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1    **The Agri-food chain and Antimicrobial Resistance: a review**

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15    **ABSTRACT**

16    **Background**

17    Antimicrobial resistance is becoming a major threat to public health and there is much current

18    activity to ameliorate that threat. However, the relative contributions that potential sources of

19    antimicrobial resistant (AMR) bacteria represent are not well established. Over-prescription of

20    antimicrobials by clinicians is one source of selection for AMR bacteria/genes, but antimicrobials are

21    used in greater quantities in food production. These bacteria/genes can then reach humans via food,

22    the environment, or other means.

23    Scope and approach

24    Summarised in this review are potential transmission routes of AMR bacteria/genes from

25    agricultural production to human infections. The situation is complicated, and it is difficult to

26  compare studies because of different methodologies and definitions of resistance being used. Data

27  and examples to illustrate each transmission route are provided where available.

28  Key findings and conclusions

29  Quantitative data for defined organism/phenotype/gene combinations for exposure assessment are

30  rare. Another problem is the identification of indistinguishable AMR bacteria in foods and human

31  cases, which is invariably taken to show that food consumption is a source of infections. However,

32  these data do not show the direction in which the flow of the organism/gene occurred nor do they

33  rule out another source(s), and such data are scant. Case control studies could identify food

34  exposures associated with particular organism/gene infections. The construction of models

35  representing potential transmission pathways may help to reveal their relative contributions.

36  However, the data may not be available to support these models. The lack of coherent data hampers

37  the development of effective policy.

38

39  **Keywords.** Antimicrobial resistance; food; agriculture; transmission; environment: societal drivers

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41

## 1  Introduction

44

45  The discovery and introduction of antibiotics prior to the Second World War marked a pivotal point

46  in the ability of humanity to combat bacterial infections. Formerly life-threatening infections became

47  easily treatable, although the oft-quoted comment by a US surgeon general "it is time to close the

48  book on infectious diseases, and declare the war against pestilence won" appears to be an urban

49  myth (Spellberg & Taylor-Blake, 2013). However, ever since the discovery of antibiotics, the

50  phenomenon of antimicrobial resistance (AMR) has been recognised (Davies & Davies, 2010) and in

51  1945 Sir Alexander Fleming warned of the potential for AMR to become a public health threat "then

52  there is the danger that the ignorant man may easily under dose himself and by exposing his

53  microbes to non-lethal quantities of the drug make them resistant"[1] . Of concern is the fact that

54  AMR can readily be transmitted from bacterium to bacterium on segments of DNA by several means

55  including phages, transposons and plasmids, so resulting in horizontal gene transfer (HGT)

56  (Djordjevic, Stokes, & Chowdhury, 2013). The three predominant processes at play include "the

57  emergence, invasion and occupation" (Baquero, Lanza, Cantón, & Coque, 2015) of environments,

58  this process involving mobility in both bacteria and the genes themselves. HGT has been shown to

59  occur in the environment, food (Jahan & Holley, 2016) and the gastrointestinal tract. These

60  environments also act as reservoirs of AMR genes - the "resistome" (Forsberg, et al., 2012).

61        The emergence of AMR in clinically important bacteria has continued at the same time as

62  the pipeline of new antibiotics has dwindled to the point where phrases such as "we are in the midst

63  of an emerging crisis of antibiotic resistance for microbial pathogens in the United States and

64  throughout the world" are appearing in the literature (Spellberg, et al., 2008). There are claims that

65  AMR infections have been increasing, for example for *Salmonella* (Su, Chiu, Chu, & Ou, 2004), but

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[1] http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf

66    the data are patchy, complex and come from countries with different surveillance systems. A recent

67    report from Canada indicates currently stable and, in some cases, decreasing incidences of AMR

68    infections (Public Health Agency of Canada, 2016). In the UK the number of methicillin-resistant

69    *Staphylococcus aureus* (MRSA) bacteraemia cases reduced by 81% from 2007/8 to 2012/13 but, in

70    contrast, the number of isolates of carbapenemase-producing *Enterobacteriaceae* increased

71    approximately ten fold between 2009 and 2014 (Department of Health antimicrobial resistance

72    strategy analytical working group, 2016). This group of organisms is rated as "Priority 1: critical" for

73    development of new antibiotics[2]. A similar increasing trend has been identified for *Klebsiella*

74    *pneumoniae* in wider Europe, and resistance to third generation cephalosporins in *Escherichia coli* is

75    also increasing (European Centre for Disease Prevention and Control, 2016). A comparison between

76    the USA, Kuwait and China between 1994 and 2000 found a growth in AMR infections of 6, 17 and

77    22%, respectively, over the period. Looking to the future the "O'Neill report" predicts 10 million lives

78    lost per year in 2050 because of AMR bacteria (O'Neill, 2016).

79        The term "antimicrobial" has a number of meanings, but in this review it is taken to mean

80    antibiotics (small compounds produced by one organism that kills or inhibits another) and their

81    chemical derivatives. There are many such chemicals and a categorization with some examples is

82    provided in Table 1.

83                    ………………………………….
84                    Table 1 about here
85                    …………………………………
86

## 2  Development and transmission of AMR bacteria in Agri-food

## settings

89    *2.1      Use of antimicrobials in the agri-food chain*

90    Antimicrobials are used for various purposes in animal production: 1) therapeutic treatment of

91    diseased animals, 2) growth promotion, 3) treating a group of animals to combat disease in a

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[2] http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf

92    proportion of them and to prevent disease from occurring in the rest (metaphylaxis) and, 4) use

93    during periods of high susceptibility to infections (prophylaxis). Of these, the use of antimicrobial

94    growth promoters (AGPs) has been banned in the EU since 2006 (http://eur-lex.europa.eu/legal-

95    content/EN/ALL/?uri=CELEX:32003R1831 ), and the cessation of AGP use is frequently suggested in

96    the literature as a means of reducing or stabilising AMR bacteria. In the US medically important

97    antimicrobials which are used in feed or water stopped being available over the counter at the end

98    of 2016[3]. The benefits of using AGPs are not clear and might only be realised when sub-optimal

99    hygiene conditions prevail (Rushton, 2015), or at early stages of production, although Hao, et al.

100   (2014) report data tending to show increased productivity with AGP use. An evaluation of the use of

101   AGPs in less affluent countries concluded that there would be "negligible effects in these countries"

102   at the national level on pork and chicken production if the use of AGPs were to be discontinued

103   (Angulo, Collignon, Wegener, Braam, & Butler, 2005). The reasons for this included likely small

104   decreases in production resulting from cessation of use of AGPs and the minor contribution that

105   meat protein makes to the diet of the poor, although this is increasing in many low to middle income

106   countries for those with increasing disposable income. A study of broiler chickens in Denmark

107   reported that the feed conversion rate increased slightly after the withdrawal of AGPs (Emborg,

108   Ersbøll, Heuer, & Wegener, 2001) suggesting that their use would, in fact, represent an economic

109   cost.

110        The risks and benefits of AGP use are still being debated (Hao, et al., 2014; Phillips, 2007).

111   However, antimicrobials are necessary for the prevention and treatment of diseases in production

112   animals with accompanying benefits to animal welfare. There may also be an effect in reducing

113   zoonotic diseases and environmental impacts such as methane production both in the growing

114   animal (by using monensin, for example) and in animal waste.

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116   *2.1.2 Antimicrobial usage*

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[3] https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm507355.htm

117

118    A recent survey reported on the veterinary use of antimicrobials in the EU broken down in to

119    antimicrobial class and the disease that they were being used to treat (De Briyne, Atkinson,

120    Pokludová, & Borriello, 2014). As an example, 40% of the citations of use of antimicrobials in cattle

121    and calves were for the control of mastitis, and for 78% of the time non-critically important

122    antimicrobials were used. Lists of critically important antimicrobials are available for veterinary[4] and

123    human clinical[5] perspectives. In China an estimated 38.5 million kg of antimicrobials were used in

124    pork and poultry production in 2012 (Krishnasamy, Otte, & Sibergeld, 2015). Estimates of the change

125    in demand for antimicrobials for animal production indicates an increase of 67% from 2010 until

126    2030, driven largely by the intensification of animal production systems in emerging economies (Van

127    Boeckel, et al., 2015). In Brazil, China, Russia, India and South Africa, the increase is predicted to be

128    99%. The ban on the use of AGPs in the EU did not necessarily result in a reduction of the veterinary

129    use of antibiotics overall for the period 2005-2009 (Woolhouse, Ward, van Bunnik, & Farrar, 2015).

130    The MARAN 2007 report noted an increase in the use of antimicrobials in the Netherlands and

131    ascribed, in part, to a possible "substitution of growth promoters" implying continued use of

132    antimicrobials in another guise, e.g. prophylaxis (Veterinary Antibiotic Usage and Resistance

133    Surveillance Working Group, 2009). However, more recent data for the Netherlands suggest a slight

134    reduction in sales of antimicrobials[6] between 2014 and 2015 at almost one third of the 2007

135    volumes.

136        Within the EU there are marked differences in the volume of antimicrobials used for animal

137    production when normalised on a mg/kg biomass basis (Grave, Torren-Edo, & Mackay, 2010). In a

138    study of ten European countries (Netherlands, France, United Kingdom, Czech Republic, Switzerland,

139    Germany, Denmark, Finland, Sweden and Norway), usage in France and the Netherlands was

140    substantially higher (more than two fold) compared to the other eight countries and around ten

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[4] http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pdf

[5] http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf
[6] http://www.wur.nl/upload_mm/0/b/c/433ca2d5-c97f-4aa1-ad34-a45ad522df95_92416_008804_NethmapMaran2016+TG2.pdf

141    times the amounts used in Norway. Several potential reasons for these differences were listed, but

142    differences of proportions of the animals produced (dairy cattle, cattle, poultry and pigs) was

143    excluded.

144          The distribution of antimicrobials sold for veterinary use compared to those prescribed for

145    human use in England is shown in Figure 1 (data from (Public Health England, 2015). Some major

146    differences were observed, for example penicillins, fluoroquinolones and 1st and 2nd generation

147    cephalosporins were used in greater proportions for human therapy, while the opposite is true for

148    tetracyclines, sulphonamides and trimethoprim, and lincosamides. Glycopeptides and

149    monobactams/carbapenems were not sold for veterinary use.

150          ……………………………….
151                         Figure 1 about here
152          ……………………………….
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## 2.2    AMR bacteria and antimicrobials in meat and dairy production

155    *2.2.1    Occurrence of AMR bacteria during production*
156
157          There is evidence that the provision of antimicrobials to livestock can result in the

158    emergence of AMR bacteria. For example, in Canadian feedlot cattle the inclusion of

159    chlortetracycline in the diets of calves resulted in the appearance of tetracycline-resistant *C. jejuni*

160    (Inglis, et al., 2005). In American feedlot cattle, administration of tylosin selected for enterococci

161    resistant to erythromycin and tylosin (Beukers, et al., 2015). This appeared to result from selection

162    for strains already present in animals arriving at the feedlot, and resistance fell at around the time

163    that tylosin was withdrawn prior to slaughter. The use of antimicrobials may also lead to the

164    selection of resistant veterinary pathogens, for example *Mannheimia haemolytica* which causes

165    bovine respiratory disease (Cameron & McAllister, 2016).

166          Antibiotic resistant bacteria have been detected in farmed animals in many studies. For

167    example, rectal swabs and faecal samples from farms in the US were tested for the presence of AMR

168    *Campylobacter* (Bae, et al., 2005). The most prevalent resistance was to doxycycline (42.3%) and

169  lesser rates of resistance being found for erythromycin, nalidixic acid and ciprofloxacin. Most *C.*

170  *jejuni* isolates (58.8%) were sensitive to all four antibiotics tested. Different results were obtained for

171  *C. coli* where resistance was more prevalent, with 72.7% of isolates being resistant to one or more of

172  these antimicrobials. This study also provided data which showed different levels of AMR bacteria

173  with different kinds of farming practice. AMR bacteria, especially *C. coli*, were more prevalent in calf

174  rearer farms. It was postulated that this may be caused by the greater use of antimicrobials in calf

175  rearing. A generally higher level of resistance in *C. coli* compared to *C. jejuni* has been reported in

176  other studies, e.g. in faecal isolates from US dairy cows (Englen, Hill, Dargatz, Ladely, & Fedorka-

177  Cray, 2007) and feedlot cattle (Englen, Fedorka-Cray, Ladely, & Dargatz, 2005). In human cases

178  infections caused by *C. jejuni* are much more common than those caused by *C. coli*.

179        A comparison was made between AMR *Salmonella* Dublin isolates from dairy and beef cattle

180  in the US (Davis, et al., 2007). This serovar was selected as it is adapted to bovines so that any

181  resistance acquired is most likely to have come from agricultural antimicrobial use rather than from

182  human therapeutics. The two kinds of animal were selected as antimicrobial use with beef cattle is

183  less than it is for dairy cattle. A problem with the study is that relatively few (19) beef isolates were

184  obtained compared to 273 for dairy sources, but for all except one of the antimicrobials tested the

185  prevalence of resistance was greater in the dairy isolates. The reported data therefore supported the

186  hypothesis that the use of antimicrobials in dairy calf rearing results in the emergence of AMR *S.*

187  Dublin.

188        Quinolone-resistant *Escherichia coli* were isolated from animals and farm environments in

189  Sweden. These organisms were isolated from 60% of calf and 28% of cow faecal samples, although

190  there was considerable farm-to-farm variability (Duse, et al., 2016). A report of 2013 UK data

191  provides information of antibiotic resistance of *Salmonella*, *Campylobacter* and *E. coli*  in veterinary

192  isolates (Public Health England, 2015).

193        A study of faecal isolates of *Campylobacter* from organic and conventional dairy herds in the

194  USA was unable to identify a difference in AMR patterns between the two types of agricultural

195 practice (Sato, Bartlett, Kaneene, & Downes, 2004), although resistance to tetracycline was higher in

196 calves than adult animals. However, an analysis of AMR *E. coli* from cows and calves showed that

197 isolates from the organic farms were less resistant for seven antibiotics, but not for an additional 10

198 (Sato, Bartlett, & Saeed, 2005). Resistance was also reported to be lower in *E. coli* from the faeces of

199 pigs from organic farms compared to those on conventional farms (Hoogenboom, et al., 2008), as

200 was the case for *E. coli* and *Ent. faecium* in broilers. In contrast no difference could be found with

201 conventional and organic poultry with respect to AMR in *Campylobacter*.

202    A greater prevalence of AMR *E. coli* isolates in calves (81.5%) compared to beef cattle

203 (39.2%) has been noted in Belgian data (Hanon, et al., 2015), and this is a common finding for a

204 range of AMR bacteria (Sato, et al., 2004; Tenhagen, et al., 2014) reflecting the greater need to treat

205 calves with antimicrobials. A comparison of veal, beef and dairy production reflected a large

206 difference in AMR *E. coli* (Catry, et al., 2016) between intensively reared veal calves compared to

207 dairy and beef animals and concluded that "intensively reared veal calves deserve special attention

208 in antimicrobial resistance monitoring and intervention programmes".

209    AMR *Salmonella* have been isolated from lairage environments in the UK and this may

210 present a means whereby resistant organisms are passed from day to day to different groups of

211 animals at slaughter (Small, et al., 2006). *Salmonella* can survive for long periods under dry

212 conditions such as might occur in dried faeces. In Spanish goat and lamb slaughtering operations,

213 some evidence has been provided to suggest that resistant bacteria are primarily introduced with

214 the animals, resistant spoilage organisms persist along the process but pathogens do not persist

215 beyond the cutting room (Lavilla Lerma, Benomar, Casado Muñoz, Gálvez, & Abriouel, 2014; Lavilla

216 Lerma, Benomar, Gálvez, & Abriouel, 2013).

217    Low prevalence rates of AMR *E. coli* were found in wild deer and small mammals tested in

218 Spain (Alonso, González-Barrio, Tenorio, Ruiz-Fons, & Torres, 2016). Similar results were obtained for

219 white-tailed deer in the USA from 1999 to 2009 (Fitzgerald, Schooley, Berry, & Kaneene, 2011), and

220 both studies suggest that carriage is lower where direct selection is minimal in wild animals. Data

221 form such sources could represent a baseline against which AMR in farmed animals could be

222 measured.

223 *2.2.2    Linkages between agricultural use of antimicrobials and human infections*
224

225 It has been shown that indistinguishable strains of AMR bacteria have been found both in food

226 isolates and human cases (Doi, et al., 2010; Kluytmans, et al., 2013; Leverstein-van Hall, et al., 2011),

227 although the evidence is patchy and not necessarily consistent between countries (Wu, et al., 2013).

228 For example, for gentamicin resistant *Campylobacter* it was concluded that chicken was not the only

229 source of human clinical resistant strains (Zhao, et al., 2015), although poultry meat was the most

230 likely source of resistant *C. coli* infections. The recovery of indistinguishable isolates of an AMR

231 bacterium from two environments does not reveal the direction in which the transmission occurred

232 (Singer & Williams-Nguyen, 2014). Evidence of a direction of flow from agriculture to humans is

233 mounting from other sources and a case in point is the detection of plasmid-borne colistin-resistant

234 *E. coli* in China (Liu, et al., 2016). This antibiotic is known as a "drug of last resort" (Al-Tawfiq,

235 Laxminarayan, & Mendelson, 2017) and is used to treat otherwise intractable infections in humans,

236 but also has use in the treatment of food animals. The fact that the resistant organism was much

237 more frequent in the agricultural environment than in the human population suggests that the

238 direction of transmission is environment to human, and not the other way round. A caveat is that

239 colistin is manufactured in China and it is possible that effluent from the process may have passed

240 into the environment, a phenomenon which has been reported for other antimicrobials in China and

241 elsewhere (Larsson, 2014).

242         Virginiamcyin, a streptogramin antimicrobial, was in use in livestock in the USA from 1975

243 while quinupristin/dalfopristin, also streptogramins, started to be used to treat Vancomycin

244 Resistant Enterococcal infections in 1999. However, a study published in 1999 (Moellering, et al.)

245 reported the detection of resistant, but not "highly resistant", strains which implies that resistance

246 could have been caused by co-selection alongside virginiamycin resistance in agricultural production.

247    There is conflicting information as to the connection between antibiotic use in animals and

248    the emergence of AMR in humans. For example the reduction in the use of avoparcin has been

249    linked to a reduction of vancomycin-resistant enterococci (VRE) in the human population (Klare, et

250    al., 2009). At a larger scale, an analysis of antimicrobial use and resistance for seven European

251    countries including Denmark has revealed a correlation between the two (Chantziaras, Boyen,

252    Callens, & Dewulf, 2014). Limited use of fluoroquinolones in Norwegian broiler production was

253    found to be associated with low levels of fluoroquinolones in Norwegian broilers and humans

254    becoming infected in Norway, in comparisons to humans infected abroad (Norström, et al., 2006).

255    However, carbapenem-resistant salmonellae were isolated from poultry and pig farms in Germany

256    even though this group of antimicrobials is not permitted for use in pig production (Fischer, et al.,

257    2013). This may have resulted from co-selection for another resistance determinant; co-selection of

258    AMR bacteria has been described in the presence of heavy metals but less so for biocides (Wales &

259    Davies, 2015). In addition, in the USA, a ban on the use of enrofloxacin in poultry production did not

260    result in a reduction in ciprofloxacin resistance in chicken or human *Campylobacter* isolates (Food

261    and Drug Administration, 2012). The potential for cattle to be a source of human *S*. Typhimurium

262    DT104 infections has been argued against (Davis, et al., 1999) because of *inter alia* a lack of correct

263    timing of the use of antimicrobials in the human population and use in animals, and the occurrence

264    of *S*. Typhimurium DT104  in wildlife.

265
266    *2.2.3    Antimicrobials and the resistome in the environment*
267
268    Antimicrobials themselves can be detected in farming environments as a large proportion of those

269    administered to animals may be excreted un-metabolised.  In China, testing of faecal samples from

270    pigs, cows and chickens showed a prevalence range of 0 to 82.1% (chlortetracycline in cow faeces)

271    and the highest concentration was 1420.76 mg enrofloxacin/kg chicken faeces (Zhao, Dong, & Wang,

272    2010), which was the highest identified in a recent review (Wohde, et al., 2016). Such contaminated

273    manure may then, in turn, be applied as a fertiliser to agricultural land and so released to soil and

274    water thus creating a greater variety of transmission routes from treated animal to humans. Wohde

275    et al (2016) includes tables of similar data for various classes of antimicrobials and discussion as to

276    their fate once excreted from the animal. Also in China, antimicrobials have been detected in animal

277    wastewater, effluent and river waters (Wei, Ge, Huang, Chen, & Wang, 2011). Only one of 18 river

278    water samples was free of any detectable antimicrobials.

279         A study of AMR genes in historical samples of Danish soils which had been amended using

280    manure or inorganic fertilisers showed found that four β-lactam AMR genes tended to increase only

281    in the manured soils at about the same time as the relevant resistance was noted  in humans

282    (Graham, Knapp, Christensen, McCluskey, & Dolfing, 2016). Their abundance ceased possibly in line

283    with reductions in their agricultural use. However, another gene, *int*1 did not decrease and this may

284    have been through co-selection as the concentration of copper increased. It was commented that

285    we must be careful not to solve one problem by creating another.

286

287    *2.3    AMR bacteria in aquaculture*

288         Antimicrobials are not confined to use in the terrestrial agri-food chain, but also in

289    aquaculture (Cabello, 2006). The similarities between both systems has been reviewed in respect to

290    the development of AMR (Done, Venkatesan, & Halden, 2015). The industry has been associated

291    with poor control of the use of antimicrobials and it has been said that this overuse was needed

292    because of poor sanitary conditions in the industry, and this may be associated with the rapid

293    increase in aquacultural production which has occurred over the last 30 years. For example, the

294    production of *Tilapia* in China has increased from close to zero in 1986 to almost 1.4 x $10^6$ tonnes in

295    2010 (Rico, et al., 2013). If the trend towards increasing aquacultural production continues, then any

296    problems connected with AMR will grow with the industry unless the pattern of antimicrobial usage

297    changes, and there is evidence that it has been reducing in some areas (Rico, et al., 2013). The use of

298    antimicrobials in aquaculture in Asia is highly variable, but 100% of Vietnamese *Pangasius* farms

299    used antimicrobials, while prawn and shrimp farms in Bangladesh were infrequent users (Rico, et al.,

300    2013). The emergence of AMR fish pathogens has been noted (Cabello, 2006) and the question as to

301    the potential to spread AMR genes to humans raised. It is of note that the accumulation of

302    tetracycline from water to plant to fish has been demonstrated experimentally (Boonsaner &

303    Hawker, 2013).

304

305    *2.4    AMR bacteria and antimicrobials in vegetable production*

306         Fruits and vegetables can also be treated with antibiotics and so potentially result in AMR

307    selection among their natural microflora, and other forms of exposure to AMR bacteria may occur

308    during irrigation as well as application to crops of manures derived from animals exposed to

309    antimicrobials (Schwaiger, Helmke, Hölzel, & Bauer, 2011). In the United States in 2009 16,465 kg of

310    antimicrobials were applied to orchards, and this represented 0.12% of those used in animal

311    production (Stockwell & Duffy, 2012). In a Chinese study, antimicrobials were reported to be higher

312    in organic than conventional vegetables, presumably because the organic vegetables were fertilised

313    with animal-derived manure (Hu, Zhou, & Luo, 2010). The addition of manure to soils has been

314    shown to enrich AMR bacteria but with no resultant increase in accumulation of AMR bacteria in the

315    vegetables themselves (Marti, et al., 2013) compared those grown in soils which had never received

316    manure. Composting and mandated offset periods were proposed as means of minimising exposure

317    of the population to AMR bacteria from vegetables.

318         Some information on the effects of agricultural uses of antimicrobials is provided by

319    comparisons of food produced under conventional and organic practices. A study of lettuces in Costa

320    Rica concluded that the organic status of one of ten farms studied "had little, if any, effect on the

321    antimicrobial resistant communities" (Rodríguez, et al., 2006). This was explained either by the AMR

322    communities identified being natural, or because the organic farm had previously been exposed to

323    antimicrobials. Similarly, there were no differences in prevalence or concentration of AMR bacteria

324    detected in French organic and conventional fruits and vegetables (Ruimy, et al., 2010). Produce

325    growing in or on the soil was more frequently contaminated than produce growing above the soil. It

13

326 was concluded that the AMR bacteria present in the food were environmental, and that the foods

327 "do not constitute a direct threat of infection of the general population". This situation contrasts

328 with the data for organic and conventional animal production.

329

## 3 Transmission routes from food production to humans

331       Essentially there are three transmission routes of AMR bacteria from agri-food systems to

332 humans 1) the consumption of contaminated food 2) contact between humans and treated animals

333 or 3) environmental contamination (which can also be of the antimicrobial itself). All would be

334 classed as zoonotic transmission routes. Complicating the picture is HGT and consideration needs to

335 be given to both bacteria and the genes that they carry. In addition, not all of the AMR bacteria

336 which need to be assessed are conventional foodborne pathogens, as some are commensals (normal

337 microflora) which may nevertheless act as a means of transmitting AMR genes and causing

338 infections in humans. The importance of the role of commensals in linking different parts of the

339 biosphere has been emphasised (Djordjevic, et al., 2013). An example is the VRE which are not

340 usually regarded as foodborne pathogens yet can cause wound infections and septicaemia.

341 Enterococci may acquire their resistance following the use of avoparcin in the production of poultry

342 as avoparcin and vancomycin are structurally similar, although the common belief of such a link is

343 not unequivocal (Phillips, et al., 2004).

344

345 *3.1 Direct Food Consumption*

346       The relative contribution between human and veterinary/food production use of

347 antimicrobials in the emergence of human clinical AMR infections is not known (Singer & Williams-

348 Nguyen, 2014). Even less is known about the proportionate role of foods containing AMR bacteria

349 which may potentially be introduced accidentally during food production, from intentionally added

350 bacteria such as lactic acid bacteria starter cultures (Aarts & Margolles, 2014), or cross

351 contamination during processing.

352    Foodborne pathogens may themselves harbour mobile resistance genes, for example *tet*M,

353    *erm*B and IS1542 in *L. monocytogenes* (Gelbíčová, Pantůček, & Karpíšková, 2016; Haubert,

354    Mendonça, Lopes, de Itapema Cardoso, & da Silva, 2016; Yan, et al., 2010). Such resistance can be at

355    a very low prevalence amongst isolates tested, for example 2% of 204 French isolates (Granier, et al.,

356    2011). where resistance to tetracycline, cotrimoxazole and erythromycin was recorded. In addition

357    spoilage and commensal organisms may also be resistant (Toomey, Bolton, & Fanning, 2010).

358    A study of virulence factors in AMR and non-AMR *E. coli* isolates from poultry, healthy

359    vegetarians and hospital inpatients found that the human resistant strains were more like the

360    poultry resistant and sensitive strains than human sensitive strains (Johnson, et al., 2007). Strains

361    from the vegetarians were more like those from the poultry, and this group would not have been

362    directly exposed to the food. It is possible that the *E. coli* was passed on to them by a family member

363    or other meat-eating contact.

364    A Finnish study concluded that the *Enterobacteriaceae* in vegetables were different from

365    those of the human faecal flora with respect to their AMR profiles and concluded that these

366    organisms did not "contribute substantially" to high levels of AMR organisms in the human faecal

367    flora (Österblad, Pensala, Peterzéns, Heleniusc, & Huovinen, 1999). In the UK ESBL *E. coli* isolates

368    from chicken and turkey production were found to be distinct from those causing disease in humans

369    (Randall, et al., 2010), although transfer of AMR might be occurring between the two. Vancomycin

370    resistant enterococci (VRE) detected in German minced pork and beef were different to clinical

371    isolates (Klein, Pack, & Reuter, 1998).

372    Another means of linking human colonisation with food consumption is by using a case-

373    control approach. For relatives of cases with community-acquired urinary tract ESBL-producing *E.

374    coli* eating outside of the home was shown to be protective, which might imply that eating at home

375    was a risk factor which, in turn, might imply cross contamination within the home (Rodríguez-Baño,

376    López-Cerero, Navarro, Díaz de Alba, & Pascual, 2008). A comparison of vegetarians and newly

377    hospitalised patients in the USA focused on risk factors for colonisation by AMR *E. coli*  (Sannes, et

al., 2008). Poultry meat contact and/or consumption was not predictive, and vegetarians were more

frequently colonised by AMR *E. coli*. Travel and recent visits to a "developing nation" were risk

factors. For campylobacteriosis in Denmark, risk factors for quinolone resistant infections included

foreign travel, eating poultry other than chicken and turkey, and swimming. Eating chicken was

protective (Engberg, Neimann, Nielsen, Aarestrup, & Fussing, 2004). In contrast poultry consumption

and touching raw poultry were risk factors for colonisation by *Ent. faecium* with inducible

quinupristin-dalfopristin resistance (Kieke, et al., 2006).

Tracking of antibiotic resistant *E. coli* and *Salmonella* in the beef production chain in America

found that resistant organisms could be detected on hides, decreasingly present along the chain,

and they were not present in 103 striploin purge samples at the end of production (Schmidt, et al.,

2015). In another study the diversity of AMR genes reduced during meat processing with no AMR

genes present on beef products (Noyes, et al., 2016). Similarly the prevalence of AMR bacteria was

greater, when differences were noted, on vegetables obtained from the farm compared to those

tested at retail (Schwaiger, et al., 2011). In Italy, resistant *Enterobacteriaceae* were present in 52.2%

of pig rectal swab isolates, but in only 3% of minced pork isolates, and the species composition was

different (Sabia, et al., 2017). Similar data were produced for Canadian samples where the

prevalence of MRSA was 61.9% in nasal swabs reducing to 1.2% in retail pork (Aslam, Diarra,

Checkley, Bohaychuk, & Masson, 2012). Italian data demonstrated a reduction of AMR bacteria in

traditional mozzarella production, with the final product containing no AMR bacteria (Devirgiliis,

Caravelli, Coppola, Barile, & Perozzi, 2008). It would be expected that the prevalence of AMR

organisms of a given species would decline along the food chain in tandem with general increases in

food hygiene.

Most reports of the presence of AMR bacteria in foods do not provide prevalence or

concentration data for particular types of resistant bacteria. Usually they provide data on the

proportion of isolates of a given taxon which are resistant to different panels of antibiotics

(Schroeder, White, & Meng, 2004), and use different criteria to define what constitutes resistance.

404 These data therefore need further processing and interpretation if they are to be used in exposure

405 assessments.

406        Example papers and summary information on the prevalence of AMR bacteria in raw (Table

407 2) and ready-to-eat (RTE) foods are provided (Table 3). In addition, a recent review commissioned

408 for the UK Food Standards Agency provides prevalence data for AMR *Campylobacter*, *Salmonella*, *E.*

409 *coli* and *Enterococcus* in pork, poultry, dairy products, seafood, and vegetables and fruit (Royal

410 Veterinary College, 2016).  It would be expected that the prevalence of pathogens in raw food would

411 be higher than in RTE/cooked foods, but there is no reason for the proportion of AMR among

412 isolates from the two kinds of food to be different unless, for example, AMR also conferred

413 resistance to a physico-chemical characteristic used in food processing. It has been shown that AMR

414 does not confer additional cross resistance to *L. monocytogenes* in respect to survival at high or low

415 pH (Cunha, et al., 2016).

416                           ……………………………
417                           Table 2 about here
418                           …………………………….
419                           ………………………………
420                           Table 3 about here
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422
423        AMR organisms have been isolated in high concentrations in a variety of foods (Boehme,

424 Werner, Klare, Reissbrodt, & Witte, 2004; Rodríguez, et al., 2006; Wang, et al., 2006). However,

425 there is a need for some caution when considering these data. For example cefotaxime-resistant *L.*

426 *monocytogenes* are common among isolates from food, but this resistance is natural since it results

427 from the lack of a specific penicillin binding protein (Yan, et al., 2010). Other organisms are, likewise,

428 naturally resistant to certain antibiotics (Fitzgerald, et al., 2011; Haubert, et al., 2016) and so the

429 identification of generic AMR bacteria in a food may be of little or no consequence, especially if the

430 resistance is not capable of undergoing HGT.

431        Outbreaks of foodborne disease caused by AMR pathogens are known to occur (Dechet, et

432 al., 2006). For example an outbreak of 58 cases of multidrug-resistant *Salmonella* Typhimurium DT

433  104 infections associated with the consumption of contaminated minced beef.  The same serovar of

434  *Salmonella* also caused an outbreak  in Denmark of 25 culture confirmed cases of whom 11 were

435  hospitalised and two died (Mølbak , et al., 1999). The source was identified as two Danish pig herds.

436  Interestingly the veterinarian claimed that fluoroquinolones had not been used on the farms yet the

437  isolates were nalidixic acid resistant. The consequence of infection by AMR pathogens to humans are

438  more severe than infection by their susceptible counterparts, including higher mortality rates

439  (Helms, Vastrup, Gerner-Smidt, & Mølbak, 2002) and duration of illness (Engberg, et al., 2004).

440       The consumption of a contaminated food could result in foodborne disease caused by

441  antibiotic-resistant variants of foodborne pathogens such as *Salmonella* (Su, et al., 2004) and

442  *Campylobacter* (Zhao, et al., 2015). Different modelling exercises have resulted in very different

443  estimates of risk, but the potential for AMR transmission by this route must be considered as

444  possible (Chang, Wang, Regev-Yochay, Lipsitch, & Hanage, 2015). A review of publically available risk

445  assessments concerning the use of antimicrobials in animal production and the emergence of AMR

446  infections in humans has been published (McEwen, 2012). A great deal of heterogeneity of approach

447  was noted, making comparisons difficult, and a lack of necessary data was noted. Differences in the

448  outcomes of risk assessment will therefore reflect real differences, as well as differences in the

449  availability of data and approach taken. A later discussion paper describes the data needs and

450  complexities of carrying out a holistic human health risk assessment for AMR bacteria (Ashbolt, et

451  al., 2013), which would be a larger task than a standard quantitative risk assessment for a defined

452  food/hazard combination. A Swiss semi-quantitative risk assessment did, however, compare relative

453  risks of AMR bacteria in chicken, beef, pork and veal (Presi, et al., 2009), and the order was (in % "of

454  the overall risk") was chicken (6.7%), pork (4.0%), beef (0.4%) and veal (0.1%).

455       Another potential source of contamination of foods by AMR bacteria is contact with infected

456  food handlers at any point in the food chain. This may be especially important for AMR

457  *Staphylococcus aureus* where it is known that the strains of the organism involved in human

458  foodborne disease are those introduced onto food during handling, as opposed to strains present on

459    the food animal (Hudson, 2014), although livestock associated strains can be isolated from foods

460    (Fox, et al., 2017). This is reflected in a study of MRSA in minced beef and pork in the USA which

461    concluded that some of the MRSA present in beef were introduced by human contact (Jackson,

462    Davis, & Barrett, 2013) and may represent a source of infection for consumers of that beef. This

463    possible transmission route was attributed to a fatal hospital outbreak of MRSA infections where an

464    infected health care worker was concluded to have contaminated food eaten by affected patients,

465    and subsequent transmission occurred (Kluytmans, et al., 1995).

466         Foods produced from animals treated with antimicrobials may themselves contain residual

467    concentrations of them and such foods are subject to testing programmes. Some data are reported,

468    but results for other samples which contain antimicrobials but at concentrations beneath regulatory

469    maxima are not necessarily reported. Foods containing antibiotics may therefore act as niches for

470    the selection of AMR bacteria which are capable of growing on them under normal storage

471    conditions. In the UK a survey of waste milk (which can be derived from animals being treated with

472    antimicrobials) samples for β-lactam antibiotics found that 66/103 (64.1%) contained at least one

473    member of the antibiotic groups penicillins and cephalosporins (Randall, et al., 2014). The maximum

474    concentration was 4.6 mg/l cefquinome which was also detected up to 27 mg/l in a follow up study.

475    The presence of antimicrobials was correlated to reported antibiotic use in the herds tested. Culture

476    for AMR bacteria found that resistant bacteria were 20 times more likely to be present in

477    cefquinome-containing milk. The use of waste milk to feed calves has been proposed as an

478    explanation for why AMR *E. coli* gradually decreases during fattening once exposure to the milk has

479    been removed (Hordijk, et al., 2013).

480         A study of the accumulation of antimicrobials by vegetables has shown that the leaves

481    accumulate the most (Hu, et al., 2010). The paper also reported values for antimicrobials in various

482    herb and vegetable plants finding 10 of the 11 antimicrobials sought to be present, and their origin

483    was likely to be organic fertilisers applied to growing crops. It has been found that the presence of

484    antimicrobials at even low concentrations (several hundred fold less than the lethal concentration)

485    can lead to the selection of resistant bacteria (Sandegren, 2014).

486

487    *3.2 Non-Food Transmission Routes associated with the agri-food chain*

488    AMR bacteria may be excreted in the faeces to contaminate the wider environment. Therefore non-

489    food environmental transmission routes may result from antimicrobial use in food production.

490    Transmission might occur via environmental contamination (e.g. manure to water to humans)

491    (Thanner, Drissner, & Walsh, 2016) or via insects, such as flies, to ready-to-eat foods (Zurek & Ghosh,

492    2014). The incidence of campylobacteriosis appears to be correlated with fly development time in

493    the UK (Nichols, 2005). A high throughput sequencing study of the resistome of feedlot cattle

494    showed "environmental connectivity" between pens and feedlots indicating the potential for

495    transmission to humans through the environment (Noyes, et al., 2016).

496        Food contact surfaces may also become contaminated. In Malaysian wet markets 38.8% of

497    poultry contact surfaces were contaminated with Extended Spectrum β-Lactamase-producing (ESBL)

498    *E. coli* (Aliyu, Saleha, Jalila, & Zunita, 2016). Logistic regression analysis identified two factors which

499    predicted the contamination of poultry; stall sanitation and counter top material, with wood

500    associated with the greatest risk. Interestingly, cross-resistance to antimicrobials resulted from

501    exposure to increasing concentrations of quaternary ammonium compounds in *Salmonella* and, to a

502    greater extent, *E. coli*, but not in *L. monocytogenes* or *C. coli* (Soumet, et al., 2016) indicating that

503    food processing sanitation operations could lead to co-selection  of AMR bacteria which could then

504    contaminate foods. A similar variability in the potential for cross-resistance to occur has been found

505    for *E. coli* and enterococci (Wieland, et al., 2017).

506        Transmission of AMR *Staphylococcus aureus* (methicillin-resistant *S. aureus*, MRSA, which is

507    resistant to penicillins and cephalosporins) can occur via direct contact between livestock and

508    humans, with potential subsequent person-to-person transmission. The dynamics of the spread of

509    MRSA between humans and pig herds have been shown for one particular genotype, although in this

510    case the direction of transmission appeared to be from humans to animals (Grøntvedt, et al., 2016).

511    A review of livestock-associated MRSA reported that 77-86% of those with occupational exposure to

512    colonised pigs will themselves be colonised in the nasal cavity (Cuny, Wieler, & Witte, 2015) and

513    further transmission can result in 3% of nosocomial MRSA infections and higher proportions of

514    septicaemia and wound infection cases. An analysis of clonal complex 398 MRSA cases found that

515    contact with livestock and residence on a pig farm were risk factors (Deiters, Günnewig, Friedrich,

516    Mellmann, & Köck, 2015). For those cases without livestock contact there were still livestock-

517    associated risk factors, as well as risk factors such as prior hospital stays and contact with MRSA

518    carriers. Butchers have also been shown to be colonised by livestock associated MRSA (Boost, Ho,

519    Guardabassi, & O'Donoghue, 2013). There are flows between humans and pigs in both directions as

520    well as person-to-person transmission of MRSA, but the evidence for foodborne transmission is not

521    apparent.

522            Another potential route might be the HGT of resistance genes from foodborne commensal

523    or starter bacteria to recipient cells in the guts, as shown in humans (Devirgiliis, Barile, & Perozzi,

524    2011; Huddleston, 2014) and mice (Sparo, et al., 2012). Ingestion of AMR *E. faecium* isolates resulted

525    in transient colonisation of human volunteers, and all twelve were clear of their inoculum 35 days

526    post exposure (Sørensen, et al., 2001), and only one person was shedding 14 days post-exposure.

527    The organism could be isolated at concentrations up to $10^7$-$10^8$/g faeces, depending on the strain.

528    The potential for AMR strains to be present for significant periods and high concentration in the gut

529    was therefore shown.

## 4.    Farmer and stakeholder behaviour and AMR

531

532    It has been noted that, as part of the process of developing effective policy interventions to combat

533    the emergence of AMR, the (interactive) behaviours of multiple actors, including farmers, but also

534    veterinarians, policy makers and the public, result in antimicrobials being used either to facilitate or

535    restrict the development of resistance to important drugs in both animals and humans (Garforth,

536    2015). However, there is a limited empirical evidence base to help understand the relevant issues,

537    the most relevant being the understanding of farmer and veterinarian behaviours in relation to

538    decision-making associated with antimicrobial use and AMR (Morris, Helliwell, & Raman, 2016).

539    Understanding societal drivers of, and responses to, the restricted prescription of antimicrobials in

540    human medicine is more extensive. Garforth (2015) notes that classical agricultural economics

541    would predict that farmers only make decisions based on net income or profit,  However, this is not

542    supported by the associated evidence base. Understanding the relative importance of financial

543    incentivisation for farmer antimicrobial usage, as opposed to other motivating factors, is important

544    as it will allow the development of policy interventions targeting the drivers of farmer behaviour.

545         Farmers are the ultimate decision makers when deciding whether to use antimicrobials as

546    part of animal production practices, and they may subsequently put pressure on other agricultural

547    stakeholders to maintain existing animal husbandry practices which are reliant on antimicrobial use

548    (Speksnijder et al, 2015).  Understanding the behaviours of all stakeholders is central to developing

549    effective policy interventions targeting farmer use of antimicrobials. Farmer decision-making may be

550    motivated by multiple sets of values, for example in relation to traditional practices, or the

551    embedding of the farm itself within the social structure of the family (Gasson, 1973). However, farm

552    businesses need to be profitable to survive, which arguably may incentivise greater use of

553    antimicrobials on farms. In reality, the evidence regarding financial incentivisation is somewhat

554    mixed. For example, Speksnijder, Jaarsma, van der Gugten, Verheij, and Wagenaar (2015) suggest

555    that economic factors are an important driver of whether farmers put pressure on veterinarians to

556    prescribe antimicrobials. In this context, they report that some farmers perceive diagnostic tests as

557    expensive, and that preventive use of antibiotics is a financially "safer" option. An additional

558    pressure on veterinarians is the perception that farmers will blame them for not prescribing

559    preventative antimicrobials if animal diseases arise at a later date, with concomitant impacts on

560    animal welfare and/or economic functioning of the farm (Gibbons, et al., 2012). In addition, farmers

561    may be unwilling to change existing animal husbandry practices, which they perceive have resulted

562 in risk avoidance, or because they are unaware of the benefits of adopting alternative strategies

563 (Gunn, Heffernan, Hall, McLeod, & Hovi, 2008; Klerkx & Jansen, 2010). Coyne, et al. (2016) explored

564 the drivers and motivators behind antimicrobial use and prescribing by veterinary surgeons and

565 farmers in the pig industry in the UK. The results indicated that veterinarians responded to pressure

566 from clients, legislation and public perception when deciding whether to prescribe antibiotics. In

567 contrast, farmers may consider issues surrounding farming systems and management to be

568 important drivers of antimicrobial use. Lack of awareness of the consequences of inappropriate or

569 overzealous use of antimicrobials may also be a driver of farmer decision-making.  For example,

570 Friedman, et al. (2007) report that most cattle farmers included in their South Carolinian sample

571 (86%) were not concerned that overuse of antibiotics in animals could result in AMR, in particular

572 failing to recognise that this could result in antibiotic resistance among farm workers.

573　　　　Understanding why different actors are making decisions will facilitate the development of

574 effective communication interventions targeting different stakeholder groups. While this is by no

575 means only driven by economic motivation, it needs to be considered as part of  a broader set of

576 potentially interacting socio-economic and animal production system related drivers, including, *inter*

577 *alia*, lack of knowledge about the effects of antimicrobials, and motivations for using antimicrobials

578 as a preventative measures. Both factors may link to understandings of animal welfare in the context

579 of animal husbandry, in particular in relation to disease prevention, and represent a driver of social

580 pressure to use and prescribe antimicrobials. It is also important to note that AMR represents a

581 transboundary risk (Gebreyes , et al., 2014; You, Bong, & Lee, 2016), which does not respect

582 regulatory or national barriers to migration to other regions or areas. Communication needs to

583 address stakeholder and end-user requirements in different geographical locations, which requires

584 not only international cooperation across policy and industry communities, but harmonisation of

585 cultural, regulatory and policy objectives, and animal production system requirements

586 internationally. Furthermore, an important policy objective is to ensure that a critical mass of

587 individuals are  changing use behaviours to reduce the risks of AMR, and prevent economic

588  disadvantages and production losses having a negative impact on affecting  compliant farmers alone.

589  The question of whether policies focused on incentivisation, for example, subsidizing farmers who

590  can demonstrate appropriate use of antimicrobials, or enforcement (e.g. financial penalties  for non-

591  compliance following AMR testing) is the optimal approach to ensure effective risk mitigation

592  measures are implemented requires further investigation. Without international harmonisation of

593  approaches any risk mitigation policies may remain ineffective (Kendall, et al., Submitted).

594

595  *4.1     Illegal use of antimicrobials*
596

597  Although more difficult to assess from the perspective of famer behaviour, and an issue representing

598  a difficult policy dilemma, the issue of illegal use needs to be addressed (Donoghue, 2003). There are

599  examples in the literature demonstrating that illegal antimicrobial administration is widespread.

600  For example, feed and fish from an aquaculture farm in eastern Sicily (Italy) were tested using

601  commercial ELISA kits. Levels of antimicrobials exceeding the method's detection capability were

602  found in all feed and tissue samples (Oliveri Conti, et al., 2015). In China, overuse and illegal use of

603  antimicrobials across the entire farming sector are well documented (Hu & Cheng, 2016; Zhong,

604  Huang, & Wu, 2017). Similar patterns of illegal use in animal production systems have been

605  identified, *inter alia*, in Vietnam (Kim, et al., 2013), Cameroon (Gondam Kamini, Tatfo Keutchatang,

606  Yangoua Mafo, Kansci, & Medoua Nama, 2016), and the US (Alvy, 2014).

607         There are reports that illegal antimicrobial use is also prevalent in specific sectors, either as a

608  preventative measure or a growth promoter. Prominent examples include within aquaculture

609  (Tuševljak, et al., 2013) and pig sectors (Došen, et al., 2014). Regulatory and industry action is

610  required to prevent illegal use: ignoring it may be viewed as supplying tacit approval (Morley, et al.,

611  2005). However, a major barrier to understanding the motivations for famers to use antimicrobials

612  illegally is obviously that their use is illegal, and farmers are unlikely to be honest about illegal use

613  and their motivations for doing so when interviewed by researchers. Monitoring illegal use may be

614 possible, but understanding why antimicrobials are being used, may represent a particularly difficult

615 research problem. Answering it will require the application of social science research methods which

616 guarantee the anonymity of participants, allow them to develop trust in researchers, and engage

617 with the problems of AMR bacteria.

618

619 *4.2     The importance of effective communication*
620
621 A recent report, published by the UK Food Standards Agency (Royal Veterinary College, 2016),

622 highlighted the need to adopt "clear transparent reporting standards that help consumers have

623 access to and understand information about the responsible use of antibiotics in the food chain".

624 Increased consumer recognition of problems associated with antimicrobial usage may increase

625 demand for products with certified and reduced antimicrobial use. Certain segments of the

626 population may be willing to pay more for such products. For example, it has been proposed that

627 labelling and marketing may demonstrate how policy makers can develop a verified antimicrobial-

628 free labelling program that would allow consumers to purchase meat products from animals that

629 had never received antimicrobials, although this would require considerable risk communication and

630 public education efforts to ensure that the general public  know the importance of the issue

631 (Centner, 2016). Although there is a substantial body of literature focused on understanding

632 consumer attitudes towards animal welfare and welfare indicators on products, the issue of

633 antimicrobial use in animal production systems has not been extensively researched, (Clark, Stewart,

634 Panzone, Kyriazakis, & Frewer, 2016) and, as a consequence, little is understood regarding the

635 extent to which consumers prioritise their reduction nor are willing to pay for products produced

636 from animals raised without the use of, or with reduced use of, antimicrobials. While there is

637 evidence that consumers express concerns about the use of antimicrobials in animal production

638 systems, for example in relation to farm animal welfare and food safety, concern about AMR has not

639 been reported, although this may reflect the construction of investigative methodologies (i.e. the

640    question was not asked) rather than lack of consumer and societal concern about the issue. For a

641    review please see (Clark, Stewart, Panzone, Kyriazakis, & Frewer, 2017).

642

## 5   Mitigation and intervention strategies

644    A number of alternatives/mitigation strategies have been proposed and these are summarised in

645    Table 4. A detailed consideration of many potential interventions is given by Baquero, et al. (2015),

646    and reviews of alternatives (Czaplewski, et al., 2016) and management options (Pruden, et al., 2013)

647    published.

648                                  …………………………………………
649                                  Table 4 about here
650                                  …………………………………………
651

652    One strategy that is often highlighted in the literature is the cessation of use of antimicrobials as

653    AGPs and allied to this a general reduction in their use whenever possible. However, there is

654    conflicting evidence as to whether such bans result in a general decrease in AMR bacteria. The

655    outcome may be determined by factors such as co-selection or a fitness cost to possession of the

656    resistance gene. In co-selection multiple resistance determinants may be present on the same

657    genetic structure such that if the selective pressure to one is removed then resistance may still be

658    maintained if one of the other selective pressures endures. In contrast, vancomycin-resistant

659    *Staphylococcus aureus* lacking *mecA* (methicillin resistance) was shown to out-compete an

660    homologous strain which possessed the gene (Noto, Fox, & Archer, 2008) so here the sensitive strain

661    should be selected for over the resistant one. Resistance to macrolides and glycopeptides did,

662    however, reduce in *Ent. faecium* consistently between 1997 and 2003 following a ban on their use as

663    growth promoters in 1995-1998 in Denmark (Hasman & Aarestrup, 2005).

664    To know whether mitigations are effective it is necessary to have in place robust surveillance

665    systems such that effects can be measured. Several national and international programmes releasing

666    data online are now in existence, for example The National Antimicrobial Resistance Monitoring

667  System (NARMS) in the US[7] and the European Antimicrobial Resistance Surveillance Network (EARS-

668  Net)[8]. However, currently such programmes may be disjointed, especially where they cross

669  jurisdictions (McNulty, Soon, Wallace, & Nastasijevic, 2016). Clearly policy needs to be founded on

670  reliable data, and so such data need to be compatible and use the same criteria (e.g. definition of

671  "resistant"). Similarly policy needs to be based on a sound understanding "of those practices that are

672  truly contributing to the antibiotic resistance problem (Singer & Williams-Nguyen, 2014).

673

674  ## 6  Economics of resistance

675

676      The selection pressures leading to resistance are heavily influenced by the behavioural

677  responses of individual actors who may not have an incentive to take into account the negative

678  impact on the future effectiveness of antimicrobials being used. The costs and benefits of

679  antimicrobial use and the magnitude of resistance can be estimated using economic approaches.

680  However, economic analysis can go much further than this in understanding the evolution of

681  resistance and developing policy responses.

682  The response to resistance occurs on two fronts:

683  1)  Need to manage existing portfolio on antimicrobials to maximise the value from their use

684  2)  Develop new products to replace those that resistance has made ineffective

685      These two strategies are linked, somewhat paradoxically, in that better use of existing products

686  reduces potential returns from developing new products.

687          The economics literature has considered antimicrobial effectiveness as a societal resource

688  and how use of this resource might be optimised. As an example, in agricultural economics there has

689  long been a consideration of the impacts of pesticide resistance. For example, Hueth and Regev

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7
https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/
[8] http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial_resistance/EARS-Net/Pages/EARS-Net.aspx

690    (1974), considered pest susceptibility to pesticides as a non-renewable resource that is privately

691    costless to use in the short run but very costly longer term to society when new products are

692    required. Treating susceptibility as an exhaustible resource and the temporal mismatch between the

693    costs and benefits of the product are central characteristics of the economic problem.

694        The use of products to control harmful biological organisms has two side-effects neither of

695    which is considered by users:

696    •    The effective use of the product by a farmer reduces the spread of the pest/disease elsewhere

697          producing a positive outcome for other farmers;

698    •    On the negative side, the use of the product engenders greater resistance in the future

699          Unless the perceived value of negative future impacts is greater than the value of disease

700    reduction, end users will deploy the product at a greater level than is best from a societal

701    perspective. The likelihood of a farmer using antimicrobials is a function of the perceived

702    consequences of non-use, the probability of these consequences occurring, how effective the

703    therapy is likely to be, and the cost (Lhermie, Gröhn, & Raboisson, 2016). In essence this suggests

704    that, in economic terms, the farmer will use antimicrobials when it is profitable to do so (although

705    see previous section on alternative drivers of farmer behaviour with respect to antimicrobial use).

706    Veterinarians may profit from the sales of antimicrobials and this driver for potential over use can be

707    negated by legislating for the reduction in such profits; in Denmark a 40% reduction in overall use

708    between 1994 and 1995 resulted from such an action (Dar, et al., 2016).

709

710    ## 7  Conclusions

711    The continued emergence of AMR bacteria will mean that infections which are currently treatable by

712    the use of antimicrobials may become untreatable in the future. It seems clear that the rise of AMR

713    is, in part, attributable to overuse of antimicrobials in the treatment of human diseases. However,

714    the link between the emergence of AMR bacteria in food production and transmission through the

715    food chain to potentially susceptible human hosts is less clear (Chang, et al., 2015) and described as

716 "a prominent and contentious issue" (Schmidt, et al., 2015). There is evidence, though, that the use

717 of antimicrobials in animal production does result in an increase in the presence of AMR bacteria in

718 food animals. The degree of subsequent transmission to humans is less clear.

719     The AMR situation is more complicated than is the case for tracking contamination pathways

720 of pathogenic bacteria in food production as account needs to be taken of the epidemiology of both

721 the organisms containing AMR genes and the genes themselves, as part of the complexity lies in the

722 ability of the genes to transfer between taxa. Commensal organisms in foods also have a role to play

723 in conveying resistance from food production to human infections. More data to demonstrate, or

724 otherwise, the flow of AMR bacteria/genes from food and/or the food production environment to

725 clinical cases, and to provide data to satisfy the many identified data gaps (Thanner, et al., 2016)

726 would provide much needed evidence to establish the size of the role of the agri-food chain in the

727 transmission of AMR to humans.

728     For food to transmit AMR bacteria the bacteria need to be present in the food in the first

729 place, and the food industry goes to great lengths to ensure that food is prepared in as hygienic

730 manner as possible, and free of bacterial pathogens. Some food is brought into the household raw

731 and could therefor harbour AMR bacteria. For example, red meats may be contaminated by

732 *Salmonella* or *E. coli* O157:H7. These foods are normally cooked prior to consumption, markedly

733 reducing the risk but not eliminating it, as cross contamination might occur prior to cooking. The

734 controls needed to prevent transmission of AMR bacteria via food are the same as those needed to

735 control foodborne pathogens and spoilage organisms *in toto* and involve all stakeholders along the

736 food chain, including everyone from the grower to the consumer. Data for the prevalence and

737 concentration of AMR bacteria on ready-to-eat foods are scarce and to assist with exposure

738 assessment the acquisition of such data should preferably focus on defined

739 bacterium/phenotype/genotype combinations. Prevalence data would be of more use of they were

740 expressed as the proportion of each food type containing the bacterium/gene in question instead of

741 as a proportion of the isolates obtained from a variety of foods as granularity is lost when this is

742  done (although the data are no doubt available from the authors of such studies). To gain the

743  maximum benefit data need to be collected in a consistent and comparable manner according to

744  agreed and registered protocols.

745      A recent review concluded that: 1) both the risks and benefits of the use of antimicrobials in

746  animals need to be considered, 2) currently available data are inadequate to enable (1) to be

747  considered properly and that,  3) relevant policy making is impaired because of this (Rushton, 2015).

748  There does seem to be a bias in that often only the risks of AGP use are considered and

749  comparatively little consideration of the benefits is given. A first step might be to assess the

750  economics of AGP use, as well as the benefits and risks perceived by farmers and veterinarioans,

751  including biological and socio-economic factors. If it is a cost then this will need to be countered by

752  benefits such as animal welfare and reduced zoonoses. Reduction in the use of AGPs would seem to

753  be of little use if the overall antimicrobial usage does not decrease in tandem, as seems to be the

754  case in the EU, or at least for some countries.

755      Generalisations in respect to control of AMR are very difficult to make as consistent patterns

756  are hard to discern since particular organism/resistance combinations do not necessarily behave the

757  same as one another and are driven by human behaviours which are poorly understood. This

758  compounds the complex web of routes by which humans might become exposed/infected/colonized

759  by AMR bacteria. Reducing the use of antimicrobials in animal production is unlikely to reduce MRSA

760  infections of humans, for example. For some organism/gene combinations withdrawal of

761  antimicrobials seems to be effective, and for others not.

762      It was not the intent of this review to examine data on the emergence of AMR veterinary

763  pathogens. However, it would be expected that if agricultural use of antimicrobials is causing AMR

764  bacteria to become a problem in human clinical cases then the same should apply to veterinary

765  pathogens.

766      The transmission of AMR genes is a large and complex area involving agriculture, medicine,

767  the environment, food and the interfaces of each with each other. Human behaviour, whether on

768    the part of farmers, veterinarians, other stakeholders, or consumer demand, represents an

769    important driver of agricultural antimicrobial use and emergence of resistance. This complex picture,

770    alongside the increasing recognition that there is a significant risk to human health, has meant that

771    the volume of publications in this area has increased greatly. For example a search in Google Scholar

772    for all of the words "antimicrobial resistance beef" anywhere in the article over the last 20 years

773    returned publication numbers shown in Figure 2. Clearly it is not possible for a review to cover this

774    volume of material and this in itself presents a problem with respect to understanding the

775    complexities of the issue.

776                                    …………………………………
777                                    Figure 2 about here
778                                    …………………………………..
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780

781            The large volume of literature and need for an interdisciplinary systems approach pose

782    challenges for evidence synthesis which might be better met with structured model development

783    than traditional systematic review and meta-analysis (Stewart, Meader, & Mengersen, 2014).

784    Another potential approaches might include computer-based ways such as text mining. Text mining

785    is useful when the volume of data available is so extensive that effective and efficient critical

786    evaluation/review is impractical and/or very time consuming on a manual basis. Furthermore, text

787    mining can provide the facility to add new knowledge and understanding quickly. An alternative to

788    text mining would be the establishment of an AMR data repository with *de facto* pre-registration

789    and use of common agreed outcome measurement, reporting and meta-language. This would

790    address problems relating to selective reporting and publication bias in addition to facilitating access

791    but would require increased investment in comparison to text mining.

792

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Table 4. Some examples of potential alternatives/interventions to negate AMR bacteria.

| Alternative/intervention | Effect | Examples | References |
|---|---|---|---|
| Antibacterial peptides | Alternative to antibiotics | Structurally nanoengineered antimicrobial peptide polymers to treat Gram negative infections | (Lam, et al., 2016) |
| Antibodies | Bind to and inactivate pathogens | Avian Antibodies (IgY) | (Kollberg, 2015) |
| Bacteriophages | Antimicrobial replacement | Treatment of AMR *Pseudomonas* otitis | (Wright, Hawkins, Änggård, & Harper, 2009) |
| Competitive exclusion | A benign bacterium is able to outcompete a pathogen | Control of *E. coli* infections in weaned pigs | (Harvey, Anderson, Genovese, Callaway, & Nisbet, 2005) |
| Decontamination of waste/irrigation water | Breaking the cycle of environmental transmission | AMR bacteria have been detected in tap water and grew in the distribution system | (Xi, et al., 2009) |

| Diagnostics | Provide rapid information to aid decision making in antimicrobial prescription | C-reactive protein testing to inform prescribing in lower respiratory tract infections | (Cals, Schot, de Jong, Dinant, & Hopstaken, 2010) |
| --- | --- | --- | --- |
| Incentives for stakeholders (farmers/veterinarians) | Subsidies for appropriate AMR use; fines for inappropriate use; standards for traded foods; increased surveillance; retailer pressure | McDonald's goal set in 2015 to "only serve chicken not treated with antibiotics important in human medicine" | http://news.mcdonalds.com/us/news-stories/2016/mcdonald-s-usa-announces-big-changes-to-its-food |
| Infection prevention and control interventions | Minimise the spread of pathogens regardless of antimicrobial susceptibility | "all-in-all-out" animal rearing systems | (Schuppers, et al., 2005) |
| Phage endolysins | Antimicrobial replacement | Various clinical applications to replace use of antibiotics and, for example, killing MRSA. For treatment of Gram positive infections. | (Schmelcher, Donovan, & Loessner, 2012) |

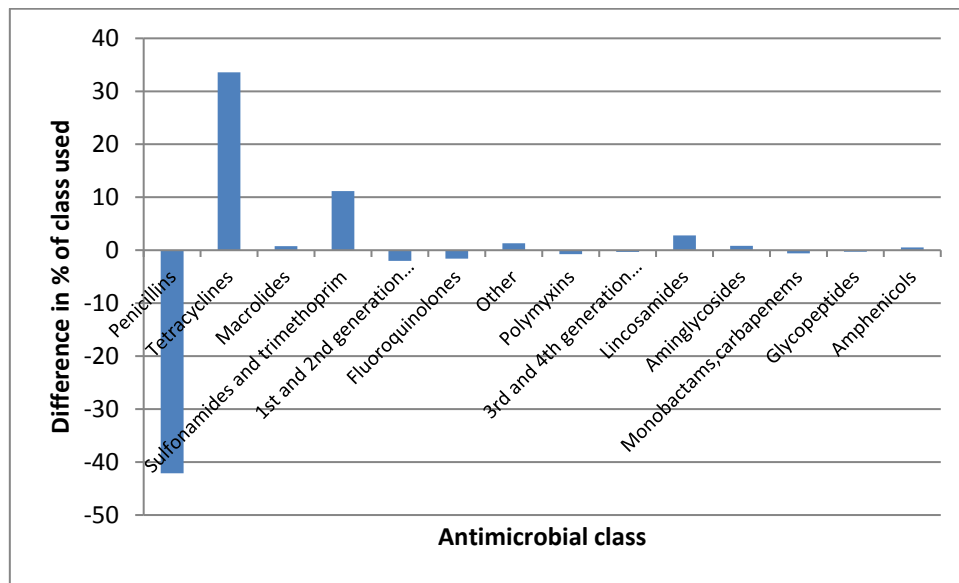| Probiotics/prebiotics/syn biotics | Improve animal health | Treatment of Clostridium difficile infections | (Lau & Chamberlain, 2016) |
|---|---|---|---|
| Risk/benefit communication for consumers | Consumers drive demand for foods produced with reduced use of antimicrobials | Introduction of front of pack labelling, public education programmes | (Centner, 2016) |
| Use of alternative food animals | Hardier species need reduced applications of antibiotics to remain healthy | Replacement of the black tiger shrimp with the white leg shrimp in Asian shrimp farms | (Rico, et al., 2013) |
| Strategic use of antimicrobials | Using antimicrobials in a controlled to stop emergence of AMR bacteria | Prevent animal use of an antimicrobial while clinical resistance is rare | (Smith, Harris, Johnson, Silbergeld, & Morris, 2002) |
| Vaccination | Prevents disease occurring and hence mitigates the need to use antibiotics | Norwegian salmon industry | (Burridge, Weis, Cabello, Pizarro, & Bostick, 2010) |

Figure 1. Example of the growth in AMR-related publications over the last two decades. The search was for all of the words "antimicrobial risk beef" anywhere in the record.
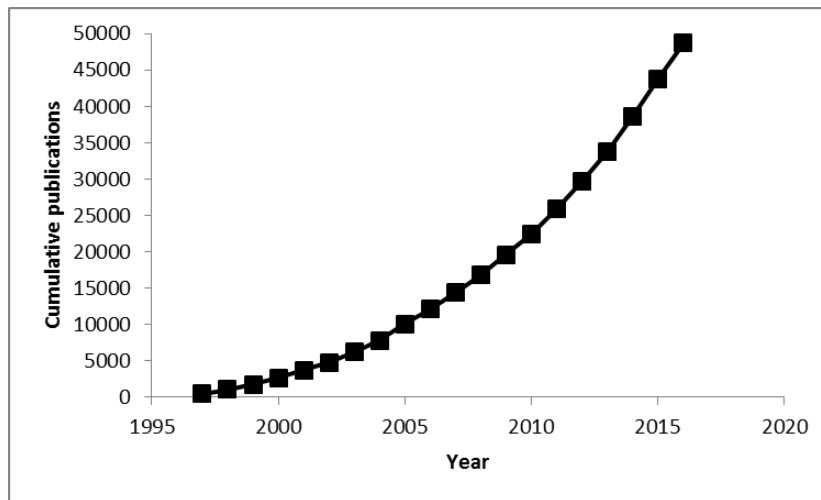
Figure 2. Comparison of the proportion of antibiotics prescribed for human use and sold for

veterinary use. A positive number indicates a greater proportion sold for veterinary purposes.

# Table 1. A taxonomy of antimicrobial families

| Major Group | Sub groups | Site of action | Examples |
|---|---|---|---|
| β-lactams | Penicillins | Cell wall synthesis | ampicillin, methicillin, penicillin G, amoxicillin |
|  | Cephalosporins |  | 1st generation: cefalothin, cefalonium |
|  |  |  | 2nd generation: cefuroxime |
|  |  |  | 3rd generation: cefotaxime, ceftriaxone, ceftiofur, ceftazidime |
|  |  |  | 4th generation: cefquinome |
|  | Monobactams |  | aztreonam |
|  | Carbapenems |  | ertapenem, imipenem, meropenem |
| Aminoglycosides |  | Protein synthesis | kanamycin, streptomycin, tobramycin, gentamicin, neomycin, amikacin, |
| Sulphonamides |  | Folic acid synthesis | sulphonamide, sulfamethoxazole, sulfamethazine, sulfamerazine, sulfadimethoxine |
| Quinolones/Fluoroquinolones |  | DNA synthesis | enrofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin , nalidixic acid, flumequine, pefloxacin |
| Macrolides |  | Protein synthesis | azithromycin, clarithromycin, dirithromycin, erythromycin, azithromycin, clindamycin, tylosin, spiramycin, carbomycin, oleandomycin, kitsamycin, tiamulin |
| Polypeptides |  | Cell membranes | colistin, polymixin B, bacitracin |
| Other: |  |  |  |
| Glycopeptides |  | Cell wall synthesis (Gram +ve) | avoparcin, vancomycin, teicoplanin, ardacin |
| Rifampin/Rifampicin |  | RNA synthesis |  |
| Linezolid |  | Protein synthesis (Gram +ve) |  |
| **Tetracyclines** |  | Protein synthesis | Tetracycline, doxycycline, oxytetracycline, chlortetracycline |
| Trimethoprim/ sulfamethoxacole |  | Folate synthesis |  |
| Coccidiostats |  | Ionophore | Lasolacid, monensin, salinomycin, narasin. Not used in human medicine. |
| Streptograminins |  | Protein synthesis | virginiamycin, quinupristin, dalfopristin (last two combined=synercid) |

TABLE 2. Examples of the Prevalence of AMR Isolates in Raw Foods

| Organism | Food, country | Criteria | Number (%) of samples containing AMR bacteria and phenotype tested | Reference |
|---|---|---|---|---|
| *Campylobacter* | Beef, Poland | EUCAST | 0 (0) N = 153 panel | (Wieczorek, Szewczyk, & Osek, 2012) |
| | Pork, Poland | | 0 (0) N = 85 panel | |
| *Escherichia coli* | Beef, UK | http://eurl-ar.eu/233-protocols.htm | 2 (0.6) N=312 ESBL, AMPC | (Animal and Plant Health Agency, 2016) |
| | Pork, UK | | 6 (2) N=312 ESBL, AMPC | |
| | Chicken, Thailand | Not related to external standards | 4 (29) N=14 ESBL | (Boonyasiri, et al., 2014) |
| | Meat, Thailand | | 8 (31)N=26 ESBL | |
| | Seafood, Thailand | | 0 (0) N = 9 ESBL | |
| | Chicken, UK domestic | Not related to external standards | 1 (2) N =62 CTX M ESBL enzymes | (Warren, et al., 2008) |
| | Chicken, Imported into the UK | Not related to external standards | 10 (37) N = 27 CTX M ESBL enzymes | |
| | Retail poultry meat in wet markets, Malaysia | CLSI | 86 (54) N = 160 ESBL | (Aliyu, et al., 2016) |
| | Minced meat, Austria | EUCAST | 20 (20) N = 100 ESBL | (Petternel, et al., 2014) |
| | Retail chicken, Netherlands | Not related to external standards | 92 (94) N = 98 ESBL | (Leverstein-van Hall, et al., 2011) |
| *Enterobacteriaceae* | Minced pork, Italy | CLSI | 3 (0.5-1.5)[1] N=200 AMPC | (Sabia, et al., 2017) |
| | | | 0 (0) N =200 ESBL | |
| *Enterococcus faecium* | Conventional retail poultry, USA | NCCLS | 43 (56) N = 77 quinupristin-dalfopristin R | (Kieke, et al., 2006) |
| | Antibiotic-free poultry, USA | | 3 (13) N =23 | |
| *Klebsiella* spp. | Chicken, Thailand | Not related to external standards | 2 (22) N=9 ESBL | (Boonyasiri, et al., 2014) |
| | Meat, Thailand | | 8 (31) N=26 ESBL | |
| | Seafood, Thailand | | 4 (20) N=20 ESBL | |
| | Vegetables, Thailand | | 4 (15) N=15 ESBL | |
| Methicillin-resistant *Staphylococcus aureus* | Minced meat, Austria | EUCAST | 9 (9) N = 100 | (Petternel, et al., 2014) |
| | Beef products, USA | CLSI | 4 (4) N = 100 *mec*A | (Jackson, et al., 2013) |
| | Pork products, USA | CLSI | 3 (3) N = 100 *mec*A | |
| | Beef, Netherlands | Not related to external standards | 42 (10.6) N = 395 | (de Boer, et al., 2009) |
| | Veal, Netherlands | | 39 (15.2) N = 257 | |
| | Lamb/mutton, Netherlands | | 20 (6.2) N = 324 | |
| | Pork, Netherlands | | 33 (10.7) N = 309 | |

| | | | | |
|---|---|---|---|---|
| | Chicken, Netherlands | | 83 (16.0) N = 520 | |
| | Turkey, Netherlands | | 41 (35.3) N = 116 | |
| | Fowl, Netherlands | | 4 (3) N = 118 | |
| | Game, Netherlands | | 4 (2) N = 178 | |
| | Beef, USA | CLSI | 0 (0) N = 29 | (Hanson, et al., 2011) |
| | Turkey, USA | | 0 (0) N = 36 | |
| | Pork, USA | | 2 (4) N = 55 | |
| | Chicken, USA | | 0 (0) N = 45 | |
| | Beef, USA | CLSI | 1 (3) N = 38 | (Waters, et al., 2011) |
| | Turkey, USA | | 1 (4) N = 26 | |
| | Pork, USA | | 1 (4) N = 26 | |
| | Chicken, USA | | 0 (0) N = 46 | |
| | Pork, USA | CLSI | 5 (6) N = 90 | (Pu, Han, & Ge, 2009) |
| | Beef, USA | | 1 (3) N = 30 | |
| | Pork, Netherlands | CLSI | 2 (3) N = 64 | (van Loo, et al., 2007) |
| | Beef, Netherlands | | 0 (0) N = 15 | |
| | Beef, USA | CLSI | 2 (1) N = 156 | (Bhargava, et al., 2011) |
| | Chicken, USA | | 3 (4) N = 76 | |
| | Turkey, USA | | 1 (2) N = 57 | |
| | Chicken, UK | EUCAST | 4 (8) N = 50 | (Fox, et al., 2017) |
| | Pork, UK | | 3 (5) N = 63 | |
| | Turkey, UK | | 2 (18) N = 11 | |
| *Salmonella* | Beef, Ireland | Not related to external standards | 0 (0) N=22 | (Duffy, et al., 1999) |
| | Lamb, Ireland | Not related to external standards | 0 (0) N =10 | |
| | Minced beef, USA | NCCLS | 1 (2) N = 50 | (White , et al., 2001) |
| | Live freshwater finfish, China | CLSI | 5 (5) N =100. All 5 resistant to erythromycin and penicillin | (Broughton & Walker, 2009) |
| Vancomycin-resistant enterococci | Minced meat, Austria | EUCAST | 0 (0) N =100 | (Petternel, et al., 2014) |
| | Chicken, Turkey | NCCLS | 2 (8) N = 25 | (Koluman, Akan, & Çakiroğlu, 2009) |
| | Beef, Turkey | | 0 (0) N = 25 | |
| | Spices, Turky | | 0 (0) N = 30 | |
| | Seafood, Spain | NCCLS | 0 (0) N = 24 | (Valenzuela, Benomar, Abriouel, Cañamero, & Gálvez, 2010) |
| | Beef, Denmark (*E. faecium*) | Not related to external standards | 0 (0) N = 128[2] | (Wegener, Madsen, Nielsen, & Aarestrup, 1997) |

[1] Between 0.5 and 1.5% of the samples were positive

[2] Enrichment was not used

ESBL = extended spectrum β-lactamase producers

AMPC = Class C β-lactamase producing

N = number sampled tested

NCCLS = National Committee for Clinical Laboratory Standards

EUCAST = European Committee on Antimicrobial Susceptibility Testing

CLSI = Clinical and Laboratory Standards Institute

*mec*A = gene indication MRSA

TABLE 3. Examples of the Prevalence of AMR Isolates in RTE Foods

| Organism | Food, country | Criteria | Results (% of isolates resistant) and phenotype | Reference |
|---|---|---|---|---|
| *Escherichia coli* | Lettuce leaves, Belgium | CLSI | 58 (22) N= 264 Antibiotic panel | (Holvoet, Sampers, Callens, Dewulf, & Uyttendaele, 2013) |
| | Market foods, Thailand | Not related to external standards | 2 (6.7) N= 30 ESBL | (Boonyasiri, et al., 2014) |
| | Street vended hamburgers, Portugal | CLSI/EUCAST | 2 (20) N = 10; 1 R to tetracycline, 1 R to amoxicillin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline | (Campos, Gil, Mourão, Peixe, & Antunes, 2015) |
| | Street vended hot dogs, Portugal | | 2 (20) N = 10; 1 R to nalidixic acid, 1 R to amoxicillin, chloramphenicol, ciprofloxacin, streptomycin, kanamycin, nalidixic acid, tetracycline, trimethoprim | |
| *Listeria* spp. | Retail foods, Turkey | Not related to external standards | 13 (13) N = 100. All S to chloramphenicol, trimethoprim, tetracycline and tobramycin; all R to rifampicin | (Şireli & Gücükoğlu, 2008) |
| | Vegetable products, Brazil | CLSI | 2 (2) N = 132. R to Penicillin G and tetracycline. S to cefoxitin, ciprofloxacin, erythromycin, streptomycin, oxacillin, vancomycin | (de Vasconcelos Byrne, Hofer, Vallim, & de Castro Almeida, 2016) |
| | Dairy products | CLSI | 0 (0) N = 65 | (Chen, Wu, Zhang, Yan, & Wang, 2014) |
| | Cold noodles in sauce | | 0 (0) N = 24 | |
| | Cooked beef | | 0 (0) N = 3 | |
| | Miscellaneous ready-to eat foods | | N/A (1) N = 131 | |
| *Salmonella* | Retail turkey products, USA | NARMS/FDA | 6 (1) N =614 R ≥ 2 antibiotics | (Khaitsa, Kegode, & Doetkott, 2007) |
| Vancomycin resistant enterococci | Cheese (different types), Turkey | NCCLS | 0 (0) N =50 | (Koluman, et al., 2009) |
| | Yoghurt | | 0 (0) N =20 | |
| | RTE cooked foods | | 0 (0) N = 50 | |

N = number sampled tested R resistant S susceptible

NCCLS = National Committee for Clinical Laboratory Standards

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| Diagnostics | Provide rapid information to aid decision making in antimicrobial prescription | C-reactive protein testing to inform prescribing in lower respiratory tract infections | (Cals, Schot, de Jong, Dinant, & Hopstaken, 2010) |
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| Infection prevention and control interventions | Minimise the spread of pathogens regardless of antimicrobial susceptibility | "all-in-all-out" animal rearing systems | (Schuppers, et al., 2005) |
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