Environment International 116 (2018) 60–73

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Antibiotics and antibiotic resistance genes in global lakes: A review and meta-analysis

Yuyi Yang[a,b,*,1], Wenjuan Song[c,1], Hui Lin[d], Weibo Wang[a], Linna Du[e], Wei Xing[a,**]

[a] Key Laboratory of Aquatic Botany and Watershed Ecology, Wuhan Botanical Garden, Chinese Academy of Sciences, Wuhan 430074, China
[b] School of Life Sciences, University of Dundee, Dundee DD1 5EH, Scotland, UK
[c] Xinjiang Institute of Ecology and Geography, Chinese Academy of Sciences, Urumqi 830011, China
[d] Institute of Environmental Resources and Soil Fertilizers, Zhejiang Academy of Agricultural Sciences, Hangzhou 310021, China
[e] Department of Agriculture and Biotechnology, Wenzhou Vocational College of Science and Technology, Wenzhou 325006, China

A R T I C L E I N F O

Keywords:
Species sensitivity distributions
Niche
Aquatic biota
Antibiotics
Antibiotic resistance genes
Meta-analysis

A B S T R A C T

Lakes are an important source of freshwater, containing nearly 90% of the liquid surface fresh water worldwide. Long retention times in lakes mean pollutants from discharges slowly circulate around the lakes and may lead to high ecological risk for ecosystem and human health. In recent decades, antibiotics and antibiotic resistance genes (ARGs) have been regarded as emerging pollutants. The occurrence and distribution of antibiotics and ARGs in global freshwater lakes are summarized to show the pollution level of antibiotics and ARGs and to identify some of the potential risks to ecosystem and human health. Fifty-seven antibiotics were reported at least once in the studied lakes. Our meta-analysis shows that sulfamethoxazole, sulfamerazine, sulfameter, tetracycline, oxytetracycline, erythromycin, and roxithromycin were found at high concentrations in both lake water and lake sediment. There is no significant difference in the concentration of sulfonamides in lake water from China and that from other countries worldwide; however, there was a significant difference in quinolones. Erythromycin had the lowest predicted hazardous concentration for 5% of the species (HC_5) and the highest ecological risk in lakes. There was no significant difference in the concentration of sulfonamide resistance genes (*sul1* and *sul2*) in lake water and river water. There is surprisingly limited research on the role of aquatic biota in propagation of ARGs in freshwater lakes. As an environment that is susceptible to cumulative build-up of pollutants, lakes provide an important environment to study the fate of antibiotics and transport of ARGs with a broad range of niches including bacterial community, aquatic plants and animals.

1. Introduction

The discovery of penicillin by Sir Alexander Fleming in 1928 opened the modern era of antibiotic innovation and development (Fleming, 1929). Today, antibiotics are not only used as medicine for humans but are also widely used in animal husbandry and aquaculture. However, antibiotics that are unintentionally discharged into the environment pose a great threat to ecosystems and human health. These antibiotics can accumulate in food webs and, even more alarming, antibiotic resistance genes (ARGs) can be transferred between environmental bacteria and human pathogens (Bengtsson-Palme and Larsson, 2015; Du and Liu, 2012; Li et al., 2015; Martinez et al., 2015; Van Boeckel et al., 2015). Antibiotic resistance is not a new phenomenon (D'Costa et al., 2011; Wright and Poinar, 2012), but the rapid and widespread increase of ARGs has been accelerated in recent years with the increase in discharge of antibiotics and other pollutants (e.g., heavy metals) into the environment (Bengtsson-Palme et al., 2014; Czekalski et al., 2014; Yang et al., 2017b; Yin et al., 2013). In fact, ARGs have recently been regarded as an emerging pollutant (Pruden et al., 2006). As such, antibiotics and their effects on the environment (ARGs, antibiotic resistant bacteria (ARB), etc.) have become an important theme in environmental science.

Aquatic environments are major pools for antibiotics and ARGs. Effluents from wastewater treatment plants, industry, hospitals and pig farms, for example, will all eventually reach some water source (Lavilla Lerma et al., 2014; Liu et al., 2012; W. Zhang et al., 2009; Zhu et al., 2013). The effects of antibiotics on aquatic micro-organisms, the nitrogen cycle and natural ecosystems have been summarized (Grenni

* Correspondence to: Y. Yang, School of Life Sciences, University of Dundee, DD1 5EH, Scotland, UK.
** Correspondence to: W. Xing, Wuhan Botanical Garden, Chinese Academy of Sciences, Wuhan 430074, China.
E-mail addresses: ytyang@dundee.ac.uk (Y. Yang), xingwei108@wbgcas.cn (W. Xing).
[1] The authors contributed equally to this paper.

https://doi.org/10.1016/j.envint.2018.04.011
Received 18 November 2017; Received in revised form 6 April 2018; Accepted 6 April 2018

et al., 2018; Roose-Amsaleg and Laverman, 2016; Välitalo et al., 2017). The distribution and environmental behaviour (e.g., adsorption and degradation) of antibiotics in aquatic environments have also been reviewed (Bu et al., 2013; Kümmerer, 2009a, 2009b; Liu and Wong, 2013). However, some aquatic environments, specifically lakes and rivers, behave differently due to their different hydraulic characteristics. In rivers, the concentration of pollutants in sediments gradually decreases downstream of a source due to hydraulic characteristics (Pruden et al., 2012; Reuther, 2009). Rivers seem to have received most attention among aquatic environments, likely due to their rapid transport of antibiotics and ARGs and the obvious identification of pollution sources and landscapes in different reaches (Chen et al., 2013; Pruden et al., 2012; Rodriguez-Mozaz et al., 2015; Storteboom et al., 2010). In lakes, the residence time of contaminants increases because of the long water retention time relative to rivers. This means that pollutants from discharges slowly circulate around the lakes and makes pollution control in lake basins especially critical (Lyandres, 2012; Reuther, 2009). Due to these characteristics, lakes are predicted to have the potential to store and accumulate ARGs to a greater extent than rivers (Czekalski et al., 2015). Lakes serve as an important drinking source of freshwater, containing nearly 90% of the liquid surface fresh water worldwide; in contrast, rivers contain only 2% (McConnell and Abel, 2013).

Until now, no comprehensive review of antibiotics and ARGs in lakes has been conducted. In this review, we collated the occurrence, distribution and risk of antibiotics and ARGs in lakes. The objectives were to (1) identify antibiotics with high concentrations through a meta-analysis and prioritize antibiotics with potential ecological risk in lakes; (2) examine the difference in antibiotic pollution between lakes in China and in other countries worldwide, as well as the temporal trend of antibiotics in the most-studied lake, Taihu Lake; and (3) reveal the ARG pollution status in lakes. Factors influencing ARG propagation, potential risks of ARGs to human health, and the bioaccumulation of antibiotics in lakes were also discussed.

2. Methodology

2.1. Data collection

To survey antibiotics and ARGs in lakes worldwide, we used the Web of Knowledge database (http://apps.webofknowledge.com) to retrieve publications. Our search terms included [lake AND antibiotic] AND/OR [lake OR river AND/OR antibiotic resistance genes] AND/OR [lake OR river AND/OR antimicrobial resistance genes]. The database was searched for studies published up to 18 January 2018. Publications were then checked individually to eliminate any duplicates or irrelevant articles. Ultimately, 45 relevant papers reporting antibiotics in global lakes met our criteria. The name, country, antibiotic and/or ARG concentrations, and sampling dates are provided in Tables S1–S5, Supplementary material I. Seventeen and forty-seven studies respectively reported ARG analysis using culture-independent methods in lakes and rivers (Tables S1–S3, Supplementary material II). Trimethoprim/sulfamethoxazole (TMP/SMX), also known as co-trimoxazole, is used to treat a variety of bacterial infections, and TMP/SMX concentrations were included with sulfonamides. It should be noted that several anonymous lakes in India that receive effluent from treatment plants had concentrations of quinolone antibiotics at $\mu g\,L^{-1}$ or $mg\,L^{-1}$ levels (Fick et al., 2009), concentrations that are 10^3 to 10^4 times higher than those detected in other lakes (Table S3, Supplementary material I). Therefore, these lakes were not included in the meta-analysis. Toxicology data for antibiotics on aquatic organisms were retrieved from the United States Environmental Protection Agency (USEPA) ECOTOX database (https://cfpub.epa.gov/ecotox/). The search criteria used to gather the appropriate toxicity data included the following: freshwater medium, endpoint of lethal concentration required to kill 50% of the population (LC_{50}) or half maximal effective concentration (EC_{50}), exposure duration of $<$ 10 days, and test location of the laboratory. Toxicity data for samples without concentration ranges were not used in this study.

2.2. Statistical analysis

2.2.1. Meta-analysis

The mean concentrations of antibiotics were either provided in the publications or calculated using the original data. Concentrations that were "not detected" or "below detection limit" were entered as zero values, similar to a recent meta-analysis on organic contaminants (Meng et al., 2016). Antibiotic concentrations from the same lake but from different sampling years were considered as different data entries; however, antibiotic concentrations from the same lake but from different seasons in the same year were used to obtain a single mean value. The concentrations of antibiotics in the water and sediment were recorded in $ng\,L^{-1}$ and $ng\,g^{-1}$, respectively. Only antibiotics with at least two values were included in the meta-analysis. The median values and their confidence intervals for the mean concentrations of antibiotics in lakes across the Earth were calculated with the wilcox.test function in R software (R Foundation for Statistical Computing, Vienna, Austria). Comparisons of the concentrations of antibiotics in lakes from China and other countries worldwide were examined by a Mann-Whitney *U* test in R software. The temporal trend of antibiotics in Taihu Lake, China was analysed with a Pearson correlation analysis. Mann-Whitney *U* tests were used to compare the maximum relative abundances of *sul1* and *sul2* between lakes and rivers, and the absolute abundances of *sul1* between lakes and rivers.

2.2.2. Ecological risk assessment of antibiotics

Information on the toxicological impacts of many potentially harmful antibiotics is lacking (Välitalo et al., 2017). Therefore, as shown by Staples et al. (2008), antibiotics that had EC_{50} or LC_{50} data for at least four aquatic species within the ECOTOX database were analysed for species sensitivity distribution (SSD) analysis. The hazardous concentrations for 5% of the species (HC_5) derived from SSD were accompanied by a confidence limit that conveys information about the shape of the statistical distribution of toxicity values and their variance (Belanger et al., 2016). The values of HC_5 for antibiotics were calculated with R software. HC_5 values were then used to calculate the predicted no effect concentrations (PNEC) with an application factor of 5. The ecological risk of antibiotics in lake water was analysed with a hazard quotient (HQ), which is the ratio of the measured environmental concentration (MEC) and PNEC.

3. Antibiotics in lakes

3.1. Overview of antibiotics detected in global lakes

The detection of antibiotics in lakes began in 2002 in Lake Ontario with the use of liquid chromatography-mass spectrometry (LC-MS) and liquid chromatography fluorescence detection (LC-FLD) (Nakata et al., 2005). Most later studies used the LC/MS/MS system, which is more efficient than only using the parent ions as in LC-MS analysis (Tables S1–S5, Supplementary material I). There were 57 antibiotics reported at least once in the water and sediments (Tables S1–S5, Supplementary material I). Antibiotics detected in lakes were classified into the following categories: sulfonamides, tetracyclines, quinolones, macrolides, lincosamides, and others (β-lactam, quinoxalines, and polyether and amphenicol antibiotics) (Table 1). The detection frequency may be related with the degradation and adsorption behaviour of antibiotics in lake water and sediments. Tetracyclines, fluoroquinolones and macrolides have a strong adsorption on particles and sediments (Huang et al., 2011; Kümmerer, 2009a). Partitioning in the sediment could be one of the main reasons for the frequent detection of tetracyclines and fluoroquinolones in Chinese rivers (Zhou et al., 2011). β-Lactam antibiotics are easily hydrolysed in weakly acidic or alkaline conditions (Braschi