Review

Tracking Change: A Look at the Ecological Footprint of Antibiotics and Antimicrobial Resistance

Patricia L. Keen [1],* and David M. Patrick [2]

[1] Department of Civil Engineering, University of British Columbia, 2002-6250 Applied Science Lane, Vancouver, BC V6T 1Z4, Canada

[2] School of Population & Public Health, University of British Columbia, 2206 East Mall Vancouver, BC V6T 1Z3, Canada; E-Mail: David.Patrick@bccdc.ca

* Author to whom correspondence should be addressed; E-Mail: plkeenpl@civil.ubc.ca; Tel.: +1-604-822-2637; Fax: +1-604-822-6901.

Abstract: Among the class of pollutants considered as 'emerging contaminants', antibiotic compounds including drugs used in medical therapy, biocides and disinfectants merit special consideration because their bioactivity in the environment is the result of their functional design. Antibiotics can alter the structure and function of microbial communities in the receiving environment and facilitate the development and spread of resistance in critical species of bacteria including pathogens. Methanogenesis, nitrogen transformation and sulphate reduction are among the key ecosystem processes performed by bacteria in nature that can also be affected by the impacts of environmental contamination by antibiotics. Together, the effects of the development of resistance in bacteria involved in maintaining overall ecosystem health and the development of resistance in human, animal and fish pathogens, make serious contributions to the risks associated with environmental pollution by antibiotics. In this brief review, we discuss the multiple impacts on human and ecosystem health of environmental contamination by antibiotic compounds.

Keywords: antibiotics; environment; antimicrobial resistance; health

1. Introduction

For millennia, long before humans made footprints on the earth's surface, bacteria have been performing crucial biological services in diverse ecological niches. Humankind learned of the advantageous use of many natural processes in which bacteria play a pivotal role and forged a relationship that has served human enterprise ever since. However, the consequences of this relationship are not exclusively positive. A comparatively small proportion of bacterial species are pathogens but some of these are responsible for infectious diseases that can have devastating impacts on human and animal health. Humans have exploited the activities of antibiotic compounds, many of which are derived from nature, to fight bacterial infections for centuries. Despite human efforts to manipulate nature, our unintended consequences on ecological processes in the natural environment can influence human health outcomes. Development of antibiotic resistance in pathogens is a shining example of health issues in which understanding the central role of the environment is crucial to managing this potential risk. Here we discuss recent contributions to our understanding of relationships between health, antibiotic resistance and the environment.

Although widespread use of antibiotic drugs to treat human infections grew tremendously since penicillin was introduced into medical therapy [1], the beneficial antibiotic properties of many bacteria and plant species have been known for a very long time. Recent advances in analytical chemistry have provided evidence that tetracycline derived from *Streptomyces* bacteria in beer fermentation was used for medical treatment of infection in ancient (350–550 AD) Nubian patients [2]. The ancient Greeks and Romans valued wild indigo root as both a blue dye and for its ability to treat respiratory tract infections and some soft tissue infections [3]. Interestingly, woad obtained from the plant *Isatis tinctoria* produces blue dye similar to indigo and has antibiotic properties [4] for which historical documents confirm its use in traditional Chinese medicine and in European medicine to treat certain infections since the 14th century. *Chromobacterium violaceum* is a Gram-negative, heterotrophic bacterium common in soil or aquatic ecosystems in many tropical regions and frequently found in black water in the Amazon River [5]. This particular bacterial species is well-known for its purple pigment and has demonstrated antimicrobial properties that have activity against *Leishmania* species, *Mycobacterium tuberculosis* and some viruses [6]. Although many plant species are known to produce compounds with antibiotic activity, few show promise for applications in human medicine as potent broad-spectrum antimicrobials [7].

Processes that lead to the development of antibiotic resistance have likely occurred throughout all of microbial evolutionary history. Microbial analyses of rock surfaces of the Lechuguilla cave system in New Mexico, dating back some 4 million years, has revealed the presence of bacteria that are resistant to many structurally and chemically diverse antibiotics currently used in human medicine [8]. Phylogenetic analyses showed that the OXA genes which encode a class of β-lactamases that confers resistance to a broad range of β-lactam antibiotics have existed on plasmids for millions of years [9]. This evidence counters the popular argument that mobilization of antibiotic resistance genes is completely due to modern use of antibiotics in medical therapy. However, despite evidence that the evolutionary processes responsible for development of antibiotic resistance in environmental bacteria probably occurred for billions of years, it is clear that selection pressure has become more intense with increasing use and disposal of antibiotics and that this selection is geared more towards ensuring

survival in hostile environments rather than improving fitness in slowly evolving populations [10–12]. Development of antibiotic resistance in bacteria is yet another example for which the metaphor of the 'ecological footprint' [13] aptly describes the increase in impacts on natural processes that occur as a result of human activities—in this case via underuse, overuse and misuse of antibiotics in medical therapy.

2. Why the Environment Matters

Ever-changing environmental conditions influence the biological, chemical, physical and ecological processes that govern the health of all ecosystem species. Just as humans must adapt to environmental stressors, the survival of healthy populations of bacteria depends on their ability to respond quickly to overcome environmental threats. Gene exchange is a common property of all bacteria. When human activities amplify the effects of exposure to stressors, the development of resistance to these represents one of the most striking illustrations of Darwinian selection and survival. Scale is an important factor in considering the response of organisms to environmental change. The effects of processes that occur at the cellular level often translate to effects at different environmental scales. For example, the mechanisms of development of antibiotic resistance in bacteria resident in biofilms lining the catheter tubes of a human patient can be very similar to those in the biofilms lining a wastewater treatment reactor. Microbes interact with a myriad of small molecules in their lifetime and it is likely that resistance develops as a self-defense mechanism, an altered response to chemical signals or as a way to metabolize molecules as a food source.

It is now accepted that resistance is a natural property of all bacteria [14–16] and the term 'resistome' is used to describe the framework that encompasses all forms of resistance and precursor elements [17]. More and more evidence is being collected to support the idea that the environment acts both as a reservoir for antibiotic resistance and a means by which this resistance can be broadly disseminated. Genes can move quickly through a bacterial population via vertical or horizontal transfer mechanisms and combined with the grand magnitude of the resistome, it is no wonder that bacteria can quickly adapt to resist new drugs soon after they are introduced for medical or agricultural use. Resistant bacteria, antibiotic resistance genes, degradative enzymes that work to inactivate antibiotics, and antibiotic molecules are present in the environment at all times and thus distinguishing naturally occurring resistance in organisms from resistance as a result of environmental pollution is a complicated task. Each of these contributors adds a layer of complexity to our understanding of the environmental footprint of antibiotics.

3. Resistant Pathogens as Environmental Contaminants

Superbugs exist everywhere in nature. Several well-known pathogens have demonstrated disturbing trends for developing resistance to antimicrobials. Since Snow's first epidemiological study of cholera in 1854 [18], water contamination with toxigenic *Vibrio cholerae* has been a well-understood risk to public health of ongoing relevance in many developing countries. *Vibrio cholerae* exists in the environment and, during its quiescent stage, distribution of the pathogen through bodies of water spreads the threat to human health, particularly when strains are resistant to multiple classes of antibiotics. Outbreaks of cholera are wide-spread in the developing world (particularly after natural

disasters) and among the recent examples of emergence of multi-drug resistant strains of the pathogen are reports from India [19], China [20], and Haiti [21]. Although comparatively few of the species of bacteria in the environment are pathogens, those that have earned the reputation as 'superbugs' make substantial contributions to the environmental footprint of antibiotics by increasing the amount and diversity of drugs needed to combat infection, increasing the cost of treating illness and altering the ecological conditions of healthy functioning ecosystems.

Emergence of multi-drug resistance in community acquired pathogens such as *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* illustrates a worrisome scenario in which the effectiveness of the antibiotics that previously successfully treated the infections has deteriorated over time. Nocosomial pathogens associated with hospital acquired infections, such as methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and Vancomycin-resistant *Enterococcus faecium* occur with high frequency of drug-resistance traits and have been detected in wastewater treatment plants that receive hospital effluent discharge [22–25]. The discharge of effluents from wastewater treatment plants provides the pathway for introduction of contaminants into the receiving environment. Given that secondary treatment of municipal wastewater depends on maintaining conditions for healthy populations of useful bacteria in reactors to degrade sewage, it is highly likely that some resistant pathogens could also be among the organisms released after waste processing.

Environment has multiple meanings. Ecosystems describe communities of living organisms and their relationship to the non-living environmental condition in which they reside. Hospitals and each of their sub-units represent unique ecosystems that, in some cases, have environmental conditions that facilitate rapid development of antibiotic resistance in pathogens. Among the hospital acquired pathogens, the emergence and spread of resistant strains of *Clostridium difficile* is demonstrating a disturbing upward trend. Increased multi-drug resistance and virulence in *Clostridium difficile* is well-documented [26–28] and this is of concern since outbreaks of *C. difficile* infections occur in long-term care facilities with increased frequency [29,30]. In addition, zoonotic transfer of pathogens via companion animals may be an under-recognized mode of transmission of organisms including *Clostridium difficile*. Although a common pathogen among several animal species, within the past decade, *C. difficile* has become accepted as an enteric pathogen in horses [31–33]. Humans and pets often share the same environment in close proximity making transmission of bacteria likely but particularly problematic if the same species of enteric pathogen can thrive in human and animal hosts. When infections that were previously associated with the hospital environment occur in the community, the implications connected with development of resistance in the pathogens responsible for these outbreaks amplify the public health concern.

Another important pathogen that has a long history of association with hospital acquired infections is *Acinetobacter baumaii*. This species of gram negative bacilli are common soil dwelling organisms that are widely distributed in nature. Because they can survive under a broad range of environmental conditions and can exist for long periods of time on dry surfaces, the risk of transmission between individuals is high. Multi-drug resistant *Acinetobacter baumaii* is a rapidly emerging pathogen in health care settings where antimicrobial resistance has seriously limited options for treatment [34]. As a last resort for multi-drug infections, carbapenems are used to treat *Acinetobacter baumaii* associated infections however, carbapenem-resistant strains of the pathogen are being reported at an alarmingly high rate [35–38]. Outbreaks of severe multi-drug resistant *A. baumannii* were observed in military

personnel active in the conflicts in Iraq and Afghanistan [39–43]. Originally, environmental exposures to soil-dwelling strains of the pathogen were thought to be responsible for the outbreaks. However, subsequent culture-based studies suggested that exposure in health care facilities is the more likely pathway of transmission between patients [44–48]. Environmental contamination plays a critical role as an important reservoir in outbreaks of *A. baumannii* and in extending the need for more frequent use and higher potency antibiotic drugs.

Microbes travel. Environmental transport of antibiotic resistant bacteria, especially human and animal pathogens, extends opportunities for exposure of non-target organisms in air, water, soil and sediment. People travel. Increased global mobility of humans and animals has influenced the rates of exposure to pathogens in unprecedented ways.

4. Antimicrobial Resistance Genes as Environmental Contaminants

Environmental contamination by antibiotic compounds is inextricably linked to development of antimicrobial resistance in non-target species of bacteria. Whether the bacteria perform critical ecosystem services, pose a health threat as pathogens or have incompletely understood functions in nature, development of antimicrobial resistance as a result of human activities is problematic. Susceptibility characteristics of microbes can be altered by incorporation of genetic information encoding for resistance or by mutation in their DNA. Antibiotic resistance genes are recognized as important environmental contaminants [49–51]. Bacteria strains containing genes that code for resistance to fluoroquinolones [52–56], macrolides [57–59], sulfonamides [60–62] and trimethoprim [63,64] have been isolated from environmental samples. Resistance can spread as a result of distribution of resistant bacterial strains or genetic elements of resistance throughout the receiving environment, evolution and selection of new resistant strains or the amplification of pre-existing resistant strains of bacteria. Introduction of antibiotics as environmental contaminants have important influences on these processes that alter abundance of resistance genes in the environment in multiple ways.

Genes of some strains of bacteria encode for the production of enzymes that are responsible for resistance to antibiotics which have the four-carbon beta lactam ring in their chemical structure. These enzymes, known as beta lactamases, are capable of breaking the ring structure that is common to antibiotics, such as penicillins, cephamycins and carbapenems, thereby inactivating the antimicrobial properties of the molecule. Extended-spectrum beta lactamases (ESBLs) are a sub-group of this class of enzymes that are often plasmid encoded and also carry genetic traits for resistance to cephalosporins and other antibiotic drugs used for treatment of serious pathogenic infections of human patients. These classes of antibiotics represent the last resort in treatment for some infections. Incidence of infection by ESBL-producing organism is being reported with increasing frequency [65–67]. This is an extremely important concern in the medical community since the range of antibiotic treatment options is progressively shrinking. One of the latest examples of this disturbing trend is the emergence of New Delhi metallo-beta-lactamase (NDM-1) in some strains of Gram negative bacteria that have demonstrated resistance to virtually all antibiotic drugs in common use. The role of the environment in the transport and dissemination of bacteria producing deactivating enzymes cannot be overlooked given that ESBL-producing *Escherichia coli* has already been isolated in samples collected from wastewater treatment effluents [68] and in isolates collected from household pets [69].

5. Antibiotic Drugs as Environmental Contaminants

It is accepted knowledge that antibiotics are present as contaminants in a variety of environmental systems [70–77]. Among the class of pollutants referred to as 'emerging contaminants', antibiotic compounds have a suspicious reputation because their biological activity is an intrinsic characteristic of their functional design. Antibiotics are introduced into the environment via multiple pathways that include effluents from disposal of human waste, waste from agricultural food animal production and aquaculture of finfish, direct application to some plants, industrial effluents from pharmaceutical production, agricultural run-off and disposal of ethanol production waste products. Acute and chronic bioassays have provided evidence that environmental exposure to low concentrations of some antibiotic drugs have toxic effects in species such as *Daphnia magna* [78], *Selenastrum capricornutum* [79] and *Artemia* [80]. Toxicity evaluations of enrofloxacin and ciprofloxacin using representatives of four photoautotrophic aquatic species found that enrofloxacin did not inhibit growth although toxic responses in some of the macrophytes were observed for exposure to ciprofloxacin at the same environmentally relevant concentrations [81].

Failure to detect antibiotics in environmental samples (especially those with high organic content) does not mean antibiotic residues are not present. The diverse chemical and structural properties of antibiotic compounds in environmental sample matrices make chemical determination problematic in many circumstances. Biodegradation [82–84], photodegradation [85–89], chemical complexation or chelation [90–94] and adsorption to particulate matter [95–105] alter the concentrations of antibiotic residues that can be reliably measured in samples of environmental origin. The current analytical method of choice is liquid chromatography combined with tandem mass spectrometry using a variety of extraction methods, frequently solid phase extraction techniques. Despite excellent improvements in analytical determination of antibiotic residues in environmental samples, analyte recoveries, detection limits and reproducibility can be highly variable.

The discharge of effluents from wastewater treatment plants represents important point sources of contaminants in the environment. Wastewater treatment plants have been described as 'hotspots' for antibiotics [106] and for antimicrobial resistance [107] although some treatment options appear promising for reducing the load of antibiotic residues that could be delivered to the receiving environment. Processes for the removal of oxytetracycline [108], sulfamethoxazole [109,110], trimethoprim [111], and some fluoroquinolones [112,113] have been demonstrated. Biological waste treatment processes rely on complex ecological interactions among the microbial species present in the system reactors. Our understanding of these ecological factors is growing and processes to treat wastewater have been shown to influence the contribution of antimicrobial resistance elements and resistant strains of bacteria released into the environment [114–116].

Direct application of antibiotic compounds can contribute to the contaminant load on the receiving environment. Oxytetracycline and streptomycin are frequently used in orchards to prevent Erwinia infection in apples and pears. Alternatives to the application of antibiotics on trees to control conditions such as fire blight include spraying orchards with a copper sulphate solution known as 'Bordeaux mixture'. Although the practice is common and effective in the treatment of fire blight, recent studies have demonstrated that long-term application of copper to agricultural soil altered microbial community structure and altered gene expression in some soil macrofauna [117]. As in the

case of human and veterinary medicine, treatment of infections in plants requires judicious use of antimicrobials such that the beneficial ecosystem services provided by a plethora of bacteria in the environment are not compromised.

The original concept behind the ecological footprint model was to compare human demands on nature with nature's ability to regenerate the resources needed to accommodate human consumption for lifestyle needs. Under the rubric of mitigating anthropogenic impacts on climate change and reducing human dependence on limited resources of fossil fuels, production of ethanol is one case where effects to reduce human ecological footprint may contribute to the increase in the microbial 'resistance footprint'. Conversion of corn starch to ethanol is highly susceptible to contamination by bacteria that will compete with yeast during the fermentation process [118]. In order to control excessive growth of bacterial populations in the production process, antibiotics such as penicillin, erythromycin, virginiamycin and tylosin are frequently added to the tanks where corn mash is mixed with warm water to ferment ethanol. The waste by-product of the ethanol fermentation is nutrient-rich corn mash known as 'distillers grains' and is a common ingredient in livestock or poultry feed. Evidence supports the hypothesis that macrolide antibiotics in dried distillers' grains can persist through the fermentation process and remain active after incorporation in livestock feed [119–121].

6. Conclusion

Environmental contamination by antibiotics is but one factor in the equation that defines the health consequences of antibiotic resistance in bacteria. The combined impact of resistant strains of bacteria, antibiotic resistance genes, degradative enzymes that inactivate antibiotics, and antibiotic compounds can have profound influence on human and ecosystem health. It will take a concerted effort involving antibiotic stewardship, judicious use of antibiotics in human and animal medicine, surveillance of drug use and the incidence of antimicrobial resistance, public awareness campaigns, and government commitment to leading coordinated initiatives for society to be protected from the deleterious consequences of excessive development of antibiotic resistance in pathogens. The environmental footprint of antibiotics must be minimized to ensure that the drugs that we use in human and veterinary medicine remain effective. This is our path of "least resistance".

References and Notes

1. Fleming, A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae*. *Br. J. Exp. Pathol.* **1929**, *10*, 226–236.
2. Nelson, M.; Dinardo, A.; Hochberg, J.; Armelagos, G. Brief communication: Mass spectroscopic characterization of tetracycline in the skeletal remains of an ancient population from Sudanese Nubia 350–550 CE. *Am. J. Phys. Anthropol.* **2010**, *143*, 151–154.
3. Wustenberg, P.; Henneicke-von Zepelin, H.H.; Kohler, G.; Stammwitz, U. Efficacy and mode of action of an immunomodulator herbal preparation containing *Echinacea*, wild indigo, and white cedar. *Adv. Ther.* **1999**, *16*, 51–70.
4. Oberthür, C.; Jaggi, R.; Hamburger, M. HPLC based activity profiling for 5-lipoxygenase inhibitory activity in *Isatis tinctoria* leaf extracts. *Filoterapia* **2005**, *76*, 324–332.

5. Hungria, M.; Astolfi-Filho, S.; Chueire, L.M.O.; Nicolás, M.F.; Santos, E.B.P.; Bulbol, M.R.; Souza-Filho, A.; Assunção, E.N.; Germano, M.G.; Vasconcelos, A.T.R. Genetic characterization of *Chromobacterium* isolates from black water environments in the Brazilian Amazon. *Lett. Appl. Microbiol.* **2005**, *41*, 17–23.

6. Dall'Agnol, L.T.; Martins, R.N.; Vallinoto, A.C.R.; Ribeiro, K.T.S. Diversity of *Chromobacterium violaceum* isolates from aquatic environments of state of Pará, Brazilian Amazon. *Mem. Inst. Oswaldo Cruz Rio de Janeiro* **2008**, *103*, 678–682.

7. Lewis, K.; Ausubel, F.M. Prospects for plant-derived antibacterials. *Nat. Biotechnol.* **2006**, *24*, 1504–1507.

8. Bhullar, K.; Waglechner, N.; Pawlowski, A.; Koteva, K.; Banks, E.D.; Johnston, M.D.; Barton, H.A.; Wright, G.D. Antibiotic resistance is prevalent in an isolated cave microbiome. *PLoS One* **2012**, *7*, e34953.

9. Barlow, M.; Hall, B.G. Phylogenetic analysis shows that the OXA beta-lactamase genes have been on plasmids for millions of years. *J. Mol. Evol.* **2002**, *5*, 314–321.

10. Davies, J.E.; Davies, D. Origins and evolution of antibiotic resistance. *Microbiol. Mol. Biol. Rev.* **2010**, *74*, 417–433.

11. Martínez, J.-L. Natural antibiotic resistance and contamination by antibiotic resistance determinants: The two ages in the evolution of resistance to antimicrobials. *Front. Microbiol.* **2012**, *3*, doi:10.3389/fmicb.2012.00001.

12. Knapp, C.W.; Dolfing, J.; Ehlert, P.A.I.; Graham, D.W. Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940. *Environ. Sci. Technol.* **2010**, *44*, 560–587.

13. Wackernagel, M.; Rees, W. *Our Ecological Footprint: Reducing Human Impact on the Earth*; New Society Publishers: Gabriola Island, Canada, 1996.

14. Wright, G.D. The antibiotic resistome: The nexus of chemical and genetic diversity. *Nat. Rev. Microbiol.* **2007**, *5*, 175–186.

15. Martinez, J.-L. Antibiotics and antibiotic resistance genes in natural environments. *Science* **2008**, *321*, 365–367.

16. Allen, H.K.; Donato, J.; Wang, H.H.; Cloud-Hansen, K.A.; Davies, J.; Handelsman, J. Call of the wild: Antibiotic resistance genes in natural environments. *Nat. Rev. Microbiol.* **2010**, *8*, 251–259.

17. Wright, G.D. The antibiotic resistome. *Expert Opin. Drug Discov.* **2010**, *5*, 779–788.

18. Snow, J. The cholera near Golden Square, and at Deptford. *Med. Times Gaz.* **1854**, *9*, 321–322.

19. Das, S.; Saha, R.; Kaur, I.R. Trends of antibiotic resistance of *Vibrio cholerae* strains from East Dehli. *Indian J. Med. Res.* **2008**, *127*, 478–482.

20. Wang, R.; Lou, J.; Liu, J.; Zhang, L.; Li, J.; Kan, B. Antibiotic resistance of *Vibrio cholera* O1 EI Tor strains from the seventh pandemic in China, 1961–2010. *Int. J. Antimicrob. Agents* **2012**, *40*, 361–364.

21. Sjölund-Karlsson, M.; Reimer, A.; Folster, J.P.; Walker, M.; Dahourou, G.A.; Batra, D.G.; Martin, I.; Joyce, K.; Parsons, M.B.; Boncy, J.; *et al*. Drug resistance mechanisms in *Vibrio cholerae* O1 outbreak strain, Haiti, 2010. *Emerg. Infect. Dis.* **2011**, *17*, 2151–2154.

22. Börjesson, S.; Matussek, A.; Melin, S.; Löfgren, S.; Lindgren, P.E. Methicillin-resistant *Staphylococcus aureus* (MRSA) in municipal wastewater: An uncharted threat? *J. Appl. Microbiol.* **2010**, *108*, 1244–1251.

23. Fuentefria, D.B.; Ferreira, A.E.; Corção, G. Antibiotic-resistant *Pseudomonas aeruginosa* from hospital wastewater and superficial water: Are they genetically related? *J. Environ. Manag.* **2011**, *92*, 250–255.

24. Araújo, C.; Torres, C.; Silva, N.; Carneiro, C.; Gonçalves, A.; Radhouani, H.; Correia, S.; da Costa, P.M.; Paccheco, R.; Zarazaga, M.; *et al*. Vancomycin-resistant enterococci from Portuguese wastewater treatment plants. *J. Basic Microbiol.* **2010**, *50*, 605–609.

25. Sahlström, L.; Rehbinder, V.; Albihn, A.; Aspan, A.; Bengtsson, B. Vancomycin resistant enterococci (VRE) in Swedish sewage sludge. *Acta Vet. Scand.* **2009**, *51*, 24–33.

26. Bartlett, J.G. Historical perspectives on studies of *Clostridium difficile* and *C. difficile* infection. *Clin. Infect. Dis.* **2008**, *46* (Suppl. 1), S4–S11.

27. Huang, H.; Weintraub, A.; Fang, H.; Nord, C.E. Antimicrobial resistance in *Clostridium difficile*. *Int. J. Antimicrob. Agents* **2009**, *34*, 516–522.

28. Spigaglia, P.; Barbanti, F.; Mastrantonio, P. Multidrug resistance in European *Clostridium difficile* clinical isolates. *J. Antimicrob. Chemother.* **2011**, *66*, 2227–2234.

29. Aslam, S.; Hamill, R.J.; Musher, D.M. Treatment of *Clostridium difficile*-associated disease: Old therapies and new strategies. *Lancet Infect. Dis.* **2005**, *5*, 549–557.

30. Riggs, M.M.; Sethi, A.K.; Zabarsky, T.F.; Eckstein, E.C.; Jump, R.L.P.; Donskey, C.J. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. *Clin. Infect. Dis.* **2007**, *45*, 992–998.

31. Weese, J.S.; Staempfli, H.R.; Prescott, J.F. A prospective study of the roles of *Clostridium difficile* and enterotoxigenic *Clostridium perfringens* in equine diarrhoea. *Equine Vet. J.* **2001**, *33*, 403–409.

32. Båverud, V. *Clostridium difficile* diarrhea: Infection control in horses. *Vet. Clin. North Am. Equine Pract.* **2004**, *20*, 615–630.

33. Thean, S.; Elliott, B.; Riley, T.V. *Clostridium difficile* in horses in Australia—A preliminary study. *J. Med. Microbiol.* **2011**, *60*, 1188–1192.

34. Eliopoulos, G.M.; Maragakis, L.L.; Perl, T.M. *Acinetobacter baumannii*: Epidemiology, antimicrobial resistance, and treatment options. *Clin. Infect. Dis.* **2008**, *46*, 1254–1263.

35. Corbella, X.; Montero, A.; Pujol, M.; Domínguez, M.A.; Ayats, J.; Argerich, M.J.; Garrigosa, F.; Ariza, J.; Gudiol, F. Emergence and rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant *Acinetobacter baumannii*. *J. Clin. Microbiol.* **2000**, *38*, 4086–4095.

36. Aygün, G.; Demirkiran, O.; Utku, T.; Mete, B.; Urkmez, S.; Yilmaz, M.; Yaşar, H.; Dikmen, Y.; Oztürk, R. Environmental contamination during a carbapenem-resistant *Acinetobacter baumannii* outbreak in an intensive care unit. *J. Hosp. Infect.* **2002**, *52*, 259–262.

37. Poirel, L.; Nordmann, P. Carbapenem resistance in *Acinetobacter baumannii*: Mechanisms and epidemiology. *Clin. Microbiol. Infect.* **2006**, *12*, 826–836.

38. Lambiase, A.; Piazza, O.; Rossano, F.; Del Pezzo, M.; Tufano, R.; Catania, M.R. Persistence of carbapenem-resistant *Acinetobacter baumannii* strains in an Italian intensive care unit during a forty-six month study period. *New Microbiol.* **2012**, *35*, 199–206.

39. Davis, K.A.; Moran, K.A.; McAllister, C.K.; Gray, P.J. Multidrug-resistant *Acinetobacter* extremity infections in soldiers. *Emerg. Infect. Dis.* **2005**, *11*, 1218–1224.

40. Hujer, K.M.; Hujer, A.M.; Hulten, E.A.; Bajaksouzian, S.; Adams, J.M.; Donskey, C.J.; Ecker, D.J.; Massire, C.; Eshoo, M.W.; Sampath, R.; *et al*. Analysis of antibiotic resistance genes in multidrug-resistant *Acinetobacter* sp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center. *Antimicrob. Agents Chemother.* **2006**, *50*, 4114–4123.

41. Yun, H.C.; Murray, C.K.; Roop, S.A.; Hospenthal, D.R.; Gourdine, E.; Dooley, D.P. Bacteria recovered from patients admitted to a deployed US military hospital in Baghdad, Iraq. *Mil. Med.* **2006**, *171*, 821–825.

42. Hawley, J.S.; Murray, C.K.; Griffith, M.E.; McElmeel, L.; Fulcher, L.C.; Hospenthal, D.R.; Jorgensen, J.H. Susceptibility of *Acinetobacter* strains isolated from deployed US military personnel. *Antimicrob. Agents Chemother.* **2007**, *51*, 376–378.

43. Scott, P.; Deye, G.; Srinivasan, A.; Murray, C.; Moran, K.; Hulten, E.; Fishbain, J.; Craft, D.; Riddell, S.; Lindler, L.; *et al*. An outbreak of multidrug-resistant *Acinetobacter baumannii-calcoaceticus* complex infection in the US military health care system associated with military operations in Iraq. *Clin. Infect. Dis.* **2007**, *44*, 1577–1584.

44. Griffith, M.E.; Ceremuga, J.M.; Ellis, M.W.; Guymon, C.H.; Hospenthal, D.R.; Murray, C.K. *Acinetobacter* skin colonization of US Army Soldiers. *Infect. Control Hosp. Epidemiol.* **2006**, *27*, 659–661.

45. Jones, A.; Morgan, D.; Walsh, A.; Turton, J.; Livermore, D.; Pitt, T.; Green, A.; Gill, M.; Mortiboy, D. Importation of multidrug-resistant *Acinetobacter* spp. infections with casualties from Iraq. *Lancet Infect. Dis.* **2006**, *6*, 317–318.

46. Turton, J.F.; Kaufmann, M.E.; Gill, M.J.; Pike, R.; Scott, P.T.; Fishbain, J.; Craft, D.; Deye, G.; Riddell, S.; Lindler, L.E.; *et al*. Comparison of *Acinetobacter baumannii* isolates from the United Kingdom and the United States that were associated with repatriated casualties of the Iraq conflict. *J. Clin. Microbiol.* **2006**, *44*, 2630–2634.

47. Tien, H.C.; Battad, A.; Bryce, E.A.; Fuller, J.; Mulvey, M.; Brisebois, R.; Doucet, J.J.; Rizoli, S.B.; Fowler, R.; Simor, A. Multi-drug resistant *Acinetobacter* infections in critically injured Canadian Forces soldiers. *BMC Infect. Dis.* **2007**, *7*, e95.

48. Griffith, M.E.; Lazarus, D.R.; Mann, P.B.; Boger, J.A.; Hospenthal, D.R.; Murray, C.K. *Acinetobacter* skin carriage among US army soldiers deployed in Iraq. *Infect. Control Hosp. Epidemiol.* **2007**, *28*, 720–722.

49. Chee-Sanford, J.C.; Aminov, R.I.; Krapac, I.J.; Garrigues-JeanJean, N.; Mackie, R.I. Occurrence and diversity of tetracycline resistance genes in lagoons and groundwater underlying two swine production facilities. *Appl. Environ. Microbiol.* **2001**, *67*, 1494–1502

50. Kümmerer, K. Resistance in the environment. *J. Antimicrob. Chemother.* **2004**, *54*, 311–320.

51. Pruden, A.; Pei, R.; Storteboom, H.; Carlson, K.H. Antibiotics resistance genes as emerging contaminants: Studies in northern Colorado. *Environ. Sci. Technol.* **2006**, *40*, 7445–7450.

52. Kehrenberg, C.; Friederichs, S.; de Jong, A.; Michael, G.B.; Schwarz, S. Identification of the plasmid-borne quinolone resistance gene *qnrS* in *Salmonella enterica* serovar Infantis. *J. Antimicrob. Chemother.* **2005**, *58*, 18–22.

53. Garnier, F.; Raked, N.; Gassama, A.; Denis, F.; Ploy, M.-C. Genetic environment of quinolone resistance gene qurB2 in a complex sul1-type integron in the newly described *Salmonella enterica* serovar Keurmassar. *J. Antimicrob. Chemother*. **2006**, *50*, 3200–3202.

54. Cattoir, V.; Poirel, L.; Aubert, C.; Soussy, C.-J.; Nordmann, P. Unexpected occurrence of plasmid-mediated quinolone resistance determinants in environmental *Aeromonas* spp. *Emerg. Infect. Dis*. **2008**, *14*, 231–237.

55. Poirel, L.; Cattoir, V.; Nordmann, P.; Amábile-Cuevas, C.F.; Arredondo-García, J.L.; Cruz, A.; Rosas, I. Fluoroquinolone resistance in clinical and environmental isolates of *Escherichia coli* in Mexico city. *J. Appl. Microbiol*. **2010**, *108*, 158–162.

56. Poirel, L.; Cattoir, V.; Nordmann, P. Plasmid-mediated quinolone resistance: Interactions between human, animal, and environmental ecologies. *Front. Microbiol*. **2012**, *3*, doi:10.3389/fmicb.2012.00024.

57. Jensen, L.; Agersø, Y.; Sengeløv, G. Presence of *erm* genes among macrolide-resistant Gram-positive bacteria isolated from Danish farm soil. *Environ. Int*. **2002**, *28*, 487–491.

58. Soge, O.O.; Tivoli, L.D.; Meschke, J.S.; Roberts, M.C. A conjugative macrolide resistance gene, mef(A), in environmental *Clostridium perfringens* carrying multiple macrolide and/or tetracycline resistance genes. *J. Appl. Microbiol*. **2009**, *106*, 34–40

59. Roberts, M.C. Environmental macrolide-lincosamide-streptogramin and tetracycline resistant bacteria. *Front. Microbiol*. **2011**, *2*, doi:10.3389/fmicb.2011.00040.

60. Antunes, P.; Machado, J.; Sousa, J.C.; Peixe, L. Dissemination of sulfonamide resistance genes (sul1, sul2, and sul3) in Portuguese *Salmonella enterica* strains and relation with integrons. *J. Antimicrob. Agents Chemother*. **2005**, *49*, 836–839.

61. Schmitt, H.; Beelen, P.V.; Tolls, J.; Leeuwan, C.L. Pollution-induced community tolerance of soil microbial communities caused by the antibiotic sulfachloropyridazine. *Environ. Sci. Technol*. **2004**, *38*, 1148–1153.

62. Heuer, H.; Solehati, Q.; Zimmerling, U.; Kleineidam, K.; Schloter, M.; Tanja Müller, T.; Focks, A.; Thiele-Bruhn, S.; Smalla, K. Accumulation of sulfonamide resistance genes in arable soils due to repeated application of manure containing sulfadiazine. *Appl. Environ. Microbiol*. **2011**, *77*, 2527–2530.

63. Sköld, O. Resistance to trimethoprim and sulfonamides. *Vet. Res*. **2001**, *32*, 261–273.

64. Granier, S.A.; Moubareck, C.; Colaneri, C.; Lemire, A.; Roussel, S.; Dao, T.-T.; Courvalin, P.; Brisabois, A. Antimicrobial resistance of *Listeria monocytogenes* isolates from food and the environment in France over a 10-year period. *Appl. Environ. Microbiol*. **2011**, *77*, 2788–2790.

65. Mulvey, M.R.; Bryce, E.; Boyde, D.; Ofner-Agostini, M.; Christianson, S.; Simor, A.E.; Paton, S. Ambler class A extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* spp. in Canadian hospitals. *Antimicrob. Agents Chemother*. **2004**, *48*, 1204–1214.

66. Hawser, S.P.; Bouchillon, S.K.; Hoban, D.J.; Badal, R.E.; Hsueh, P.-R.; Paterson, D.L. Emergence of high levels of extended-spectrum-β-lactamase-producing Gram-negative bacilli in the Asia-Pacific region: Data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) Program, 2007. *Antimicrob. Agents Chemother*. **2009**, *53*, 3280–3284.

67. Hansen, D.S.; Schumacher, H.; Hansen, F.; Stegger, M.; Hertz, F.B.; Schønning, K.; Justesen, U.S.; Frimodt-Møller, N. DANRES Study Group. Extended-spectrum β-lactamase (ESBL) in Danish clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae*: Prevalence, β-lactamase distribution, phylogroups, and co-resistance. *Scand. J. Infect. Dis*. **2012**, *44*, 174–181.

68. Diwan, V.; Chandran, S.P.; Tamhankar, A.J.; Stålsby Lundborg, C.; Macaden, R. Identification of extended-spectrum β-lactamase and quinolone resistance genes in *Escherichia coli* isolated from hospital wastewater from central India. *J. Antimicrob. Chemother*. **2012**, *67*, 857–859.

69. Shaheen, B.W.; Nayak, R.; Foley, S.L.; Kweon, O.; Deck, J.; Park, M.; Rafii, F.; Boothe, D.M. Molecular characterization of resistance to extended-spectrum cephalosporins in clinical *Escherichia coli* isolates from companion animals in the United States. *Antimicrob. Agents Chemother*. **2011**, *55*, 5666–5675.

70. Daughton, C.; Ternes, T. Pharmaceuticals and personal care products in the environment: Agents of subtle change. *Environ. Health Perspect*. **1999**, *107*, 907–938.

71. Diaz-Cruz, M.S.; Lopez de Alda, M.J.; Barcelo, D. Environmental behavior and analysis of veterinary and human drugs in soils, sediments and sludge. *Trends Anal. Chem.* **2003**, *22*, 340–351.

72. Golet, E.M.; Xifra, I.; Seigrist, H.; Adler, A.; Giger, W. Environmental exposure assessment of flouroquinolone antibacterial agents from sewage to sludge. *Environ. Sci. Technol.* **2003**, *37*, 3243–3249.

73. Halling-Sørensen, B.; Nors Nielsen, S.; Lanzky, P.F.; Ingerslev, F.; Holten Lützhøft, H.C.; Jørgensen, S.E. Occurrence, fate and effects of pharmaceutical substances in the environment— A review. *Chemosphere* **1998**, *36*, 357–393.

74. Hirsch, R.; Ternes, T.; Haberer, K.; Kratz, K.-L. Occurrence of antibiotics in the aquatic environment. *Sci. Total Environ*. **1999**, *225*, 109–118.

75. Jjemba, P.K. The potential impact of veterinary and human therapeutic agents in manure and biosolids on plants grown on arable land: A review. *Agric. Ecosyst. Environ.* **2002**, *93*, 267–278.

76. Kolpin, D.W.; Furlong, E.T.; Meyer, M.T.; Thurman, E.M.; Zaugg, S.D.; Barber, L.B.; Buxton, H.T. Pharmaceuticals, hormones, and other organic wastewater contaminants in US streams, 1999–2000: A national reconnaissance. *Environ. Sci. Technol.* **2002**, *36*, 1202–1211.

77. Kümmerer, K. Significance of antibiotics in the environment. *J. Antimicrob. Chemother.* **2003**, *52*, 5–7.

78. Wollenberger, L.; Halling-Sørensen, B.; Kusk, K.O. Acute and chronic toxicity of veterinary antibiotics to *Daphnia magna*. *Chemosphere* **2000**, *40*, 723–730.

79. Lanzky, P.F.; Halling-Sørensen, B. The toxic effect of the antibiotic metronidiazole on aquatic organisms. *Chemosphere* **1997**, *35*, 2553–2561

80. Migliore, L.; Civitareale, C.; Bramnilla, G.; di Delupis, G.D. Toxicity of several important agricultural antibiotics to *Artemia*. *Water Res*. **1997**, *31*, 1801–1806.

81. Ebert, I.; Bachmann, J.; Kühnen, U.; Küster, A.; Kussatz, C.; Maletzki, D.; Schlüter, C. Toxicity of the fluoroquinolone antibiotics enrofloxacin and ciprofloxacin to photoautotrophic aquatic organisms. *Environ. Toxicol. Chem*. **2011**, *30*, 2786–2792.

82. Wu, C.; Spongberg, A.L.; Witter, J.D. Sorption and biodegradation of selected antibiotics in biosolids. *J. Environ. Sci. Health Part A* **2009**, *44*, 454–461.

83. Wen, X.; Jia, Y.; Li, J. Degradation of tetracycline and oxytetracycline by crude lignin peroxidase prepared from *Phanerochaete chrysosporium*—A white rot fungus. *Chemosphere* **2009**, *75*, 1003–1007.

84. Li, B.; Zhang, T. Biodegradation and adsorption of antibiotics in the activated sludge process. *Environ. Sci. Technol.* **2010**, *44*, 3468–3473.

85. Lunestad, B.T.; Samuelsen, O.B.; Fjelde, S.; Ervik, A. Photostability of eight antibacterial agents in seawater. *Aquaculture* **1995**, *134*, 217–225.

86. Boreen, A.L.; Arnold, W.A.; McNeill, K. Photodegradation of pharmaceuticals in the aquatic environment: A review. *Aquat. Sci. Res. Across Boundaries* **2004**, *65*, 320–341.

87. Werner, J.J.; Arnold, W.A.; McNeill, K. Water hardness as a photochemical parameter: Tetracycline photolysis as a function of calcium concentration, magnesium concentration and pH. *Environ. Sci. Technol.* **2006**, *40*, 7236–7241.

88. Ge, L.; Chen, J.; Zhang, S.; Cai, X.; Wang, Z.; Wang, C. Photodegradation of flouroquinolone antibiotic gatifloxacin in aqueous solutions. *Chin. Sci. Bull.* **2010**, *55*, 1495–1500.

89. Yuan, F.; Hu, C.; Hu, X.; Wei, D.; Chen, Y.; Qu, J. Photodegradation and toxicity changes of antibiotics in UV and UV/H(2)O(2) process. *J. Hazard. Mater.* **2011**, *185*, 1256–1263.

90. Gu, C.; Karthikeyan, K.G. Sorption of the antimicrobial ciprofloxacin to aluminum and iron hydrous oxides. *Environ. Sci. Technol.* **2005**, *39*, 9166–9173.

91. Wang, Y.-J.; Jia, D.-A.; Zhu, H.-W.; Zhou, D.-M. Adsorption and cosorption of tetracycline and copper (II) on montmorillonite as affected by soil pH. *Environ. Sci. Technol.* **2008**, *42*, 3254–3259.

92. Aristilde, L.; Sposito, G. Molecular modeling of metal complexation by a flouroquinolone antibiotic. *Environ. Toxicol. Chem.* **2008**, *27*, 2304–2310.

93. Zhang, Y.; Cai, X.; Lang, X.; Qiao, X.; Li, X.; Chen, J. Insights into aquatic toxicities of the antibiotics oxytetracycline and ciprofloxacin in the presence of metal: Complexation *versus* mixture. *Environ. Pollut.* **2012**, *166*, 48–56.

94. Tias, P.; Machesky, M.L.; Strathmann, T.J. Surface complexation of the zwittterionic flouroquinolone antibiotic ofloxacin to nano-anatase TiO$_2$ photocatalyst surfaces. *Environ. Sci. Technol.* **2012**, *46*, 11896–11904.

95. Rabølle, M.; Spliid, N. Sorption and mobility of metronidazole, olaquindox, oxytetracycline and tylosin in soils. *Chemosphere* **2000**, *40*, 715–722.

96. Cardoza, L.A.; Knapp, C.W.; Larive, C.K.; Belden, J.B.; Lydy, M.; Graham, D.W. Factors affecting the fate of ciprofloxacin in aquatic field systems. *Water Air Soil Pollut.* **2005**, *161*, 383–398.

97. Jia, D.-A.; Zhou, D.-M.; Wang, Y.-J.; Zhu, H.-W.; Chen, J.-L. Adsorption and cosorption of Cu(II) and tetracycline on two soils with different characteristics. *Geoderma* **2008**, *146*, 224–230.

98. Ji, L.; Chen, W.; Zheng, S.; Xu, Z.; Zhu, D. Adsorption of sulfonamide antibiotics to multiwalled carbon nanotubes. *Langmuir* **2009**, *25*, 11608–11613.

99. Ji, L.; Liu, F.; Xu, Z.; Zheng, S.; Zhu, D. Adsorption of pharmaceutical antibiotics on template-synthesized ordered micro- and mesoporous carbons. *Environ. Sci. Technol.* **2010**, *44*, 3116–3122.

100. Zhang, D.; Pan, B.; Zhang, H.; Ning, P.; Xing, B. Contribution of different sulfamethoxazole species to their overall adsorption on functionalized carbon nanotubes. *Environ. Sci. Technol.* **2010**, *44*, 3806–3811.

101. Chen, W.-R.; Huang, C.-H. Adsorption and transformation of tetracycline antibiotics with aluminum oxide. *Chemosphere* **2010**, *79*, 779–785.

102. Ji, L.; Shao, Y.; Xu, Z.; Zheng, S.; Zhu, D. Adsorption of monoaromatic compounds and pharmaceutical antibiotics on carbon nanotubes activated by KOH etching. *Environ. Sci. Technol.* **2010**, *44*, 6429–6436.

103. Marc Teixidó, M.; Pignatello, J.J.; Beltrán, J.L.; Granados, M.; Peccia, J. Speciation of the ionizable antibiotic sulfamethazine on black carbon (biochar). *Environ. Sci. Technol.* **2011**, *45*, 10020–10027.

104. Ji, L.; Wan, Y.; Zheng, S.; Zhu, D. Adsorption of tetracycline and sulfamethoxazole on crop residue-derived ashes: Implication for the relative importance of black carbon to soil sorption. *Environ. Sci. Technol.* **2011**, *45*, 5580–5586

105. Haham, H.; Oren, A.; Chefetz, B. Insight into the role of dissolved organic matter in sorption of sulfapyridine by semiarid soils. *Environ. Sci. Technol.* **2012**, *46*, 11870–11877.

106. Michael, I.; Rizzo, L.; McArdell, C.S.; Manaia, C.M.; Merlin, C.; Schwartz, T.; Dagot, C.; Fatt-Kassino, D. Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: A review. *Water Res.* **2013**, *47*, 957–995.

107. Rizzo, L.; Manaia, C.M.; Merlin, C.; Schwartz, T.; Dagot, C.; Ploy, M.C.; Michael, I.; Fatta-Kassinos, D. Urban wastewater treatment plants as hotspots for antibiotic resistance spreading into the environment. *Sci. Total Environ.* **2013**, *447*, 345–360.

108. Zhao, C.; Pelaez, M.; Duan, X.; Deng, H.; O'Shea, K.; Fatta-Kassinos, D.; Dionysiou, D.D. Role of pH on photolytic and photocatalytic degradation of antibiotic oxytetracycline in aqueous solution under visible/solar light: Kinetics and mechanism studies. *Appl. Catal. B Environ.* **2013**, *134–135*, 83–92.

109. Trovó, A.G.; Nogueira, R.F.P.; Agüera, A.; Fernandez-Alba, A.R.; Sirtori, C.; Malato, S. Degradation of sulfamethoxazole in water by solar photo-Fenton. Chemical and toxicological evaluation. *Water Res.* **2009**, *43*, 3922–3931.

110. Xekoukoulotakis, N.P.; Drosou, C.; Brebou, C.; Chatzisymeon, E.; Hapeshi, E.; Fatta-Kassinos, D.; Mantzavinos, D. Kinetics of UV-A/TiO$_2$ photocatalytic degradation and mineralization of the antibiotic sulfamethoxazole in aqueous matrices. *Catal. Today* **2011**, *161*, 163–168.

111. Sirtori, C.; Agüera, A.; Gernjak, W.; Malato, S. Effect of water-matrix composition on Trimethoprim solar photodegradation kinetics and pathways. *Water Res.* **2010**, *44*, 2735–2744.

112. Vasquez, M.I.; Hapeshi, E.; Fatta-Kassinos, D.; Kümmerer, K. Biodegradation potential of ofloxacin and its resulting transformation products during photolytic and photocatalytic treatment. *Environ. Sci. Pollut. Res.* **2013**, *20,* 1302–1309.

113. Sturini, M.; Speltini, A.; Maraschi, F.; Pretali, L.; Profumo, A.; Fasani, E.; Albini, A.; Migliavacca, R.; Nucleo, E. Photodegradation of fluoroquinolones in surface water and antimicrobial activity of the photoproducts. *Water Res.* **2012**, *46*, 5575–5582.

114. Novo, A.; Manaia, C.M. Factors influencing antibiotic resistance burden in municipal wastewater treatment plants. *Appl. Microbiol. Biotechnol*. **2010**, *87*, 1157–1166.

115. Da Silva, M.F.; Tiago, I.; Veríssimo, A.; Boaventura, R.A.R.; Nunes, O.C.; Manaia, C.M. Antibiotic resistance of enterococci and related bacteria in an urban wastewater treatment plant. *FEMS Microbiol. Ecol*. **2005**, *55*, 322–329.

116. Michael, I.; Hapeshi, E.; Michael, C.; Varela, A.R.; Kyriakou, S.; Manaia, C.M.; Fatta-Kassinos, D. Solar photo-Fenton process on the abatement of antibiotics at a pilot scale: Degradation kinetics, ecotoxicity and phytotoxicity assessment and removal of antibiotic resistant enterococci. *Water Res*. **2012**, *46*, 5621–5634.

117. De Boer, T.E.; Taş, N.; Martin Braster, M.; Temminghoff, E.J.M.; Röling, W.F.M.; Roelofs, D. The influence of long-term copper contaminated agricultural soil at different pH levels on microbial communities and springtail transcriptional regulation. *Environ. Sci. Technol*. **2012**, *46*, 60–68.

118. Bischoff, K.M.; Liu, S.; Leathers, T.D.; Worthington, R.E.; Rich, J.O. Modeling bacterial contamination of fuel ethanol fermentation. *Biotechnol. Bioeng*. **2009**, *103*, 117–122.

119. Basaraba, R.J.; Oehme, F.W.; Vorhies, M.W.; Stokka, G.L. Toxicosis in cattle from concurrent feeding of monensin and dried distillers grains contaminated with macrolide antibiotics. *J. Vet. Diagn. Invest*. **1999**, *11*, 79–86.

120. Islam, M.; Toledo, R.; Hamdy, M.K. Stability of virginiamycin and penicillin during alcohol fermentation. *Biomass. Bioenergy* **1998**, *17*, 369–385.

121. Jacob, M.E.; Fox, J.T.; Narayanan, S.K.; Drouillard, J.S.; Renter, D.G.; Nagaraja, T.G. Effects of feeding wet corn distillers grains with solubles with or without monensin and tylosin on the prevalence and antimicrobial susceptibilities of fecal foodborne pathogenic and commensal bacteria in feedlot cattle. *J. Anim. Sci.* **2008**, *86*, 1182–1190.