

Impact of antibiotics as anthropogenic stressor for influencing bacterial evolutionary process – A review

Sanjib Ghosh

Department of Zoology, Jangipur College, Murshidabad, West Bengal, India
Corresponding author e-mail: sanjibzoology@gmail.com

Received: 2 June 2020 / Accepted: 12 September 2020

Abstract. A large number of human induced stressors are affecting natural evolutionary process through altering ecosystems and biodiversity. Antibiotics are one of the most commonly excreted pollutants released in environment since last eight decades. Antibiotics can alter genetic orientation of bacterial population and can exert selection pressure for emerging new taxon. In environments like soil and water, antibiotics directly or indirectly may affect many aspects of natural systems like biogeochemical cycles, nitrifications and decomposition process. All these may bring new selection pressure for bacteria not only in community or population level but also in species level.

Key words: antibiotics, bacteria , evolution, population, community.

1. Introduction

Since industrial revolution human activities has had a great impact on ecosystem and biodiversity of this planet. Directly or indirectly human is acting as one of the most potential driving force that can modify ecosystems as well as biodiversity resulting in vast evolutionary changes in different species around us (Palumbi, 2001). As a hyper-keystone species human dominates over a large number of other keystone species and this hyper-dominance also creates different types of selection pressure on the other component species of the existing biodiversity (Worm & Paine, 2016). Human activities are causing permanent changes in ecosystems and creating new ecosystems called Anthropogenic Biomes or Anthromes (Ellis, 2011). Rapid evolution has been observed in microbes to vertebrates (Dlugosch & Parker, 2008) due to anthropogenic causes. Antibiotics (Baquero & Blazquez, 1997), pesticides (Tabashnik, 1994) and climate change (Parmesan, 2006) are the major anthropogenic stressors that have potential responses to direct evolutionary changes in various ways in different forms of life. In this review I will try to draw a scenario how anthropogenic activities in the form of antibiotics exert

evolutionary pressure on microbial communities of different ecosystems and force them to adapt in various selection pressure. Antibiotics act as a potential ecological stressor in the environment that have the potentiality to alter the structure and composition of microbial communities through resistance expansion and ecological function disturbances in the micro-habitat (Ding & He, 2010).

Antibiotics are used to manage various infectious diseases caused by bacteria in humans, animals, livestock, and aquacultures all over the world (Cycoń et al., 2019). Alexander Fleming (in 1929) discovered penicillin that have inhibitory effect on bacterial cell wall biosynthesis and thus able to stop infectious pathogens like *Staphylococcus aureus*. Antibiotics are used in large scale since last 80 years to treat a variety of infectious diseases of human and animals. Antibiotics are also used in non-medical purposes like Animal Husbandry and Aquaculture, Bee-keeping, Horticulture, Food preservation, Alcohol production and Boat and hull paint (Meek et al., 2015).

Use of antibiotics both in medical and non-medical purposes increases rapidly. It is reported that total global antibiotic consumption has been increased by more than 30 percent between 2000 to 2010 (Van Boeckel et al., 2014). In 2010, 63,200 tons of antibiotics were used in animal farming and aquaculture which was more than all human consumption of that year (Van Boeckel et al., 2015). It has been predicted that in 2030 global antibiotics consumption will be 200% higher than in 2015 (Cycoń et al., 2019).

2. Classes of antibiotic

Antibiotics are complex molecules with different functional groups in their chemical structures and are divided into several classes depending on the mechanisms of action, i.e., inhibition of cell wall synthesis, alteration of cell membranes, inhibition of protein synthesis, inhibition of nucleic acids synthesis, competitive antagonism, and antimetabolite activity (Kümmerer, 2009).

Antibiotics are of three types based on their source of production- natural, synthetic and semi-synthetic molecules. Natural antibiotics are produced by bacteria to inhibit or kill other competitor microorganisms. Semi-synthetic compounds are natural antibiotics chemically altered by inserting different groups to improve its effectiveness (Grenni et al., 2018).

Table 1. Types of antibiotics (Grenni et al., 2018)

Antibiotic class	Mode of action	Example
Aminoglycosides	Inhibition of protein synthesis	Dihydrostreptomycin, Neomycin, Spectinomycin, Streptomycin
Actinomycines	Inhibition of the synthesis of nucleic acids (anticancer drugs)	Actinomycin D
β -Lactams	Inhibition of cell wall synthesis	Amoxicillin, Ampicillin, Cefotaxim, Flucloxacillin, Nafcillin, Oxacillin, Nafcillin, Penicillin G
Diaminopyrimidine	Inhibition of purine and pyrimidine synthesis	Trimethoprim
Glycopeptides	Acting on the wall or membrane cell	Polymyxins, Teicoplanin, Vancomycin
Macrolides	Inhibition of protein synthesis by reversibly binding to the 50S ribosomal subunit	Azithromycin, Clarithromycin, Erythromycin
Nitroimidazole	Inhibition of nucleic acids synthesis	Metronidazole, Tinidazole
Phenicol and amphenicols	Inhibition of protein synthesis	Chloramphenicol, Thiamphenicol
Quinolones and Fluoroquinolones	Inhibition of DNA replication	Ciprofloxacin, Enrofloxacin, Nalidixic acid, Ofloxacin
Rifamycins	Inhibition of nucleic acids synthesis	Rifampicin, Rifapentine
Sulfonamides	Inhibition of the folic acid synthesis	Sulfachloropyridazine, Sulfanilamide, Sulfadimethoxine, Sulfathiazole
Tetracyclines	Inhibition of the protein synthesis	Chlortetracycline, Doxycycline, Oxytetracycline, Tetracycline

3. Source of Antibiotic in the Environment

Antibiotics are widely used for treatment of bacterial infections in humans and animals. Moreover, they are used in Animal Husbandry and Aquaculture, Bee-keeping, Horticulture, Food preservation, Alcohol production, Boat and hull paint (Meek et al., 2015). Only a minute portion of the administered antibiotics are metabolized in human and animal bodies and rest of the drugs are excreted out and discharged into water and soil through municipal wastewater, animal manure, sewage sludge, and biosolids (Bouki et al., 2013; Daghri & Drogui, 2013; Wu et al., 2014). It has been reported that 75–80% of tetracyclines, 50–90% of erythromycin and 60% of lincomycin are excreted in urine and feces (Kumar et al., 2005; Sarmah et al., 2006). The concentrations of antibiotic residues in manure, sewage sludge and biosolids show large variations. Tetracyclines are the most frequently reported antibiotics found in manure (Pan et al., 2011; Chen et al., 2012; Massé et al., 2014). Other groups of antibiotics with considerable concentrations found in manure are fluoroquinolones (Zhao et al., 2010; Van Doorslaer et al., 2014) and sulfonamides (Martínez-Carballo et al., 2007).

Table 2. Maximum reported concentrations of selected antibiotics detected in manure and sewage sludge (Cycoń et al., 2019)

a) MANURE, µg/kg			
Class	Antibiotics	Concentration	Reference
Fluoroquinolones	Ciprofloxacin	45,000	Zhao et al., 2010
	Enrofloxacin	1,420	
	Fleroxacin	99,000	
	Norfloxacin	225,000	
Sulfonamides	Sulfadiazine	91,000	Martínez-Carballo et al., 2007
Tetracyclines	Chlortetracycline	764,000	Massé et al., 2014
	Oxytetracycline	354,000	Chen et al., 2012
	Tetracycline	98,000	Pan et al., 2011
b) SEWAGE SLUDGE, µg/kg dry weight			
Class	Antibiotics	Concentration	Reference
Diaminopyrimidines	Trimethoprim	133	Göbel et al., 2005
Macrolides	Azithromycin	1.3–158	Göbel et al., 2005; Li et al., 2013
Sulfonamides	Sulfadimethoxine	0–20 (22.7)	Lillenberg et al., 2010; Li et al., 2013

4. Fate of Antibiotics in the Environment

In the environment, antibiotics have to face different biotic and abiotic processes like transformation and degradation (Reichel et al., 2013; Cui et al., 2014; Manzetti & Ghisi, 2014; Duan et al., 2017). Molecular structure and physicochemical properties of antibiotics govern their transformation and degradation processes (Thiele-Bruhn, 2003; Pan & Chu, 2017). Degradation process of antibiotics in natural environment is controlled by various biotic and abiotic factors. For this reason variation is found in the rate of degradation of different groups of antibiotics. Long-term persistence of azithromycin, ofloxacin, and tetracycline in soils (with half-lives of 408–3466 days, 866–1733days and 578 days, respectively) were reported by Walters et al. (2010).

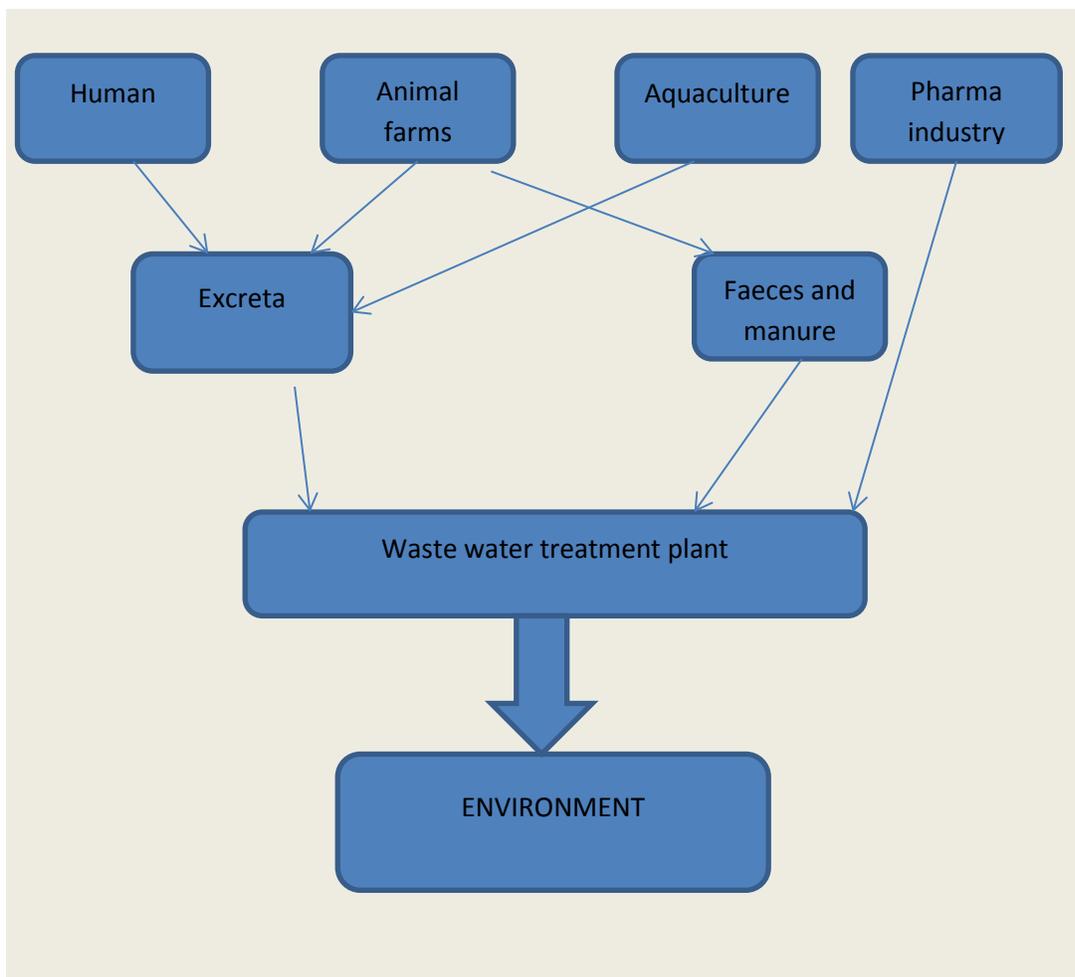


Figure 1. Fate of antibiotics in the environment

5. Impact of Antibiotics

Uncontrolled usage of antibiotics imposes strong selection pressure for resistance development. Emergence of resistance results in adaptation (Sultan et al., 2018). Both antibiotics and antibiotic resistant genes (ARG) directly or indirectly can affect bacterial community (Grenni et al., 2018) structure. Here some direct impact of antibiotics on different aspects of bacterial ecosystem and biodiversity are discussed in short.

5.1. Bacterial ecosystem

Bacterial diversity is mostly governed by their ecosystems. Soil and aquatic ecosystems are more or less loaded with antibiotics and have severe consequences in terms of habitat modification and

interaction with other living forms. Soil plays a pivotal role in ecosystems serving the primary nutrient source and habitat for plants and other organisms. Soil receives a large portion of excreted antibiotics through application of manure and sewage sludge as fertilizers in agricultural fields and for this reason soil acts as hotspots for antibiotics to affect its indigenous microbial populations (Thiele-Bruhn & Beck, 2005). Higher density of bacteria in the soil ecosystem may involve in genetic exchanges, which could result in the development of microbial resistance in the presence of antibiotics (Murray, 1997). Two studies on sulfadiazine (Kotzerke et al., 2008; Schauss et al., 2009) have demonstrated the effects of antibiotics on soil nitrification and denitrification processes. Various antibiotics like ciprofloxacin (Naslund et al., 2008), sulfadiazine (Zielezny et al., 2006; Kotzerke et al., 2008) and tylosin (Müller et al., 2002; Demoling & Bååth, 2008) have been reported to affect soil biomass production soil respiration rates. Nitrogen transformation process has been studied by Tomlinso et al. (1966). They reported that streptomycin (at 400 mg/L) was required to achieve 75% inhibition of ammonia oxidation in activated sludge in 2~4 h. It has also been reported that antibiotics such as oxytetracycline inhibit nitrification process in surface water (Klaver & Matthews, 1994). Methanogenesis has been reported to respond to antibiotics like sulfamethoxazole and ofloxacin (Fountoulakis et al., 2004).

5.2. Bacterial community structure

Microbial biodiversity plays an important role in the maintenance of biological processes in water and soil. Most biogeochemical cycles are exclusively regulated by microorganisms. Antibiotics can act as an ecological stressor in the environment by driving changes in the structure of natural bacterial communities through disappearance of some bacterial groups (Allen et al., 2010). The effects can be found even in non-target organisms with important ecological functions (Pallecchi et al., 2008; Martinez, 2009). Many studies have revealed that the presence of antibiotics may result in a reduction in microbial biodiversity. Moreover, they can influence the growth and enzyme activities of bacterial communities and ultimately ecological functions such as biomass production and nutrient transformation, leading to loss of functional stability (Martinez, 2009; Koike et al., 2007; Pauwels & Verstraete, 2006; Świącilo & Zych-Wężyk, 2013). Antibiotics may have a selective effect on various microbial groups that can alter the relative abundance of different bacterial species and interfere in interactions between different

species (Grenni et al., 2018). Various ecological processes like nitrogen transformation, methanogenesis, sulfate reduction, nutrient cycling and organic matter degradation may be changed due to the presence of different groups of antibiotics in natural environment that individually or altogether may result in severe alteration in the structure and composition of bacterial community (Roose-Amsaleg & Laverman, 2016). Sulfonamides have been reported to induce a change in microbial diversity by reducing not only microbial biomass, but also affecting the relationship between bacteria and fungi (Underwood et al., 2011).

5. 3. Bacterial population structure

Antibiotics can affect the structure and composition of bacterial populations. Any bacterial species has specific type of susceptibility to any given antibiotic (Olivares et al., 2013; Cox & Wright, 2013; Girgis et al., 2009). For any given concentration of antibiotic, a part of the population present in the micro biota (the most susceptible one) will be inhibited and another part will consequently increase their number. It is reported by several workers that a strong stressor (such as the presence of an antibiotic) will reduce diversity (Abeles et al., 2016; Cleary et al., 2016). Presence of mild concentrations of antibiotics may produce an apparent increase in biodiversity by the emergence of new taxons whose presence was very little before antibiotic stress (Zhang et al., 2015). The most significant studies of the effect of antibiotics on the composition of the microbiota have been performed through studying the gut microbiota of humans and other experimental mammal models (Looft & Allen, 2012; Jernberg et al., 2010; Forslund et al., 2013; Robinson & Young, 2010). Most of the researchers observed some misbalances in the bacterial composition upon treatment with antibiotics. Once treatment ends, a recovery of the composition of the microbiome is observed after some time. Recent evidences show that the bacterial groups present in the microbiome before and after the treatment are not same (Raymond et al., 2016). This means that while the overall structure of the population remains constant, the overall genomic content largely varies (Raymond et al., 2016).

5. 4. Bacterial genetic system

Genetic diversity in bacterial population may be increased due to exposure to low levels of antibiotics through activation of the bacterial SOS response which in turn may result in an increased rate of mutation throughout the genome (Foster, 2007; Andersson & Hughes, 2014).

Antibiotics were also found to increase the horizontal transfer of genetic material between bacteria either by conjugation (Maiques et al., 2006) or by increasing competence resulting in the uptake of extracellular DNA (Slager et al., 2014). A large number of antibiotics were found to affect the process of gene regulation at the transcription level (Davies et al., 2006; Goh et al., 2002), either via direct binding or through other regulatory mechanisms such as riboswitches (Blount & Breaker, 2006) and quorum sensing (Rémy et al., 2018), resulting in increased phenotypic variability. Together, these mechanisms increase the available pool of genetic and phenotypic diversity in bacterial populations exposed to antibiotic.

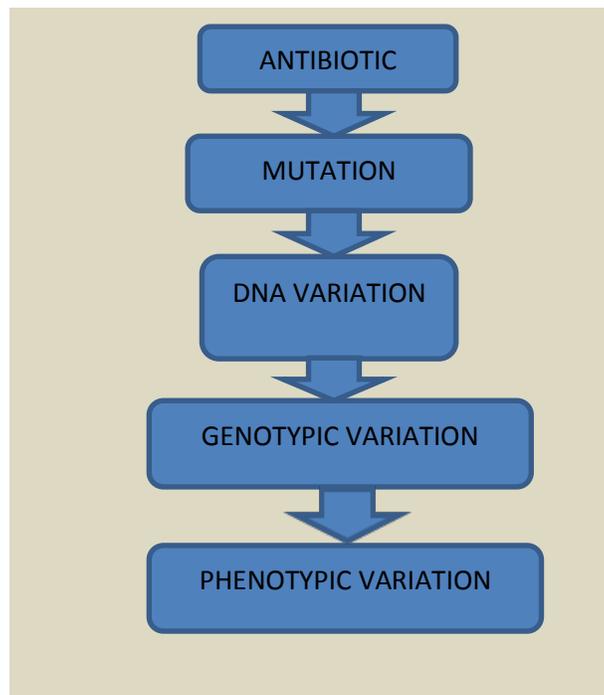


Figure 2. Impact of antibiotics on bacterial Genetic system

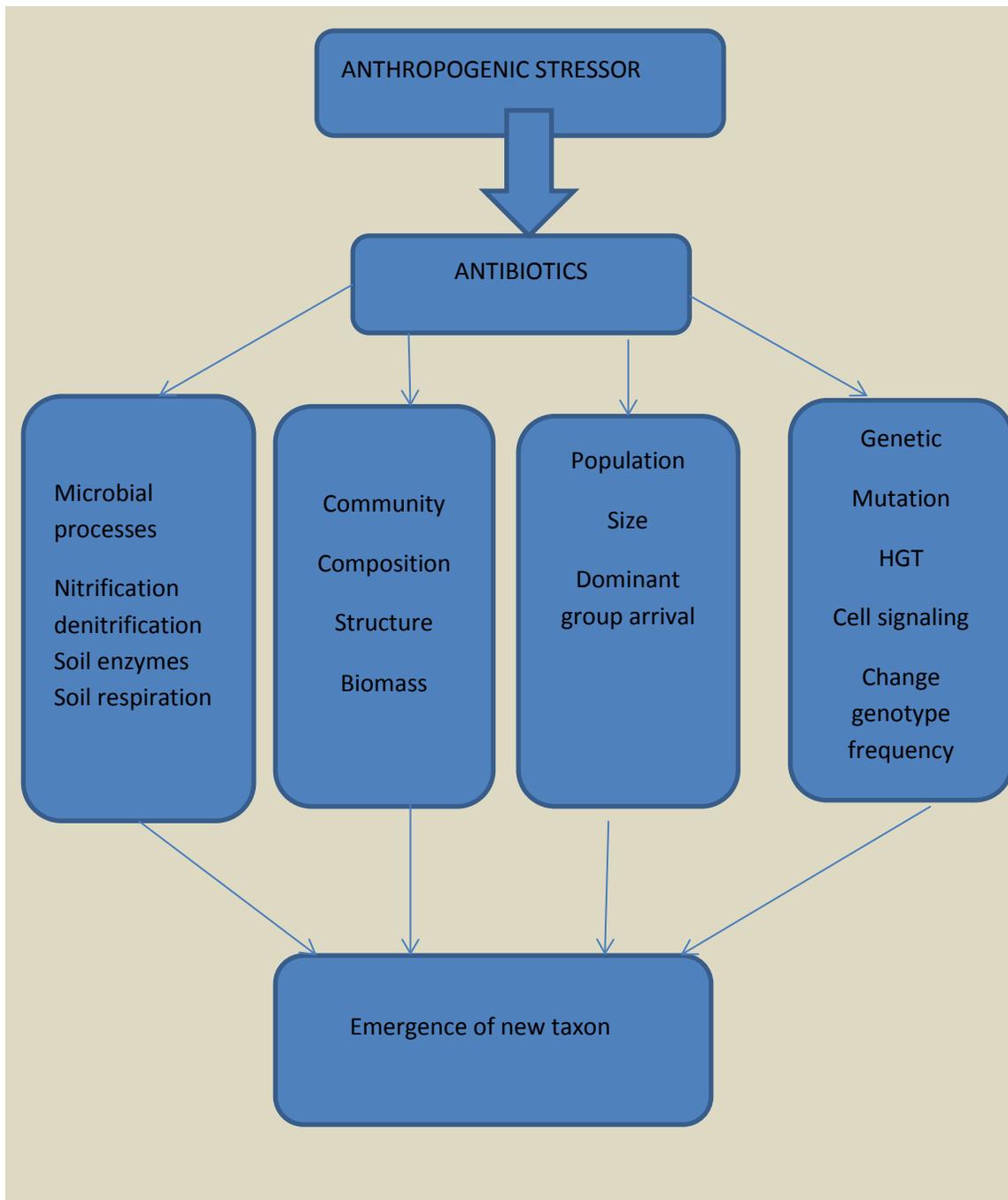


Figure 3. How antibiotics influence emergence of new Taxa

6. Discussion

Antibiotics are naturally produced compounds and most of the bacterial populations are well adapted to the presence of the natural concentrations of these antimicrobials (Kelsic et al., 2015).

Antibiotics are most successful compounds ever discovered to treat infectious diseases caused by bacterial infection. Since last eight decades we have increased the usage of this magical drugs in various medical purposes as well as in non-medical purposes. Uncontrolled and unethical use of antibiotics are now a critical concern of health care providers as most of the antibiotics become resistant to their target organisms. Huge amount of antibiotics are now documented to present in different ecosystems like soil and water. Now a days another voices from the side of ecologists and environmentalists are raised as a large number of studies and reports are coming in light evidenced with severe impacts of antibiotics beyond their target organisms. The selective pressures imposed by antibiotic pollution can impact on the evolutionary dynamics observed in microbial populations in different ways (Martínez, 2017).

Different bacterial species or lineages within a species harbor phenotypic heterogeneity in their response to antibiotics. Certain bacterial populations have been reported to exhibit different levels of tolerance to antibiotics due to changes in gene expression or fluctuations in critical physiological traits (Sanchez-Romero & Casadesus, 2013; Sanchez-Romero & Dunlop, 2018). Bacteria and fungi inhabiting soil and aquatic environments are not only the foundation of the most diverse and densely populated ecosystems on Earth (Lozupone & Knight, 2007; Caporaso et al., 2011) but are also crucial for the performance of important ecological processes like nutrient cycling, decomposition, and primary productivity (Torsvik et al., 2002; Gibbons & Gilbert, 2015; Van Bruggen et al., 2019). Selective pressures associated with antibiotic pollution can act on the overall microbial community composition by reducing taxa diversity or by shifting microbial composition. Antibiotic exposure tends to favour an increase in Gram-negative bacteria as opposed to Gram-positive bacteria. The latter showing increased susceptibility to antibiotics due to the absence of an outer cell membrane (Delcour, 2009). Exposure to antibiotics may thus result in the loss of key microbial taxa with important ecological roles. Antibiotic pollution in aquatic environments was found to reduce overall microbial diversity, including taxa responsible for carbon cycling and primary productivity (Grenni et al., 2018; Eckert et al., 2019; Ding & He, 2010). Similarly, the presence of antibiotics in soil was found to alter microbial community structure, leading to a loss of biomass and a reduction in microbial activity including nitrification, denitrification, and respiration (Thiele-Bruhn & Beck, 2005; Westergaard et al., 2001; Cycoń et al., 2019). Moreover, antibiotics can also affect bacterial enzyme activity, including dehydrogenases, phosphatases, and ureases, which are considered important indicators

of soil activity (Cycoń et al., 2019). Finally, antibiotic disruption of microbial communities can also lead to an increased abundance of parasites and pathogens in both soil and water environments. For example, the presence of antibiotic pollution in aquatic environment was shown to lead to an increase frequency of toxic Cyanobacteria species, causing eutrophication in freshwater environments (Drury et al., 2013).

7. Conclusions

It can be summarized that antibiotic load on environment is created by human and the effect of antibiotic is continuous alteration in genetic combinations of bacterial populations resulting in selection of new taxon in different ecosystems. Global impact of antibiotics may be extended onto their beneficial interactions with plants and organisms. Alteration in the composition of bacterial community may create selection pressure for other higher organisms too. Though it needs more study and data, theoretically it can be hypothesized that anthropogenic activities like imposing antibiotic load in environment may alter the global evolutionary process in bacterial population to some extent.

References

- Abeles S.R., Jones M.B., Santiago-Rodriguez T.M., Ly M., Klitgord N., Yooseph S., Nelson K.E. & Pride D.T., 2016, Microbial diversity in individuals and their household contacts following typical antibiotic courses. *Microbiome* 4(1): 39.
- Allen H.K., Donato J., Wang H.H., Cloud-Hansen K.A., Davies J. & Handelsman J., 2010, Call of the wild: antibiotic resistance genes in natural environments. *Nat. Rev. Microbiol.* 8: 251–259.
- Andersson D.I. & Hughes D., 2014, Microbiological effects of sublethal levels of antibiotics. *Nat. Rev. Microbiol.* 12(7): 465–478.
- Baquero F. & Blazquez J., 1997, Evolution of antibiotic resistance. *Trends Ecol. Evol.* 12: 482–87.
- Blount K.F. & Breaker R.R., 2006, Riboswitches as antibacterial drug targets. *Nat. Biotechnol.* 24: 1558–1564.
- Bouki C., Venieri D. & Diamadopoulos E., 2013, Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: a review. *Ecotoxicol. Environ. Saf.* 91: 1–9.
- Caporaso J.G., Lauber C.L., Walters W.A., Berg-Lyons D., Lozupone C.A., Turnbaugh P.J., Fierer N. & Knight R., 2011, Global patterns of 16S rRNA diversity at a depth of millions of sequences per sample. *Proc. Natl. Acad. Sci. USA* 108: 4516–4522.
- Chen Y.S., Zhang H.B., Luo Y.M. & Song J., 2012, Occurrence and assessment of veterinary antibiotics in swine manures: a case study in East China. *Chinese Sci. Bull.* 57: 606–614.

- Cleary D.W., Bishop A. H., Zhang L., Topp E., Wellington E.M.H. & Gaze W.H., 2016, Long-term antibiotic exposure in soil is associated with changes in microbial community structure and prevalence of class 1 integrons. *FEMS Microbiol. Ecol.* 92(10): fiw159. Doi: 10.1093/femsec/fiw159
- Cox G. & Wright G.D., 2013, Intrinsic antibiotic resistance: mechanisms, origins, challenges and solutions. *Int. J. Med. Microbiol.* 303(6–7): 287–92.
- Cui H., Wang S.-P., Fu J., Zhou Z.-Q., Zhang N. & Guo L., 2014, Influence of ciprofloxacin on microbial community structure and function in soils. *Biol. Fertil. Soils* 50: 939–947.
- Cycoń M., Mroziak A. & Piotrowska-Seget Z., 2019, Antibiotics in the Soil Environment—Degradation and Their Impact on Microbial Activity and Diversity. *Front. Microbiol.* 10: 338. Doi: 10.3389/fmicb.2019.00338
- Daghrir R. & Drogui P., 2013, Tetracycline antibiotics in the environment: a review. *Environ. Chem. Lett.* 11: 209–227.
- Davies J., Spiegelman G.B. & Yim G., 2006, The world of subinhibitory antibiotic concentrations. *Curr. Opin. Microbiol.* 9: 445–453.
- Delcour A.H., 2009, Outer membrane permeability and antibiotic resistance. *Biochim. Biophys. Acta Proteins Proteom.* 1794: 808–816.
- Demoling L.A. & Bååth E., 2008, No long-term persistence of bacterial pollution-induced community tolerance in tylosin-polluted soil. *Environ. Sci. Technol.* 42: 6917–6921
- Ding C. & He J., 2010, Effect of antibiotics in the environment on microbial populations. *Appl. Microbiol. Biotechnol.* 87: 925–941.
- Dlugosch K.M. & Parker I.M., 2008, Invading populations of an ornamental shrub show rapid life history evolution despite genetic bottlenecks. *Ecol. Lett.* 11: 701–9.
- Drury B., Scott J., Rosi-Marshall E.J. & Kelly J.J., 2013, Triclosan exposure increases triclosan resistance and influences taxonomic composition of benthic bacterial communities. *Environ. Sci. Technol.* 47: 8923–8930
- Duan M., Li H., Gu J., Tuo X., Sun W., Qian X. & Wang X., 2017, Effects of biochar on reducing the abundance of oxytetracycline, antibiotic resistance genes, and human pathogenic bacteria in soil and lettuce. *Environ Pollut.* 224: 787–795.
- Eckert E.M., Quero G.M., Di Cesare A., Manfredini G., Mapelli F., Borin S., Fontaneto D., Luna G.M. & Corno G., 2019, Antibiotic disturbance affects aquatic microbial community composition and food web interactions but not community resilience. *Mol. Ecol.* 28: 1170–1182.
- Ellis E.C., 2011, Anthropogenic transformation of the terrestrial biosphere. *Philos. Trans. R. Soc. A: Math. Phys. Eng. Sci.* 369: 1010–1035.
- Forslund K., Sunagawa S., Kultima J.R., Mende D.R., Arumugam M., Typas A. & Bork P., 2013, Country-specific antibiotic use practices impact the human gut resistome. *Genome Res.* 23(7): 1163–1169.
- Foster P., 2007, Stress-induced mutagenesis in bacteria. *Crit. Rev. Biochem. Mol. Biol.* 42: 373–397.
- Fountoulakis M.S., Drillia P., Stamatelatos K. & Lyberatos G., 2004, Toxic effect of pharmaceuticals on methanogenesis. *Water Sci. Technol.* 50: 335–340.
- Gibbons S.M. & Gilbert J.A., 2015, Microbial diversity-exploration of natural ecosystems and microbiomes. *Curr. Opin. Genet. Dev.* 35:66–72.
- Girgis H.S., Hottes A.K. & Tavazoie S., 2009, Genetic architecture of intrinsic antibiotic susceptibility. *PLoS One* 4(5): e5629.

- Göbel A., Thomsen A., McArdell C.S., Alder A.C, Giger W., Theiss N., Löffler D. & Ternes T.A., 2005, Extraction and determination of sulfonamides, macrolides, and trimethoprim in sewage sludge. *J. Chromatogr. A* 1085: 179–189.
- Goh E.-B., Yim G., Tsui W., McClure J., Surette M.G. & Davies J., 2002, Transcriptional modulation of bacterial gene expression by subinhibitory concentrations of antibiotics. *Proc. Natl. Acad. Sci. USA* 99: 17025–17030.
- Grenni P., Ancona V. & Barra Caracciolo A., 2018. Ecological effects of antibiotics on natural ecosystems: a review. *Microchem. J.* 136: 25–39.
- Jernberg C., Löfmark S., Edlund C. & Jansson J.K., 2010, Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology* 156(1): 3216–23.
- Kelsic E.D., Zhao J., Vetsigian K. & Kishony R., 2015, Counteraction of antibiotic production and degradation stabilizes microbial communities. *Nature* 521(7553): 516–519.
- Klaver A.L. & Matthews R.A., 1994, Effects of oxytetracycline on nitrification in a model aquatic system. *Aquaculture* 123: 237–247.
- Koike S., Krapac I.G., Oliver H.D., Yannarell A.C., Chee-Sanford J.C., Aminov R.I. & Mackie R.I., 2007, Monitoring and source tracking of tetracycline resistance genes in lagoons and groundwater adjacent to swine production facilities over a 3-year period. *Appl. Environ. Microbiol.* 73: 4813–4823.
- Kotzerke A., Sharma S., Schauss K., Heuer H., Thiele-Bruhn S., Smalla K., Wilke B.M. & Schloter M., 2008, Alterations in soil microbial activity and N-transformation processes due to sulfadiazine loads in pig-manure. *Environ. Pollut.* 153: 315–322.
- Kumar K., Gupta C.S., Chander Y. & Singh A.K., 2005, Antibiotic use in agriculture and its impact on the terrestrial environment. *Adv. Agron.* 87: 1–54.
- Kümmerer K., 2009, Antibiotics in the aquatic environment—a review—part I. *Chemosphere* 75: 417–434.
- Li W., Shi Y., Gao L., Liu J. & Cai Y., 2013, Occurrence, distribution and potential affecting factors of antibiotics in sewage sludge of wastewater treatment plants in China. *Sci. Tot. Environ.* 445–446: 306–313.
- Lillenbergh M., Yurchenko S., Kipper K., Herodes K., Pihl V., Löhmus R., Ivask M., Kuu A., Kutti S., Litvin S.V. & Nei L., 2010, Presence of fluoroquinolones and sulfonamides in urban sewage sludge and their degradation as a result of composting. *Int. J. Environ. Sci. Technol.* 7: 307–312.
- Looft T. & Allen H.K., 2012, Collateral effects of antibiotics on mammalian gut microbiomes. *Gut Microbes* 3(5): 463–467.
- Lozupone C.A. & Knight R., 2007, Global patterns in bacterial diversity. *Proc. Natl. Acad. Sci. USA* 104: 11436–11440.
- Maiques E., Úbeda C., Campoy S., Salvador N., Lasa Í., Novick R.P., Barbé J. & Penadés J.R., 2006, Beta-lactam antibiotics induce the SOS response and horizontal transfer of virulence factors in *Staphylococcus aureus*. *J. Bacteriol.* 188: 2726–2729.
- Manzetti S. & Ghisi R., 2014, The environmental release and fate of antibiotics. *Mar. Pollut. Bull.* 79: 7–15.
- Martinez J.L., 2009, Environmental pollution by antibiotics and by antibiotic resistance determinants. *Environ. Pollut.* 157: 2893–2902.
- Martínez J.L., 2017, Effect of antibiotics on bacterial populations: A multi-hierarchical selection process. *F1000Research* 6(F1000 Faculty Rev.): 51.

- Martínez-Carballo E., González-Barreiro C., Scharf S. & Gans O., 2007, Environmental monitoring study of selected veterinary antibiotics in animal manure and soils in Austria. *Environ. Pollut.* 148: 570–579.
- Massé D.I., Saady N.M.C. & Gilbert Y., 2014, Potential of biological processes to eliminate antibiotics in livestock manure: an overview. *Animals* 4: 146–163.
- Meek R.W., Vyas H. & Piddock L.J.V., 2015, Nonmedical Uses of Antibiotics: Time to Restrict Their Use? *PLoS Biol.* 13(10): e1002266.
- Müller A.K., Westergaard K., Christensen S. & Sørensen S.J., 2002, The diversity and function of soil microbial communities exposed to different disturbances. *Microb. Ecol.* 44: 49–58.
- Murray B.E., 1997, Antibiotic resistance. *Adv. Intern. Med.* 42: 339–367.
- Naslund J., Hedman J.E. & Agestrand C., 2008, Effects of the antibiotic ciprofloxacin on the bacterial community structure and degradation of pyrene in marine sediment. *Aquat. Toxicol.* 90: 223–227.
- Olivares J., Bernardini A., Garcia-Leon G., Corona F., Sanchez M.B. & Martinez J.L., 2013, The intrinsic resistance of bacterial pathogens. *Front. Microbiol.* 30(4): 103. Doi: 10.3389/fmicb.2013.00103
- Pallecchi L., Bartoloni A., Paradisi F. & Rossolini G.M., 2008, Antibiotic resistance in the absence of antimicrobial use: mechanisms and implications. *Expert Rev. Anti-Infect. Ther.* 6: 725–732.
- Palumbi S.R., 2001, Humans as the world's greatest evolutionary force. *Science* 293: 1786–1790.
- Pan X., Qiang Z., Ben W. & Chen M., 2011, Residual veterinary antibiotics in swine manure *Chemosphere* 84: 695–700.
- Pan M. & Chu L.M., 2017, Leaching behavior of veterinary antibiotics in animal manure-applied soils. *Sci. Total Environ.* 579: 466–473.
- Parmesan C., 2006, Ecological and evolutionary responses to recent climate change. *Annu. Rev. Ecol. Evol. Syst.* 37: 637–669.
- Pauwels B. & Verstraete W., 2006, The treatment of hospital wastewater: an appraisal. *J. Water Health* 4: 405–416.
- Raymond F., Deraspe M., Boissinot M., Bergeron M.G. & Corbeil J., 2016, Partial recovery of microbiomes after antibiotic treatment. *Gut Microbes* 7(5): 428–434.
- Reichel R., Rosendahl I., Peeters E.T.H.M., Focks A., Groeneweg J., Bierl R., Schlichting A., Amelung W. & Thiele-Bruhn S., 2013, Effects of slurry from sulfadiazine- (SDZ) and difloxacin- (DIF) medicated pigs on the structural diversity of microorganisms in bulk and rhizosphere soil. *Soil Biol. Biochem.* 62: 82–91.
- Rémy B., Mion S., Plener L., Elias M., Chabrière E. & Daudé D., 2018, Interference in bacterial quorum sensing: A biopharmaceutical perspective. *Front. Pharmacol.* 9: 203.
- Robinson C.J. & Young V.B., 2010, Antibiotic administration alters the community structure of the gastrointestinal microbiota. *Gut Microbes* 1(4): 279–84.
- Roose-Amsaleg C. & Laverman A.M., 2016, Do antibiotics have environmental side-effects? Impact of synthetic antibiotics on biogeochemical processes. *Environ. Sci. Pollut. Res.* 23: 4000–4012.
- Sanchez-Romero M.A. & Casades J., 2013, Contribution of phenotypic heterogeneity to adaptive antibiotic resistance. *Proc. Natl. Acad. Sci. USA* 111: 355–360.

- Sanchez-Romero I. & Dunlop M.J., 2018, Heterogeneity in efflux pump expression predisposes antibiotic-resistant cells to mutation. *Science* 362: 686–690.
- Sarmah A.K., Meyer M.T. & Boxall A.B.A., 2006, A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. *Chemosphere* 65: 725–759.
- Schauss K., Focks A., Leininger S., Kotzerke A., Heuer H., Thiele-Bruhn S., Sharma S., Wilke B.M., Matthies M., Smalla K., Munch J.C., Amelung W., Kaupenjohann M., Schloter M. & Schleper C., 2009, Dynamics and functional relevance of ammonia-oxidizing archaea in two agricultural soils. *Environ. Microbiol.* 11: 446–456.
- Slager J., Kjos M., Attaiech L. & Veening J.W., 2014, Antibiotic-induced replication stress triggers bacterial competence by increasing gene dosage near the origin. *Cell* 157: 395–406.
- Sultan I., Rahman S., Jan A.T., Siddiqui M.T., Mondal A.H. & Haq Q.M.R., 2018, Antibiotics, Resistome and Resistance Mechanisms: A Bacterial Perspective. *Front. Microbiol.* 9: 2066. Doi: 10.3389/fmicb.2018.02066
- Święciło A. & Zych-Węzyk I., 2013, Bacterial stress response as an adaptation to life in a soil environment. *Pol. J. Environ. Stud.* 22: 1577–1587.
- Tabashnik B.E., 1994, Evolution of resistance to *Bacillus thuringiensis*. *Annu. Rev. Entomol.* 39: 47–79.
- Thiele-Bruhn S., 2003, Pharmaceutical antibiotic compounds in soils - a review. *J. Plant Nutr. Soil Sci.* 166: 145–167.
- Thiele-Bruhn S. & Beck I.C., 2005, Effects of sulfonamide and tetracycline antibiotics on soil microbial activity and microbial biomass. *Chemosphere* 59: 457–465.
- Tomlinso T.G., Boon A.G. & Trotman C.A.N., 1966, Inhibition of nitrification in activated sludge process of sewage disposal. *J. Appl. Bacteriol.* 29: 266–291.
- Torsvik V., Øvreås L. & Øvreås L., 2002, Microbial Diversity and Function in Soil: From Genes to Ecosystems. *Curr. Opin. Microbiol.* 5: 240–245.
- Underwood J.C., Harvey R.W., Metge D.W., Repert D.A., Baumgartner L.K., Smith R.L., Roane T.M. & Barber L., 2011, Effects of the antimicrobial sulfamethoxazole on groundwater bacterial enrichment. *Environ. Sci. Technol.* 45: 3096–3101.
- Van Boeckel T.P., Gandra S., Ashok A., Caudron Q., Grenfell B.T., Levin S.A. & Laxminarayan R., 2014, Global Antibiotic Consumption 2000 to 2010: An Analysis of National Pharmaceutical Sales Data. *The Lancet Infectious Diseases* 3099(14): 1–9.
- Van Boeckel T.P., Brower C., Gilbert M., Grenfell B.T., Levin S., Robinson T.P., Teillant A. & Laxminarayan R., 2015, Global Trends in Antimicrobial Use in Food Animals. *Proc. Natl Acad. of Sci. USA* 112(18): 5649–5654.
- Van Bruggen A.H.C., Goss E.M., Havelaar A., Van Diepeningen A.D., Finckh M.R. & Morris J.G., 2019, One Health—Cycling of diverse microbial communities as a connecting force for soil, plant, animal, human and ecosystem health. *Sci. Total Environ.* 664: 927–937.
- Van Doorslaer X., Dewulf J., Van Langenhove H. & Demeestere K., 2014, Fluoroquinolone antibiotics: an emerging class of environmental micropollutants. *Sci. Total Environ.* 500–501: 250–269.
- Walters E., McClellan K. & Halden R.U., 2010, Occurrence and loss over three years of 72 pharmaceuticals and personal care products from biosolids-soil mixtures in outdoor mesocosms. *Water Res.* 44: 6011–6020.

- Westergaard K., Müller A.K., Christensen S., Bloem J. & Sørensen S.J., 2001, Effects of tylosin as a disturbance on the soil microbial community. *Soil Biol. Biochem.* 33: 2061–2071.
- Worm B. & Paine R.T., 2016, Humans as a Hyper keystone Species. *Trends Ecol. Evol.* 31: 600–607.
- Wu X.-L., Xiang L., Yan Q.-Y., Jiang Y.-N., Li Y.-W., Huang X.-P., Li H., Cai Q.-Y. & Mo C.H., 2014, Distribution and risk assessment of quinolone antibiotics in the soils from organic vegetable farms of a subtropical city, Southern China. *Sci. Total Environ.* 487: 399–406.
- Zhang Y., Tian Z. & Liu M., 2015, High Concentrations of the Antibiotic Spiramycin in Wastewater Lead to High Abundance of Ammonia-Oxidizing Archaea in Nitrifying Populations. *Environ. Sci. Technol.* 49(15): 9124–32.
- Zhao L., Dong Y.H. & Wang H., 2010, Residues of veterinary antibiotics in manures from feedlot livestock in eight provinces of China. *Sci. Total Environ.* 408: 1069–1075.
- Zielezny Y., Groeneweg J., Vereecken H. & Tappe W., 2006, Impact of sulfadiazine and chlorotetracycline on soil bacterial community structure and respiratory activity. *Soil Biol. Biochem.* 38: 2372–2380.