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Mini Review

Antimicrobial Resistance in the Food Chain: Significance, Risks, Control

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Abstract

Antimicrobial resistance linked to the food chain represents an important public health issue worldwide. Resistant bacteria, often of zoonotic origin, are selected because of improper use of antimicrobial molecules in the breeding of livestock and the selective pressure operated by antibiotics present in the environment. In the plant-derived food, resistant bacteria are present as consequences of contaminated irrigation water and soil. In addition, food handlers could be carriers of these organisms and where poor hygiene procedures occur, they could transfer resistant bacteria on food. These organisms can reach humans through contact with animals and their environment or through contaminated food causing difficult-to-treat, potentially fatal, infections. The problem of antimicrobial resistance in the food chain is briefly described below and the main actions to be taken to stem the phenomenon are also reported.

Keywords: *Antimicrobial Resistance; Food Chain; MRSA; Colistin-Resistance*

Antimicrobial resistance: the impact on the public health

Antimicrobial resistance (AMR) is a worldwide critical issue of public health, and it has emerged as one of the most important challenges for the sanitary systems for the 21st century. In fact, AMR led to a large number of deaths; to get a clear idea of the problem, it is sufficient to report some data and a forecast deriving from an international survey on AMR, the O'Neill AMR Review: in the EU alone 400,000 citizens are affected by infections caused by resistant bacteria annually and about 33,000 die [1]; the forecast for 2050, in the absence of actions to mitigate the phenomenon, is 10 million deaths recorded annually globally [2]. In addition, recent reports suggest that this forecast may be more pessimistic due to the pandemic of Covid-19 where more antimicrobials have been administered for the control of the bacterial opportunistic infections; at the same time AMR have probably caused more Covid-19 deaths as secondary bacterial infection [3]. AMR has important implications from a clinical point of view, since it causes an increase in the morbidity, in the duration of the disease as well as the possibility of developing complications and epidemics and, determines an increase in the lethality of infections: in the EU there are 33,000 deaths a year due to infections caused by resistant bacteria [1]. More recently, in the 2019, a systematic analysis on the burden of AMR has been published: the authors reported that for the considered year, there were an estimated 4.5 million deaths associated with bacterial AMR and 1.27 million deaths caused by bacterial AMR [4]. CDC estimates that about 400,000 U.S citizen fall ill every year for antimicrobial resistant foodborne bacterial infections [5]. AMR has also had such a negative impact because of the economic loss due to healthcare cost, as well as the additional cost required for the use of more expensive drugs and therapeutic procedures, because of the lengthening of hospitalization, ~~for~~ the increase of the disability-adjusted life-years (DALYs) and the loss of working days of the hospitalized patients.

Antimicrobial resistance and food chain: which link and risks?

The genesis of resistant bacterial variants can occur both in primary production and in the environment, where the presence of antibiotics makes a selective pressure that leads to the emergence of resistant mutant strains and their subsequent spread. For plant based food the main source of contamination are irrigation water and soil fertilized with animal manure, instead, for food of animal origin, the contamination is due mainly to feed, water, humans, dust, rodents, arthropods and equipment [6]. For aquaculture, among others, water, sediments and feed are identified as main source of AMR bacteria [6]. The use of antimicrobials in animal production, especially in the intensive systems, where they can be used for therapeutic, metaphylactic and prophylactic purposes, is associated with the emergence, selection and spread of resistant pathogenic and commensal bacteria in the intestinal tract of food animals. In EU the use of antimicrobial as growth promoter is not allowed but this use of antimicrobials is still utilized in some non-European countries [7]. From primary productions (animals and plants) resistant bacteria can reach humans who can become infected by handling or consuming contaminated food; the CDC estimates that one in every 5 cases of infection with resistant bacteria is caused by eating or handling food [5]. What is the global situation in relation to the interconnection between AMR and the food chain? While in the EU the Reg (EU) 6/2019 that governs the production the production, marketing and use of veterinary drugs is in force [8], whereas in many non-European countries there is no specific legislation and the marketing of antimicrobials is often uncontrolled; this favors the conditions for the development and spread of resistant microorganisms which, with the globalization of trade and the free movement of people, can spread them everywhere. In fact, as reported by the annual reports on the use of antimicrobial drugs in animal production prepared by the World Organization of Animal Health, it emerges that the use of antimicrobials as growth promoters is still widespread: in 2017 in 41% of Countries included in the monitoring were allowed to use antimicrobials as growth promoters! Fortunately, between 2017 and 2019 there was a decrease of 14% in the countries that use antimicrobials for this purpose, but the phenomenon remains a concern [9]. In fact, some “last resort” antimicrobials and indicated by the WHO as Critically Important Antimicrobials (CIA) are still used as growth promoters; this is the case, for example, of colistin, an antimicrobial of last resort in the treatment of some human infections. Compounding the problem was the discovery in 2014 of the transferability through plasmid genes (*mcr* genes) coding for resistance to colistin; this family of genes is easily transferable at the intra and inter specific level [10]. This discovery has raised a global alarm and many investigations have highlighted that the food chain can act as a vehicle for these genes in turn hosted in some enterobacteria such as *Escherichia coli* and *Klebsiella pneumoniae* [11]. Some reports have documented the presence in foods of animal origin of bacteria resistant to molecules never used in veterinary medicine and animal husbandry, asking questions about the sources of contamination and the level of consumer exposure. Recently these questions were answered by EFSA with the publication of one Scientific Opinion on the role played by the environment in the emergence and spread of antimicrobial resistance (AMR) thorough the food chain [6]. The authors of this Opinion stated that the environmental spread of resistant organisms is now ubiquitous and that there is a sort of “cycle” of these bacteria that are introduced from the environment into food production plants (for example by slaughtered animals or by plants irrigated with contaminated water) and that from there can be transferred in the *post* primary food chain [6].

Antimicrobial resistance and food chain: the case of methicillin-resistant *Staphylococcus aureus* (MRSA)

A paradigmatic example of the interconnection between AMR and the food chain is given by the case of methicillin-resistant *Staphylococcus aureus* (MRSA) Methicillin resistance is due to the presence of the penicillin binding protein 2a (PBP2a) encoded by the *mec*A gene or its homologue *mec*C, with a low affinity for methicillin and oxacillin and virtually for all the β-lactams antibiotics

[12,13]. MRSA is present in the list of bacteria for which the WHO indicates the urgent need to develop new antibiotics to be used in human therapy [14], as it is able to cause nosocomial and community infections that can lead to severe diseases (septicemia, necrotizing pneumonia, pyoderma, etc.), sometimes fatal. MRSA colonizes both human and animal hosts; in the latter, variants have developed that have adapted to many species of food producing animals including pigs, ruminants and poultry. The consequence is that this AMR variant of *S. aureus* has been isolated with different levels of prevalence in many foods of animal origin such as meat, raw milk and table eggs, representing a potential risk for consumer who, by handling or consuming these foods, could get infected [15]. Furthermore, it should be emphasized that some operators, such as veterinarians, slaughterers and others who have an occupational exposure to the animals have a greater risk of getting infected by MRSA and other AMR bacteria.

Here, the briefly reported results of surveys conducted in southern Italy, aimed at assessing the presence and characteristics of MRSA in some locally produced foods. The isolates were characterized from a phenotypic and molecular point of view for the detection of the AMR pattern and the genetic virulence markers, as well as, for their attribution to specific Clonal Complexes (CC) by Multi Locus Sequence Typing (MLST). Already in 2007, the contamination of raw milk and dairy products by MRSA was highlighted for the first time in Italy; some isolates were enterotoxigenic, highlighting the potential for food poisoning caused by Staphylococcal Enterotoxin(s) [16]. After, MRSA strains were detected in the 37% of pig carcasses and in 9 of 113 slaughterhouse operators [17], then in the 2.5% of raw milk samples [18] and in 7% of slaughtered horses [19]. Finally, for the first time in Europe, MRSA was isolated in 4% of raw buffalo milk samples [20]. Interestingly, some MRSA isolates from the above investigations belonged to human CCs, others to animal CCs. In fact, a continuous interchange of AMR strains occurs between humans and animals; in addition, because of the exchanges of prophages and other mobile genetics elements between human and animal *S. aureus* CC398 clades, a new host adaptation could occur [21].

Conclusion

In conclusion, the phenomenon of AMR in the food chain is a complex and multifactorial public health problem that requires a One Health approach for its understanding and management. At the same time, the spread of AMR bacteria must be continuously monitored and required a worldwide coordinated action plan [7]. It is very important to become aware of the problem in human and veterinary medicine, in the animal husbandry sector and among operators in the food sector. In the quality control of the food chain, the presence of pathogenic AMR bacteria should be considered as a real biohazard to be taken into consideration in food safety assessment processes and for the assessment of the occupational risk. In order to limit the further selection and spread of AMR bacteria in the food chain, it is necessary to act at the source, for example by reducing the impact of the selective pressure caused by mass antibiotic treatments in food animals and to use antimicrobials following the directives of Reg. (EU) 6/2019 which sets out the principles and prescriptions for the correct and prudent use of antibiotic medicines in the veterinary field and which requires that these molecules not be used systematically in animals. Finally, consumers should be aware of the problem and should be informed about the proper hygiene management in the kitchen in order to avoid the spread of AMR bacteria from raw food, particularly raw meat, to other food or domestic surfaces.

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