Veterinary Administration in 1999, and is designed to investigate, on a continuous basis, the resistance behaviour of zoonotic pathogens and indicator bacteria from slaughtered pigs, cattle and broilers and from bulk milk of cattle (Kofer et al., 2002). The analysis of resistance of *E. coli*

from pig faeces (n = 131) revealed no resistance to amoxicillin-clavulanic acid, while a low percentage was found (0.7%; n = 421) among *Enterococcus* spp. isolated from cows (milk samples; Kofer and Pless, 2003). Faecal isolates of *Salmonella* spp. from broiler faeces showed low resistance rates to amoxicillin-clavulanic acid (6.8%, 6.7% and 8.3%, respectively, in 2001, 2002 and 2003; Kofer et al., 2004). On the other hand, the analysis of bulk milk samples from cattle showed a 25% resistance to amoxicillin-clavulanic acid in the isolated *E. coli*.

An antibiotic resistance monitoring system has also been developed in Hungary (Kaszanyitzky et al., 2002). Susceptibility testing of bacteria from carcasses and different samples of animal origin has been carried out in veterinary institutes in this country for a long time, but using an inconsistent methodology. Since January 2001 the antibacterial susceptibility of *E. coli*, *Salmonella*, *Campylobacter* and *Enterococcus* strains isolated from the colons of slaughtered cows, pigs and broiler chickens has been examined among samples submitted to a central laboratory from each of the 19 counties of Hungary. In spite of the fact that ampicillin/amoxicillin are often used for treating animals, ampicillin resistance was infrequent among enterococci isolated from broilers, pigs and cattle through the period from 2001 to 2004 (percentages between 0% and 2.8%; Kaszanyitzky et al., 2007) while no resistance was found for amoxicillin-clavulanic acid in *Staphylococcus* isolated from food and different animal species (Kaszanyitzky et al., 2003).

In Slovenia, Kurincic et al. (2005) analyzed sixty samples of poultry meat (skin from legs and chicken liver) between 2001 and 2003. Most (90%) of the tested samples were found to be positive for *Campylobacter* spp., and no strains resistant to amoxicillin-clavulanic acid were found in their study.

Although **Greece** monitors antimicrobial resistance in isolates from humans and, occasionally, in isolates from livestock, food and animals (Editorial Committee, 1997), a specific veterinary antimicrobial resistance-monitoring program has not yet been established and there is scant information regarding this issue (Minas et al., 2007). In 2003, Burriel et al. studied the susceptibility of 262 strains of enterobacteriaceae from animal and human sources to the action of 15 antimicrobials frequently used in animal prophylaxis and metaphylaxis. The antibiotics with the highest proportion of resistant strains from animal sources were amoxicillin, colistin, erythromycin, penicillin G and spectinomycin. Finally, the above-mentioned work carried out by Minas et al. in 2007, aimed to assess the antimicrobial resistance of indicator bacteria (*E. coli*, *E. faecalis*, *E. faecium*) isolated from cattle and swine in Greece to different antimicrobial agents. Although neither amoxicillin nor amoxicillin-clavulanic acid were included in this study, the results obtained indicated a high level of resistance in these bovine and porcine indicator bacteria, suggesting that a veterinary antimicrobial resistance-monitoring program is needed in Greece to monitor bacterial resistance in animals.

Switzerland, has implemented a monitoring programme for antimicrobial resistance in farm animals since 2006 (Lederberger et al., 2005).

Faecal samples from 500 healthy calves were collected at Swiss slaughterhouses (Di Labio et al., 2007). Samples were cultured for *E. coli*, *Enterococcus* spp. and *Campylobacter* spp. Isolated strains were tested for antimicrobial susceptibility. The results for amoxicillin-clavulanic acid showed low resistance rates. Thus, the percentages of resistance obtained were as follows: *E. coli* (n = 467): 2.6%; *Enterococcus* spp. (n = 413): 1.5%; *E. faecalis* (n = 195): 0%; *E. faecium* (n = 160): 2.5%; *Campylobacter* spp. (n = 202): 0%; *Campylobacter jejuni* (n = 129): 0% and *Campylobacter coli* (n = 27): 0%.

Throughout Switzerland and **Liechtenstein**, raw poultry meat samples (n = 415) were collected at retail level and examined for the foodborne pathogen *Campylobacter* spp. (Ledergerber et al., 2003). Regarding the resistance data found for amoxicillin, five strains (5.9%) out of 85 tested were resistant to this compound. There was a tendency for a higher level of resistance in imported *versus* Swiss products, which was the same as when comparing conventional *versus* free range housing production systems. In this country, the resistance of *Campylobacter* spp. in broiler fowl has been monitored continuously since 2002. According to the Swiss Zoonoses Report 2007, the proportion of *Campylobacter* spp. resistant to amoxicillin has remained at a constantly low level. Moreover, antibacterial resistance data from 2006 showed that in *Salmonella* isolates from chicken meat, 4% of strains showed resistance to amoxicillin-clavulanic acid (Buttner, 2007).

In this same country, a study on a large number (n = 6589) of diarrhoeic dogs revealed the presence of *Salmonella* in 69 (1%) animals tested. Amongst the 80 canine isolates analysed, 14% were resistant to amoxicillin-clavulanic acid (Wissing et al., 2001).

3. Conclusion

In order to minimize the risk of the emergence of antimicrobial resistance in bacteria, and the negative public health impact, recommendations have been made to reduce the overuse and misuse of antimicrobials in animals whilst at the same time providing for their safe and effective use in veterinary medicine. Moreover, in order to assess the risks of antimicrobial resistance occurring in animals and its potential transfer to humans, monitoring antimicrobial resistance is essential (Anonymous, 1999, 2000, 2002).

Thus, an important basis for the prudent use of antimicrobials is an awareness of resistance in populations of bacteria coupled with data on the use of antimicrobials.

To reduce the selection for resistance, treatment should be directed against the most likely causative agents and narrow spectrum antimicrobials should be a first priority. Moreover, treatment strategies should be optimised by means of the use of PK/PD data.

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Received: 2011–08–03
Accepted after corrections: 2011–11–07

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