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40 years of veterinary papers in JAC – what have we learnt?

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Abstract

This review, for the occasion of the 40th anniversary of the Journal of Antimicrobial Chemotherapy (JAC), gives an overview of the manuscripts related to veterinary bacteriology in the past 40 years with a focus on “One Health” aspects. From 1975 to 2000 the number of manuscripts related to veterinary medicine was limited, but thereafter, the number steadily increased. Most manuscripts published were related to food-producing animals, but companion animals and minor species were also covered. Subjects included antimicrobial usage in animals and the consequences for human medicine, new resistance genes and mechanisms, prevalence and epidemiology of antimicrobial resistance and emergence of resistant bacteria in animals with zoonotic potential such as livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA), methicillin-resistant *S. pseudintermedius* (MRSP) and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. The manuscripts added to our knowledge on the risks of transmission of resistant bacteria from animals to humans and the importance of prudent use of antimicrobial agents in veterinary medicine.

Introduction

The Journal of Antimicrobial Chemotherapy (JAC) publishes primarily articles in the field of antimicrobial chemotherapy related to human medicine, but also articles from veterinary medicine, especially those likely to have an impact on public health. The objective of this review is to give an overview of JAC manuscripts in the field of veterinary microbiology, especially veterinary bacteriology, during the past 40 years. An editorial published earlier this year marked the starting point for a series of articles to celebrate the 40th anniversary of JAC.[1] The focus of this review is on bacteria from animals, their resistance genes and mechanisms as well as antimicrobial chemotherapy of bacterial diseases in animals from 1975 until 2015. Manuscripts reporting antiviral, antifungal, and antiparasitic aspects related to veterinary medicine were not included, neither were studies using animal models to study antimicrobials for human use. Using these exclusion criteria, a total of 379 'veterinary' papers were published in JAC during 1975-2015. This corresponds to approximately 2.4% of the total number of 15,584 papers published in JAC during that time period.

The history of veterinary papers in JAC

During the first two years 1975 and 1976, all manuscripts published in JAC were about human medicine and no veterinary manuscripts were published. During the period 1977–2000 papers dealing with veterinary medicine and antimicrobial resistance in bacteria from animals were sporadic (usually less than 10 manuscripts per year), although the total number of manuscripts published each year steadily increased from 94 in 1977 to 450 in 2000 (Figure 1).[1] The first manuscript related to veterinary microbiology was a manuscript about the relationship between antibiotics as feed additives in animals and the emergence of bacterial resistance in man by

Pohl in 1977.[2] It concluded that antibiotics as feed additives resulted in resistant bacteria in the gut flora of animals and that these resistant bacteria could potentially be transmitted to man. Pohl further concluded that many resistant bacteria in humans probably have no animal origin and therefore, the total prohibition of antibiotics in animal feed would be unlikely to result in a significant decrease of resistant bacteria in humans.[2] In 1986, Linton reviewed the evidence available at the time and concluded "… that antibiotic resistant *E. coli* reach man from animal sources, and colonize the human gut for a number of days, is beyond doubt" and that "carriage of multiple plasmids, many of which carry multiple resistance determinants, must constitute an important potential source of plasmids for indigenous *E. coli* in the human gut and, subsequently, to human pathogens".[3] The topic of antimicrobial use in livestock and pet animals and the consequences for human medicine has been the subject of various papers in JAC during the following decades and reflects an important aspect of the "One Health" principle.[4-14]

During 2001-2015, the number of manuscripts related to veterinary microbiology steadily increased exceeding 10 per year in 2003 and reaching a peak of 45 in 2014 (Figure 1). Most of the veterinary manuscripts were about food-producing animals, especially pigs, cattle and chickens. Manuscripts relating to companion animals like dogs, horses and cats were less frequent. Minor numbers of manuscripts dealt with fish, wild animals, and sheep, whereas only a few manuscripts dealt with turkeys, ducks, geese, or goats (Figure 2). Many manuscripts dealt with more than one animal species and most manuscripts were about Enterobacteriaceae (mainly *Escherichia coli* and *Salmonella enterica*), staphylococci, enterococci and *Campylobacter* spp. though several studies also included animal-specific bacteria, such as *Rhodococcus equi* from horses and *Bartonella henselae* from cats.

Topics of the veterinary papers in JAC

Popular topics of veterinary papers in JAC reflect changing research trends over time, which in turn are influenced by overall thinking in the field of antimicrobial agents and the availability of new technologies such as molecular typing and DNA sequencing. As mentioned above, in the 1970s and 1980s, veterinary papers in JAC were rare on the whole and the topics discussed were mixed. The relationship between antimicrobial resistance and use of antimicrobial agents in humans and animals was an early theme that has steadily continued to draw the interest of researchers publishing in JAC.

In the 1990s, JAC started publishing veterinary articles on topics such as mechanisms of resistance and studies on the prevalence and epidemiology of resistance among bacteria from animals. From 2001-2005, the number of veterinary papers increased substantially, as did the number of the different topics covered with larger scale surveillance and prevalence studies predominating often covering several countries and animal species.[15-22] Researchers investigated not only the prevalence of phenotypic resistance but also the spread of certain resistance mechanisms and genes among bacteria isolated from animals.[17,18,20,22]

Prevalence studies and resistance mechanisms continued to be popular topics from 2006-2010. This period also saw a substantial increase in the number of studies carrying out detailed molecular characterization of strains, integrons,[23-25] and/or mobile genetic elements (MGEs).[26-31] Detailed molecular characterizations of strains and MGEs continued to be popular in 2011-2015[32-37], alongside the characterization of resistance mechanisms and genes[38-42] Prevalence and surveillance studies were still being published in 2011-2015,[43-47] but were proportionally less popular than in preceding years. This undoubtedly reflected the increasing accessibility of molecular techniques such as whole genome sequencing, enabling molecular characterization to be performed with ease and at a relatively low cost. Between 2006-2015, there was also a substantial number of papers investigating levels of antimicrobial use in animals and its impact on resistance in both the animals themselves as well as humans.[48-51] This probably reflects increasing calls for better monitoring of antimicrobial use in animals and calls to reduce unnecessary antibiotics in farming.

New emerging resistant bacteria of animal origin

Livestock-associated methicillin-resistant Staphylococcus aureus

The first papers in JAC about the occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) of animal origin were published in 2005[52,53] and 2006.[54-56] These initial reports focused mainly on companion animals such as dogs, cats and horses.[53-56] Later on, livestock-associated MRSA (LA-MRSA) isolates of clonal complex (CC) 398 from pigs were identified[57] and characterized in detail using a variety of molecular methods.[58] The close similarity between the isolates from humans and animals strongly suggested these LA-MRSA isolates were being exchanged and, though the direction of transfer – zoonosis or humanosis – was questioned,[59] proof of transfer in both directions was found. Indeed reports followed about the presence of LA-MRSA CC398 in other animals (e.g. cattle, broiler chickens), people in occupational contact with animals, and in food of animal origin.[60-67]

Methicillin-resistant *Staphylococcus pseudintermedius*

Methicillin resistance also occurs in *S. pseudintermedius* (formerly identified as *S. intermedius*), an opportunistic pathogen that causes infections in pet animals, particularly dogs but also in cats.[68-70] Since 2006, there has been a significant emergence of methicillin-resistant *S. pseudintermedius* (MRSP).[68] Although infections in humans with MRSP are uncommon, canine infections or carriage of such organisms represent a potential hazard for people in contact with dogs.[68] MRSP often display resistance to almost all classes of antimicrobial agents used in veterinary medicine and several reports published in JAC have investigated the occurrence of resistance and/or resistance mechanisms to various antimicrobials.[68-72] Other reports focus on the evolution and clonal relationship of MRSP isolates in different countries.[69-74]

Extended-spectrum β-lactamase-producing Enterobacteriaceae from animals

In mid-2000s, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae from animal sources were described. The first report published in JAC referred to ESBL-producing *Salmonella* isolates from poultry, poultry products and human patients in The Netherlands.[22] Soon thereafter, first reports about the occurrence of ESBL-producing *E. coli* in meat and from various animal and environmental sources were published.[75,76] During the following years, ESBL-producing Enterobacteriaceae were reported from different countries, different food and food animal sources, including apparently healthy animals, and also from food-borne outbreaks.[23,27,44-46,77-88] In these studies different types of ESBL genes were detected with $bla_{\text{CTX-M}}$ variants, $bla_{\text{SHV-2}}$ and $bla_{\text{TEM-52}}$ genes being most predominant. The first report about ESBL genes in *E. coli* from companion animals was published in JAC in 2010,[89] followed by reports that described the presence of ESBL-producing *E. coli* and *Klebsiella pneumoniae* in dogs, cats and horses in different countries.[90-93] In addition, free-living birds were also identified as carriers of ESBL-producing Enterobacteriaceae.[94,95] Many of the studies on ESBL-producing Enterobacteriaceae also provided a detailed strain characterization and a characterization of the ESBL gene-carrying plasmids.[28,44-46,78,79,84,88-93,96]

(Fluoro)quinolone-resistant bacteria of animal origin

Increasing levels of quinolone resistance among Enterobacteriaceae and *Campylobacter* spp. has been a particular cause for concern since the mid-1990s.[97-100] In 1998, Piddock *et al*. demonstrated that *gyrA* and *parC* mutations were responsible for quinolone resistance among veterinary isolates of *Salmonella enterica*.[101] Such mutations were also detected in *Salmonella* Typhimurium from fish and *E. coli* from turkeys, ruminants, other food animals and food of animal origin.[18,102-106] In addition to Enterobacteriaceae, mutations in the quinolone resistance determining region of the target genes were also identified in other bacteria, including *Campylobacter* spp.,[98,107,108] *Bartonella henselae*,[109] *Pasteurella multocida*,[33] *Haemophilus parasuis*,[110] and *S. aureus*.[111] Soon, it was demonstrated that (i) isolates harbouring first-step mutations towards quinolone resistance also exhibited reduced susceptibility to fluoroquinolones and (ii) fluoroquinolone exposure selects for resistant mutants.[112-115] It was shown that other mechanisms, such as active efflux, also play a role in fluoroquinolone resistance and that the mechanisms of fluoroquinolone resistance are more complex than initially thought.[115,116]

Reports about plasmid-mediated quinolone resistance (PMQR) genes in bacteria of animal origin were published in JAC from the mid-2000s on. The first paper dated from 2006 and described a *qnrS* gene in an avian *Salmonella* Infantis isolate.[117] Soon thereafter, the first complete nucleotide sequence of a small *qnrS1*-carrying plasmid from *Salmonella* Typhimurium was published.[118] The *qnrS1* gene was also detected in the *Salmonella* serovars Corvallis, Virchow, and Saintpaul, whereas a *qnrB5* gene was found in the *Salmonella* serovars Newport, Hadar, and Saintpaul, all from various European countries.[119-121] A study from China identified the PMQR genes *aac(6')-Ib-cr*, *qepA*, *qnrA3*, *qnrB6*, *qnrB10* and *qnrS1* among 30 isolates of Enterobacteriaceae. One to three mutations in the QRDRs of the genes *gyrA* and *parC* were detected in all but one of the PMQR-positive isolates.[122] Further PMQR genes identified in bacteria of animal origin were *qnrB2* in *Salmonella* Bredeney from poultry,[123] *qnrB19*, *qnrS1* and *qnrB6* together with *aac(6')-Ib-cr* in various *Salmonella* serovars from reptiles,[124] *qnrA1*, *qnrB6* and *aac(6')-Ib-cr* in *H. parasuis* from pigs,[110] as well as *qnrS1*, *qnrB19*, *qnrB10* and *qepA* in *E. coli* from pigs and chickens.[125] A large-scale study on PMQR genes in *Salmonella enterica* and *Escherichia coli* isolated from animals, humans, food and the environment in 13 European countries revealed the presence of *qnrA1*, *qnrB2, qnrB4, qnrB6, qnrB7, qnrB12, qnrB19*, *qnrS1*, *aac(6')-1b-cr*, and *qnrD* genes in *Salmonella enterica* as well as *qnrS1* and *qnrB19* in *E. coli*.[126] An additional PMQR gene *oqxAB* was detected on a plasmid in *E. coli* from a chicken.[32] Complete sequences of larger plasmids carrying PMQR genes were also published.[35,127]

Novel and unusual resistance genes in bacteria of animal origin

New resistance genes in LA-MRSA and other staphylococci

The novel *mecA* homologue, initially described as $mecA_{LGA251}$, but later renamed as *mecC*, was found in MRSA isolates from a domestic dog, brown rats, a rabbit, a common seal, sheep and a chaffinch.[38] This gene was also detected in a MRSA isolate of a cat suffering from chronic conjunctivitis.[128] Further studies identified this gene in methicillin-resistant staphylococci from wildlife, including MRSA from European brown hares, an otter, and a hedgehog as well as in a methicillin-resistant *Staphylococcus stepanovicii* from a Eurasian lynx,[129] common voles, wood mice and a brown rat,[130] and from captive maras in a zoo.[131] The *mecC* gene was also detected in MRSA from cases of bovine mastitis.[132]. A new allotype, *mecC2*, was identified in a methicillin-resistant *Staphylococcus saprophyticus* from a common shrew.[133]

The multiresistance gene *cfr*, which confers resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A antibiotics, was initially found on plasmid pSCFS1 from a bovine *Staphylococcus sciuri* isolate.[39] The complete sequence of this first *cfr*-carrying plasmid was published in JAC in 2004.[134] Later on, *cfr* was also found on a small plasmid in an LA-MRSA ST9 isolate from a case of bovine mastitis.[36] A review was published in 2013 which illustrated the wide dissemination of the *cfr* gene in Gram-positive and Gram-negative bacteria from animals and humans.[39] The complete sequence of the 135,615 bp *cfr*-carrying plasmid pSCEC2 from *Escherichia coli* was reported in 2014.[135]

A multiresistance gene cluster of suspected enterococcal origin has been identified on plasmids and in the chromosomal DNA of *S. aureus* isolates from pigs and chickens, but also humans.[136] This cluster comprised the novel ABC transporter gene *lsa*(E) for combined resistance to pleuromutilins, lincosamides and streptogramin A antibiotics,[137,138] the novel spectinomycin resistance gene *spw*,[138,139] as well as the streptomycin resistance gene *aadE* and the lincosamide resistance gene *lnu*(B).[136-139] Another novel plasmid-borne spectinomycin resistance gene, *spd*, was identified in MRSA ST398 from various animal and human sources.[140] This gene was also identified in MSSA ST433 of porcine origin,[141] and a variant of this gene was detected in *Staphylococcus hyicus* and coagulase-negative staphylococci from pigs.[142] A variant of the pleuromutilin-lincosamide-streptogramin A-resistance gene *vga*(E), which showed only 85.7% identity to the original *vga*(E) gene from Tn*6133*, was detected on identical plasmids in *Staphylococcus cohnii* and *Staphylococcus simulans* from pigs.[143]

Carbapenemase genes in bacteria of animal origin

The first carbapenemase gene *bla*$_{VIM-1}$ was found in a multiresistance class 1 integron of an *E. coli* isolate on a pig farm in 2012.[34] A year later, the *bla*$_{VIM-1}$ gene was also found in *Salmonella* Infantis from pig and poultry farms in Germany,[144] and the *bla*$_{NDM-1}$ gene was found in a *Salmonella* Corvallis from a wild bird.[145] Other carbapenemase genes found so far in animals and published in JAC include *bla*$_{OXA-48}$ in *E. coli* and *K. pneumoniae* from dogs,[146] *bla*$_{IMP-4}$ in *Pseudomonas aeruginosa* from a dog,[147] *bla*$_{VIM-2}$ in *P. aeruginosa* from cattle and fowl as well as *bla*$_{OXA-23}$ and *bla*$_{OXA58}$ in *Acinetobacter baumannii* from cattle, pig and fowl,[148] the *bla*$_{NDM-1}$ gene in *A. baumannii* of porcine origin,[149] and *bla*$_{NDM-1}$-producing *Acinetobacter calcoaceticus* and *Acinetobacter junii* from environmental samples from livestock farms.[150] These findings provoked a controversial debate about the role of animals in the dissemination of carbapenemase genes which has resulted in publication of reviews and editorials.[151-153]

Novel resistance genes in bovine and porcine Pasteurellaceae

The first description of florfenicol resistance in a target bacterium was published in 2005.[154] This report described the presence of the phenicol exporter gene *floR* on a plasmid in bovine *Pasteurella multocida* from the UK. A few years later, the *floR* gene was also detected on plasmids in bovine *Pasteurella trehalosi* (meanwhile renamed as *Bibersteinia trehalosi*) from France and in porcine and bovine *P. multocida* from Germany.[31,155] The *floR* gene has also been detected on a small plasmid in porcine *H. parasuis*.[156] This phenicol resistance gene was also part of the multiresistance integrative and conjugative element ICE*Pmu1* from bovine *P. multocida*, which carried a total of twelve resistance genes, including the novel macrolide resistance genes *erm*(42), *msr*(E) and *mph*(E).[33] Macrolide resistance in *Mannheimia haemolytica* was shown to be caused by the mutation A2058G in the the 23S rRNA and in *P. multocida* by the mutation A2059G in 23S rRNA.[41] The tetracycline resistance gene *tet*(L), which is widespread among Gram-positive bacteria, was identified on plasmids and in the chromosomal DNA of *M. haemolytica*, *Mannheimia glucosida* and *P. multocida*.[157] Another *tet* gene, *tet*(H) was detected on novel plasmids in *Actinobacillus pleuropneumoniae*.[158] The trimethoprim resistance gene *dfrA1* was found in a partially truncated class 2 integron in a porcine *Pasteurella aerogenes* isolate.[159] The trimethoprim resistance gene *dfrA14* was identified on different plasmids in *A. pleuropneumoniae*.[37]

New resistance genes and resistance-mediating mutations in other bacteria of animal origin

A novel chloramphenicol exporter gene, *cmlB1*, has been identified in the porcine respiratory tract pathogen *Bordetella bronchiseptica*.[160] Another novel chloramphenicol/florfenicol exporter gene, designated *fexB*, was identified in

Enterococcus faecium and *Enterococcus hirae* of porcine origin.[161] Both, CmlB and FexB belong to the Major Facilitator Superfamily of exporters. A novel *floR* gene variant was detected as part of a multiresistance genomic island in a porcine *Stenotrophomonas maltophila* isolate. This FloRv protein showed only 84.1%-91.8% amino acid identity to the various described FloR proteins.[162] A novel ABC transporter, OptrA, that confers combined resistance to phenicols and oxazolidinones was identified in *E. faecalis* and *E. faecium* from humans, pigs and chickens.[42] Other new resistance genes reported in JAC include the aminoglycoside resistance genes *armA* and *rtmB*. Gonzalez-Zorn *et al*. investigated the genetic environment of the *armA* gene in an *E. coli* isolate from a pig and showed that it was embedded in a novel transposon composite facilitating spread between Enterobacteriaceae of human and animal origin.[163] The *rtmB* gene was isolated from porcine *E. coli* and *Enterobacter* isolates as well as from *E. coli* chicken isolates in China.[164-166] A novel macrolide efflux gene *mef*(B) was found in porcine *E. coli* isolates.[167] Wang *et al*. reported the novel $fosX^{CC}$ gene conferring fosfomycin resistance in *Campylobacter coli* from swine faeces.[168] Novel gentamicin resistance genes were found in *Campylobacter* from humans and retail food.[169]

Novel mutations in the *rpoB* gene responsible for rifampicin resistance have been identified in canine MRSP and in equine *Rhodococcus equi*.[170,171]

Relationship between antimicrobial use and resistance in animals and humans

It is a generally accepted fact that the use of antimicrobial agents in both humans and animals results in a selective pressure under which bacteria can either develop resistance mediating mutations or acquire resistance genes. Indeed the use of antimicrobial agents is perhaps the major driving force in resistance development and dissemination. Consequently, several studies have analysed sales patterns of antimicrobial agents used in veterinary medicine in Europe as well as their consumption in various animal species.[50,51,172,173] The latest data from 2011, published in 2014, showed that in all 25 EU countries analysed, tetracyclines, penicillins and sulphonamides accounted for more than half (53%–88%) of the total amount of antimicrobial agents sold by country.[50] Another study also evaluated the appropriateness of use compared with prudent use guidelines in Switzerland.[174] The authors concluded that most prescriptions corresponded well to guidelines on prudent use of antimicrobials. However, there was a wide variation in prescriptions between different veterinarians which might indicate that the usage and amount of antimicrobials used for group medication lacking a specific indication could be further reduced.[174] Several papers investigated the levels of antimicrobial use in animals and its impact on resistance in both the animals themselves as well as humans.[14,49,175-180] Some studies demonstrated a correlation between antimicrobial usage in animals and the occurrence of resistant bacteria in animals.[14,49,175-177] Others also found a relationship between the antimicrobial usage and the occurrence of antimicrobial resistant bacteria not only in animals, but also in humans with close contact to animals.[178-179] For instance, a study on enterococci revealed that the overall resistance in broiler isolates corresponded with resistance in the isolates of broiler farmers and poultry slaughterers.[178] A more recent study also showed that MRSA of the same MLST, *spa* and *dru* types with very similar resistance patterns were seen among chickens at slaughter and abattoir workers and underlines the exchange of resistant isolates between animals and people in occupational contact with them.[66] A study of Danish pigs and their farmers and families showed that ESBL-producing *E. coli* was detected in pigs on 79% of the farms with a high consumption of cephalosporins compared to 20% of the pigs on farms that did not use these drugs. At four farms ESBL-producing *E. coli* isolates with the same CTX-M enzyme, phylotype, PFGE type and MLST type were detected in both pigs and farmers.[179] These examples underline the interrelationship of antimicrobial use and dissemination of resistant bacteria.

Conclusion

Despite the fact that veterinary papers in JAC represent only a minority of all manuscripts published in JAC during 1975-2015 (Fig. 1), they address important aspects of antimicrobial usage and antimicrobial resistance in various animal species. Antimicrobial resistance remains an important public health issue and that needs an integrated global perspective as bacteria do not respect geographical or species borders. The 'One Health' concept states that human health, animal health, environmental health, agriculture as well as food safety and security are closely linked. The focus of the veterinary papers in JAC often included links to human health, but also to food safety and security, especially when dealing with bacteria of zoonotic importance. Clearly, veterinary papers are indispensable in helping provide a more complete picture of the complex interactions between humans and animals in the field of antimicrobial chemotherapy. Consequently, their continued publication in the JAC is assured for the foreseeable future.

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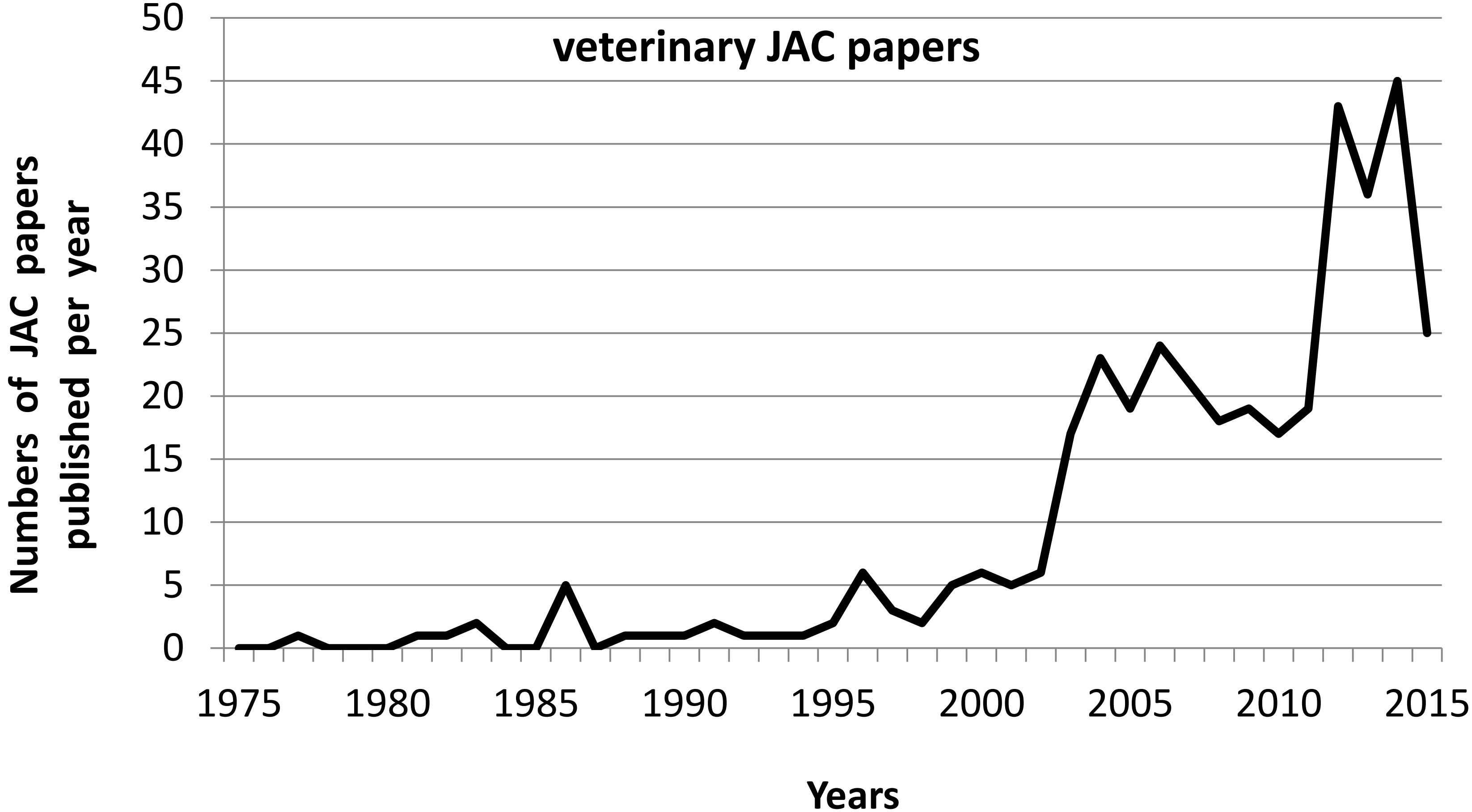
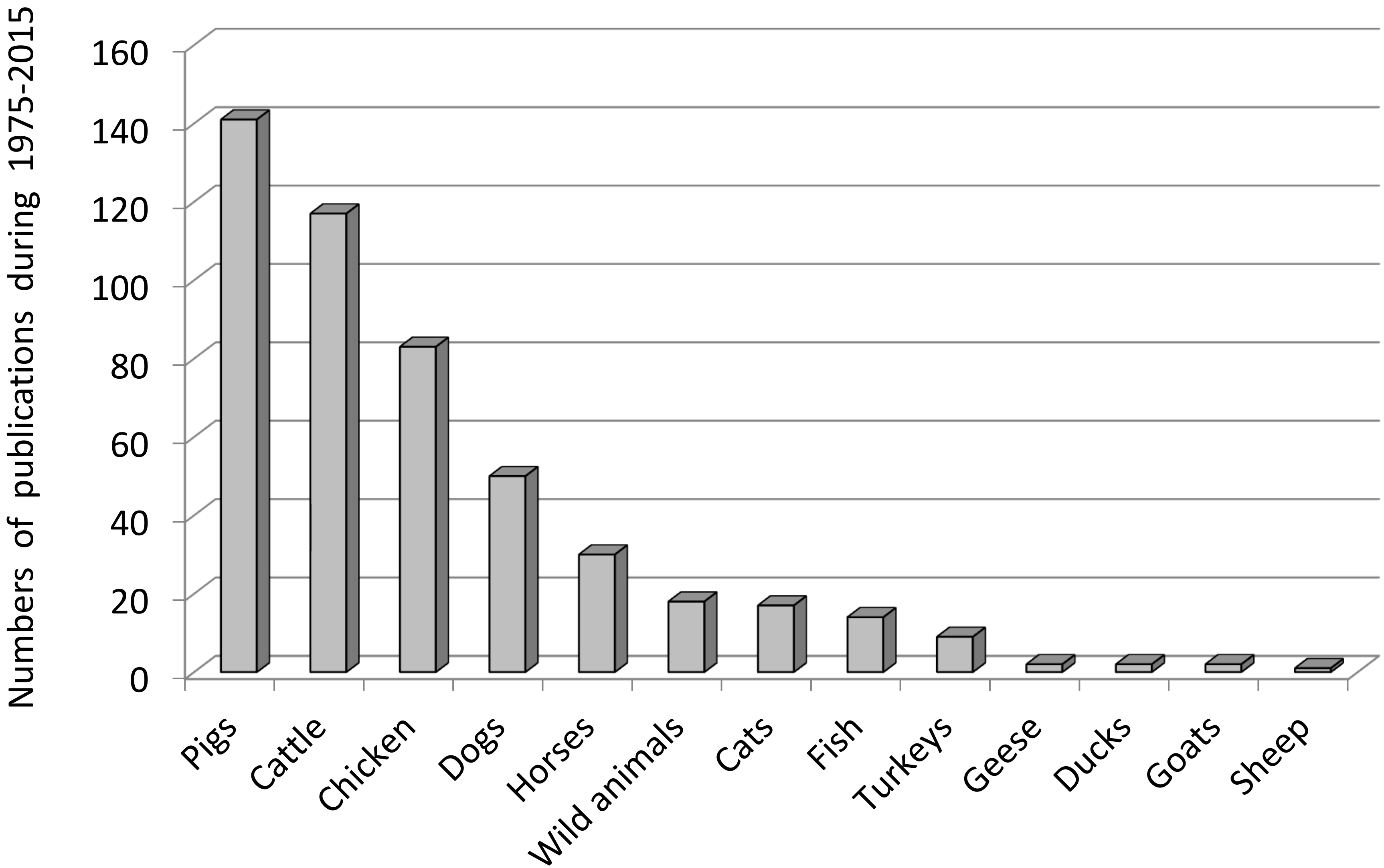
Figure 1. Numbers of ‘veterinary’ papers published in JAC during 1975-2015.

Figure 2. Numbers of veterinary papers published in JAC during 1975-2015 according to the animals species involved. It should be noted that papers which dealt with more than one animal species, are separately listed for each animal species involved. Consequently, the total number of the papers listed in Fig. 2 exceeds the actual total number of the ‘veterinary’ papers published in JAC during 1975-2015.


veterinary JAC papers
Numbers of JAC papers published per year
0
5
10
15
20
25
30
35
40
45
50
1975
1980
1985
1990
1995
2000
2005
2010
2015
Years


Numbers of publications during 1975-2015
160
140
120
100
80
60
40
20
0
Pigs
Cattle
Chicken
Dogs
Horses
Wild animals
Cats
Fish
Turkeys
Geese
Ducks
Goats
Sheep