

Emerging policies on antimicrobial resistance, the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food producing animals

Catherine C. Adley*, Aideen Dowling, Harald Handschuh and Michael P. Ryan

Microbiology Laboratory, Department of Chemical and Environmental Sciences, University of Limerick, Limerick, Ireland

* Corresponding author: email: catherine.adley@ul.ie; Tel: +353 61 202646; Fax: +353 61 202568

Emerging antimicrobial resistance is one of the barriers in controlling pathogenic bacteria. In attempting to understand the emergence of antimicrobial resistance, European Member States are obliged to monitor and report antimicrobial resistance in zoonotic *Salmonella* spp., and *Campylobacter* spp., isolates from food-producing animals since 2003. Reporting on actual consumption of antimicrobial agents has been underway since 2010, together with monitoring and reporting of sales of veterinary antimicrobial agents since 2009, by some countries and encompassing most of the EU/EEA in later years. The first integrated report by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) suggesting possible relationships between the consumption of antimicrobial agents and the occurrence of antimicrobial resistance was published in 2015. The scope of the report was limited to a comparison of consumption of antimicrobials in food-producing animals including *Campylobacter* spp., *Salmonella* spp., and *Escherichia coli* as an indicator pathogen. The antimicrobials tested for emerging resistance due to consumption were the fluoroquinolones, 3rd and 4th generation cephalosporins and the tetracyclines. Monitoring has been from, healthy animals and food for *Campylobacter* spp., while for *Salmonella* spp., monitoring has been on the prevalence of the bacteria. Macrolides against *Campylobacter* spp., only were also monitored. The data provides a baseline for emerging antimicrobial resistance knowledge and when and if control measures are working.

Keywords: antimicrobial consumption; food borne bacteria; antimicrobial resistance

1. Introduction

The use (particularly the misuse) of antimicrobials in human and animal medicine has been highly associated with the spread of antimicrobial resistance in human and animals [1]. However, there is some evidence that exposure to antimicrobials has not been limited to the modern ‘antimicrobial era’. Evidence has been reported in the form of traces of tetracycline found in human skeletal remains from ancient Sudanese (Kush) Nubia dating back to 350–550 CE and in samples taken from the femoral mid-shafts of the late Roman period skeletons, from the Dakhleh Oasis in Egypt [2].

Multiple reports spanning the past 40 years, consistently highlighted the issue of increasing antimicrobial resistance since the Swann Report in 1969 [3] and the SMAC report of 1998 [4] in the UK. The rapid spread of antimicrobial resistance has led to various control measures especially in the agricultural use of antimicrobials. A timeline of these measures is outlined below. The relationship between antimicrobial consumption and growth in resistance levels for certain bacterial species (*Campylobacter* spp., *Salmonella* spp., and *Escherichia coli*) is also discussed.

1.1 Timeline on antimicrobial control measures in Europe

The European Union (EU) took up the mantle and a strong approach was taken and some landmark regulations have been enforced on the use of antimicrobial agents on European farms. Sweden banned antimicrobials in animal feed, following a 1984 report, which showed that consumer confidence in meat safety dropped after it emerged that 30 tons per year of antimicrobials were being used in Sweden in food animal production [5]. In the early 1990s, vancomycin-resistant *Enterococcus* (VRE) was first found in patients in Europe [6], resulting in an EU wide ban on the use of avoparcin in agriculture in 1997 (Directive 97/6/EC amending Directive 70/524 [7]). In 1999, the Steering Committee of the European Commission (EC) recommended phasing out the use of medically important antimicrobials as growth promoters and implementing disease prevention methods [8]. Since 2006, all veterinary use of antimicrobials requires a prescription (POM status, prescription-only medicines), and that all licensed veterinary antimicrobial products are prescription only drugs [9].

A communication from the EC in 2011, outlined a plan to address the growing issue of antimicrobial resistance and finalised in 2014 [10]. Some countries have been more active including developing their own country-specific reports from committees that look at both antimicrobial use information and susceptibility levels e.g. Denmark [11], the Netherlands [12], Germany [13], Sweden [14], and Norway [15]. The British Prime Minister commissioned a ‘Review on Antimicrobial Resistance’, under the auspices of the Wellcome Trust and the British Government [16], to raise awareness of antimicrobial misuse. The EU began to host an Antimicrobial Awareness Day on 18th November every year (starting in 1998), across Europe.

1.2 Timeline on antimicrobial control measures in the US

In the United States, new animal antimicrobial labelling was adopted when the Food and Drug Association (FDA) prohibited the extra-label use of fluoroquinolones and glycopeptides in food-producing animals in 1997 [17] another class of antimicrobials (cephalosporins) was added to this list in April of 2012 [18].

In 2003 an entirely new approach was undertaken to address the microbial safety of new antimicrobial drugs in the form of Guidance for Industry (GFI) 152 [19]. This procedure outlined a risk assessment based approach for evaluating the microbial food safety of antimicrobial animal drugs. In 2003, the National Antimicrobial Resistance Monitoring System – Enteric Bacteria (NARMS) was set up, coordinated by the Centre for Disease Control (CDC) in partnership with the FDA and US Department of Agriculture (USDA), together with health departments at both state and local level [20]. This new monitoring system exposed some general trends in antimicrobial resistance, including a rise in resistance levels for beta-lactam antimicrobials amongst *Enterobacteriaceae*. Conversely, resistance to several other classes of antimicrobial, including critically important classes such as fluoroquinolones exhibited very low levels of resistance in salmonella, suggesting that the new policy measures were having an effect. Doyle et al [21] and Barclay [22] provide a comprehensive summary of the US activities on antimicrobial use and monitoring policies. The CDC-US issued a substantial report on antimicrobial resistance threats in 2013 [23].

1.3 Global approaches to tackling emerging antimicrobial resistance

A host of intergovernmental agencies worldwide have taken an interest in the emerging antimicrobial resistance threat, such as the World Health Organisation (WHO), whose activities in this area started in 1971, with a collaborative study on antimicrobial sensitivity testing methodologies [24]. National bodies have their own antimicrobial susceptibility testing systems in operation [25], with harmonised methods only now beginning to develop across Europe e.g. with EUCAST [26].

In 1981, the WHO established a scientific working group on antimicrobial resistance [27]. Workshops on global strategy approaches occurred in 2001 and 2002 [28, 29] with options for action, incorporating five domains, based on the 2001 global strategy recommendations [30]. This eventually led to the six-point policy package that was presented on World Health Day, April 2011 [31], under the theme "Combat Drug Resistance". WHO called for urgent and concerted action by governments, health professionals, industry, civil society and patients to slow down the spread of drug resistance, to limit the impact of drug resistance today and preserve medical advances for future generations [31]. The WHO six point policy package included: Monitoring of antimicrobial resistance and use; the rational use and regulation of antimicrobials; Antimicrobial use in animal husbandry; Infection prevention and control; the nurturing of innovation and political commitment [32].

The World Health Assembly (WHA) Resolution of 1998 [33], pressed Member States to develop procedures to encourage the suitable and cost effective use of antimicrobials. At the 67th World Health Assembly, in May 2014, Member States approved a resolution, WHA67.25, requesting the WHO to draft a global plan of action on antimicrobial resistance. At the 68th World Health Assembly in March 2015, this global plan was formulated [34].

The building blocks that are considered prerequisites to combat antimicrobial resistance include:

- Comprehensive plans at national level,
- Laboratory capacity to undertake surveillance for resistant microorganisms,
- Access to safe, effective antimicrobial medicines,
- Control of the misuse of these medicines,
- Awareness and understanding among the general public and effective infection prevention and control programmes [35].

The Codex Alimentarius Commission (CAC) is recognized by the World Trade Organization, as an international reference body for the resolution of disputes that concern both food safety and consumer protection. As of 2012, there were 186 members of the CAC: 185 member countries and one member organization, the European Union (EU). The CAC has published many reports on use of veterinary drugs [36, 37] and on minimizing and containing antimicrobial resistance [38]. A task force on antimicrobial resistance was set up in 2007 which formulated strategies for undertaking risk analysis for food borne antimicrobial resistance [39].

The OIE (Office International des Epizooties), now known, as the World Organization for Animal Health, was established in 1920, due to an infection of rinderpest which occurred suddenly in Belgium as a consequence of infected zebra that originated in India and intended for Brazil, transiting via the port of Antwerp [40]. The OIE reports on infection worldwide, so that countries can take precautionary preventative measures. Information is also provided by OIE on diseases transmissible to humans and international introduction of pathogens. The OIE also has a role in highlighting antimicrobial resistance and set up committees in 2003 to consolidate and update its publication on *Terrestrial Animal Health Codes* [41] and proposed a list of critically important antimicrobials for veterinary use in 2007 [42]. The OIE organised the first Global Conference “*On the Responsible and Prudent use of Antimicrobial Agents for Animals*”, in Paris in March 2013, where all the national, regional and global experts and stakeholders in the

field of pharmacology, epidemiology, animal and human, discussed the situation on antimicrobial use worldwide and antimicrobial resistance, all the presentations are available on the OIE website [43]. Suggested alternatives to antimicrobials at the conference included; metals; host antimicrobial peptides (recombinant); essential oils; bacteriophage; immunomodulants etc. An OIE report published in 2014, outlined standards, recommendations and work to date of the OIE on antimicrobial resistance [44]. The OIE recommends permanent risk assessment is carried out in parallel with the use of antimicrobials which will ensure the health and welfare of animals [45].

The World Economic Forum has identified antimicrobial resistance as a global risk [46]. The growing global threat of antimicrobial resistance was recognised by US President Obama, the Swedish Prime Minister and then-European Council President Reinfeldt and European Commission President Barroso at the 2009 US–EU summit. The summit declaration called for the establishment of - “*a transatlantic taskforce on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us*”. The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was constituted, based on this declaration [47].

However, multiple factors can influence antimicrobial decision-making in different jurisdictions around the world; there are many different ethical, social and cultural bases for the use of these products in farming [48]. It is commonly accepted that greater levels of antimicrobial usage leads to greater selective pressure that favours resistance, and consequently, lower usage levels favour susceptible bacteria [49]. Antimicrobial resistance is a complex global issue which cannot be solved by any one country acting in isolation. A target for the G20 summit in Hangzhou, China in November 2011 is to reunite the world in the fight against antimicrobial resistance [50].

1.4 Monitoring of the spread of antimicrobial resistance

Monitoring programmes on the incidence and progress of antimicrobial resistance and consumption of antimicrobial agents are extremely desirable. The EU set out 12 key actions (Road Map) for a successful fight against antimicrobial resistance in its action plan against the rising threats from antimicrobial resistance. Actions 9 and 10 are requests to “*Strengthen surveillance systems on AMR [antimicrobial resistance] and antimicrobial consumption in human medicine (action no 9) and in animal medicine (action no 10)*” [51].

European and international professional bodies have developed several strategies, recommendations and treatment guidelines on responsible use of antimicrobials, these include EPRUMA (European Platform for the Responsible Use of Medicines in Animals) [52], FVE (Federation of Veterinarians of Europe) [53] and HMA (Heads of Medicine Agencies) [54]. National antimicrobial resistance programmes have also been established in the EU Member States.

The bacterial species monitored and the antimicrobial agents tested, as well as the methodology used differ between agencies making comparison difficult. For instance, some agencies report clinical breakpoints, whereas others report antimicrobial susceptibility by means of epidemiological cut-off values for most of the antimicrobials tested. Additionally some of the agencies may have included reports on consumption of antimicrobials, but as for resistance the level of detail differs. Hence for example, in the Danish reports, data can be obtained down to the individual herd level and are reported by drug class and animal species each year. In the majority of other countries e.g. Ireland, only total consumption for all animal species can be obtained.

However, the data still provides useful information regarding trends that may occur over time and the potential differences between countries. Data that contains further information on animal population, along with antimicrobial agents and a relationship between resistance and consumption of the antimicrobials can be established [55]. The European Medicines Agency (EMA) estimates the amount of antimicrobial products consumed in treatment and growth promotion in food animals. These reports allow for studies to examine the feasibility of associations between the presence of resistant organisms and the consumption of antimicrobials. EU countries are obliged, but to date it is based on voluntary reporting, to submit data on antimicrobial resistance in humans based on the EU Directive No 1082 [56].

2. Monitoring Consumption of Antimicrobials in the EU

Monitoring the use of antimicrobials and the level of antimicrobial resistance has been underway in Europe since 2003, and of consumption of antimicrobials since 2010, by the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) and published by the European Centre for Disease Control (ECDC). The reports are based on antimicrobial consumption data from the community (primary care sector) and the hospital sector. The report for 2010 was from data from 24 EU Member States and two European Economic Area (EEA) non-EU countries, Iceland and Norway [57]. Two further reports for 2011 [58] and for 2012 [59], from the 28 EU Member States and again the two EEA countries are available.

Much of the concern about inappropriate antimicrobial prescribing and the possible emergence of antimicrobial resistance in animals is focused on the potential transfer of resistance via the food chain. Antimicrobials may only be supplied for use in animals under veterinary prescription in accordance with European Commission directive 2001/82/EC [60]. The major aims of these strategies and legislative regulations are to encourage veterinarians to

prescribe prudently and responsibly and furthermore to reduce antimicrobial use. Decisions made by veterinarians in treating animals reflect an ethical requirement to improve and maintain animal health. There are multiple situations for limiting antimicrobial usage under a variety of voluntary, regulatory and legal policy frameworks going back to the first feed additive directive 70/524 in 1970 [61] that was amended in 1997 [62].

2.1 Consumption of antimicrobials in humans and food-producing animals in the EU in 2012

An in-depth analysis and summary by the ECDC, the European Food Safety Authority (EFSA) and the EMA was compiled for 2012 and published in January 2015 [63]. This, the first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals, suggested that there is a possibility of a connection between the consumption of antimicrobial agents and the incidence of antimicrobial resistance in humans and food-producing animals. The countries providing information included, the 28 Member States (MS). The EU Member States include: Austria; Belgium; Bulgaria; Croatia; Cyprus; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Luxembourg; Malta; Netherlands; Poland; Portugal; Romania; Slovakia; Slovenia; Spain; Sweden; United Kingdom. In addition data from Iceland, Norway and in some cases Switzerland was obtained. The scope of this study was restricted to a comparison of antimicrobial consumption in both food-producing animals and humans and to the analysis of the occurrence of antimicrobial resistance to certain types of antimicrobial in selected bacterial species. Examples are outlined in Table 1. An in-depth analysis was also carried out on the association between consumption of carbapenems in human medicine and carbapenems resistance in bacteria isolated from humans.

Table 1 Antimicrobials consumed and bacteria tested for antimicrobial resistance in the EU analysis.

Species tested	Antimicrobial tested
<i>Campylobacter</i> spp.	Fluoroquinolones
<i>Salmonella</i> spp.	3 rd - and 4 th -generation cephalosporins
<i>Escherichia coli</i> (indicator /pathogen)	Tetracycline
	Macrolides (<i>Campylobacter</i> spp., only)

The information for the report was obtained from laboratories which submitted data to the following networks: ECDC; European Antimicrobial Resistance Surveillance Network (EARS-Net); The European Surveillance Antimicrobial Consumption Network (ESAC-Net) and the Food and Waterborne Diseases and Zoonosis Network (FWD-Net).

The ECDC submitted the final report for approval to agencies who supplied the data and to the EFSA's Scientific Network for Zoonosis Monitoring Data and its BIOHAZ Panel. To the European Surveillance of Veterinary Antimicrobial Consumption network (ESVAC) and to the Committee for Medicinal Products for Veterinary Use (CVMP). An outline of the results presented in this report follows.

2.2 Comparison of biomass corrected consumption of antimicrobials in humans and food-producing animals in the EU in 2012

In 2012, 3400 tonnes of antimicrobials were sold for human use and 7982 tonnes of antimicrobials were sold for food producing animals in the 26 EU/EEC, where data was available. The use of antimicrobials in humans is reported by ESAC-Net by use of the indicator DDD (defined daily dose) per 1000 inhabitants and per day. Veterinary monitoring is reported by ESVAC as milligrams per PCU (population correction unit) (mg/PCU). Data from ESAC-Net was converted into milligrams per kilogram estimated antimicrobials consumed (Figure 1). Results to note include: Estimated biomass was on average 116.4 mg/kg in humans (range 56.7 in the Netherlands – 175.8 France mg/kg); estimated biomass was 144 mg/kg in animals (range 3.8 in Norway - 396.5 mg/kg in Cyprus); consumption was lower in animals (<56 mg/kg), than humans in 12 of the 26 countries. (The Netherlands was lowest at 56.7 mg/kg); in eight countries there was a higher consumption in animals than in humans.

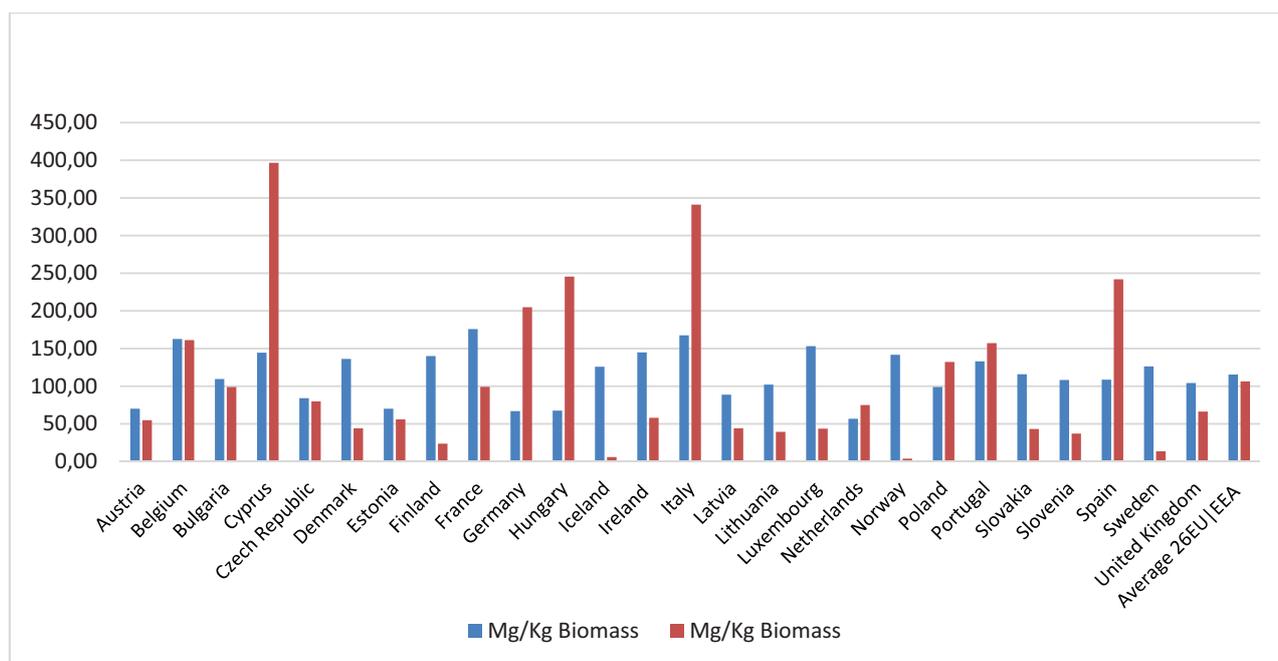


Fig. 1 Comparison of biomass corrected consumption of antimicrobials in Humans (blue) and Food-Producing Animals (red) by Country in 26 EU\EEA in 2012. Data sourced from ref 63.

The crude comparison of consumption of selected antimicrobials in humans and animals has limitations in its determination and must be interpreted with caution. It was shown that antimicrobials of the penicillin, macrolide and fluoroquinolones class were the main selling antimicrobial classes in human medicine, with tetracycline, penicillin and sulphonamide classes the highest selling for food-producing animals. In determining a method for presentation of the data obtained from the EU countries, the data was analysed using logistic regression, to predict if select organisms developed resistance correlated to consumption of antimicrobials by country.

The 3rd and 4th-generation cephalosporins are regarded by WHO [64] as Critically Important Antimicrobials (CIA) and were analysed for the report. Over 70% of the consumption of the 3rd and 4th-generation cephalosporins was reported for hospital/human use (range 30-98%). The average consumption (population-weighted mean) for humans was 3.50 mg/kg (range 0.02–12.52 mg/kg) and for food-producing animals 0.24 mg/kg (range < 0.01–0.68 mg/kg) estimated biomass. No significant correlation could be found within countries between the use of 3rd - and 4th-generation cephalosporins for humans and for food-producing animals (Spearman's rank correlation, rho = 0.32).

Fluoroquinolones are also CIAs of highest priority and are mostly used in the community. The population-weighted mean consumption of fluoroquinolones (mg) per estimated biomass (kg) in humans was 7.04 mg/kg and in food-producing animals was 2.47 mg/kg estimated biomass. The corresponding ranges were 2.24–16.03 (human) and 0.01–10.98 mg/kg (food-producing animals). A weak correlation was found within countries between consumption of fluoroquinolones in humans and food-producing animals (Spearman's rank correlation, rho = 0.63).

2.3 Comparison of consumption of selected antimicrobial classes in food-producing animals and resistance of bacteria in food-producing animals in 26 EU\EEA in 2012

Analysis was carried out on consumption of tetracycline, 3rd and 4th-generation cephalosporins, macrolides and for fluoroquinolones and other quinolones and emerging resistance in *E. coli* and *Salmonella* spp., from cattle, domestic fowl and pigs and for *C. coli* and *C. jejuni* from cattle and domestic fowl.

The logistic regression analysis of the data to predict association between consumption and resistance, showed a positive association between the national consumption of tetracycline and emerging resistance observed by the bacteria monitored. With regard to the 3rd-4th generation cephalosporins, reduced susceptibility to cefotaxime was analysed, and a significant association observed. For macrolides consumption, resistance to erythromycin was analysed and again a positive association was observed. *Campylobacter* spp., tested (*C. coli* and *C. jejuni*) showed a significant positive association. The national consumption of fluoroquinolones and other quinolones and the risk of reduced susceptibility to ciprofloxacin were assessed and positive associations for both fluoroquinolones and other quinolones recorded in *E. coli*, *Salmonella* spp., and *C. jejuni*.

These results did not consider areas such as: dosing age regime; time of treatment in the animal life and interval between slaughter. In addition old drugs e.g. tetracyclines have been used therapeutically (50 years) and as growth promoters (25 years), so history or exposure and co-selection of resistance genes need to be considered.

2.4 Comparison of consumption of selected antimicrobial classes in humans and resistance of bacteria in humans in 26 EU/EEA in 2012

The 3rd and 4th-generation cephalosporin consumption in hospitals and in the community analysed showed significant association between resistance and consumption for all countries. A positive correlation between the 3rd and 4th-generation cephalosporins use from eight countries in hospitals and occurrence of resistance in *Salmonella* spp., was found.

The quinolone consumption by humans was almost exclusively fluoroquinolones with there being a strong correlation between resistance to this class of antimicrobials and consumption in the community being observed from blood stream infections (BSI) isolated *E. coli* (Table 2). With regards to emerging resistance in *Salmonella* spp., (*S. Enteritidis* and *S. Typhimurium*) no correlation on consumption 3rd and 4th-generation cephalosporin in humans and resistance in humans could be found.

For fluoroquinolones resistance in *C. coli*, a positive correlation was found between consumption of fluoroquinolones and consumption in the community. This is thought to occur due to potential cross contamination from poultry or possibly from imported companion animal, food treats e.g. pig ear treats [65]. Macrolide consumption in humans and the incidence of erythromycin resistance was analysed from the community, hospitals and in total. For *C. coli* (in 14 countries) a positive correlation was observed. For *C. jejuni* (16 countries), no correlation was observed. However, as only a small number of countries provided data, therefore the outcomes should be interpreted with caution.

No significance for tetracycline use in humans and resistance in *S. Typhimurium* ($p=0.96$) (Table 2), or other *Salmonella* spp., in humans or for *Campylobacter* spp., (*C. coli* and *C. jejuni*) was observed. The high level of resistance to tetracycline could be due to co-selection and the spread of clones from food-producing animals. An unusual occurrence of a tetracycline reservoir from imported mice for pet (e.g. reptiles) food has been put forward as an example [66].

Carbapenems possess a very broad spectrum of activity and are active against both Gram-positive and Gram-negative bacteria and are considered as antimicrobials of last resort in recent emergence of multidrug-resistant cases. Resistance to carbapenems is increasing throughout the world [67]. Overall 16282 *Klebsella pneumonia* isolates from BSI's were reported of which 1235 were resistant to carbapenems. Greece, with the highest consumption of carbapenems, showed the highest resistance to *K. pneumonia* (60.5%), with Italy (28.8%) and Romania (13.7%) following. The logistic regression analysis of the data showed a positive correlation between consumption in humans and resistance in human isolates. Some argue that resistance was obtained from travel to high incident countries outside the EU. Other concerns include the reported presence of carbapenemases producing *Acinetobacter* spp., in both cattle from France and horses from Belgium [68, 69]. Carbapenems resistance has also been reported in *Salmonella* spp., and *E. coli* from livestock and pigs [70, 71]. This has resulted in extending the monitoring and reporting to extended spectrum beta-lactamases (ESBL'S), AmpC beta-lactamases (AmpC) and carbapenemases in *Salmonella* spp., and *E. coli* by the EU for Member States [72].

Table 2 Antimicrobial consumption in humans and probability of antimicrobial resistance in bacteria from humans.

Organism	Antimicrobial consumed	p- value
<i>E. coli</i> *	3 rd -4 th Generation Cephalosporins	<0.005
<i>E. coli</i>	Fluoroquinolones	<0.001
<i>Salmonella</i> Typhimurium	Tetracycline	0.96
<i>Klebsella pneumonia</i>	Carbapenems	0.002

*tested for 3rd generation cephalosporins resistance

2.5 Comparison of consumption of selected antimicrobial classes in food-producing animals and resistance of bacteria in humans in 26 EU/EEA in 2012

The most prevalent food borne pathogen in the EU Member States in 2013 was *Campylobacter* spp., caused by broiler meat with *C. jejuni* being the most prevalent in humans. In 2013, a total of 5196 food-borne outbreaks, including waterborne outbreaks, were reported in the EU [73]. Most of these food-borne outbreaks were caused by *Salmonella* spp., followed by viruses, bacterial toxins and *Campylobacter* spp., in 28.9% of all outbreaks the causative agent was unknown [73]. The common *Salmonella* serovar was Enteritidis which is often resistant to fluoroquinolones and Typhimurium which is multi-resistant. *Campylobacter* species were, *C. jejuni* which is the most dominant and *C. coli*. The analysis therefore was based on these organisms (Table 3).

Table 3 Antimicrobial consumption in food producing animals and antimicrobial resistance in bacteria from humans.

Organism from Humans	Antimicrobial consumed in animals	<i>p</i>
<i>E. coli</i>	3 rd -4 th Generation Cephalosporins	NS*
<i>E. coli</i>	Fluoroquinolones	<0.05
<i>E. coli</i>	Other quinolones	<0.001
<i>S. Typhimurium</i>	Tetracycline	<0.05
<i>Salmonella</i> spp.	Tetracycline	<0.001
<i>Campylobacter jejuni</i>	Tetracycline	<0.001
<i>Campylobacter jejuni</i>	Macrolides	<0.05

NS: Not Significant

For 3rd-4th generation cephalosporins consumption in food-producing animals and probability of cephalosporin resistance in *E. coli* from BSI's in humans, no significance (NS) was found. A slight positive correlation for *Salmonella* spp., was observed, however, it was not statistically significant. Similarly for fluoroquinolones resistance in *Salmonella* spp., and *Campylobacter* spp., no significant was found for consumption in food-producing animals and resistance in human isolates. However, for *E. coli* from BSI's, a positive association was observed for fluoroquinolones and other quinolones. Again travel or transmission between humans could be a factor.

For tetracycline a positive association was seen for *Salmonella* spp., and *Campylobacter* spp., (Table 3). Possible relationships between occurrence of resistance to erythromycin in *C. jejuni* isolates from humans and total consumption of macrolides in animals in 2011-2012, demonstrated a significant positive association.

3. Conclusions

In summary, although the data analysed in the first integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals [63], should be used with caution, due to reporting vigilance in some countries as against others to date. Factors such as co-selection of antimicrobial resistance genes and cross resistance; movement of people and animals; importation of contaminated food from outside the EU; cross contaminating from pets and pet food and the increasing prevalence of exotic pets in homes across Europe, could have misrepresented the results. More than 200 million pets are estimated to be in the EU [74]. Overall, the association between consumption of selected antimicrobials and the occurrence of resistance in the selected bacteria monitored were mostly observed. The on-going collaboration by the ECDC, EFSA and EMA on developing harmonising approaches to the collection of data and antimicrobial susceptibility methodologies, more detailed enhanced data on consumption of antimicrobials in specific animal species and hospital usage will allow for standardised data and conclusions to be more authentic. The EUCAST programme for harmonising and standardisation of antimicrobial testing methods and interpretation of breakpoints will allow for comparative European wide results to be analysed.

The ECDC/EFSA/EMA (2015) [63] report can be summarised as follows:

Consumption of antimicrobials in humans and resistance in bacteria from humans

- A positive association between 3rd-4th generation cephalosporins consumption in humans and cephalosporin resistance in *E. coli* from humans was observed.
- A strong association between consumption of fluoroquinolones in humans and resistance in *E. coli* was observed. No correlating was found for *Salmonella* spp. Some correlating was found for community consumption of fluoroquinolones and resistance to *C. coli* in humans. For *Salmonella* spp., and *Campylobacter* spp., low numbers of human isolated were tested.

Consumption of antimicrobials in food-producing animals and resistance in bacteria from food-producing animals

- Overall, a strong association was found for consumption of antimicrobials tested and resistance in the organism tested. In particular for *E. coli* and less so for *Salmonella* spp., and *Campylobacter* spp.

Consumption of antimicrobials in food-producing animals and resistance in bacteria from humans

- The incidence of resistance in *E. coli* that have caused blood stream infections could be correlated with consumption of antimicrobials in food-producing animals and also in humans.
- A positive association between consumption of cephalosporins in humans (use in hospitals and in total) and resistance was observed in the organisms tested.
- For fluoroquinolones a positive correlation was observed with consumption in the community but not with consumption in hospitals.

Can the outbursts of concerns since the Swan report in 1969 [3] to the present day national and numerous intergovernmental and professional body reports on antimicrobial resistance emergence, make any difference or will they sit on the shelf? Alternative to antimicrobials including novel agents e.g. metals, antimicrobial peptides (recombinant), essential oils, bacteriophage, immunomodulants and the recent isolation of a novel antimicrobial teixobactin, which was isolated from uncultivable organisms in soil and shows a new path for antimicrobial discovery [75]. A political as well as corporate will is required together with target involvement of medical and veterinary professionals and with societal attitudes taking the challenge on board. But as global crisis's emerge including; income disparity and financial failure, natural catastrophes from climate and water shortages, population ageing and war and refugee migration, the emerging antimicrobial problem moves down the global risk priority.

Acknowledgements The support of the Department of Chemical and Environmental Sciences, University of Limerick, is gratefully acknowledged.

References

- [1] Dowling, A., O' Dwyer, J., Adley, CC. Alternatives to antimicrobials: future trends. In: Mendez-Vilas, A, Editor. Microbial pathogens and strategies for combating them: science, technology and education. Formatex Research Centre, Badajoz, Spain. 2013. Volume 1: pp 216-226. ISBN (13) Volume 1: 978-84-939843-9-7
- [2] Aminov RI. A brief history of an antimicrobial era: lessons learned and challenges for the future. *Frontiers in Microbiology*, 2010, 1: 134: 1-7
- [3] Swann MM, Baxter KL, Field HI, Howie, JW, Lucas, IAM., Millar ELM., Murdoch, JC, Parsons, JH, White, EG. Report of the Joint Committee on the Use of Antimicrobials in Animal Husbandry and Veterinary Medicine. CMND. 4190. Published by HMSO, 1969
- [4] SMAC (Scientific Medical Advisory Committee) Report. The Path of Least Resistance. Standing Medical Advisory committee, subgroup antimicrobial resistance. Scientific Medical Advisory Committee. 1998 Department of Health UK.
- [5] Cogliani C, Goossens H, Greko C. Restricting antimicrobial use in food animals: Lessons from Europe. *Microbe*, 2010, 6:274-279.
- [6] Bates J. Epidemiology of vancomycin-resistant enterococci in the community and relevance of farm animals to human infections. *Journal of Hospital Infection*, 1997; 37:89-101.
- [7] EU. Commission Directive 97/6/EC of 30 January 1997 amending Council Directive 70/524/EEC concerning additives in feeding stuffs. *Official Journal of the European Communities*, 1997, 5.2.97: L 35:11-13
- [8] EC. Opinion of the Scientific steering committee on antimicrobial resistance Directorate General XXIV. Consumer Policy and Consumer Health Protection. Directorate B - Scientific Health Opinions 1999. http://ec.europa.eu/food/fs/sc/ssc/out50_en.pdf (Accessed 1 June 2015)
- [9] Owens B. Strategies to reduce the use of antimicrobials in animals. *The Pharmaceutical Journal*, 2014, 293: 7836
- [10] EC Proposal for a Regulation of the European Parliament and of the Council on veterinary medicinal products COM (2014) 558 Final 2014/0257 (COD) http://ec.europa.eu/health/files/veterinary/vet_2014-09/regulation/reg_part1_en.pdf (Accessed 6 July 2015)
- [11] Danmap: DANMAP is the Danish Programme for surveillance of antimicrobial consumption and resistance in bacteria from animals, food and humans. 2015. <http://www.danmap.org/> (Accessed June 7 2015)
- [12] NethMap/ MARAN (2014) NethMap- consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands and MARAN- monitoring of antimicrobial resistance and antimicrobial usage in animals in the Netherland in 2013. http://www.wageningenur.nl/upload_mm/1/a/1/0704c512-5b42-4cef-8c1b-60e9e3fb2a62_NethMap-MARAN2014.pdf (Accessed Jun 7 2015)
- [13] Germap: Antimicrobial Resistance and Consumption Report on the consumption of antimicrobials and the spread of antimicrobial resistance in human and veterinary medicine in Germany 2012 http://www.bvl.bund.de/SharedDocs/Downloads/08_PresseInfothek/Germap_2012_en.pdf?__blob=publicationFile&v=2 or homepage at <http://www.bvl.bund.de/> (accessed 7 June 2015)
- [14] SwedRES: Annual reports available on Swedish antimicrobial utilisation and resistance in human and veterinary medicine 2015. www.smittskyddsinstitutet.se (accessed 7 June 2015)
- [15] NORM/ NORM-VET: Norwegian National Veterinary Institute 2015 <http://www.vetinst.no/eng/Publications/NORM-NORM-VET-Report> (accessed June 7 2015)
- [16] O'Neill J: Antimicrobial resistance: Tackling a crisis for the health and wealth of nations. The Review on Antimicrobial Resistance, 2014. <http://amr-review.org/Publications> (Accessed June 29 2015)
- [17] FDA. Extra label animal drug use; fluoroquinolones and glycopeptides: order of prohibition. 1997, Federal Register 62(99): 27944-27947
- [18] FDA. Food and Drug Administration, 2012: 21 CFR Part 530: [Docket No. FDA-2008-N-0326] New Animal Drugs; Cephalosporin Drugs; Extra label Animal Drug Use; Order of Prohibition. pp 735-745. Available at: <http://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf> (Accessed 4 June 2015)
- [19] FDA. Food and Drug Administration, 2003: Guidance for Industry #152. Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern. U.S. Food and Drug Administration, Rockville, MD. <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf> (Accessed 4 June 2015).

- [20] CDC NARMS National antimicrobial resistance monitoring system. 2015 <http://www.cdc.gov/narms/about/index.html>. (Accessed 4 June 2015)
- [21] Doyle MP, Loneragan GH, Scott HM, Singer RS. Antimicrobial resistance: challenges and perspectives. *Comprehensive Reviews in Food Science and Food Safety*, 2013; 12:234-248.
- [22] Barclay E. Subtherapeutic use of antimicrobials in animal feed: In light of an unresolved clash of expert paradigms should we punt to the consumer in decade four? [Internet] 1998. <http://dash.harvard.edu/bitstream/handle/1/8965587/eb Barclay.pdf?sequence=1>
- [23] CDC 2014 Antibiotic resistance threats in the United States, 2013 CDC Atlanta, Georgia
- [24] Ericsson HM., Sherris JC. WHO International Collaborative Study of Antimicrobial Sensitivity Testing (1968–1970) published as "Antimicrobial Sensitivity Testing. Report of an International Collaborative Study", *Acta Pathologica et Microbiologica Scandinavica*, 1971, Supplement No. 217:1-90.
- [25] Cotter G., Adley CC. Comparison and evaluation of antimicrobial susceptibility testing of enterococci performed in accordance with six national committee standardised disk diffusion procedures. *Journal of Clinical Microbiology*, 2001; 39: 3753-3756.
- [26] Kahlmeter G., Brown DFJ., Goldstein FW., MacGowan AP., Mouton JW., Österlund A., Rodloff A., Steinbakk M., Urbaskova P., Vatopoulos A. European harmonization of MIC breakpoints for antimicrobial susceptibility testing of bacteria. *Journal of Antimicrobial Chemotherapy*, 2003, 52: 145-148.
- [27] WHO Consultation Group for Surveillance of Antimicrobial Resistance, Geneva, 22–26 November 1982. WHO/BVI/PHA/ANT/82.2
- [28] WHO Global Strategy for Containment of Antimicrobial Resistance. Geneva, World Health Organization, 2001, WHO/CDS/CSR/DRS/2001.2. Geneva, WHO Press
- [29] WHO. Implementation Workshop on the WHO Global Strategy for Containment of Antimicrobial Resistance. Geneva, 25-26 November 2002 WHO/CDS/CSR/RMD/2003.7. 2003 Geneva, WHO Press
- [30] WHO. Antimicrobial resistance: synthesis of recommendation by expert policy groups. Alliance for the prudent use of antimicrobials. Geneva, World Health Organization, 2001; WHO/CDS/CSR/DRS/2001.10
- [31] WHO/WHA. World Health Day 2011: Policy briefs. Geneva, World Health Organization, 2011 <http://www.who.int/world-health-day/2011/policybriefs/en/> (Accessed June 11 2015).
- [32] WHO. Evolving threat of antimicrobial resistance: options for action. 2012. http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf (Accessed 4 June 2015)
- [33] WHO/WHA World Health Assembly (fifty-first). Emerging and other communicable diseases: antimicrobial resistance. WHA51.17, 1998, agenda item 21.3. 2. <http://apps.who.int/medicinedocs/documents/s16334e/s16334e.pdf> (Accessed 6 June 2014)
- [34] WHO/WHA. Antimicrobial resistance. Sixty-eighth World Health Assembly Resolution A68-20. 27 March 2015 http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_20-en.pdf?ua=1 (Accessed 11 June 2015)
- [35] WHO. Worldwide country analysis: response to antimicrobial resistance. 2015 http://apps.who.int/iris/bitstream/10665/163468/1/9789241564946_eng.pdf?ua=1&ua=1 (Accessed 29 June 2015)
- [36] CAC. Report of the fifth session of the Codex committee on residues of veterinary drugs in food. Washington DC. 16-19 October 1990 ALINORM 1991/31A 1991 file:///C:/Users/Home/Downloads/al91_31Ae%20(1).pdf (Accessed 6 June 2015)
- [37] CAC. Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38-1993.
- [38] CAC. Code of practice to minimise and contain antimicrobial resistance. Codes 2005_ CAC/RCP 61-2005, Paris, CAC publishers.
- [39] CAC. Guidelines for risk analysis of foodborne antimicrobials resistance. CAC/GL 77- 2011 Paris, CAC publishers.
- [40] OIE History of OIE. The OIE home web page. www.oie.ie (Accessed 6 June 2015)
- [41] OIE: The OIE Terrestrial Animal Health Code. 2014a. 23rd edition Paris, OIE publishers.
- [42] FAO/WHO/OIE. Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials Report of the FAO/WHO/OIE. Expert Meeting FAO Headquarters, Rome 26-30 November 2007. <ftp://ftp.fao.org/docrep/fao/010/i0204e/i0204e00.pdf>. (Accessed 23 June 2015)
- [43] OIE. Conference on the responsible and prudent use of antimicrobials agents for animals. Paris March 2013, presentations available at: http://www.oie.int/eng/A_AMR2013/presentations.htm (Accessed 6 June 2015)
- [44] OIE. International symposium on alternatives to antimicrobials (ATA): challenges and solutions in animal production. Paris 25-28, 2012. <http://www.ars.usda.gov/alternativestoantimicrobials/Symposium2012/index.html> (Accessed 6 June 2015).
- [45] OIE. Antimicrobial resistance; standards, recommendations and work of the World Organisation for Animal Health (OIE) http://www.oie.int/fileadmin/Home/eng/Media_Center/docs/foll-AMR-Chatham-v19115-sansphrase_Final.pdf (Accessed 6 June 2014)
- [46] Howell L. Global Risks 2013. 8th ed. Geneva: Insight report: World Economic Forum, 2013. pp 28-35
- [47] EU. Recommendations for future collaboration between the U.S. and EU. Transatlantic Taskforce on Antimicrobial Resistance, 2011. http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/210911_TATFAR_Report.pdf (Accessed 6 June 2015)
- [48] Scott HM, Midgley G, Loneragan GH: Antimicrobials in animal agriculture: Parables and policy. *Zoonosis and Public Health*, 2015, 62:3-9.
- [49] WHO global principles for the containment of antimicrobial resistance in animals intended for food. 2000. WHO/CDS/CSR/APH/2000.4. http://whqlibdoc.who.int/hq/2000/who_cds_csr_aph_2000.4.pdf (Accessed 6 June 2015)
- [50] O'Neill J. Tackling a global health crisis: initial steps. Review of antimicrobial Resistance. 2015 <http://amr-review.org/Publications> (Accessed 23 June 2015)
- [51] EU Action plan against the rising threats from antimicrobial resistance: Road Map. 2015. http://ec.europa.eu/health/antimicrobial_resistance/docs/roadmap_amr_en.pdf (Accessed 23 June 2015)

- [52] EPRUMA. Introducing EPRUMA (European Platform for the Responsible Use of Medicines in Animals), Promoting best practices and responsible use of medicines in animals - Ensuring animal health, animal welfare and public health. 2012. <http://www.epruma.eu>.
- [53] FVE. Federation of Veterinarians of Europe. Position paper on AMR: Veterinarians are an important part of the solution to the urgent matter of antimicrobial resistance. FVE/14/doc/023. Adopted on 21 November 2014 http://www.fve.org/uploads/publications/docs/023_fve_vets_part_of_solution_amr_adopted.pdf (Accessed 3 July 2015)
- [54] HMA (Heads of Medicine Agencies) -V Action plan on antimicrobial issues. 2011. http://www.hma.eu/uploads/media/HMA_AMR_Action_Plan_Feb_2011.pdf (Accessed 2 July 2015)
- [55] Garcia-Migura, L, Hendriksen RS, Fraile L, Aarestrup F.M. Antimicrobial resistance of zoonotic and commensal bacteria in Europe: The missing link between consumption and resistance in veterinary medicine. *Veterinary Microbiology*, 2014, 170: 1-9.
- [56] EU. Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC. *Official Journal of the European Communities* 2013, 5.11.2013. L293:1-15.
- [57] ECDC. European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2010. Stockholm: ECDC; 2013
- [58] ECDC. European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2011. Stockholm: ECDC; 2014a
- [59] ECDC. European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC; 2014b
- [60] EU 2001 DIRECTIVE 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. *Official Journal of the European Communities* 28.11.2001 L311/1-64
- [61] EU. Council Directive of 23 November 1970, concerning additives in feeding-stuffs (70/524/EEC Directive 70/524/EEC. *Official Journal of the European Communities*. 1970, 14.12.1970: No L 270/1-pp 840-856.
- [62] EU Commission Directive 97/6/EC of 30 January 1997 amending Council Directive 70/524/EEC concerning additives in feeding stuffs. *Official Journal of the European Communities*, 1997. 5.2.97: L 35:11-13.
- [63] ECDC/EFSA/EMA: ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority) and EMA (European Medicines Agency). ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. Stockholm/Parma/London: ECDC/EFSA/EMA, 2015. *EFSA Journal* 2015, 13(1):4006, 114 pp.
- [64] WHO advisory group on integrated surveillance of antimicrobial resistance (AGISAR): Critically Important antimicrobials for human medicine. 3rd Revision 2012b. Geneva, Switzerland. WHO publishers.
- [65] Adley CC, Dillon C, Morris C, DeLappe N, Cormican M. Prevalence of *Salmonella* in pig ear pet treats. *Food Research International*. 2011; 44(1):193-197.
- [66] Harker KS, Lane C, De Pinna E, Adak GK. An outbreak of *Salmonella Typhimurium* DT191a associated with reptile feeder mice. *Epidemiology and Infection*, 2011, 139:1254-1261.
- [67] Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA: Carbapenems: Past, present, and future. *Antimicrobial Agents and Chemotherapy*, 2011, 55:4943-4960.
- [68] Poirel L, Berot B, Millemann Y, Bonnin RA, Pannaux, G, Nordmann P. Carbapenemase producing *Acinetobacter* spp. in cattle, France. *Emerging Infectious Disease*. 2012; 18(3):523-525.
- [69] Smet A, Boyen F, Pasmans F, Butaye P, Martens A, Nemeč A, Deschaght P, Vaneechoutte M, Haesebrouck F. OXA-23-producing *Acinetobacter* species from horses: a public health hazard? *Journal of Antimicrobial Chemotherapy*, 2012; 67:3009-3014.
- [70] Fischer J, Rodríguez I, Schmoger S, Friese A, Roesler U, Helmuth R, Guerra B. *Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm. *Journal of Antimicrobial Chemotherapy*, 2012; 67:1793-1795.
- [71] Fischer J, Rodríguez I, Schmoger S, Friese A, Roesler U, Helmuth R, Guerra B. *Salmonella enterica* subsp. Enterica producing VIM-1 carbapenemase isolated from livestock farms. *Journal of Antimicrobial Chemotherapy*, 2013; 68: 478-480.
- [72] EC. Commission Implementing Decision of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (notified under document C(2013) 7145) (2013/652/EU). *Official Journal of the European Union*. 14.11.2013. L 303:26-39
- [73] EFSA: The European Union Summary Report on Trends and Sources of Zoonosis, Zoonotic Agents and Food-borne Outbreaks in 2013. *European Food Safety Authority Journal*, 2015, 13:3991
- [74] Euro Group for Animal's: European exotic pet campaign. 2015 <http://eurogroupforanimals.org/> (Accessed 5 July 2015)
- [75] Ling LL, Schneider T, Peoples AJ, Spoering AL, Engels I, Conlon BP, Mueller A, Schaberle TF, Hughes DE, Epstein S, Jones M, Lazarides L, Steadman VA, Cohen DR, Felix CR, Fetterman KA, Millett WP, Nitti AG, Zullo AM, Chen C, Lewis K: A new antimicrobial kills pathogens without detectable resistance. *Nature*, 2015; 517: 455-459.