

OXFORD  
UNIVERSITY PRESS

Journal of Antimicrobial Chemotherapy

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

Journal:	<i>Journal of Antimicrobial Chemotherapy</i>
Manuscript ID	JAC-2016-1206.R1
Manuscript Type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Schwarz, Stefan; Friedrich-Loeffler-Institute (FLI), Institute of Farm Animal Genetics; Enne, Virve; University College London, Centre for Clinical Microbiology; Queen Mary University of London, Centre for Immunology and Infectious Disease van Duijkeren, Engeline; National Institute for Public Health and the Environment (RIVM), Laboratory for zoonoses and Environmental Microbiology
Keywords:	Antimicrobial resistance, antimicrobial consumption, zoonotic pathogens, mobile genetic elements, Resistance genes, Mutations

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Manuscripts

# 40 years of veterinary papers in JAC

## – what have we learnt?

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**Running title:** Veterinary medicine in JAC

**Keywords:** antimicrobial resistance, antimicrobial consumption, zoonotic pathogens, mobile genetic elements, resistance genes, mutations

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25 **Abstract**

26 This review, for the occasion of the 40<sup>th</sup> anniversary of the Journal of Antimicrobial  
27 Chemotherapy (JAC), gives an overview of the manuscripts related to veterinary  
28 bacteriology in the past 40 years with a focus on “One Health” aspects. From 1975 to  
29 2000 the number of manuscripts related to veterinary medicine was limited, but  
30 thereafter, the number steadily increased. Most manuscripts published were related  
31 to food-producing animals, but companion animals and minor species were also  
32 covered. Subjects included antimicrobial usage in animals and the consequences for  
33 human medicine, new resistance genes and mechanisms, prevalence and  
34 epidemiology of antimicrobial resistance and emergence of resistant bacteria in  
35 animals with zoonotic potential such as livestock-associated methicillin-resistant  
36 *Staphylococcus aureus* (LA-MRSA), methicillin-resistant *S. pseudintermedius*  
37 (MRSP) and extended-spectrum  $\beta$ -lactamase (ESBL)-producing Enterobacteriaceae.  
38 The manuscripts added to our knowledge on the risks of transmission of resistant  
39 bacteria from animals to humans and the importance of prudent use of antimicrobial  
40 agents in veterinary medicine.

41

## 42 Introduction

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

57

## 58 The history of veterinary papers in JAC

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

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

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

92

93 **Topics of the veterinary papers in JAC**

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

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

110 Prevalence studies and resistance mechanisms continued to be popular topics  
111 from 2006-2010. This period also saw a substantial increase in the number of studies  
112 carrying out detailed molecular characterization of strains, integrons,<sup>23-25</sup> and/or  
113 mobile genetic elements (MGEs).<sup>26-31</sup> Detailed molecular characterizations of strains  
114 and MGEs continued to be popular in 2011-2015<sup>32-37</sup>, alongside the characterization  
115 of resistance mechanisms and genes<sup>38-42</sup> Prevalence and surveillance studies were  
116 still being published in 2011-2015,<sup>43-47</sup> but were proportionally less popular than in

117 preceding years. This undoubtedly reflected the increasing accessibility of molecular  
118 techniques such as whole genome sequencing, enabling molecular characterization  
119 to be performed with ease and at a relatively low cost. Between 2006-2015, there  
120 was also a substantial number of papers investigating levels of antimicrobial use in  
121 animals and its impact on resistance in both the animals themselves as well as  
122 humans.<sup>48-51</sup> This probably reflects increasing calls for better monitoring of  
123 antimicrobial use in animals and calls to reduce unnecessary antibiotics in farming.

124

## 125 **New emerging resistant bacteria of animal origin**

### 126 ***Livestock-associated methicillin-resistant Staphylococcus aureus***

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

139

#### 140 **Methicillin-resistant *Staphylococcus pseudintermedius***

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

#### 153 **Extended-spectrum $\beta$ -lactamase-producing Enterobacteriaceae from animals**

154 In mid-2000s, extended-spectrum  $\beta$ -lactamase (ESBL)-producing  
155 Enterobacteriaceae from animal sources were described. The first report published in  
156 JAC referred to ESBL-producing *Salmonella* isolates from poultry, poultry products  
157 and human patients in The Netherlands.<sup>22</sup> Soon thereafter, first reports about the  
158 occurrence of ESBL-producing *E. coli* in meat and from various animal and  
159 environmental sources were published.<sup>75,76</sup> During the following years, ESBL-  
160 producing Enterobacteriaceae were reported from different countries, different food  
161 and food animal sources, including apparently healthy animals, and also from food-  
162 borne outbreaks.<sup>23,27,44-46,77-88</sup> In these studies different types of ESBL genes were  
163 detected with *bla*<sub>CTX-M</sub> variants, *bla*<sub>SHV-2</sub> and *bla*<sub>TEM-52</sub> genes being most predominant.  
164 The first report about ESBL genes in *E. coli* from companion animals was published



165 in JAC in 2010,<sup>89</sup> followed by reports that described the presence of ESBL-producing  
166 *E. coli* and *Klebsiella pneumoniae* in dogs, cats and horses in different countries.<sup>90-93</sup>  
167 In addition, free-living birds were also identified as carriers of ESBL-producing  
168 Enterobacteriaceae.<sup>94,95</sup> Many of the studies on ESBL-producing Enterobacteriaceae  
169 also provided a detailed strain characterization and a characterization of the ESBL  
170 gene-carrying plasmids.<sup>28,44-46,78,79,84,88-93,96</sup>

171

### 172 **(Fluoro)quinolone-resistant bacteria of animal origin**

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

188 Reports about plasmid-mediated quinolone resistance (PMQR) genes in  
189 bacteria of animal origin were published in JAC from the mid-2000s on. The first

190 paper dated from 2006 and described a *qnrS* gene in an avian *Salmonella* Infantis  
191 isolate.<sup>117</sup> Soon thereafter, the first complete nucleotide sequence of a small *qnrS1*-  
192 carrying plasmid from *Salmonella* Typhimurium was published.<sup>118</sup> The *qnrS1* gene  
193 was also detected in the *Salmonella* serovars Corvallis, Virchow, and Saintpaul,  
194 whereas a *qnrB5* gene was found in the *Salmonella* serovars Newport, Hadar, and  
195 Saintpaul, all from various European countries.<sup>119-121</sup> A study from China identified  
196 the PMQR genes *aac(6')-Ib-cr*, *qepA*, *qnrA3*, *qnrB6*, *qnrB10* and *qnrS1* among 30  
197 isolates of Enterobacteriaceae. One to three mutations in the QRDRs of the genes  
198 *gyrA* and *parC* were detected in all but one of the PMQR-positive isolates.<sup>122</sup> Further  
199 PMQR genes identified in bacteria of animal origin were *qnrB2* in *Salmonella*  
200 Bredeney from poultry,<sup>123</sup> *qnrB19*, *qnrS1* and *qnrB6* together with *aac(6')-Ib-cr* in  
201 various *Salmonella* serovars from reptiles,<sup>124</sup> *qnrA1*, *qnrB6* and *aac(6')-Ib-cr* in *H.*  
202 *parasuis* from pigs,<sup>110</sup> as well as *qnrS1*, *qnrB19*, *qnrB10* and *qepA* in *E. coli* from pigs  
203 and chickens.<sup>125</sup> A large-scale study on PMQR genes in *Salmonella enterica* and  
204 *Escherichia coli* isolated from animals, humans, food and the environment in 13  
205 European countries revealed the presence of *qnrA1*, *qnrB2*, *qnrB4*, *qnrB6*, *qnrB7*,  
206 *qnrB12*, *qnrB19*, *qnrS1*, *aac(6')-Ib-cr*, and *qnrD* genes in *Salmonella enterica* as well  
207 as *qnrS1* and *qnrB19* in *E. coli*.<sup>126</sup> An additional PMQR gene *oqxAB* was detected on  
208 a plasmid in *E. coli* from a chicken.<sup>32</sup> Complete sequences of larger plasmids  
209 carrying PMQR genes were also published.<sup>35,127</sup>

210

## 211 **Novel and unusual resistance genes in bacteria of animal origin**

### 212 ***New resistance genes in LA-MRSA and other staphylococci***

213 The novel *mecA* homologue, initially described as *mecA*<sub>LGA251</sub>, but later renamed as  
214 *mecC*, was found in MRSA isolates from a domestic dog, brown rats, a rabbit, a

215 common seal, sheep and a chaffinch.<sup>38</sup> This gene was also detected in a MRSA  
216 isolate of a cat suffering from chronic conjunctivitis.<sup>128</sup> Further studies identified this  
217 gene in methicillin-resistant staphylococci from wildlife, including MRSA from  
218 European brown hares, an otter, and a hedgehog as well as in a methicillin-resistant  
219 *Staphylococcus stepanovicii* from a Eurasian lynx,<sup>129</sup> common voles, wood mice and  
220 a brown rat,<sup>130</sup> and from captive maras in a zoo.<sup>131</sup> The *mecC* gene was also  
221 detected in MRSA from cases of bovine mastitis.<sup>132</sup> A new allotype, *mecC2*, was  
222 identified in a methicillin-resistant *Staphylococcus saprophyticus* from a common  
223 shrew.<sup>133</sup>

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

233 A multiresistance gene cluster of suspected enterococcal origin has been  
234 identified on plasmids and in the chromosomal DNA of *S. aureus* isolates from pigs  
235 and chickens, but also humans.<sup>136</sup> This cluster comprised the novel ABC transporter  
236 gene *Isa(E)* for combined resistance to pleuromutilins, lincosamides and  
237 streptogramin A antibiotics,<sup>137,138</sup> the novel spectinomycin resistance gene *spw*,<sup>138,139</sup>  
238 as well as the streptomycin resistance gene *aadE* and the lincosamide resistance  
239 gene *Inu(B)*.<sup>136-139</sup> Another novel plasmid-borne spectinomycin resistance gene, *spd*,

240 was identified in MRSA ST398 from various animal and human sources.<sup>140</sup> This gene  
241 was also identified in MSSA ST433 of porcine origin,<sup>141</sup> and a variant of this gene  
242 was detected in *Staphylococcus hyicus* and coagulase-negative staphylococci from  
243 pigs.<sup>142</sup> A variant of the pleuromutilin-lincosamide-streptogramin A-resistance gene  
244 *vga(E)*, which showed only 85.7% identity to the original *vga(E)* gene from Tn6133,  
245 was detected on identical plasmids in *Staphylococcus cohnii* and *Staphylococcus*  
246 *simulans* from pigs.<sup>143</sup>

247

### 248 **Carbapenemase genes in bacteria of animal origin**

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

262

### 263 **Novel resistance genes in bovine and porcine Pasteurellaceae**

264 The first description of florfenicol resistance in a target bacterium was published in  
265 2005.<sup>154</sup> This report described the presence of the phenicol exporter gene *floR* on a  
266 plasmid in bovine *Pasteurella multocida* from the UK. A few years later, the *floR* gene  
267 was also detected on plasmids in bovine *Pasteurella trehalosi* (meanwhile renamed  
268 as *Bibersteinia trehalosi*) from France and in porcine and bovine *P. multocida* from  
269 Germany.<sup>31,155</sup> The *floR* gene has also been detected on a small plasmid in porcine  
270 *H. parasuis*.<sup>156</sup> This phenicol resistance gene was also part of the multiresistance  
271 integrative and conjugative element ICEPmu1 from bovine *P. multocida*, which  
272 carried a total of twelve resistance genes, including the novel macrolide resistance  
273 genes *erm(42)*, *msr(E)* and *mph(E)*.<sup>33</sup> Macrolide resistance in *Mannheimia*  
274 *haemolytica* was shown to be caused by the mutation A2058G in the the 23S rRNA  
275 and in *P. multocida* by the mutation A2059G in 23S rRNA.<sup>41</sup> The tetracycline  
276 resistance gene *tet(L)*, which is widespread among Gram-positive bacteria, was  
277 identified on plasmids and in the chromosomal DNA of *M. haemolytica*, *Mannheimia*  
278 *glucosida* and *P. multocida*.<sup>157</sup> Another *tet* gene, *tet(H)* was detected on novel  
279 plasmids in *Actinobacillus pleuropneumoniae*.<sup>158</sup> The trimethoprim resistance gene  
280 *dfrA1* was found in a partially truncated class 2 integron in a porcine *Pasteurella*  
281 *aerogenes* isolate.<sup>159</sup> The trimethoprim resistance gene *dfrA14* was identified on  
282 different plasmids in *A. pleuropneumoniae*.<sup>37</sup>

283

#### 284 ***New resistance genes and resistance-mediating mutations in other bacteria of*** 285 ***animal origin***

286 A novel chloramphenicol exporter gene, *cmlB1*, has been identified in the porcine  
287 respiratory tract pathogen *Bordetella bronchiseptica*.<sup>160</sup> Another novel  
288 chloramphenicol/florfenicol exporter gene, designated *fexB*, was identified in

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

306 Novel mutations in the *rpoB* gene responsible for rifampicin resistance have  
307 been identified in canine MRSP and in equine *Rhodococcus equi*.<sup>170,171</sup>

308

309

## 310 **Relationship between antimicrobial use and resistance in animals** 311 **and humans**

312 It is a generally accepted fact that the use of antimicrobial agents in both humans  
313 and animals results in a selective pressure under which bacteria can either develop

314 resistance mediating mutations or acquire resistance genes. Indeed the use of  
315 antimicrobial agents is perhaps the major driving force in resistance development and  
316 dissemination. Consequently, several studies have analysed sales patterns of  
317 antimicrobial agents used in veterinary medicine in Europe as well as their  
318 consumption in various animal species.<sup>50,51,172,173</sup> The latest data from 2011,  
319 published in 2014, showed that in all 25 EU countries analysed, tetracyclines,  
320 penicillins and sulphonamides accounted for more than half (53%–88%) of the total  
321 amount of antimicrobial agents sold by country.<sup>50</sup> Another study also evaluated the  
322 appropriateness of use compared with prudent use guidelines in Switzerland.<sup>174</sup> The  
323 authors concluded that most prescriptions corresponded well to guidelines on  
324 prudent use of antimicrobials. However, there was a wide variation in prescriptions  
325 between different veterinarians which might indicate that the usage and amount of  
326 antimicrobials used for group medication lacking a specific indication could be further  
327 reduced.<sup>174</sup> Several papers investigated the levels of antimicrobial use in animals and  
328 its impact on resistance in both the animals themselves as well as humans.<sup>14,49,175-180</sup>  
329 Some studies demonstrated a correlation between antimicrobial usage in animals  
330 and the occurrence of resistant bacteria in animals.<sup>14,49,175-177</sup> Others also found a  
331 relationship between the antimicrobial usage and the occurrence of antimicrobial  
332 resistant bacteria not only in animals, but also in humans with close contact to  
333 animals.<sup>178-179</sup> For instance, a study on enterococci revealed that the overall  
334 resistance in broiler isolates corresponded with resistance in the isolates of broiler  
335 farmers and poultry slaughterers.<sup>178</sup> A more recent study also showed that MRSA of  
336 the same MLST, *spa* and *dru* types with very similar resistance patterns were seen  
337 among chickens at slaughter and abattoir workers and underlines the exchange of  
338 resistant isolates between animals and people in occupational contact with them.<sup>66</sup> A

339 study of Danish pigs and their farmers and families showed that ESBL-producing *E.*  
340 *coli* was detected in pigs on 79% of the farms with a high consumption of  
341 cephalosporins compared to 20% of the pigs on farms that did not use these drugs.  
342 At four farms ESBL-producing *E. coli* isolates with the same CTX-M enzyme,  
343 phylotype, PFGE type and MLST type were detected in both pigs and farmers.<sup>179</sup>  
344 These examples underline the interrelationship of antimicrobial use and  
345 dissemination of resistant bacteria.

346

347

## 348 Conclusion

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

362

363



364 **Transparency declarations**

365 None to declare.

366

367

368 **Funding**

369 No funding was obtained for this study.

370

371

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920 **Figure 1.** Numbers of 'veterinary' papers published in JAC during 1975-2015.

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925 **Figure 2.** Numbers of veterinary papers published in JAC during 1975-2015

926 according to the animals species involved. It should be noted that papers which dealt

927 with more than one animal species, are separately listed for each animal species

928 involved. Consequently, the total number of the papers listed in Fig. 2 exceeds the

929 actual total number of the 'veterinary' papers published in JAC during 1975-2015.





