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INVITED REVIEW – OPEN ACCESS

Spreading of Antimicrobial Resistance Across Clinical Borders

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ABSTRACT

Spreading of antibiotic resistance is effective via many routes and is dependent on the setting. Moreover, poor hygiene conditions, poor sanitation, as well as inadequate infection control contribute to the spreading of resistant bacteria in health care and industrial facilities, in the community as well as in animal production. Bacteria are present in any environment and bacterial resistance disseminate across the world. Animals receiving antibiotics, they carry antibiotic resistant bacteria and are spread to humans through food or animal contact. Vegetables may be contaminated with antibiotic-resistant bacteria coming from animal manure fertilizers. Overuse or misuse of antibiotics by humans is another major issue. Production of safe food especially of animal origin is important. In this vein, a holistic controlling in all different steps of the production line must be done as microorganisms manifest their presence in foods. Bacterial biofilms dominion our lives, as they are ubiquitous in every environment. Conjugation seems to be the mechanism related in biofilms transfer genes within biofilms or between bacterial communities. Eradicating the problem of antibiotic resistance could be approached by collaboration of authorities, bodies, industrials, veterinarians and doctors as the economic and social challenges emerging from AMR are important. Hereby, we expose the major ways across clinical borders resistant bacteria can sprea.

Keywords: Antimicrobial resistance, biofilms, food chain, resistant bacteria, antibiotics

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INTRODUCTION

Undoubtedly, there is a crucial necessity to gain an extensive understanding of the threat related to antimicrobial resistance (AMR) and global health. Human, animal, and environmental issues are involved.

The Scottish microbiologist Fleming in 1928 discovered Penicillin, the world's first antibiotic substance, for which he received a Nobel prize. Penicillin was broadly used to treat infections since 1945 in soldiers with sepsis resulting from wounds (1).

In the late 1930s, several sulfonamides were introduced, and thereafter many antibacterial substances were discovered, which highly contributed to the decrease in the mortality and morbidity levels.

However, the use of antibiotic compounds is compromised by the potential risk of resistance to the antibiotic since it was first used (2).

Biochemical and physiological mechanisms may be involved in the development of resistance. Antimicrobial agents seem to follow multifarious and complex processes, which emerge and disseminate resistance. Owing to the limited knowledge, the control of the resistance patterns is dubious, and prevention recommendations are not systematically established.

Another important concern is the impact of economic and social challenges emerging from AMR (3).

The pharmaceutical industry continually invests and attempts to develop new antibiotics following the demand from physicians. The willingness of several physicians to prescribe the latest antimicrobial compounds has increased the frequency of resistance. Overuse or misuse of antibiotics is another major issue. Yet, promptitude to directly buy from several pharmacists without a medical prescription is another challenge.

Hospitals, health organizations, private sector, and consumers truly recognize the importance of the problem. Clearly, a collaboration between the different bodies involved on an intergovernmental level is crucial for developing appropriate actions toward the increasing antibiotic resistance. The problem is not only related to humans, but it is extrapolated to animals, environment, and foods.

In this vein, a tripolar collaboration between the World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), and World Organization for Animal Health (OIE) was established in 2015 as the Global Action Plan on (AMR) (4). This association aims to generate antibiotic awareness through policies of international standards harmonization, systematic monitoring and assessment, and initiatives for sensitizing the people and involved bodies toward the rational use of antibiotics. Additionally, as an action plan, the Interagency Coordination Group on Antimicrobial Resistance was formed by the United Nations in 2016.

Antimicrobial agents are known to destroy or inhibit the growth of microorganisms and are necessary for protecting human and animal health. When antibiotics are given to battle bacterial infections, most of the bacteria are killed. However, it is well established that antimicrobial drugs can alter the host indigenous microbiota selecting the resistant organisms, which can appear as opportunistic pathogens.

Antimicrobial-resistant microorganisms can growth and move from food-producing animals to humans by direct exposure or through the ingested food and environment. Therefore, it is evident that the issue of AMR consists of a multifarious problem enclosing the interconnection between humans, animals. and the environment (5).

Likewise, antibiotics are fed to terrestrial and aquatic animals not only for treating infection but mainly promoting a faster flesh growth of the animal for commercial purposes.

In addition, antibiotic resistance has been observed in plant pathogenic bacteria. Hospital, industrial and domestic sewage worsen the situation. Surviving resistant bacteria may be transmitted to other hosts in different ways or on their mutations may be transformed to the new multiplying bacterial generations. As a result, "pathogenicity islands" are formed harboring multiple drug-resistant genes.

The spread of antibiotic resistance is a universal problem, as the observed resistance arises from one geographical location to another through food, water, movement of animals and/or people.

Consumer demands worldwide are based on safe and ethically produced food, particularly of animal origin. To ensure that the food is safe, a holistic control of the different steps involved in the production line must be followed (6).

Lapses in the handling, processing, and distribution of foods cannot be resolved through obsolete methods and inadequate proposals. They require positive approaches and resolution through the pooling of accumulated knowledge. Owing to the rapid evolution in the industrial domain and the pressures for continual improvement of both products and processes, the introduction of predictive modeling in the food industry can provide a considerable competitive advantage. Research and development capital concerns of the industry have been preserved by investigating a plethora of factors able to react on the final product. The presence of microorganisms in foods is strictly associated with the food quality. Microorganisms manifest through food spoilage, foodborne illness in consumers, or a final transformation of food in a beneficial form, which is called food fermentation (6).

Microbial growth is highly associated with food attributes, such as water activity, pH, temperature, relative humidity and conditions of storage (6). The effect of these features on the behavior of microbes in foods can be seen by the implementation of prognostic mathematical modeling derived from quantitative studies on microbial numbers. Predictive modeling is a useful tool, which gives prognostic information, and it is applied for a quantitative risk assessment. Herein, predictive models have been adapted for improving the food industry chain through a built virtual prototype of the final product or a process reflecting real-world conditions (7). Quality control issues are also applied in the pharmaceutical industry (8). Industries are engaged through the Industry Declaration signed in 2016. Since 2017, the established AMR Industry Alliance records data and traces the common line to be adapted. In this regard, the primary purpose of Alliance is focused on actions or conducts leading to the reduction of AMR. Yet, investments in research as well as cross industry effective measures for preserving contamination should be another issue that requires development or improvement.

Microbes can adapt to almost all environments, such as soil, water, air, animals, plants, rocks, and humans. The environmental impact of antibiotics has been given particular attention since their misuse and overuse could spread multidrug resistance in the environment and waters, thereby compromising human and veterinary health (9).

Antibiotics excreted by humans are non-completely metabolized. Additionally, resistant bacteria from the human microbiota could be shaded into the natural ecosystems causing harm. Environmental antibiotic resistance seems to be a tripolar issue. As stated, the administered antibiotics are partially metabolized, and consequently they are excreted through feces or urine in an unaltered or active metabolite form.

Resistant bacteria in the environment could spread and persist. Studies have found methicillin-resistant *Staphylococcus aureus* (MRSA) in marine waters from temperate and warmer climates (10).

Lastly, horizontal gene transfer among bacteria of different species could carry antibiotic resistance to different species. When compared with clinical strains, the environmental ones seem to possess many multidrug resistant efflux pumps. The comparative genomics of environmental and clinical *Stenotrophomonas maltophilia* strains strains are presented with different antibiotic resistance profiles. different antibiotic resistance profiles (11). Specifically, the presence of the MDR RND efflux pump (EbyCAB) on a genomic island seems to be accessed through horizontal gene transfer for *S. maltophilia* (11).

Another study comparing similar species coming from different environments (clinical and environmental ecosystems) showed higher antibiotic resistance in the environmental ecosystem (12). Likewise, the study was concerning the new antibiotic Tigecycline after 7 years of clinical use in Greece, showing its rapid spread in the environment.

As stated, antibiotics used in veterinary medicine for not only treating animal infections but also as growth factors in animal feed are metabolized in part and then excreted in the environment. Moreover, treatment using sub-lethal antibiotic doses could select bacterial species. Plant, soil, and water environments are absorbing non-metabolized drugs.

Concerning animals, antibiotics are accumulated in their tissues and when meat is consumed by humans, the resistant strains could potentially be acquired, which is a major public health concern. Studies performed at a molecular level have shown the transfer of resistant bacteria from food to humans through the food chain (13).

Yet, it is well known that antimicrobial drugs can produce alterations in the host indigenous microbiota selecting resistant organisms, which can appear as opportunistic pathogens. A multiple antibiotic-resistant profile was shown for most bacterial strains isolated in foods and environment (9). Clearly, high resistance was observed for the currently used antibiotics, such as ampicillin, penicillin, cephalothin, and streptomycin followed by ceftriaxone and gentamycin (9). In contrast, amikacin, aztreonam, chloramphenicol, and tylosin practically exhibited absence of resistance. Tylosin exhibited high resistance in soil specimens. Fish coming from aquacultures exhibited a low resistance profile, whereas cultured mussels showed enhanced resistance to almost all antibiotics.

Human microbiota have been clearly colonized by high numbers of *Lactobacillus* spp. Nonpathogenic *Lactobacillus* spp. were shown to be sensitive to the beta lactams, second generation cephalosporins, and carbapenems. However, *Lactobacillus* spp. resistance was observed toward metronidazole and its combination with aztreonam (14).

As known, probiotics are beneficial live microorganisms originating from the human intestinal tract. When given as foods ingredients, they could procure health profits for the host as functional foods. Those foods are largely consumed during the recent years, as consumers are believing in their benefits. Moreover, they are given in animal food as supplements to regularize their intestinal microflora and protect them from putrefactive infections. Nonetheless, several probiotic strains exhibit resistance to antimicrobials agents (14). In a study, *Lactobacillus* spp. coming from "Kopanisti" artisan cheese were shown to be alarmingly multidrug resistant (15).

Human habits and peculiarities of every household, such as number and species of animals bred, household microenvironment, hygienic habits, and others, seem to determine the food microflora, which permits selective growth of several microbial species against others. Rural household microenvironment plays a key role as strengtheners of antibiotic resistance when bacteria bear resistance genes. However, several expressed phenotypes were against usually used veterinarian antibiotics. In this light, it seems that resistance was developed due to environmental bacterial contamination during the ripening of the artisan cheese. The risk of resistance transmission to humans consuming these products should be evaluated.

Another issue is focused on the genetically modified crops with antibiotic resistance marker genes (ARMGs). Concerns were raised on the use of ARMGs in genetically modified crops, as it was believed that the consumption of such foods might cause antibiotic resistance in the human bacterial microbiota compromising antibiotic therapy. Yet, if ARMGs are taken by pathogens, a potential health risk could occur. However, WHO and *Codex Alimentarius* Commission stated that there are extremely low transfer chances of ARMGs from plants to intestinal microbiota bacteria due to the complexity of the transferring process (16).

Traces of antibiotic-resistant DNA were detected in wastewater treatment plants. The antibiotic-resistant DNA forms are introduced in the aquatic and terrestrial environments, thereby spreading antibiotic resistance.

Lastly, wastewater treatment is implemented by using the improved Anaerobic Membrane Bioreactors (AnMBRs) technology. However, no information is provided about the involvement of the antibiotic resistance genes in the procedure (17).

Bacterial biofilms sway our lives, as they are ubiquitous from the medicine, environment, and pharmaceutical, and food industries as well as biotechnological applications (18, 19).

Their presence could be associated with positive effects in the natural settings, whereas it could be negative in other settings. In natural ecosystems, bacteria reside within biofilms, and in this case, conjugation is one of the probable mechanisms of gene transfer within biofilms or between bacterial communities (20).

Biofilms are recognized as a primordial form of cellular differentiation expressing the prokaryotic genome. They are metabolically active and possess a cell-to-cell communication system, i.e., quorum sensing. This communication system permits several pathogens to vanquish the host defenses. Moreover, they are resistant to stress and develop immunomodulatory mechanisms (19).

Microbial biofilms become resistant to a plethora of antibiotics and antimicrobial substances used in clinical medicine, veterinary medicine, industries, or environmental setting. In environmental ecosystems, biofilms could have some beneficial actions, whereas bacterial biofilms formation is always deleterious in medicine or industry.

Specifically, an Extracellular Polymeric Substances (EPS) matrix obstructs the inlet of certain antimicrobial agents impeding drug diffusion into the biofilm. Hydrophilic and positively charged antibiotics, such as aminoglycosides, are more restricted than others (21).

As previously discussed, the extensive use of antibiotics to promote growth in domestic animals, livestock, and agriculture resulted in the selection of antibiotic-resistant bacteria (22, 23). The presence of plasmids in bacteria from various environments and gene transfer through conjugation has resulted in spreading of the gene pool.

Biofilm formation is possible on food matrices or food industry infrastructures. Mixed bacterial biofilms show higher resistance to several antimicrobial substances, such as quaternary ammonium compounds and other biocides, used for the disinfection of the industry infrastructures (24).

In the food industry, biofilm formation offers physical and mechanical resistance, such as protection from desiccation and impedance to the liquid waves during pipelines other infrastructure disinfection. Resistance against chemicals, specifically disinfectant agents and antibiotics, are additional issues. Bacterial biofilms are formed on not only the different locations inside the industrial plant, such as cutting tables, surfaces, pipelines, packing material, equipment and machines, and utensils, but also in water and humid areas (19, 25). Nevertheless, the major concern for the food industry is that bacteria-forming biofilms could be pathogenic to humans. These biofilms could be formed on different surfaces and materials, such as polyethylene, glass, polypropylene, stainless steel, wood, caoutchouc, and plastic. Biofilms are formed in 4 stages: (1)

bacterial adhesion to the surface, (2) formation of microcolonies, (3) maturation of the biofilm, and (4) dispersion of the biofilm to contaminate other surfaces (26).

The secretion of lipases, proteases, and toxins from bacteria alters the organoleptic properties of foods and corrodes the surfaces. Bacterial biofilms are associated with foodborne diseases due to infections or intoxications from food matrices or industrial equipment (27).

Unfortunately, *S. aureus* and particularly MRSA in hospitals can resist several classes of antibiotics (28). Hitherto, *S. aureus* and MRSA were associated with foods and (29) industrial plants. MRSA adheres to multiple surfaces forming biofilms. Temperature, pH, nutrients. and other factors favor the adherence of microorganisms to the equipment and foods. Food handlers seem to be the reservoir, which enables bacteria to form biofilms rather than from food itself. Polysaccharides and proteins are the major compounds of the EPS matrix of MRSA strains (30); however, some authors have predominantly reported proteinaceous components in the MRSA biofilm matrix (31).

Bacillus cereus is considered responsible for the association with foodborne diseases due to the contamination from surfaces, pipelines, and equipment in the food industry (32). Yet, *B. cereus* is a spore-producing bacteria, and its resistant spore forms contaminate dairy products and even escape pasteurization processes. Similarly, *Coxiella burnetti*, the agent of Q-fever, could escape pasteurization (33).

Raw milk and poultry are known vehicles for outbreaks associated with *Campylobacter jejuni*. The intestine of bovines and poultry are the source of the microorganism (34). However, it is not registered as a major problem in the dairy industry when hygienic measures are followed. Post-pasteurization contamination could occur in the finished dairy products.

In contrast, checking for the presence of *Listeria monocytogenes* is imposed due to the ability of this bacterium to grow and form biofilms at refrigeration temperatures in the cold chain industries and those dealing with cold, refrigerated foods and dairies. Moreover, *L. monocytogenes* is involved in gastroenteritis acquired from inappropriate hygienic conditions of the food chain line of some other foods, such as seafood, meat, minced meat, ready-to-eat products, fruits, soft cheeses, ice cream, cold cuts, candied apples, frozen vegetables, and poultry. Nevertheless, the occurrence of the disease seems to be more severe in immunocompromized persons and lastly in pregnant women, where listeriosis can lead to spontaneous abortion or fetal malformation (35).

Poultry meat is a common vehicle for *Salmonella* in processed foods. The *S. enterica* biofilm formation on food surfaces is reported (36), as the microorganism is able to grow on stainless steel surfaces in the industry. Survival of the bacterium for over a year under dry conditions was observed to contaminate the food chain (37). It consists of a major risk of outbreaks, when particularly associated with refrigerated poultry and other products during food processing or in shelves in a supermarket (38). It is also involved in waterborne outbreaks.

Finally, we discuss the involvement of *Escherichia coli* strains, which are major constituents of human intestinal microbiota. The organism is transmitted through drinking water, vegetables, fruits, and fresh meat. During harvest, contamination occurs from inappropriate water sources used during cultivation of vegetables. Post-harvest contamination occurs when vegetables are exposed to the shelves in the industrial plant, as the organism can attach to abiotic and biotic surfaces, which is followed by biofilm development. Inappropriate storage temperatures will also permit its rapid growth (39). *E. coli* O157:H7 is isolated from beef- or ground beef-processing surfaces, forming biofilms and causing a severe infection.

More rarely, *Yersinia enterocolitica*, an agent of acute gastroenteritis. has been reported to survive in raw milk and in hard cheeses for long time periods. Its presence is ubiquitous in different environments, such as soil, water, and animals. The primary source of pathogenic *Y. enterocolitica* is fattening pigs and offal. *Yersinia* is sensitive to the acidic environment, which destroys the microorganism. The organism has the ability to propagate and form biofilms at refrigeration temperatures (40).

Enterobacter sakazakii is an emerging pathogen and food contaminant. It is implicated in severe cases of necrotizing enterocolitis, sepsis, and meningitis in low-birth-weight preterm neonates. The organism shows a ubiquitous distribution in dry food products, such as milk powder, rice, vegetables, teas, and various spices, as it is resistant to desiccation. Besides, *E. sakazakii* has been associated with dried infant formula and infant bottles, its survival is reported even after a 2.5-year period of storage (41).

Biofilms are also colonizing water systems. In most cases the same bacterial species are involved as stated previously for food industries. Nevertheless, biofilms are formed in pharmaceutical water systems. Poor design or maintenance can lead to this biofilm formation. The material of construction, temperature of the system, and water flow are capital to the prevention of biofilm formation. Stainless steel seems to be the preferred material in most cases.

In pharmaceutical industries, medicine preparations require maximum hygienic and safety conditions. Cosmetics industry follows the same rules as food industry. Bacterial colonization is frequently coming from handler's skin and industrial infrastructures. Psychrophiles are the most frequently isolated contaminants. These microorganisms have their sources in the water used for the preparation of medical solutions. *Acinetobacter*, *Alcaligenes*, *Alteromonas*, and *Flavobacterium* are commonly found in contaminations. These organisms are associated with severe nosocomial infections due to their capacity to form biofilms and develop antibiotic resistance.

Besides, the same bacterial genus, as in food industry, seems to be a concern for the pharmaceutical industry. It should be mentioned that policies and procedures in the pharmaceutical industry is spotty, as the domain comprises different companies producing sterile compounded products (42) to the other drugs, healthy foods, and formula milk. As discussed, guidelines matching a particular core process but deviations based on the required degree of sterility are adapted depending on the product.

S. aureus, *Salmonella*, *Yersinia*, *E. coli*, *Bacillus*, and *Pseudomonas* are involved. Contamination is usually associated with handler's hands or intestinal microbiota. *Pseudomonas* is colonizing a variety of ecological niches and specifically parts of plants. Contamination frequently comes from plant products used in cosmetics preparation.

Unusual contaminations are reported due to the following genera: *Listeria*, *Erysipelothrix*, *Propionibacterium acnes*, *Mycobacterium*, *Bacillus anthracis*, *Clostridium perfringens*, and *Clostridium tetani*. These contaminations usually occur through humans during the use of the product or ingredients, such as placenta or amniotic fluid.

Two main strategies were proposed for the eradication of biofilms formation. The first one embeds on the prevention of bacterial adhesion to the surfaces either by antimicrobial coating of the surface or modification of surface properties. The second one focused on destroying biofilm by mechanical (physical pressure, photocatalysis, twitching, and electrostatic interactions) or chemical methods (antimicrobials, enzymes, phages, essential oils, bacteriocins, and biosurfactants) (43).

In an attempt to save the situation from the emerging antibiotic resistance, a strong strategy reducing the use of antibiotics and spreading of resistant microorganisms must be applied (44).

Likewise, vaccination when vaccines are available is an important tool for protecting human health from bacterial infections and reducing inappropriate antibiotic prescriptions and their upcoming resistance effects at the same time.

Despite the problems in eradicating antibiotic resistance, successful solutions could be envisaged by a tight collaboration of authorities, bodies, and doctors. The interplay of the food and pharmaceutical industry, healthcare providers, physicians, academic institutions, universities, and government bodies is crucial to regularize the situation. Governments should spread sufficient information and educate people involving professionals in these issues for successfully controlling the emergence of antibiotic-resistant infectious diseases.

In conclusion, a global prevention policy should be designed to fight antibiotic resistance as a complement to the correct use of antibiotics.

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