

The Phenomenon of Antibiotic Resistance in the Polar Regions: An Overview of the Global Problem

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Abstract: The increasing prevalence of antibiotic resistance is a global problem in human and animal health. This leads to a reduction in the therapeutic effectiveness of the measures used so far and to the limitation of treatment options, which may pose a threat to human health and life. The problem of phenomenon of antibiotic resistance affects more and more the polar regions. This is due to the increase in tourist traffic and the number of people staying at research stations, unmodernised sewage systems in inhabited areas, as well as the migration of animals or the movement of microplastics, which may contain resistant bacteria. Research shows that the presence of antibiotic resistance genes is more dominant in zones of human and wildlife influence than in remote areas. In a polluted environment, there is evidence of a direct correlation between human activity and the spread and survival of antibiotic-resistant bacteria. Attention should be paid to the presence of resistance to synthetic and semi-synthetic antibiotics in the polar regions, which is likely to be correlated with human presence and activity, and possible steps to be taken. We need to understand many more aspects of this, such as bacterial epigenetics and environmental stress, in order to develop effective strategies for minimizing the spread of antibiotic resistance genes. Studying the diversity and abundance of antibiotic resistance genes in regions with less anthropogenic activity could provide insight into the diversity of primary genes and explain the historical evolution of antibiotic resistance.

Keywords: antibiotic resistance, polar regions, bacteria, bacterial community and diversity, Antarctica, Arctic

Introduction

Antibiotic resistance of bacterial pathogens is an increasing public health threat. The overuse and misuse of antibiotics is primarily responsible for the emergence and spread of resistant pathogens.¹ For example, the cases of methicillin-resistant *Staphylococcus aureus* (MRSA) were identified in the United Kingdom in 1962 and in the United States in 1968.^{1,2} In addition, bad sanitation in poorer countries, displacement, tourism, medicine, lack of access to clean water, poor hygiene, intensive trade and climate change contribute to the global spread of resistant pathogens.^{3–7} The lack of infection control programs as well as the lack of an antibiotic policy also play an important role.

The loss of efficacy of antibiotics poses a threat to public health, especially when it comes to the ability to treat infections.⁸ Antibiotics play a significant role in medicine and surgery. Many medical advances correlate with the ability to fight infection with antibiotics. These include joint replacements, cardiac surgery, organ transplants, cancer treatment, and treatment of chronic diseases like diabetes, asthma, end-stage renal disease and rheumatoid arthritis.^{1,7} Due to greater treatment options for bacterial infections, antibiotics have contributed to an increase in life expectancy.⁹ Natural selection allows antibiotic-resistant bacteria to spread because antibiotics do not work against them. At the same time, antibiotics remove their drug-sensitive competitors.¹⁰ Despite reports and warnings of overuse, antibiotics are prescribed all over the world. It has been shown that the indication for treatment, the choice of medication or the duration of antibiotic therapy are incorrect in 30% to 50% of the cases.^{1,11} One study found that the pathogen was only defined in 7.6% of 17,435 patients hospitalized with community-acquired pneumonia (CAP). In turn, a study by the Karolinska Institute in Sweden showed the possibility of identifying the pathogen in 89% of CAP patients using molecular diagnostic techniques such as

PCR and semi-quantitative PCR.¹² It has also been found that 30% to 60% of the antibiotics prescribed in intensive care units (ICUs) have been found to be unnecessary, inappropriate, or suboptimal.¹¹ Resistance to almost all developed antibiotics was observed (Figure 1).



Figure 1 A timeline of development of antibiotic resistance. Based on Ventola.¹

The antimicrobial resistance (AMR) phenomenon has a direct impact on the welfare of humans and animals, carries a large economic burden due to higher treatment costs, reduced productivity due to disease and increased mortality.¹³ An estimated 4.95 million deaths were related to AMR in 2019, while in the case of 1.27 million cases, AMR was the direct cause of deaths.¹⁴ If appropriate preventive measures are not taken immediately, the number of deaths due to antibiotic resistance in the world by 2050 could increase up to 10 million per year.¹⁵

Mechanisms of Antibiotic Resistance

In the case of bacteria, genes can be transferred by mobile genetic elements such as plasmids or they can be inherited.¹⁰ Sub-inhibitory and sub-therapeutic levels of antibiotics can cause changes in gene expression, horizontal gene transfer (HGT) or mutagenesis, thereby contributing to the development of resistance.¹⁶ The most common way of acquiring antibiotic resistance by a previously sensitive bacterial cell is through HGT. This process takes place in a mixed population of bacteria, in which antibiotic-resistant bacterial cells come into contact with bacterial cells that are sensitive to the antibiotic. The most convenient sites for HGT are certain ecosystems and the digestive tract of animals and humans. Resistance genes are passed on by transduction during which genetic material is transferred from resistant bacteria to sensitive bacteria; transformation, that is, uptake of genetic material (DNA) released by autolysis of antibiotic-resistant cells by sensitive cells; conjugation, involving the transfer of R (R resistance) plasmids or a fragment of the donor chromosome.¹⁷

In the case of a biofilm, bacteria often exchange antibiotic resistance genes, which can be encoded in mobile genetic elements (MGEs), transposons, integrative and conjugative elements (ICEs) or bacteriophages.¹⁸ It is also worth paying attention to the processes related to membrane vesicles (MVs), which constitute a reservoir of DNA in water environments.¹⁹ MV has been reported to contribute to the development of biofilm in, for example, *H. pylori* and *V. cholerae*.^{20,21} The important fact is that MVs can contain and transport biomolecules such as DNA, RNA, proteins or metabolites that can be involved in gene transfer, cell communication and nutrient acquisition. Interestingly and importantly, the DNA and proteins carried by MV show resistance to nucleases and proteinases that would normally degrade these substrates.²²

Acar and Moulin²³ share acquisition mechanisms by antibiotic-resistant bacteria into six categories:

1. efflux pumps which prevents achievement by the antibiotic of its target, that is, the site of damage function of the bacterial cell,
2. reduced bacterial cell membrane permeability, which occurs when modifications are made to its composition and function,
3. inactivation of the antibiotic by enzymes produced by bacteria; they can alter the antibiotic inside or outside the bacterial cell, rendering it uninhibited by its antibacterial effect,
4. reduction of the target substrate an antibiotic, which lowers antibiotic affinity,
5. the presence of a mixed population of sensitive and resistant bacteria at the concentration of the antibiotic selecting resistant cells,
6. mutations in bacteria with the following selection by antibiotic-resistant bacteria.

In recent years, an aspect of bacterial epigenetics has appeared more and more often, which may have an impact on the spread of antibiotic resistance. Methylation of adenines and cytosines can alter the genetic structure and affect the mutation rate in the bacterial genomes, thus modulating antibiotic sensitivity.²⁴ As evidence for the connection of epigenetic mechanisms with bacterial resistance to antibiotics, the following was indicated: adaptive resistance, phase variation (DNA inversion, methylation/demethylation of gene promoters or other regulatory sequences, transposition and slipped-strand mispairing), heteroresistance, phenotypic heterogeneity and the resulting bistability (impact on formation of persister cells).^{24–32} More research is needed on the role of bacterial epigenetics, especially as epigenetic modifications of bacterial genomes constitute new diagnostic markers as well as new drug targets. Ghosh et al²⁴ indicate that we need precise mapping of epigenetic tags on bacterial genomes and their functional analysis. Bacterial epigenetics is discussed in more detail in Ghosh et al's²⁴ review.

Antibiotic Resistance in the Polar Regions

Antibiotic resistance genes have been observed at both the North and South Poles. For this reason, studying remote natural environments that have minimal anthropogenic contribution may be beneficial in following the evolution of antibiotic resistance, as well as allowing us to understand the origins of ARGs beyond clinical conditions.^{33–35} The transfer of bacteria containing resistance genes to isolated regions where endemic microorganisms live may be mediated, for example, by anthropic activity or bird migration.³⁵ In *E. coli* isolates from Arctic birds (Western sandpiper, Vega/Glaucous gull, Emperor/Brent goose, Iceland/Glaucous gull), resistance to 14 drugs (including ampicillin, sulfamethoxazole, trimethoprim, chloramphenicol, tetracycline or fosfomycin) was detected.³⁶ In a study of the Arctic Tern (*Sterna paradisaea*), which migrates long distances along the Atlantic Ocean, the highest ARBs were observed for β -lactam and quinolone antibiotics.³⁷ Resistance phenotypes such as vancomycin-resistant enterococci (VRE) and broad-spectrum beta-lactamase-producing gram-negative bacteria (ESBL) have been isolated from bright gulls, which breed in the Arctic, but are also regular visitors to urban areas such as urban landfills and sewage near human habitats.³⁸ In Admiralty Bay in the area of Palmer Station, Miller et al³⁹ isolated from seawater samples and penguin faeces bacteria that showed multi-drug resistance to five common antibiotics such as tetracycline, kanamycin, ampicillin, nalidixic acid and streptomycin. It has also been shown that some wild reindeer (*Rangifer tarandus platyrhynchus*) in the Svalbard archipelago (Arctic) carry *E. coli* resistant to antimicrobial agents.⁴⁰

Tam et al,⁴¹ while examining lakes in Antarctica, found in isolates (inter alia *Arthrobacter* spp., *Bacillus* spp., *Flavobacterium* spp., *Pseudomonas* spp., *Rhodococcus* spp., *Sphingomonas* spp.) resistance to 10 or more antibiotics in 26 strains of selected bacteria, and in 43 strains resistance to at least 3 antibiotics.

Until recently, it was believed that the anthropogenic influence in the polar regions was negligible. However, the development of tourism, the growing number of inhabitants as well as the number of researchers in the Arctic and Antarctic may carry the risk of introducing alien microbes associated with humans with unknown consequences.³⁸ Microplastics are also potential vectors for chemical contamination, and recent discoveries show that they can also be a carrier of antibiotic-resistant bacteria.^{42,43}

Basically, two assumptions are suggested to explain the spread of antibiotic resistance. The first is the release of antibiotic-resistant exogenous bacteria into the environment through inappropriate use of antibiotics. On the other hand, the second alternative is the co-selection of bacteria carrying antibiotic resistance genes or the horizontal transfer of these genes through mobile elements, in which environmental stress is indirectly influenced by the presence of pollutants, the degree of salinity, temperature or the presence of heavy metals.⁴⁴ In a polluted environment, there is evidence of a direct correlation between human activity and the spread and survival of antibiotic-resistant bacteria.⁴⁵ The local Antarctic microflora is influenced by increasing anthropic activity. However, we must bear in mind that antibiotic resistance is a natural phenomenon and is a common defense mechanism of bacteria.⁴⁶ This review describes the current state of knowledge regarding the prevalence of antibiotic resistance in the polar regions (Figure 2).

Seawater and Freshwater

Misuse of antibiotics has contributed to the selection as well as spread of antibiotic-resistant bacteria in marine and terrestrial ecosystems.^{47,48} It is generally accepted that antibiotic resistance is a response to the increased release of antibiotics in aquatic environments, sometimes via wastewater or to other sources of contamination such as such as mining or animal husbandry.^{49–53} The relationship between the prevalence of ARG and anthropogenic activity was confirmed by Ouyang et al⁵⁴ studying the urban stream of the Jiulongjiang River. Also, Pruden et al,⁵⁵ studying the riverside areas, confirmed the relationship between the sources in wastewater treatment plants and the intensification of the phenomena of antibiotic resistance.

The aim of Jara et al³⁵ study was to evaluate the antibiotic-resistance features of bacterial isolates recovered from freshwater samples collected in regions under differential anthropic influence in Fildes Peninsula, King George Island, Antarctica. Resistance to β -lactams (mainly third-generation cephalosporins), aminoglycosides, as well as to ciprofloxacin, chloramphenicol, tetracycline and sulfamethoxazole was observed in the three studied zones differing in human influence. In the zone exposed to greater human activity, greater richness and diversity of antibiotic resistance genes



Figure 2 Diagram of cases described and associated with the occurrence of antibiotic resistance in the polar regions.

(ARGs) were observed compared to the other two zones studied, which were characterized by low human activity. In addition, from the zone exposed to greater human activity, the collected bacterial isolates were resistant to synthetic and semi-synthetic drugs, in contrast to isolates recovered from zones with little human intervention, which resulted in high susceptibility to antibiotics.³⁵ The differences in the number of bacteria in the individual zones studied can be attributed not only to human activity, but also to the presence of animals, such as migratory birds or sea mammals, that migrate long distances. Antibiotic-resistant bacteria have been reported in marine mammals and sharks on the US West Coast, where 58% of the subjects tested were resistant to at least one antibiotic and 43% to more than one drug.⁵⁶ Moreover, examples of *Salmonella enterica* serovar Enteritidis (related to salmonellosis in humans) have been reported in Papuan penguins (*Pygoscelis papua*), and in Adelia penguins (*Pygoscelis adeliae*).⁵⁷ Additionally, Jara et al³⁵ found isolates resistant to synthetic or semi-synthetic antibiotics, such as SUL and TMP, in zones with increased human activity. Research from the Davis station (Antarctica) area suggests that the discharge of insufficiently treated residual water introduces human pathogens that carry ARGs into the Antarctic ecosystem.⁵⁸ Karkman et al⁵⁹ demonstrated a correlation of the abundance of ARGs unrelated to the selective pressure of the antibiotic with contaminated faeces. Several β -lactamase genes have been identified that mediate resistance to clinically significant cephalosporins. These include the ESBL bla_{CTX-M2} and bla_{PER-2} genes and the plasmid-mediated AmpC β -lactamase genes pAmp_{CDHA}, pAmp_{CFOX} noted in zones of increased human influence. No β -lactamase genes were detected in the studied zone with the lowest human activity.³⁵ This may indicate the introduction of ARGs into the environment by humans or animals, which is consistent with research near scientific bases in Antarctica, where ESBL genes were detected in the tested isolates and no ARGs were found in native bacteria.³⁸ It is therefore believed that the local microflora is affected by human activity, and the bacterial strains found in an area exposed to human influence were more resistant to antibiotics than those collected from more remote areas without human influence.³⁵ Research by Kalinowska et al⁶⁰ studied sewage treatment plants and two arctic lakes in terms of the microbial community. One of the lakes is affected by the nesting area of birds (natural impact), and the other lake receives treated sewage from the Polish Polar Station (anthropogenic impact) in Hornsund, West Spitsbergen. *Caldilineaceae* and *Anaerolinaceae* families belonging to the Chloroflexi type, associated with municipal and domestic sewage treatment systems, were abundant in sewage samples, while in the samples from the lake being a nesting area for

birds, they did not exceed 0.1%. A similar tendency was also observed in the case of Clostridia (phylum Firmicutes), potentially human-associated clade TM7-3 of the Saccharibacteria/TM7 phylum or the B142 class from the Dojkabacteria/WS6 phylum. In the case of the lake receiving treated wastewater from the test station, it was found that the microbial community diversity was directly increased by introducing wastewater-related bacteria as well as by providing nutrients that could play a significant role in typically oligotrophic Arctic lakes. Additionally, there was an increase in the total number of prokaryotic cells, mean cell volume, prokaryotic biomass, and percentage of viable cells.⁶⁰ The wastewater management research are described in more detail in the section “Wastewater Management in the Canadian Arctic”.

Laganà et al⁶¹ undertook a study of the Pasvik River, which flows between the borders of Norway and Russia, to study the biofilm-forming capacity of river bacterial isolates and to evaluate their antibiotic sensitivity profiles. For this purpose, water and sediment samples were taken in May and July. It is believed that the ability of bacteria to form biofilm is a strategy for the survival of microorganisms in altered environmental conditions, such as in contaminated areas. Biofilm is recorded in microorganisms that are able to survive environmental stresses by colonizing various types of substrates. Moreover, studies have shown an increased tolerance to antibiotics among bacterial communities composed of biofilms.^{62,63} Compared to their plankton counterparts, bacterial cells in biofilms are 10 to 1000 times less susceptible to certain antimicrobial agents.⁶⁴ The mechanisms that protect biofilms against antimicrobials may not only limit the effects of antimicrobial agents but even increase the resistance of biofilms to antimicrobial agents or induce biofilm formation.⁶⁵ For example, it has been reported that sub-inhibitory concentrations of tetracycline and cefradin induce biofilm formation and increase the pB10 plasmid transfer rate between biofilm biomass (*E. coli* and *P. aeruginosa*) at rates 2–5 times faster than without antibiotic treatment.⁶⁶

Contamination is believed to influence the selection pressure that contributes to the spread of antibiotic resistance factors.⁶¹ In Laganà et al⁶¹ study, all strains were resistant to ampicillin (AMP), in addition, there was widespread resistance (in 90% of all strains) to the antibiotics mezlocillin (MEZ), ceftazidime (CAZ), cefotaxime (CTX), ceftazidime (CAZ), cefuroxime (CXM), fosfomicin (FOS), piperacillin (PRL), aztreonam (ATM), cefotaxime (CTX), ceftazidime (CAZ), cefuroxime (CXM), fosfomicin (FOS), pipemidic acid (PI), sulfamethoxazole + trimethoprim (SXT), amikacin (AK), chloramphenicol (C) and amoxicillin + clavulanic acid (AUG) was also observed in a large percentage (60% to 70% of the total) tested strains. All the tested strains from the Pasvik River were able to produce biofilm, but it was noted that bacterial isolates taken from polluted areas (closer to industrial areas) showed a greater biofilm formation capacity than isolates taken away from contaminated areas. This may confirm that the strategy of biofilm formation in bacterial communities offers a better chance of survival in a changed environment. Also, Sanz-Lázaro et al⁶⁷ showed changes in the accumulation of marine biofilm communities in response to organic pollutants. Interestingly, in May, both in water and sediment samples, resistance to cell wall antibiotics is the most common, while in July, resistance to nucleic acid inhibitors is predominant.

Pathogenic microorganisms that do not host the genes or antibiotic-resistant gene elements are introduced into the aquatic environment via wastewater, spread rapidly, and may form new bacterial communities or become incorporated into newly formed biofilms.⁶¹ The biofilm matrix may increase the range of mobile genetic elements, eg, plasmids, that are horizontally transferred.⁶⁸ It has also been noticed that bacteria that form communities in the form of biofilms have an increased ability to survive to cleaning or disinfection.⁶⁹

Therefore, aquatic environments can be one of the main ways that antibiotic resistance spreads.

Laganà et al⁶¹ found a significant association between biofilm formation and antibiotic resistance in water and sediment samples, but only in May and only in the more polluted area. They suggest that in the colder months (eg, May), bacterial communities, composed mainly of psychrophilic strains (which are well adapted to growing at low temperatures), are able to cope with the presence of contaminants. Since the presence of antibiotic resistance is often associated with the presence of contaminants, this result may reflect the survival strategy of bacteria under altered environmental conditions.

Wastewater Management in the Canadian Arctic

Due to their global use in medicine, animal husbandry and aquaculture, antibiotics are found in large amounts in wastewater and treatment plants.⁴⁸ To illustrate, it is estimated that the consumption of antibiotics in 228 countries in livestock reached 63,151 tonnes in 2010 and is expected to increase by another 67% by 2030.⁷⁰ Due to poor local and global regulation, antibiotics are increasingly found in terrestrial, freshwater and marine environments.⁷¹ Wastewater and sewage treatment plants have been identified as hotspots in the evolution, recombination and diffusion of antibiotic resistance.⁷²

Most communities living in the Canadian Arctic use Wastewater Stabilization Ponds (WSPs), which act as controlled discharge storage tanks, where the wastewater is held for an average of 200–250 days, followed by an annual emptying at the end of summer.⁷³ Most of the time these ponds are frozen; however, they can release sewage in an uncontrolled manner at the onset of spring thaws or floods that last throughout the summer. WSPs are often discharged into tundra wetlands where polishing of effluent has been observed prior to discharge into primarily marine receiving water environments. These wetlands have been used for sewage disposal for years and have been called Wetland Treatment Areas (WTAs).^{50,74} The removal efficiency and suppression of tundra WTA pollutants is characterized by high inter-system and intra-system variability, depending on the natural hydrology of the landscape and temperature.^{50,75} Additionally, most households do not have plumbing, so waste is collected in septic tanks and transported to WSPs located on the periphery of the community.⁷³ There are new regulations for urban wastewater treatment (Wastewater Systems Effluent Regulations [WSER]);⁷⁶ but due to many obstacles such as infrastructure, funding, community capacity, climate and the lack of appropriate design guidelines, the community would struggle to comply with the regulations, so they are not used in regions of the northern Canadian Arctic.⁷³

High concentrations of antibiotic residues have been reported in municipal wastewater from partially metabolized human drugs and the disposal of unused antibiotics.⁷⁷ Wastewater treatment plants not only create a good place for the development of microorganisms but also create conditions that facilitate the transfer of resistance genes between communities of microorganisms present in wastewater.⁷⁸ Conventional wastewater treatment systems are considered to be hotspots for the diffusion and evolution of the ARG.⁵¹ ARGs or antibiotic-resistant bacteria (ARBs) can persist in human and agricultural waste, and then may be released into, eg, aquatic environments, which is important in the Canadian Nunavut Territory, which is mainly inhabited by Inuit who collect food by hunting, fishing or collecting shellfish.^{79,80} In the Nunavut region, the presence of multiple resistance to two or more antibiotics, including ampicillin and streptomycin, has been identified in two salmonid isolates taken from remote locations away from human habitats.⁸¹ Wild animals can act as vectors and spread antimicrobial resistance from urban rural areas in Arctic environments, as exemplified by Alaskan seagulls carrying antibiotic resistance strains of *E. coli*.^{82,83} Human-environment interactions may pose a risk of exposure to wastewater-related pathogens through contact with animals or the aquatic environment, especially as natural wastewater treatment systems (WWTSs) are located close to households.⁵⁰

Neudorf et al⁷⁶ studied three wastewater treatment plants in the Canadian Arctic (two lagoon systems – Pond Inlet and Clyde River, and one mechanical treatment plant – Iqaluit) for both water quality and the presence of antibiotic-resistant genes in raw and treated sewage. Measurements of the wastewater quality parameters have shown that the current systems only provide basic treatment and are not WSER compliant. The WSP systems at Pond Inlet and Clyde River provided a higher level of treatment than the mechanical plant at Iqaluit, indicating that some biological treatment is taking place in the WSP in this region. Treatment with WSP-based systems altered the ARG profile and resulted in a reduction in the absolute number of *E. coli*, ARG and 16S rRNA GC, indicating that WSP treatment reduced the total number of bacteria, including ARG-containing bacteria in the waste water. However, the mechanical system in Iqaluit had no effect on the wastewater ARG profile, *E. coli*, ARG or bacterial load (16S GC rRNA) leaving the treatment plant, indicating no microbial removal. Although the absolute abundance of ARGs decreased across the treatment continuum in the Clyde River WSP system, they showed that the effluent samples contained a significantly ($P < 0.05$) higher relative abundance of many ARGs (ie, *sul1*, *sul2*, *mecA*, *tet(O)*, and *qnr(S)*) at the end of the purification process, compared to the inflow levels. This indicates that these ARGs were enriched across the microbial community during long persistence in secondary WSPs, which may be explained by the fact that some antibiotics (notably fluoroquinolones, trimethoprim, and

sulfonamides) are poorly cleared during primary treatment processes.⁷⁶ In this way, selective pressure may be exerted on bacteria in the sewage system, leading to the enrichment of ARB and subsequent release to the receiving waters.⁸⁴

Hayward et al⁵⁰ studied two sites which were located in Sanikiluaq and Naujaat in Nunavut, Canada. In both places it was noticed that ARG concentrations were higher in spring than in summer, which may be related to the hydrology of these areas. The target genes with the highest prevalence in wetlands are the class I integrase gene *int1*, *sul1*, *sul2* and *qnrS* in Naujaat. Earlier studies have noticed that the *int1* gene and the group of sulfa antibiotics (to which sul genes confer resistance) are among the most common in sewage.^{85,86} It is suggested that there is a selective pressure on the waste water that may contribute to the proliferation of naturally occurring ARGs, as ARGs found in the reference water were also found in greater abundance in the raw sewage and wetlands of the treatment plant. Some ARGs have also been detected in reference soils, which may indicate that they occur naturally there.⁵⁰ Total coliform, *E. coli*, VSS, and zinc were the water quality parameters that were the most strongly correlated with the gene targets. Bacteria often carry ARGs in their cell structure in a selective environment, so we expect a large number of bacteria and ARGs in the wastewater. In addition, the waste water has a high nutrient content which may allow bacteria to multiply. In conclusion, a hypothesis was made, supported by research, that system hydrology will play a large role in the concentrations and spatial distribution of ARGs in wetlands. Elevated levels of ARG in soil samples compared to water samples may indicate retention of ARG from the period of higher concentrations in water, or may provide an environment conducive to the proliferation of bacteria that can carry ARG.⁵⁰

The objectives of study by Gromala et al⁸⁷ were to examine the WSP systems of Baker Lake, Cambridge Bay, and Kugluktuk, all in Nunavut, Canada, with a particular focus on sampling Baker Lake. Identified gene families have been associated with macrolide resistance, class A beta-lactamases, protection of ABC-F ribosomes, and rRNA methyltransferases. Except for one gene family (CARB-16) associated with class A beta-lactamases, all of the most abundant gene families appeared to be associated with resistance to macrolide antibiotics, which are commonly used in the treatment of clinical infections, especially upper respiratory tract and skin infections.^{87,88} However, these genes possibly resistant to macrolide antibiotics have not been detected in large numbers in lakes below Lake Lagoon in Baker Lake, which may indicate that the microorganisms carrying these ARGs did not survive in lakes further downstream. Several ARG families identified in both samples from sites below the Baker Lake WSP and above the reference sites are likely to occur naturally in this environment. The samples were dominated mainly by representatives of Proteobacteria. Moreover, samples from sites further from the WSP had a less similar composition of microbial communities than samples from closer sites. This shows that the microbial counts decline as they move away from the WSP.⁸⁷

Interestingly, despite wastewater treatment, the determinants of antibiotic resistance may not be completely removed.⁸⁹ Antibiotic-resistant bacteria (ARB) have been reported in tap water, for example, in China, France, Japan, Scotland, Portugal and Poland.^{90–96} Most bacteria in tap water are not culturable, but this global problem should not be underestimated. More research is needed on the impact of consuming such water on the health of consumers.⁸⁹ It is worth mentioning that ingested bacteria can exchange genes with the human intestinal microflora.⁹⁷ Various methods of monitoring antibiotic resistance in wastewater, their strengths and weaknesses, as well as opportunities or threats are described in the review by Miłobedzka et al.⁹⁸

Soils

Antarctic soils considered minimally affected by anthropogenic contamination should not show (or little) genetic influence on the selection pressure caused by the introduction of synthetic or semi-synthetic antibiotics in the 20th century.³⁴ Low temperatures reduce the activity of endoenzymes that degrade cells and their DNA, which promotes the survival of DNA in cold environments.⁹⁹ Extracellular DNA containing ARGs can persist in soils, for example, by binding cations, facilitating genomic transfer between members of the soil community.¹⁰⁰

Research by Yu-Jing Zhang et al¹⁰¹ using high-throughput quantitative PCR (HT-qPCR) to profile a large spectrum of ARGs in soil samples collected from 61 ocean and river beaches in Victoria, Australia, detected a total of 110 ARGs and 8 MGEs. The two most frequently detected ARG classes, conferring resistance to multidrug and β -lactam, accounted for 32.7% and 22.7% of the total numbers of detected ARGs, respectively. The other frequently detected ARG categories included aminoglycoside (12.7%), MLSB (10.9%) and tetracycline (7.3%). Soil salinity attributes were identified as the

most important environmental factors in modulating ARG distribution patterns in beach soils, and there was a significant upward trend in ARG over soil salinity gradients. Correlation in salinity may suggest increased bacterial resistance resulting from a response to increased salinity stress. Zhang et al¹⁰¹ suggested that soil salinity may directly contribute to the evolution and diffusion of ARGs in beach soil environments. In addition, some studies have shown that salinity stress-tolerant bacteria often exhibited increased resistance to antibiotics.¹⁰² Extreme temperature, pH, and salinity can induce phenotypic and genotypic adaptations in bacteria.¹⁰³ Salinity stress may induce bacterial cells to develop antibiotic resistance through increased translation of multiple antibiotic resistance operons, transfer of ARG-containing plasmid, and increased expression of ARG-related bacterial proteins to acquire resistance to environmental stress.¹⁰¹ It was found that the synthesis and protein folding is influenced both by the high temperature and antibiotics, for example macrolides or aminoglycoside.¹⁰⁴ Cellular responses to temperature stress, nutrient starvation, oxidative and nitrosative stresses are often paralleled with concurrent responses to antibiotics, as these stresses and antimicrobials are targeting same cellular components and processes.^{101,105} However, in theory, responding to every stress encountered and the evolution of immunity is unprofitable as it requires investment in the production of proteins, genetic material and energy. Greater efficiency can be achieved if cells can choose similar pathways to respond to different stressors. An example of such a strategy in bacteria is the alternative sigma factor σ S, which regulates the expression of 70 genes conferring resistance to stresses such as temperature change, hunger, pH and DNA damage.¹⁰⁴

In addition, the occurrence of salinity stress can eliminate salt-sensitive bacteria, which at the same time may contribute to the survival and reproduction of only salt-tolerant bacteria.

In studies by Yuan et al,¹⁰⁶ no large differences were observed in the total abundance of ARGs at different soil sampling sites in King George Island, West Antarctica. Samples taken from Antarctica were compared to typical anthropogenic sources of pollution-activated sludge from a Hong Kong wastewater treatment plant and chicken and pig faeces from farms in China.

Polypeptide and multi-drug related ARGs were found much more frequently compared to other ARGs in Antarctic soils. Compared to soils, most ARGs in representative sources of contamination, ARGs (AS – active sludge, CF – chicken feces, SF – swine feces) were more specifically related to anthropogenic antibiotics (eg, amino glycosides, beta-lactams, fluoroquinolones, macrolides, sulfonamides and tetracyclines). In samples enriched with animal faeces (SF) collected from feeders, the abundance of ARG (2.7×10^3 ppm) was at least 65 times greater than in Antarctic soils (maximum 40.8 ppm). Antibiotic resistance is widespread in the polar regions, possibly due to the multifaceted role of antibiotics in nature, including interspecies competition, signaling molecules and virulence.¹⁰⁶ Also, important are the resistance mechanisms developed as a result of the influence of stress factors in the environment. However, increasing human interference, mainly in the vicinity of research stations, is changing the profile of the ARG.^{39,107} Insufficient treatment and disposal of waste water, which introduces foreign microorganisms, may contribute to this.¹⁰⁸ However, in the Yuan et al¹⁰⁶ study, soil samples collected near China's Great Wall station did not differ significantly in the ARG profile, with samples collected at remote sites and with a low probability of anthropogenic impact. Seventy-nine subtypes of ARGs have been identified in Antarctic soil samples, the most abundant of which was the *bacA* gene (the *bacA* gene product is able to circumvent the inhibition of the dephosphorylation of the isoprenyl pyrophosphate by bacitracin).^{106,109} The most common resistance mechanism was efflux pumps (about 60% of all ARGs detected), which could confer resistance to many antibiotics, such as multidrug, chloramphenicol, macrolide, and fosmidomycin. The results of the study suggest that the soil is a reservoir for *BacA*, *ceoB*, *dfrE*, *mdtB*, *amrB*, *acrB*, *mexF*, *mexB*, *vanR* and *arnA* genes, detected in over 70% of all ARGs in Antarctic soils, which were mainly associated with chloramphenicol, multidrugs, polypeptides and trimethoprim.¹⁰⁶ Culturable bacterial strains in Antarctic soils were consistently susceptible to aminoglycosides, fluoroquinolones and tetracycline but resistant to macrolide (erythromycin), rifampin, oxazolidinone and some beta-lactams (eg, ampicillin, penicillin, and cefazolin). In addition, none of the well-known beta-lactam-related ARGs in the database were detected in the genomes of breeding bacterial consortia, but were resistant to some beta-lactams. Therefore, this result suggests that these Antarctic soil consortia possess unidentified beta-lactam resistance genes. ARGs possibly present on plasmids in Antarctic soils were able to confer resistance to chloramphenicol, fluoroquinolones, multidrugs, polypeptides and tetracyclines, and ARGs associated with chloramphenicol and many

drugs could be detected in all soil samples. The multi-drug resistance genes (2.6 ± 2.1 ppm) were the most abundant of all resistance types in Antarctic soils, followed by chloramphenicol and fluoroquinolone.¹⁰⁶

In research by Gothem et al,³⁴ surface soil samples were collected from 17 sites in ice-free areas in the vicinity and to the north of Mackay Glacier, South Victoria Land, Antarctica. The research was based on metagenomics to identify the natural diversity of in silico antibiotic resistance genes from remote Antarctic regions. Most of the collected ARGs (126 out of 177; 71%) were gram-negative, 16 ARGs (9%) were assigned to gram-positive bacteria, only *Bacilli spp.* (*Firmicutes*) and Actinobacteria. The main gram-negative bacteria were Bacteroidetes (41 ARG) and Acidobacteria (37 ARG). The bacterial clusters encoding the multiple mechanisms of resistance included Proteobacteria (30 ARG), Firmicutes (16 ARG), Cyanobacteria (8 ARG), and Actinobacteria (5 ARG). The two most abundant ARG families identified are undecaprenyl pyrophosphate phosphatases (UppP) and the efflux/transporter system genes that mediate antibiotic export across the cell surface and reduce intracellular antibiotic load. UppP genes confer resistance to bacitracin and have been reported in the most numerous types of bacteria in the area under study: Bacteroidetes (9 ARG), Acidobacteria (7 ARG) and Proteobacteria (3 ARG). ORFs described as runoff mechanisms were found in 13 out of 17 metagenomes, confirming that this is a common resistance strategy for soil bacterial populations. In the metagenomes of Antarctic soils, genes responsible for antibiotic inactivation strategies have been found less frequently, in relation to the UppP genes or the efflux pump genes. Some communities have had membrane spanning domains (MDS) (2 ARGs) and multi-drug efflux pumps (11 ARGs) which can remove a wide variety of antibiotics from the cell.³⁴ Surprisingly, a single ARG-encoding resistance to trimethoprim, a synthetic antibiotic that inhibits DNA synthesis, was discovered and may support the possibility of introducing foreign microorganisms into the continent, which serve as a mechanism for introducing antibiotic resistance genes into remote and virgin soil communities.^{34,110,111} A possible explanation for this finding may be the presence of thymidylate synthetase (thyE), which converts deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) at the 5' end of the drfA sequence, which codes for trimethoprim resistance.³⁴ Gothem et al³⁴ have observed a significant correlation between the diversity of ARG, and the nitrogen content in the soil. Moreover, the number of ARGs per sample showed a significant negative correlation with the number of species in the site, which could be explained by the competitive exclusion of species by exposure to antibiotics, potentially by inhibiting the growth and activity of competing species.¹¹² This phenomenon, rather than acquiring and developing new resistance mechanisms, may favor the selection of pre-existing genotypes.^{34,113}

Summarizing the study by Gothem et al,³⁴ it is believed that most antibiotic resistance genes found here are predominantly from antibiotic-producing species, confirming the presence of antibiotic biosynthetic genes in many types of resistance. Antibiotic resistance appears to be transmitted vertically through generations with limited horizontal transfer (no mobile genetic elements found) of ARG between species. Phylogenetic analyzes have shown that the origin of some β -lactamase genes dates back more than 2 billion years ago.¹¹⁴ The results of the study (177 naturally occurring, historical genes conferring resistance to natural antibiotics were found) indicate that ARG homologues found in remote Antarctic soils represent older genes that were acquired or evolved in the distant past, which over time formed part of the necessary gene pool and passed specific selection pressure for a niche.³⁴ Therefore, the concept is confirmed, whereby a variation in the content of soil in the environment ARG corresponds phylogeny and not HGT. We need to consider and understand how direct and indirect human activities affect the composition of distant soils and changes in resistance properties.

Plastic

Human activities contribute to the production of millions of tonnes of plastic, most of which can end up in ecosystems.¹¹⁵ Plastic pollutants can reach marine environments through inland waters, wastewater, or when garbage is transported by wind. Fishing and general maritime activities are also an important factor. Due to their environmental durability, plastics are a global problem, and depending on environmental conditions, type of polymer and weathering, they undergo transformation processes, including photooxidation or mechanical cutting into smaller pieces of plastic.⁴² The presence of microplastics has already been recorded in the polar environment, not only in fresh and seawater but also in sediments, ice, snow, fish and benthic organisms.^{116–126} Plastics are known to absorb highly toxic hydrophobic organic compounds, including persistent organic pollutants (POPs), polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), phthalates, pesticides and heavy metals.^{42,127–129} In addition to the fact that such compounds can accumulate in

fatty tissue and bio-magnification through the marine trophic web, chemical contaminants can be a factor in trigger antibiotic resistance.^{42,130}

Laganà et al⁴² studied the biofilm and susceptibility of bacteria to antibiotics found on the surface of some polystyrene pieces recovered from King George Island (Antarctica) in 2016. They assumed that plastics could serve as a habitat for bacterial species exhibiting antibiotic resistance, thereby acting as a potential vector for the spread of antibiotic resistance. Polystyrene (PS) consists of about 95% of air, which makes it very mobile, easily crushed into smaller pieces, and the porous structure of PS favors the adsorption of biological and chemical pollutants, such as biological fouling microorganisms and POPs. Antarctic waters are home to psychrophilic microorganisms which are extremophiles and have adaptations that enable them to reproduce and grow at temperatures below 0°C. In a study by Laganà et al,⁴² a taxonomic analysis of bacterial isolates attached to PS revealed the presence of species belonging to the genera *Pseudoalteromonas* spp. and *Shewanella* spp., which are types of hydrocarbon bacteria commonly found in oil contaminated areas. In turn, Martins et al¹³¹ identified human waste and the combustion of fossil fuels as the main causes of the release of aliphatic and polycyclic aromatic hydrocarbons in surface sediments in areas off the southern coast of King George Island. This may indicate the proliferation of ruthless hydrocarbon-degrading bacteria, specialized members of the microflora that usually proliferate and become dominant following oil contamination. The antibiotic susceptibility profiles of the bacterial strains isolated from the analysed PS sample highlighted the occurrence by multiple AR against cefuroxime and cefazolin, two molecules that belong to cephalosporins, against cinoxacin that belongs to quinolones as well as against ampicillin, amoxicillin + clavulanic acid, carbenicillin and mezlocillin that belong to beta-lactams.⁴² Recent studies have documented the absorption of antibiotics to plastic surfaces, but there are not enough data on the potential effect of mixed microplastic and antibiotic contamination on the spread of AR. However, a correlation between ARG and the class 1 integron integrase gene (*intI1*) has recently been found and it has been suggested that *intI1* may facilitate the transfer of several ARGs such as *sulI*, *tetX*, *ermE* and *ermF* between water and microplastics through HGT, which may indicate a role for microplastic in the spread of antibiotic resistance in the environment.¹¹⁵ Recent studies have also shown that salinity may reduce the content of ARGs and antibiotics on the surface of polyethylene.¹³² Further studies, such as plasmid isolation, ARG identification, and sequencing, are recommended to investigate the potential mobility of antibiotic resistance components in the environment.

The Consequences of the Globally Widespread Problem of Antibiotic Resistance

We have to bear in mind the consequences of the globally widespread problem of antibiotic resistance. These are not only clinical consequences but also diagnostic, epidemiological, economic and psychological consequences.¹³³ The clinical consequences are associated with an increase in therapeutic failure, complications, and mortality. The emergence of new resistance mechanisms forces us to constantly search for and introduce new methods of their rapid detection, which results in an increase in the cost of microbiological diagnostics or an extension of the waiting time for the result. In turn, the rapid movement of people and wares in the globalization of resistance and the emergence of outbreaks and epidemics of multi-resistant infections, and an increase in the presence of resistance genes in the environment.¹³³ We should also pay attention to the economic consequences among which the most important are the higher cost of therapy, a longer stay in the hospital or compensation.^{133,134} It is estimated that the each year AMR cost about 1.1 billion euros to the health care systems of EU/EEA countries.¹³⁵ Additionally, in developing countries, antibiotics are found in animal products.³ For example, in Cameroon, residues of chloramphenicol and tetracycline have been reported to exceed the maximum residue limit (MRL) recommended by the European Union in 2010 in the edible tissues of chickens (muscles, stomachs, heart, liver, kidneys) and eggs.¹³⁶ Human consumption of animal products contaminated with antibiotic residues may result in drug hypersensitivity reactions, aplastic anemia, carcinogenic, hepatotoxicity, mutagenic and teratogenic, as well as disturb the intestinal flora and reproductive disorder.^{137,138}

For many years, cross-sectoral and transnational actions have been taken to reduce the occurrence of the effects of bacterial resistance. However, despite the measures taken for the prevention and control of antibiotic resistance is still, an increase in resistance to certain antibiotics is observed. It is optimistic that since 2015 in Europe, a decrease in most resistance rates was observed, including a statistically significant decrease in the percentage of *S. aureus* resistance to methicillin from 19.0% to 15.5% and the percentage of *S. pneumoniae* insensitivity to penicillin from 14.2% to 12.1%.¹³⁹

Conclusion

The problem of antibiotic resistance phenomenon is affects more and more the polar regions. The increase in tourism and people staying at research stations, unmodernised sewerage in inhabited areas, as well as animal migration or the movement of microplastics that may contain resistant bacteria contribute to this problem. Research shows that the presence of ARGs is more dominant in human and wildlife-influenced zones, compared to remote areas. It has also been suggested that the presence of resistance to synthetic and semi-synthetic antibiotics in polar regions is correlated with human presence and activity. However, we have to bear in mind that the phenomenon of antibiotic resistance existed before the era of the use of antibiotics. Further research is needed to assess the risk of antibiotic resistance in the polar environment. Studying the diversity and abundance of antibiotic resistance genes in regions of less anthropogenic activity such as the polar regions may provide insight into the diversity of primordial genes and explain the historical evolution of antibiotic resistance.

The increasing prevalence of antibiotic resistance is a global problem in human and animal health. There is also a direct relationship between an increase in antimicrobial resistance and the misuse of antimicrobials, such as taking antibiotics prophylactically – without medical indications or in the wrong way. It is necessary to implement the “One Health” strategy because only a holistic approach to the problem of antibiotic resistance can bring success. It is important not only to monitor drug resistance and the consumption of antibiotics but also to focus on the search for new drugs, vaccines and alternative treatments. Phage therapy, antimicrobial peptides (AMPs) and phagemids can be alternatives to antibiotics.

Abbreviations

AMP, antimicrobial peptide; AMR, antimicrobial resistance; AR, antibiotic resistance; ARB, antibiotic-resistant bacteria; ARG, antibiotic-resistant gene; CAP, community-acquired pneumonia; ESBL, extended-spectrum β -lactamases; HGT, horizontal gene transfer; ICE, integrative and conjugative element; MGE, mobile genetic element; MLSB, macrolide–lincosamide–streptogramin B; MV, membrane vesicles; PAH, polycyclic aromatic hydrocarbon; PCB, polychlorinated biphenyl; POP, persistent organic pollutant; PS, polystyrene; SUL, sulfonamide; TMP, trimethoprim; WSER, Wastewater Systems Effluent Regulations; WSP, wastewater stabilization pond; WTA, wetland treatment area.

Disclosure

The authors report no conflicts of interest in this work.

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