

Bacterial Resistance to Antibiotics in Aquatic Environments: Origin and Implications to Public Health

Resistencia bacteriana a antibióticos en ambientes acuáticos: origen e implicaciones para la salud pública

Resistência bacteriana a antibióticos em ambientes aquáticos: origem e implicações para a saúde pública

Erika Andrea Rodríguez¹; Judy Natalia Jiménez Quiceno²

¹ Microbiologist, MSc, PhD in Biology. Professor. Universidad de Antioquia, Colombia. Molecular Epidemiology and Bacterial Resistance Line, Basic and Applied Microbiology Group, Universidad de Antioquia. Medellín, Colombia. erika.rodriguez@udea.edu.co. ORCID: <https://orcid.org/0000-0002-8582-8776>

² Bacteriologist, MSc, PhD in Basic Biomedical Sciences. Full Professor. Molecular Epidemiology and Bacterial Resistance Line, Basic and Applied Microbiology Group, Universidad de Antioquia. Medellín, Colombia. jnatalia.jimenez@udea.edu.co. ORCID: <https://orcid.org/0000-0002-9183-1912>

Recibido:31/10/2022. Aprobado: 23/05/2023. Publicado: 14/07/2023

Rodríguez E, Jiménez JN. Resistencia bacteriana a antibióticos en ambientes acuáticos: origen e implicaciones para la salud pública. Rev. Fac. Nac. Salud Pública. 2023;41(3):e351453. doi: <https://doi.org/10.17533/udea.rfnsp.e351453>

Abstract

The alarming increase of bacterial resistance to antibiotics globally has dilucidated other sources different from the hospital and community, where water has gained great importance. The aquatic environment constitutes the source and natural habitat of a large number of microorganisms, including antibiotic-resistant bacteria; likewise, it is considered one of the principal receptors of antimicrobials, resistant bacteria, and antibiotic-resistant genes from human activities. Water contamination with these emerging contaminants has serious implications for human health, related with the dissemination of bacterial resistance and the emergence of new

resistance mechanisms. This review provides a global description of the role of aquatic environments in the problem of bacterial resistance, principal contamination sources, besides the impact to public health. Given this panorama, the need to address the problematic de la bacterial resistance is established from the perspective of “one health”, where traditional surveillance, focused on human and veterinary levels, is articulated to environmental epidemiological surveillance, principally based on wastewater.

Keywords: antibiotics, antibiotic-resistant bacteria, water contamination, wastewater-based epidemiology, antimicrobial resistance, public health.

Abstract

The alarming increase in bacterial resistance to antibiotics worldwide has exposed sources of this phenomenon other than the hospital and the community, where water has become increasingly important. Aquatic environments are the source and natural habitat of a large number of microorganisms, including antibiotic-resistant bacteria. They are also considered one of the main destinations of antimicrobials, resistant bacteria, and antibiotic-resistance genes resulting from human activities. Water contamination with these emerging contaminants has serious implications for human health associated with the spread of bacterial resistance and the emergence of new resistance mechanisms. This review

provides a general description of the role of aquatic environments in the problem of bacterial resistance, the main sources of contamination, as well as their impact on public health. Considering this panorama, the need to address the problem of bacterial resistance from a “One Health” approach is established, where traditional surveillance, which focuses on the human and veterinary level, is articulated with environmental epidemiological surveillance, mainly based on wastewater.

Keywords: antibiotics, antibiotic-resistant bacteria, water contamination, wastewater-based epidemiology, antimicrobial resistance, public health.

Resumo

O incremento alarmante da resistência bacteriana aos antibióticos no nível global tem revelado outras fontes diferentes do hospital e da comunidade, em que a água tem ganho grande importância. O ambiente aquático constitui a fonte e o habitat natural de um grande número de microrganismos, incluindo bactérias resistentes a antibióticos; é considerado, também, um dos principais receptores de antimicrobianos, bactérias resistentes e genes de resistência a antibióticos provindos das atividades humanas. A poluição da água com esses poluentes emergentes tem sérias implicações para a saúde humana, relacionadas com a disseminação da resistência bacteriana e a emergência de novos mecanismos de resistência.

Nesta revisão oferece-se uma descrição global do papel dos ambientes aquáticos na situação problemática da resistência bacteriana, as principais fontes de poluição, além do impacto para a saúde pública. Diante desse panorama, determina-se a necessidade de abordar a problemática da resistência bacteriana desde a perspectiva de “uma saúde” em que a vigilância tradicional, focada nos níveis humano e veterinário, esteja articulada com a vigilância epidemiológica ambiental, principalmente baseada em águas residuais.

Palavras-chave: antibióticos, bactérias resistentes a antibióticos, poluição da água, epidemiologia baseada em águas residuais, resistência antimicrobiana, saúde pública.

Introduction

Recently, the profound consequences of bacterial resistance to antibiotics have been evidenced in human health and the macroeconomic impact in terms of mortality (1.27-million deaths attributable to antimicrobial resistance for 2019) [1] and morbidity, with serious implications in the production force; besides, it has become one of the biggest threats to modern medicine [2]. The appearance untreatable infections, caused by multi-resistant microorganisms, warns of the arrival of a post-antibiotic era, where effective treatment will not exist to fight infectious diseases [2,3]. Among the principal causes of bacterial resistance is the excessive and inadequate use of antibiotics, which brings as consequence the selection and propagation of resistant bacteria [3]. Traditionally, hospitals have been indicated as the sou-

ce or reservoirs of this problematic; however, the alarming increase of resistant bacteria has allowed to elucidate other sources from the community and environment [4], where water has gained much importance.

The aquatic environment is the natural habitat of a large number of microorganisms, including antibiotic-resistant bacteria, and is rated as the principal receptor of antimicrobials, resistant bacteria, and antibiotic-resistant genes (ARG) from human activities [4]. All these elements are considered “emerging contaminants”, given their capacity to amplify, diffuse, and persist in aquatic environment media [5]. This water contamination has serious implications for public health, related with the dissemination of bacterial resistance and emergence of new resistance mechanisms. Studies conducted

describe, in general, the presence of these contaminants in aquatic environment media, and although studies are needed from an epidemiological approach that permit measuring or quantifying the risk for colonization or infection with resistant bacteria from contact with contaminated waters, their presence in these scenarios already supposes a motive for great concern, when understanding the role of water as source of acquisition of infectious diseases.

This topic review provides information on the role of aquatic environments on the dissemination of bacterial resistance, the reasons why they are considered favorable environments for this problematic and describes the impact for public health. This topic is important to understand the appearance and propagation of resistant microorganisms not only in hospital settings, but also in other sources or reservoirs coming from the community and environment.

The information contained in this review comes from bibliographic sources found in Medline-PubMed and Science Direct, including research and review articles from indexed scientific journals. Likewise, information was selected based on its quality and contributions to scientific knowledge.

Bacterial resistance in aquatic environments

Water constitutes a necessary and vital resource for human beings, but it is also the natural habitat of a large number and diversity of microorganisms [6]. Aquatic environments are favorable environments for the appearance and dissemination of resistant bacteria, and this is due to several reasons:

1. *The aquatic environment is the natural habitat for a large number and diversity of microorganism groups.* Water has a wide diversity of autochthonous and allochthonous microorganisms, which can exchange resistance genes through horizontal transfer of genetic material and serve as ARG reservoir [7]. Various genetic elements (plasmids, insertion sequences, transposons, integrons, genomic islands, prophages) participate in gene acquisition and dissemination and in genetic recombination among bacteria from water [8,9]. In these genetic elements, resistance genes are found to antimicrobial families, like: quinolones, tetracyclines, and beta-lactams, which can be shared between aquatic bacteria and human pathogenic bacteria [10].

Among the elements recognized for their role in the dissemination of bacterial resistance in water, there are type-I integrons. Studies on this genetic element, conducted in water, principally wastewater, show that in environments contaminated with antibiotics there is high amount of ARG [11,12] and greater prevalence of the type-I integron, compared with other classes of integrons [12]; hence, it is an indicator of antibiotic contamination in waters [13]. Likewise, an important frequency has been reported of bacteriophages carrying ARG in the water, which evidences the role as ARG vectors that favor transfer of antimicrobial resistance mechanisms in these scenarios [14].

As example of an autochthonous microorganism of the aquatic environment and recognized for its role in the dissemination of antimicrobial resistance, there is *Aeromonas* spp., which, in addition to intrinsically having ARG, carries a great diversity of mobile genetic elements that enable its capacity to exchange resistance genes with other bacteria species, including pathogens, like *Escherichia coli* or *Enterobacter aerogenes* [7].

2. *Aquatic environments are a natural source of ARG.*

Great variety of bacteria carry naturally ARG as protection mechanism against antimicrobial compounds produced by competing microorganisms [7], that is, they had ARG prior to the introduction of antibiotics.

In nature, various examples exist of the link and mobilization of resistance genes between environmental bacteria and human pathogens. One of those examples is the origin of the gene that encodes the extended-spectrum beta-lactamase *bla*CTX-M, of much importance in human pathogen bacteria, whose origin was related with species of *Kluyvera* spp., an environmental bacteria [4].

Other examples include quinolone resistance genes *qnrA* and carbapenems *bla*OXA-48, located in plasmids and found in clinical isolates of *Enterobacteriaceae*, whose origin is described in the chromosome of environmental bacteria, like *Shewanella algae* and *Vibrionaceae* [15-17]; hence, natural ecosystems are considered natural source of ARG.

3. *The aquatic environment is one of the principal antimicrobial receptors, resistant bacteria, and antibiotic-resistant genes.* Water is a resource affected by a vast variety of contaminants, among these, antimicrobials, resistant bacteria, and ARG from different anthropogenic sources (Figure 1), which contribute to the appearance and dissemination of bacterial resistance. Presence of these emerging contaminants in the aquatic environment may result in the selection of resistant bacteria or horizontal transfer of resistance genes among bacteria [10].

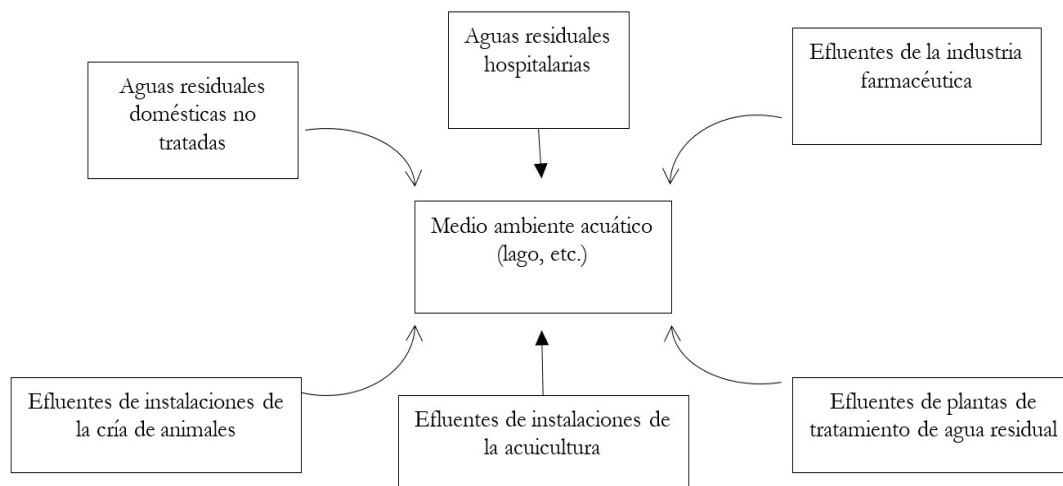


Figure 1. Contamination sources from the aquatic environment medium with antimicrobials, resistant bacteria, and antibiotic-resistant genes

Source: Elaborated by the authors.

With respect to the selection of resistant bacteria in the aquatic environment, selection experiments conducted on bacterial models, like *E. coli* and *Salmonella Typhimurium*, show that, in spite of the low concentrations of antimicrobials in water in comparison with those used in treatments for humans and animals ($\mu\text{g/L}$ in humans and ng/L in environment), these concentrations are sufficient for the selection of resistant bacteria [18,19]. Nevertheless, recent studies suggest that selective bacterial processes in water can be more complex. For example, it has been seen that according to the antimicrobial evaluated, variability exists on the magnitude of the selective effect, as well as a possible additive selective effect when various antimicrobials from the same family are found in the aquatic environment [20].

Moreover, interaction processes among microbial communities also participate in the selection of resistant bacteria in the environment. It has been observed how bacterial competition with and among microbial communities generates variable effects on selective processes [20-23]. Interaction among some natural microbial communities would avoid selection of bacterial resistance in minimum antimicrobial selective concentrations [21], contrary to what had been detected in *in-vivo* assays in single-species experiments [19,24]. This phenomenon could be explained by the increased biological cost of the resistance and a protection effect of some resistant microbial communities for the susceptible phenotype [20,21].

The following describe sources of water contamination with antimicrobials, resistant bacteria, and antibiotic-resistant genes (ARG), according with the load or selection pressure they exert on the environment (Figure 1):

1. *Hospital wastewater.* It is highly dangerous, not only due to their infectious and toxic characteristics, but also because they host large amounts of antibiotics and multi-resistant pathogenic bacteria, managing to alter even the natural microbiota present in aquatic ecosystems [25]. These waters are described as favorable settings for the exchange of resistance genes between pathogenic clinical microorganisms and environmental bacteria; that is due to the large amounts of broad-spectrum antimicrobials and resistant bacteria eliminated by colonized and infected patients [26].

The role of these effluents and their impact on the contamination of aquatic environments, compared with other contamination sources, are being studied, finding diverse results. On the one hand, a large variety of ARG types is described in hospital wastewater, even greater than that present in other community wastewater systems [25], and a high abundance of transcriptionally active resistance genes is indicated, possibly related with the level of hospital antibiotic use over time and with antibiotic residue [27].

However, on the other hand, a limited impact on the dissemination of antimicrobial resistance has also been described in hospital effluent sewer systems, in comparison with the community's wastewater treatment plants [27], or a variable effect of the hospital effluent on the bacterial resistance according with the microorganism evaluated [28]. The foregoing suggests that although hospital wastewater is not the principal factor contributing to the development and persistence of bacterial resistance in the aquatic environment, it plays an important role and it is necessary to establish strategies that contribute to its adequate management [25].

2. *Untreated domestic wastewater.* Wastewater, from the water supply system of the populations, after having been modified by diverse uses in domestic, industrial, and community activities, may be source of contamination of water bodies with bacterial resistance.

It is possible to detect large amounts of resistant microorganisms and antibiotics in wastewater. This may be due to high antibiotic use in humans. It is estimated that, globally, antibiotic use between 2000 and 2010 increased by 36%, being much higher in countries, like Brazil, Russia, India, China, and South Africa [29]. These figures raise serious concerns for public health and environmental health, given that a large part of these antibiotics is completely eliminated through the feces and urine; their broad use in people from the community could lead to selection processes of pathogenic bacteria that colonize the human intestine and, consequently, detect resistant bacteria in wastewater [30,31].

3. *Wastewater treatment plants (WWTP).* Wastewater treatment plants were not designed to reduce the load of antibiotics, resistant bacteria in water and their associated ARG arriving in wastewater [10,30]. Rather, it has been noted that they play an important role in the contamination of the aquatic environment with bacterial resistance [10,30]; this is because they constitute one of the principal receptors of bacterial resistance, from different anthropogenic sources, like domestic wastewater, hospital residue [5,32], and even aquaculture discharges, agricultural and livestock runoff in developing countries, where wastewater channeling systems are precarious or inexistent.

Further, antibiotics and resistant bacteria can concentrate in WWTP, which could favor bacterial selection processes or horizontal transfer of resistance genes among bacteria [10,33].

In turn, the WWTP effluents are referenced among the principal dispersion sources of bacterial resistance to antibiotics [33].

4. *Pharmaceutical industry.* Effluents from the pharmaceutical industry can be an important point source of antibiotics [34]. It has been demonstrated that discharges from their effluents provide conditions in which antibiotics reach concentrations selective for resistance enrichment [34]. Likewise, it has been described how antibiotic residue from the pharmaceutical industry can reach the wastewater due to the high solubility of these compounds and, often, to their poor degradability [35].

5. *Aquaculture discharges and agricultural and livestock runoff.* Residues from antimicrobials, resistant bacteria, and ARG that reach water from agriculture and cattle farming, and even from aquaculture are due to antimicrobial use in these areas, principally as growth promoters (antimicrobials to improve animal

growth or improve feeding efficiency to increase the production of animal derivatives) [10,36].

In food producing animals (livestock, pork, poultry, and in aquaculture) over 30 different antimicrobials are used [4]. A study on estimates of global consumption of antimicrobials in veterinary medicine shows high figures in countries, like China (45%), Brazil (7.9%), the United States (7.0%), Thailand (4.2%), and India (2.2%); besides predicting that between 2017 and 2030, global consumption of veterinary antimicrobials will increase, going from 93,309 tons of antibiotics in 2017, to 104,079 tons by 2030 [37]. Despite progress in reducing antibiotic use in countries, like Germany and China, it is estimated that antimicrobial use in food producing animals will increase in all continents [37].

These data are relevant because livestock has been considered an important release source, to the environment, of antibiotics, resistant bacteria, or associated genes [38]. This release occurs principally with the use of manure from animals treated with antimicrobials as fertilizer; likewise, with crop irrigation with contaminated waters from farms. It is estimated that from 75% to 90% of antimicrobials used in animal foods are excreted to the environment, through agricultural runoff [4]. From there, antimicrobials move from the field to underground waters and eventually come in contact with surface waters, through events like rainfall [7].

In aquaculture, antimicrobials are used to prevent and treat bacterial infections in fish and invertebrates [39]. In fish, antimicrobial administration is carried out with the food. Residues of foods with antibiotics and animal excretions, which generally have traces of the antibiotic, accumulate in sediments and ponds and can be disseminated by water currents [39]. In countries, like China and Chile there is broad use of antimicrobials in this area [39,40].

Finally, antimicrobial use in agriculture is scarce, and when used, their presence in the environment can be influenced by soil adsorption processes, rainfall dilution, photodegradation, and microbial degradation [41].

One of the most-used antibiotics in agriculture is streptomycin, which is used to control fire blight caused by *Erwinia amylovora* in apples and pear trees [41].

Presence of resistant bacteria and antibiotic-resistant genes in aquatic environments: impact on public and environmental health

Knowing the impact of dissemination, through water, of bacterial resistance on public and environmental health is cause for much concern. Among the important effects, or risk scenarios for public and environmental health,

there is the presence of resistant bacteria and ARG in water that can lead to the appearance of new resistance mechanisms, mobilization and transfer of resistance genes to human pathogens, and dissemination of bacterial resistance [42].

During the last decade, various studies – globally – on resistant bacteria and ARG in the aquatic environment medium have considered these environments favorable for the appearance and dissemination of bacterial resistance [7]. These studies have been conducted in tributaries and effluents of WWTP [43,44]; directly in rivers, lakes, and the sea [45]; in hospital wastewater [46]; in wastewater and its annexes (sewers, streams or puddles); recreational water [47], and drinking water [48], where there are reports, for example, of the presence of environmental microorganisms associated specifically with antibiotic resistance phenomena [49], resistant pathogenic bacteria, ARG, and mobile genetic elements linked with bacterial resistance [13,50].

The description of the presence of resident bacteria and ARG in water has been fundamental to understand the relevance and participation of environmental bacteria on the dissemination and transfer of antibiotic resistance. This is added to findings of pathogenic resistant bacteria, like *Pseudomonas aeruginosa*, *Acinetobacter*, *E. coli*, and other species of the family *Enterobacteriaceae* in water bodies, microorganisms that are multi-resistant, with resistance to more than one antibiotic, like tetracyclines, quinolones, sulfonamides, and beta-lactams [51].

It should be highlighted that most research on resistance in the aquatic environment has been conducted

in the United States, China, and Europe; however, in Africa and Latin America, studies are scarce [52]. In Latin America and the Caribbean, limitations exist, given that most of these investigations are concentrated in countries, like Brazil, Chile, Mexico, Colombia, and Argentina, hence, studies on the situation of bacterial resistance in aquatic environments in the region may not be representative [52]. Also, in Latin America, few studies quantify the presence of resistance genes in water or analyze the bacterial resistome (ARG total, including those circulating in pathogenic bacteria, antibiotic producers, and non-pathogenic bacteria) [50].

In Colombia, since 2010, progress has been made on the topic. Mostly, studies have focused on antibiotic detection and degradation. With respect to detection of resistant bacteria and ARG, in recent years (2019-2021) information in that regard has been published more frequently [44,50-55]. These studies have determined the presence of antibiotics, resistant bacteria, and resistance genes in different water sources [53], and have demonstrated the dissemination of resistant bacteria from the hospital and community to the environment [54]. This, in turn, shows the impact of the antibiotic selective pressure on environmental settings and the consequences for the emergence of new resistance mechanisms and for ecological equilibrium, which represents a big threat to public and environmental health.

In spite of this progress on the topic, questions remain that require further studies about the impact on public and environmental health of the presence of resistant bacteria and ARG in aquatic environments (Figure 2).

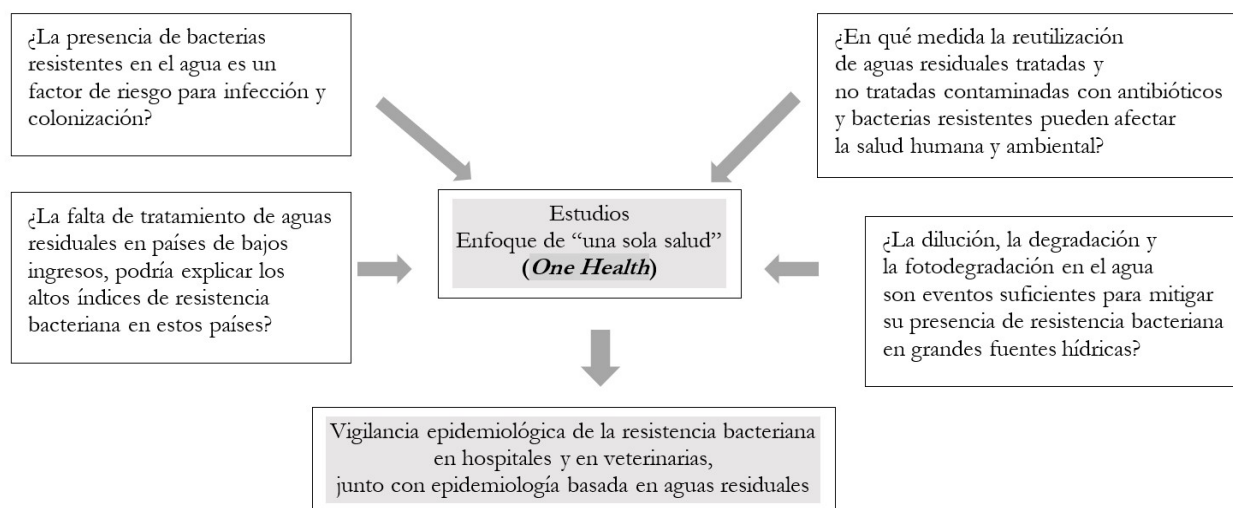


Figure 2. Questions requiring further studies about the impact on public and environmental health of the presence of resistant bacteria and antibiotic-resistant genes in aquatic environments.

For the most part, studies conducted to date tend to be descriptive on the presence of these emerging contaminants in water; few have an epidemiological, longitudinal approach, and of continuous monitoring, to permit establishing or measuring the risk of colonization or infection with resistant bacteria from contact with contaminated water with these emerging contaminants.

In reports or research seeking to evaluate the transmission of resistant bacteria from water contaminated with these microorganisms and its impact on human health, one of the most-studied models is the case of *E. coli* resistant to beta-lactams. Highlighted among the studies, is that by Dorado-García *et al.*, 2019 [56] who evaluated the molecular similarity of *E. coli* isolates producing extended-spectrum beta-lactamases (ESBL) and *AmpC* from individuals from the general population with isolates from different environments, finding greater similarity among the isolates derived from human clinical environments, surface waters, wastewater, and wild birds (similarity index 0.7-0.8), while the similarity with isolates resulting from livestock or from foods was lower (similarity index 0.3-0.6) [56].

Other research has evaluated the risk factors associated with colonization by *E. coli* resistant to antimicrobials, indicating that individuals who consume untreated water, contaminated with this bacteria, have 26% more probabilities of being colonized by it than individuals who consume uncontaminated water [57]. Likewise, the risk of being colonized by *E. coli* that produces beta-lactamases, such as *blaCTX-M*, increases in people in constant contact with water [58], as evidenced in a population that practices water sports, like surfers (RR = 4.09, 95% CI: 1.02-16.4), which, due to their profession, have greater risk of ingesting these microorganisms directly from the sea water, route through which many people could be directly exposed [59-61]. Other epidemiological studies also suggest that contact with recreational water in fresh water sources is a risk factor not only for colonization, but also for the development of urinary tract infections acquired in the community and caused by ESBL-producing Enterobacteriaceae, like *E. coli* or *Klebsiella pneumoniae* in low-prevalence countries (OR = 2.1; 95% CI: 1.0-4.0) [62,63].

During the last decade, various studies have been reported in populations colonized or infected by gram-negative carbapenemase-producing bacilli, like *blaNDM-1* or *blaIMI-2*, without hospitalization antecedents, at the same time that these microorganisms are detected in tap water, wastewater discharge, or rivers, with which these people have contact [48,64-66]. Some of these studies have used molecular typing methods, which have permitted determining genetic relations among isolates from infected individuals, isolates from colonized people and animals, with bacterial isolates from recreational water, wastewater, effluents from

WWTP, and rivers [63-65,67-70]. These genetic relations of clinical and environmental isolates have been reported in *blaNDM-1*-producing gram-negative bacilli; these have also been detected among isolates of *K. pneumoniae*, *E. coli* and other Enterobacteriaceae carrying beta-lactamases *blaSHV-83* and *blaOXA-10*, *blaCTX-M-15*, *blaVIM-1* and *blaIMI-2* [64,65,69,71]. Although in these studies it is difficult to evidence the direction of the transmission from the environment to human beings, they do provide information about the potential risk to human health of water contamination due to bacterial resistance [48], the possible propagation of multidrug-resistant microorganisms from water, and the importance of monitoring bacterial resistance, together with the incorporation of environmental sampling [66].

Another question about the impact of bacterial resistance on environmental health is related with the impact of natural phenomena, like dilution, degradation, and photodegradation, *etc.*, on mitigating the presence of antimicrobials, resistant bacteria, and ARG in large hydric sources. In the case of antimicrobials, such as beta-lactams, glycopeptides, and fluoroquinolones, these can largely be degraded, even in biological processes of the WWTP, while trimethoprim and lincosamides seem to be persistent [72]. Nevertheless, some of the intermediate products of antimicrobial degradation can also lead to co-selection of bacterial resistance in the environment [73]. Furthermore, phenomena like dilution in large hydric sources could have effect on bacteria and the capacity to carry out horizontal exchange of resistance genes, given that the probability of genetic exchange increases when there are relatively high cell densities [74]. However, this has not been fully shown because it is suggested that even if bacteria die, their DNA could remain intact at the bottom of lakes or clay, and be capable of transferring to autochthonous water bacteria and these, eventually, have contact with human microbiota [75].

Other concerns or worries about the impact of bacterial resistance in the aquatic environment medium on public and environmental health are related, on one side, with the reutilization of wastewater and application of sludge or biosolids from WWTP for crops, and how this practice can lead to their contamination. Some investigations describe the translocation of resistant bacteria and ARG to edible food crops, when crops are irrigated with treated wastewater or when they are fertilized with sludge from WWTP [76,77], and their impact depends principally on the load of ARG introduced and the irrigation intensity [20].

Moreover, lack of wastewater treatment can contribute to the dissemination of bacterial resistance. Although conventional WWTP are not designed to reduce significantly these emerging contaminants, the risk is much higher when wastewater is not treated. In low- and medium-income countries a high prevalence of bacterial

resistance exists, and of the wastewater generated, only between 8% and 28% are treated. Furthermore, tertiary treatments are scarce due to technological limitations. Within this context, the population could be more exposed to these contaminants, especially in urban areas with high levels of poverty and limited physical infrastructure of drinking water and sanitation, where animals, water, and human beings coexist and can eventually contaminate fresh water sources with wastewater [78].

Regarding this panorama, it is necessary not to underestimate the risk to human health represented by bacterial resistance in water and highlight the importance of promoting more and better residual water treatments, to reduce – in part – these effects [79]. Additionally, it shows the importance of conducting interventions in other areas of social life, given that the mere decrease of antibiotic consumption does not seem sufficient to reduce global resistance to antimicrobials due to the transmissibility of these microorganisms [80].

The findings to date on the impact to public and environmental health of the presence of resistant bacteria and ARG in aquatic environments suggest the importance of conducting interventions using the “one health” approach, proposed by the World Health Organization (WHO), defined as a “joint effort by several disciplines that unite to provide solutions for human, animal, and environmental health” [81]. These also underscore the need to articulate the traditional surveillance of bacterial resistance focused on human and veterinary levels, with surveillance in the environment, using methodologies, like the wastewater-based epidemiology [82].

The *wastewater-based epidemiology* is an approach based principally on the extraction, detection, and subsequent analysis and interpretation of biomarkers in wastewater, providing a means of data collection for epidemiological studies, to evaluate public health conditions of a population and offer information about the health of communities [82,83]. It permits obtaining information about different factors related with lifestyle, evaluating temporal trends or response to public health events in water, and monitoring and surveilling infectious diseases [82,83]. This methodology is being used to support the surveillance and monitoring of infectious diseases or pathogenic microorganisms, like in the case of the COVID-19 pandemic and detection of bacterial resistance (resistant bacteria, antibiotics, and ARG) in wastewater [82,83].

With respect to monitoring of bacterial resistance, epidemiology in wastewater raises the need to monitor clinically important genes found in mobile elements and that confer resistance to high-consumption antibiotics or to antibiotics that have been used for a long time, like tetracycline and sulfonamides. This approach is useful to detect emergent resistance mechanisms and determi-

ne resistance patterns and their extension in human and environmental communities [82,83].

There are several examples of bacterial resistance surveillance studies applying wastewater-based epidemiology. Reinthaler *et al.*, [84] between 2000 and 2009, compared the resistance patterns of *E. coli* strains isolated from human patients with strains isolated from wastewater from WWTP, finding parallel development of resistance patterns both in patients as in environmental samples, and an increase in multi-resistant *E. coli* strains over time in samples from both sources.

Another study by Majlander *et al.*, [85] on ARG prevalence and abundance in wastewater from two hospitals during nine weeks in 2020 found resistance patterns during the weeks of monitoring and different resistance profiles among hospitals, information that was useful to understand the propagation of resistance to antibiotics in hospitals and identify potential intervention areas.

Similarly, other studies have detected the presence of ARG of clinical importance in wastewater, among them resistance genes to carbapenems [50,51,86-88], ARG to treat tuberculosis [89], indicating a resistance pattern like those described in hospitals and even detecting ARG not found in hospitals [50].

Further, other research has explored the relation of the detection of bacterial resistance in wastewater with environmental and human factors. For example, exploration on how antibiotic use influences the population [90-92], population size [90], immigration or international flights [91], soil use or agriculture [93], epidemiological and climatological conditions [55,92], socioeconomic, health, and environmental factors [91]. Overall, all these investigations highlight the potential of the surveillance of wastewater to monitor the resistance to antibiotics. In addition, they point to the importance of conducting wastewater-based surveillance, on par with traditional surveillance, to answer those unsolved questions about the impact bacterial resistance in aquatic environments has on public health [86].

Conclusion

Currently, aquatic environments are principal sources and receptors of antimicrobials, resistant bacteria, and ARG from anthropogenic activities, and play an important role in disseminating and amplifying antimicrobial resistance, with serious implications to public health.

The “one health” approach, proposed by the WHO, and the use of wastewater-based epidemiology are presented as strategies that allow having an integral vision of the problematic to, thus, establish joint actions that permit designing and applying programs and policies that impact human and environmental health.

Conflict of interests

The authors declare that the review was conducted in absence of any commercial or financial relationship that could be interpreted as a potential conflict of interest.

Funding

This work was supported by the Administrative Department of Science, Technology, and Innovation – Colciencias (Minciencias), Contract FP44842-124-2017.

Declaration of responsibility

The points of view expressed are the responsibility of the authors and not of the Institution in which they work or of the funding sources.

Declaration of contribution by the authors

The authors contributed equally to the conceptualization, elaboration, and review of the final manuscript.

Reference

- Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629-55. doi: [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
- Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis*. 2013;13(12):1057-98. doi: [https://doi.org/10.1016/S1473-3099\(13\)70318-9](https://doi.org/10.1016/S1473-3099(13)70318-9)
- Vanegas Múnera J, Jiménez Quiceno J. Resistencia antimicrobiana en el siglo XXI: ¿hacia una era postantibiótica? *Rev Fac Nac Salud Pública*. 2019;38(1):1-6. doi: <https://doi.org/10.17533/udea.rfnsp.v38n1e337759>
- Marshall BM, Levy SB. Food animals and antimicrobials: Impacts on human health. *Clin Microbiol Rev*. 2011;24(4):718-33. doi: <https://doi.org/10.1128/CMR.00002-11>
- Martinez JL. Environmental pollution by antibiotics and by antibiotic resistance determinants. *Environ Pollut*. 2009;157(11):2893-902. doi: <https://doi.org/10.1016/j.envpol.2009.05.051>
- Vaz-Moreira I, Nunes OC, Manaia CM. Bacterial diversity and antibiotic resistance in water habitats: Searching the links with the human microbiome. *fems Microbiol Rev*. 2014;38(4):761-78. doi: <https://doi.org/10.1111/1574-6976.12062>
- Almakki A, Jumas-Bilak E, Marchandin H, Licznar-Fajardo P. Antibiotic resistance in urban runoff. *Sci Total Environ*. 2019;667:64-76. doi: <https://doi.org/10.1016/j.scitotenv.2019.02.183>
- Guo J, Li J, Chen H, et al. Metagenomic analysis reveals wastewater treatment plants as hotspots of antibiotic resistance genes and mobile genetic elements. *Water Res*. 2017;123:468-78. doi: <https://doi.org/10.1016/j.watres.2017.07.002>
- Szczepanowski R, Linke B, Krahn I, et al. Detection of 140 clinically relevant antibiotic-resistance genes in the plasmid metagenome of wastewater treatment plant bacteria showing reduced susceptibility to selected antibiotics. *Microbiology*. 2009;155(7):2306-19. doi: <https://doi.org/10.1099/mic.0.028233-0>
- Marti E, Variatza E, Balcazar JL. The role of aquatic ecosystems as reservoirs of antibiotic resistance. *Trends Microbiol*. 2014;22(1):36-41. doi: <https://doi.org/10.1016/j.tim.2013.11.001>
- Li D, Yu T, Zhang Y, et al. Antibiotic resistance characteristics of environmental bacteria from an oxytetracycline production wastewater treatment plant and the receiving river. *Appl Environ Microbiol*. 2010;76(11):3444-51. doi: <https://doi.org/10.1128/AEM.02964-09>
- Kristiansson E, Fick J, Janzon A, et al. Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. *PLoS One*. 2011;6(2):e17038. doi: <https://doi.org/10.1371/journal.pone.0017038>
- Zheng W, Huyan J, Tian Z, et al. Clinical class 1 integron-integrase gene – A promising indicator to monitor the abundance and elimination of antibiotic resistance genes in an urban wastewater treatment plant. *Environ Int*. 2020;135:105372. doi: <https://doi.org/10.1016/j.envint.2019.105372>
- Maganha de Almeida Kumlien AC, Borrego CM, Balcázar JL. Antimicrobial resistance and bacteriophages: An overlooked intersection in water disinfection. *Trends Microbiol*. 2021;29(6):517-27. doi: <https://doi.org/10.1016/j.tim.2020.12.011>
- Poirel L, Rodriguez-Martinez JM, Mammeri H, et al. Origin of plasmid-mediated quinolone resistance determinant QnrA. *Antimicrob Agents Chemother*. 2005;49(8):3523-5. doi: <https://doi.org/10.1128/AAC.49.8.3523-3525.2005>
- Poirel L, Liard A, Rodriguez-Martinez JM, Nordmann P. Vibrionaceae as a possible source of Qnr-like quinolone resistance determinants. *J Antimicrob Chemother*. 2005;1118-21. doi: <https://doi.org/10.1093/jac/dki371>
- Poirel L, Potron A, Nordmann P. oxa-48-like carbapenemases: The phantom menace. *J Antimicrob Chemother*. 2012;67(7):1597-606. doi: <https://doi.org/10.1093/jac/dks121>
- Gullberg E, Albrecht LM, Karlsson C, et al. Selection of a multidrug resistance plasmid by sublethal levels of antibiotics and heavy metals. *mBio*. 2014;5(5):e01918-14. doi: <https://doi.org/10.1128/mBio.01918-14>
- Gullberg E, Cao S, Berg OG, et al. Selection of resistant bacteria at very low antibiotic concentrations. *PLoS Pathog*. 2011;7(7):e1002158. doi: <https://doi.org/10.1371/journal.ppat.1002158>
- Stanton IC, Murray AK, Zhang L, et al. Evolution of antibiotic resistance at low antibiotic concentrations including selection below the minimal selective concentration. *Commun Biol*. 2020;3(1):467. doi: <https://doi.org/10.1038/s42003-020-01176-w>
- Klümper U, Recker M, Zhang L, et al. Selection for antimicrobial resistance is reduced when embedded in a natural microbial community. *ISME J*. 2019;13(12):2927-37. doi: <https://doi.org/10.1038/s41396-019-0483-z>
- Kraupner N, Ebmeyer S, Bengtsson-Palme J, et al. Selective concentration for ciprofloxacin resistance in *Escherichia coli* grown in complex aquatic bacterial biofilms. *Environ Int*. 2018;116:255-68. doi: <https://doi.org/10.1016/j.envint.2018.04.029>
- Lundström S V, Östman M, Bengtsson-Palme J, et al. Minimal selective concentrations of tetracycline in complex aquatic bacterial biofilms. *Sci Total Environ*. 2016;553:587-95. doi: <https://doi.org/10.1016/j.scitotenv.2016.02.103>

24. Andersson DI, Hughes D. Microbiological effects of sublethal levels of antibiotics. *Nat Rev Microbiol.* 2014;12(7):465-78. doi: <https://doi.org/10.1038/nrmicro3270>
25. Zhang S, Huang J, Zhao Z, et al. Hospital wastewater as a reservoir for antibiotic resistance genes: A meta-analysis. *Front Public Heal.* 2020;8:574968. doi: <https://doi.org/10.3389/fpubh.2020.574968>
26. Bouki C, Venieri D, Diamadopoulos E. Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: A review. *Ecotoxicol Environ Saf.* 2013;91:1-9. doi: <https://doi.org/10.1016/j.ecoenv.2013.01.016>
27. Rowe WPM, Baker-Austin C, Verner-Jeffreys DW, et al. Overexpression of antibiotic resistance genes in hospital effluents over time. *J Antimicrob Chemother.* 2017;72(6):1617-23. doi: <https://doi.org/10.1093/jac/dkx017>
28. Harris S, Morris C, Morris D, et al. The effect of hospital effluent on antimicrobial resistant *E. coli* within a municipal wastewater system. *Environ Sci Process Impacts.* 2013;15(3):617. doi: <https://doi.org/10.1039/C2EM30934C>
29. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. *Lancet Infect Dis.* 2014;14(8):742-50. doi: [https://doi.org/10.1016/S1473-3099\(14\)70780-7](https://doi.org/10.1016/S1473-3099(14)70780-7)
30. Hong P-Y, Al-Jassim N, Ansari M, Mackie R. Environmental and public health implications of water reuse: Antibiotics, antibiotic resistant bacteria, and antibiotic resistance genes. *Antibiotics.* 2013;2(3):367-99. doi: <https://doi.org/10.3390/antibiotics2030367>
31. Korzeniewska E, Harnisz M. Extended-spectrum beta-lactamase (esbl)-positive Enterobacteriaceae in municipal sewage and their emission to the environment. *J Environ Manage.* 2013;128:904-11. doi: <https://doi.org/10.1016/j.jenvman.2013.06.051>
32. Rizzo L, Manaia C, Merlin C, et al. Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: A review. *Sci Total Environ.* 2013;447:345-60. doi: <https://doi.org/10.1016/j.scitotenv.2013.01.032>
33. Novo A, André S, Viana P, et al. Antibiotic resistance, antimicrobial residues and bacterial community composition in urban wastewater. *Water Res.* 2013;47(5):1875-87. doi: <https://doi.org/10.1016/j.watres.2013.01.010>
34. Šimatović A, Udiković-Kolić N. Antibiotic resistance in pharmaceutical industry effluents and effluent-Impacted environments. In: Manaia C, Donner E, Vaz-Moreira I, Hong P, editors. *Antibiotic resistance in the environment. The handbook of environmental chemistry, vol 91.* Cham: Springer. pp. 101-22. doi: https://doi.org/10.1007/978_2019_389
35. Grujić S, Vasiljević T, Laušević M. Determination of multiple pharmaceutical classes in surface and ground waters by liquid chromatography-ion trap-tandem mass spectrometry. *J Chromatogr A.* 2009;1216(25):4989-5000. doi: <https://doi.org/10.1016/j.chroma.2009.04.059>
36. Maron DF, Smith TJS, Nachman KE. Restrictions on antimicrobial use in food animal production: An international regulatory and economic survey. *Global Health.* 2013;9:48. doi: <https://doi.org/10.1186/1744-8603-9-48>
37. Tiseo K, Huber L, Gilbert M, et al. Global trends in antimicrobial use in food animals from 2017 to 2030. *Antibiotics.* 2020;9(12):918. doi: <https://doi.org/10.3390/antibiotics9120918>
38. Dolliver H, Gupta S. Antibiotic losses in leaching and surface runoff from manure-amended agricultural land. *J Environ Qual.* 2008;37(3):1227-37. doi: <https://doi.org/10.2134/jeq2007.0392>
39. Cabello FC, Godfrey HP, Tomova A, et al. Antimicrobial use in aquaculture re-examined: Its relevance to antimicrobial resistance and to animal and human health. *Environ Microbiol.* 2013;15(7):1917-42. doi: <https://doi.org/10.1111/1462-2920.12134>
40. Pavón A, Riquelme D, Jaña V, et al. The high risk of bivalve farming in coastal areas with heavy metal pollution and antibiotic-resistant bacteria: A Chilean perspective. *Front Cell Infect Microbiol.* 2022;12:867446. doi: <https://doi.org/10.3389/fcimb.2022.867446>
41. McManus PS. Does a drop in the bucket make a splash? Assessing the impact of antibiotic use on plants. *Curr Opin Microbiol.* 2014;19:76-82. doi: <https://doi.org/10.1016/j.mib.2014.05.013>
42. Hernandez F, Henriques L, Pilz R, et al. Antibiotic resistance in aquatic environments of Rio de Janeiro, Brazil. In: Ahmad I, Ahmad Dar M, editors. *Perspectives in water pollution.* Croatia: In-Tech; 2013. doi: <https://doi.org/10.5772/54638>
43. Lepuschitz S, Schill S, Stoeger A, et al. Whole genome sequencing reveals resemblance between esbl-producing and carbapenem resistant *Klebsiella pneumoniae* isolates from Austrian rivers and clinical isolates from hospitals. *Sci Total Environ.* 2019;662:227-35. doi: <https://doi.org/10.1016/j.scitotenv.2019.01.179>
44. Diab M, Hamze M, Bonnet R, et al. Extended-spectrum beta-lactamase (esbl)- and carbapenemase-producing Enterobacteriaceae in water sources in Lebanon. *Vet Microbiol.* 2018;217:97-103. doi: <https://doi.org/10.1016/j.vetmic.2018.03.007>
45. Hua M, Huang W, Chen A, et al. Comparison of antimicrobial resistance detected in environmental and clinical isolates from historical data for the us. *Biomed Res Int.* 2020;2020:4254530. doi: <https://doi.org/10.1155/2020/4254530>
46. Tran NH, Chen H, Reinhard M, et al. Occurrence and removal of multiple classes of antibiotics and antimicrobial agents in biological wastewater treatment processes. *Water Res.* 2016;104:461-472. doi: <https://doi.org/10.1016/j.watres.2016.08.040>
47. Mao D, Yu S, Rysz M, et al. Prevalence and proliferation of antibiotic resistance genes in two municipal wastewater treatment plants. *Water Res.* 2015;85:458-66. doi: <https://doi.org/10.1016/j.watres.2015.09.010>
48. Martínez JL, Coque TM, Baquero F. Prioritizing risks of antibiotic resistance genes in all metagenomes. *Nat Rev Microbiol.* 2015;13:396. <https://doi.org/10.1038/nrmicro3399-c2>
49. Devarajan N, Laffite A, Graham ND, et al. Accumulation of clinically relevant antibiotic-resistance genes, bacterial load, and metals in freshwater lake sediments in Central Europe. *Environ Sci Technol.* 2015;49(11):6528-37. doi: <https://doi.org/10.1021/acs.est.5b01031>
50. Cerqueira F, Matamoros V, Bayona JM, et al. Antibiotic resistance gene distribution in agricultural fields and crops. A soil-to-food analysis. *Environ Res.* 2019;177:108608. DOI: <https://doi.org/10.1016/j.envres.2019.108608>
51. Yang L, Liu W, Zhu D, et al. Application of biosolids drives the diversity of antibiotic resistance genes in soil and lettuce at harvest. *Soil Biol Biochem.* 2018;122:131-40. DOI: <https://doi.org/10.1016/j.soilbio.2018.04.017>
52. Sato T, Qadir M, Yamamoto S, et al. Global, regional, and country level need for data on wastewater generation, treatment, and use. *Agric Water Manag.* 2013;130:1-13. doi: <https://doi.org/10.1016/j.agwat.2013.08.007>
53. World Economic Forum. *Antimicrobial resistance and water: The risks and costs for economies and societies.* Switzerland [internet]; 2021 [citado 2023 abr. 17]. Disponible en: <https://www.weforum.org/reports/the-costs-and-risks-of-amr-water-pollution/>

80. Collignon P, Beggs JJ, Walsh TR, et al. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: A univariate and multivariable analysis. *Lancet Planet Heal.* 2018;2(9):e398-405. doi: [https://doi.org/10.1016/S2542-5196\(18\)30186-4](https://doi.org/10.1016/S2542-5196(18)30186-4)
81. Velazquez-Meza ME, Galarde-López M, Carrillo-Quiróz B, Alpuche-Aranda CM. Antimicrobial resistance: One Health approach. *Vet World* 2022;15:743–9. doi: <https://doi.org/10.14202/vetworld.2022.743-749>.
82. Sims N, Kasprzyk-Hordern B. Future perspectives of wastewater-based epidemiology: Monitoring infectious disease spread and resistance to the community level. *Environ Int.* 2020;139:105689. doi: <https://doi.org/10.1016/j.envint.2020.105689>
83. Choi PM, Tschärke BJ, Donner E, et al. Wastewater-based epidemiology biomarkers: Past, present and future. *TrAC Trends Anal Chem.* 2018;105:453-69. doi: <https://doi.org/10.1016/j.trac.2018.06.004>
84. Reinthaler FF, Galler H, Feierl G, et al. Resistance patterns of *Escherichia coli* isolated from sewage sludge in comparison with those isolated from human patients in 2000 and 2009. *J Water Health.* 2013;11(1):13-20. doi: <https://doi.org/10.2166/wh.2012.207>
85. Majlander J, Anttila V-J, Nurmi W, et al. Routine wastewater-based monitoring of antibiotic resistance in two Finnish hospitals: Focus on carbapenem resistance genes and genes associated with bacteria causing hospital-acquired infections. *J Hosp Infect.* 2021;117:157-64. doi: <https://doi.org/10.1016/j.jhin.2021.09.008>
86. Flach C-F, Hutinel M, Razavi M, Åhrén C, Larsson DGJ. Monitoring of hospital sewage shows both promise and limitations as an early-warning system for carbapenemase-producing Enterobacterales in a low-prevalence setting. *Water Res.* 2021;200:117261. doi: <https://doi.org/10.1016/j.watres.2021.117261>
87. Teban-Man A, Szekeres E, Fang P, et al. Municipal wastewaters carry important carbapenemase genes independent of hospital input and can mirror clinical resistance patterns. *Microbiol Spectr.* 2022;10(2):e0271121. doi: <https://doi.org/10.1128/spectrum.02711-21>
88. Chagas TPG, Seki LM, da Silva DM, Asensi MD. Occurrence of kpc-2-producing *Klebsiella pneumoniae* strains in hospital wastewater. *J Hosp Infect.* 2011;77(3):281. doi: <https://doi.org/10.1016/j.jhin.2010.10.008>
89. Mtetwa HN, Amoah ID, Kumari S, et al. Wastewater-based surveillance of antibiotic resistance genes associated with tuberculosis treatment regimen in KwaZulu Natal, South Africa. *Antibiotics.* 2021;10(11):1362. doi: <https://doi.org/10.3390/antibiotics10111362>
90. Han S, Wang Z, Huang H, et al. Estimating antibiotics use in major cities in China through wastewater-based epidemiology. *Sci Total Environ.* 2022;826:154116. doi: <https://doi.org/10.1016/j.scitotenv.2022.154116>
91. Hendriksen RS, Munk P, Njage P, et al. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nat Commun.* 2019; 10:1124. doi: <https://doi.org/10.1038/s41467-019-08853-3>
92. Caucci S, Karkman A, Cacace D, et al. Seasonality of antibiotic prescriptions for outpatients and resistance genes in sewers and wastewater treatment plant outflow. *fems Microbiol Ecol.* 2016;92(5):fiw060. doi: <https://doi.org/10.1093/femsec/fiw060>
93. Spänig S, Eick L, Nuy JK, et al. A multi-omics study on quantifying antimicrobial resistance in European freshwater lakes. *Environ Int.* 2021;157:106821. doi: <https://doi.org/10.1016/j.envint.2021.106821>