Antibiotic overuse in farming: Impact and risks (Review Article)

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Abstract---Although antibiotic therapy is important for animal health, for the preservation of livestock and the improvement of sanitary conditions, the unrestrained use of these molecules presents great risks to public health. The aim of our research is to highlight the use of antibiotics in poultry farming and its impact on the intestinal flora of chickens as well as on consumer health. The spread of the phenomenon of uncontrolled antibiotic use, the risks become complex and multiple and the danger is increasing and intensified. All previous studies indicate that the adverse effects of non-rational usage of antibiotics in poultry are widespread and multiple, but antibiotic resistance is the most disastrous problem among these effects. All

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parts of the public and animal health sector must therefore face this phenomenon in order to control it and avoid exacerbating its effects.

**Keywords**—antibiotic therapy, public health, poultry farming, impacts, risks, danger.

1. **Introduction**

The purpose of using antibiotics (like any veterinary drug) is to protect the health and well-being of animals, these drugs control the health status and assure the quality and the productivity of the breeding. (Berghiche et al, 2017). Veterinary drugs may, if their use is followed by an insufficient withdrawal period, leave residues in food of animal origin that retain activity that inhibits the growth of bacteria.

As residues are most frequently present in very small quantities, in the range of micrograms (μg), as indicated by maximum residue limits, its toxicity is correlated with chronic exposure (consumption of contaminated food over long periods) (Jeon et al, 2008). And when this toxicity is manifested, it can produce allergic and carcinogenic health problems for the consumer, as well as the possibility of selecting antibiotic-resistant bacteria. (Kantati Y, 2011). In our work we try to spotlight the different viewpoints about risks related to the overuse of antibiotics in poultry farming.

2. **Toxicological Viewpoints**

The effects on the human organism depends on two factors, the transformation in vivo of the original molecule, which leads to the formation of a metabolite that loses its antibacterial properties but has a residual allergenic potency, the toxicity of this residue can be increased or decreased in proportion to the original compound; and toxic availability corresponding to the shape in which the residual is available in the body, It could be unattached or bound to molecules. It is accessible to the body’s immune response, and predisposed to accumulate in certain organs or to be eliminated. (Chataigner et al, 2004). According to Scippo (2008), risks presented by residues depands to the use of this molecules in animals; there are of four kinds of toxic risks, to public health, to animal health.

The direct toxicity of antibiotic residues is quite difficult to identify because it is generally chronic toxicity. The latter is expressed only after repeated consumption of foodstuffs containing residues of the same antibiotic. Some scientists then suggest possible liver toxicity, the risk of direct toxicity then depends on the dose ingested, the chemical nature of the antibiotic initially administered and the nature of the residues. (Jeon et al, 2008; Stoltz, 2008)

The case of potential toxicity frequently cited is chloramphenicol, which has been responsible for aplastic anaemia in humans (related to its use in human medicine), no maximum residue limits are set in food of animal origin for chloramphenicol and this antibiotic is now banned for use in production animals; Antibiotic residues used in therapy or prophylaxis can have a long-term
carcinogenic effect following regular consumption of food containing these residues. (Boultif, 2009) (Chestnut et al, 2004). (Benoit, 2012)

These antibiotics are then banned from use in production animals, this is the case with nitrofurans which including nitrofurazone, these antibiotics used in human medicine for a short time in patients, is well known as genotoxic carcinogen; Animal experiments have shown that their prolonged use can lead to changes in genetic material and the development of tumours and the potential of the mutagenicity and carcinogenicity of these compounds come from the nitro-reduction of the drug, leading to the formation of electrophilic metabolites and their binding to DNA. (kantatiy, 2011) (Stolz, 2008).

Carcinogenesis takes place in two complementary phases, initiation which is an irreversible modification of genetic information and promotion, that allows the initiation to express itself as a tumor, the first phase is non-dose dependent while the second phase is dose dependent. (Riana Nantenaina Randrianomenjanahary, 2006). Nitrofurans are suspected of foetotoxicity, some sulfonamides are fetotoxic in high doses and these molecules pass into breast milk, they are toxic to childes under one month of age. The adverse effects on genetic material, including DNA, reproduction, fertility, and toxicity to the nervous system and immune system (Chestnut and Stevens, 2003)

A. Health problems

Residues of veterinary drugs are incriminated in human allergy and may be implicated in certain hypersensitivity accidents in allergic people by causing either a sensitizing or triggering effect. (Benoit, 2012). In human medicine, allergy is a recognized side effect of antibiotics and in particular beta-lactams. As for macrolides, they cause few side effects and only very few of them seem to be caused by allergic mechanisms.

However, given the very low levels of residues present in the body, compared to the concentrations of antibiotics administered during treatment or prophylaxis, it is highly unlikely that they cause primary sensitization in the individual. (Chestnut et al, 2004). The mechanisms of allergy to antibiotic residues are varied and may correspond to the four types of immunological reactions in the Gell and Coombs classification (Stoltz, 2008) (Table 1)

<table>
<thead>
<tr>
<th>Type Clinical response</th>
<th>Name</th>
<th>Effector and mechanism</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hypersensitivity immediate or Anaphylactic</td>
<td>IgE anaphylaxis, mast cells and basophils</td>
<td>shock, angioedema, hives, bronchospasm</td>
</tr>
<tr>
<td>II</td>
<td>Hypersensitivity by cytotoxicity</td>
<td>IgG, IgM, complement, phagocytosis</td>
<td>Cytopenias and/or nephritis</td>
</tr>
</tbody>
</table>

Table 1: Gell and Coombs classification of immuno-allergic reactions (Stoltz, 2008)
The allergy phenomenon can then be explained by the fact that antibiotics behave like haptens, will couple to serum proteins and thus induce the formation of antibodies responsible for hypersensitivity states. Antibiotic residues are decomposed in the body and thus give rise to derivatives which certainly do not possess the power of antibiotics but are nevertheless capable, by binding to proteins, of forming antigenic complexes that can cause allergic conditions, these accidents are then characterized by a variety of symptoms, namely dermatoses, respiratory manifestations, urticaria reactions, digestive disorders, reactions edematous, but especially and in the most serious cases, a fatal anaphylactic shock (Mansouri, 2007).

**B. Effects on animal health**

Antibiotics used in therapy generally have low toxicity, this differentiates them from external antiseptics which can under no circumstances be used in a general way; Nevertheless, some antibiotics have a high general toxicity that prevents their use in many animal species, this is the case with ionophore antibiotics (monensin) that have major cardiac toxicity. Apart from the direct organ toxicities specific to each antibiotic, any antibiotic therapy must make the practitioner fear two types of adverse reactions, a disruption of the digestive flora and therapeutic failures by resistance selection, (Zeghilet, 2009).

**3. Bacteriological Viewpoint**

The bacteriological risk associated with the consumption of food containing antibiotic residues can be attributed to three phenomena, the modification of the digestive flora which can lead to undesirable disorders and symptomatology, the selection in humans of pathogen strains resistant to these antibiotics and technological risk when we talk about contaminated sub-product. (Berghiche et al, 2018) (Mohamed said, 2015), (AKODA, 2004).

**A. Antibiotic resistance**

Antimicrobial resistance is a public health problem in both human and veterinary medicine (Sinaly, 2014); It is important to note that any use of antibiotics, even if justified and judicious, may lead to the development or selection of resistant microbial strains. The risk of resistance development will be all the greater if use is frequent (continuous or repeated) and extended to a large proportion of a herd (Chevalier, 2012).
Considered as a "side effect" of antibiotics, along with toxicity (Lafon, 2010), according to the World Health Organization (WHO), antibiotic resistance is "the resistance of a microorganism to an antibiotic to which it was previously susceptible. It results from the ability of bacteria to withstand the attack of antimicrobial drugs such as antibiotics.

Resistance occurs when the microorganism mutates or acquires a resistance gene. (Vincent and al, 2015); It can also be defined in different ways, from a bacteriological point of view, it characterizes a bacterial strain whose growth is not inhibited by contact with a concentration of antibiotics, preventing the multiplication of most other strains of its species, and From a pharmacological point of view, resistance is defined as the achievement of a maximum concentration of antibacterial agents in diseased tissues that is too low to inhibit bacterial growth. (Chatellet, 2007).

From an epidemiological point of view, a bacterial strain is resistant to an antibiotic if it has a significantly different minimum inhibitory concentration than the normal population. (AFFSA, 2004); Finally, from a clinical viewpoint, a bacterium is resistant if the treatment put in place by the practitioner is ineffective in treating the infection for which it is the cause (Chatellet, 2007); The regression of bacterial resistance to antibiotics is a much slower phenomenon than its emergence and a drastic reduction in antibiotic consumption will be necessary to hopefully curb this problem, the resistance process is indeed a function of antibiotics and depends on concentration levels and therefore on the dose, duration and frequency of treatment, but it also depends on the bacterial species (density at the treated site, sensitivity to antibiotics, etc.) (Lafon, 2010; Delaere, 2001)

Genetic origin of resistance and genetic transfer modalities, bacterial resistance to an antibiotic is of genetic origin. Resistance genes are found either in the chromosome (chromosome resistance) or in a mobile element, such as plasmids, transposable elements or integrons (extra-chromosome resistance). Resistance can be either natural or acquired. (Sylvie Carle, 2009); Bacterial resistance is an inconstant property, and is expressed differently depending on the environment of the bacteria and the growth factors found there. (Chatellet, 2007); There are four main mechanisms by which microorganisms develop resistance, and they are present in the table:

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme Inhibition</td>
<td>Production of an enzyme that inactivates or destroys the antibiotic; Most widespread resistance mechanism.</td>
</tr>
<tr>
<td>Reduction in cell permeability</td>
<td>Changes in wall or membrane permeability bacterial preventing the drug from reaching its target.</td>
</tr>
<tr>
<td>Alteration of the binding sites targeted by the antibiotic</td>
<td>Decrease in the affinity of the antibiotic for its site of action.</td>
</tr>
</tbody>
</table>
Antibiotic efflux pumps are mechanisms that pump antibiotics out of the cell, making the action site inaccessible.

Natural Resistance Mechanisms is a species trait that affects all bacteria of the species under consideration; It is stable, transmitted to the offspring (its genetic support is the bacterial chromosome) but it is not or only slightly transmissible in a horizontal mode (from one bacterium to another within the same species or between different species). (Amara, 2012)

For each class of antibiotic, there are bacterial species on which the antibiotic is inactive due to lack of target or access to the target. We are talking about naturally resistant bacterial species and intrinsic resistance mechanisms, this may be due to the absence of the target (such as the absence of wall in mycoplasmas making them insensitive to beta-lactam antibiotics) or the absence of antibiotic penetration (role of the outer membrane for example in Gram negative bacteria with vancomycin) (Delaere, 2001; AFSSA, 2006).

The structure of the cell wall and cytoplasmic membrane of an organism can be impermeable to an antibiotic, this is the example of mycobacteria that are resistant to many drugs because they have a complex lipid layer outside the peptidoglycan rich in mycolic acids (Prescott et al., 2007). Acquired resistance is the mechanism that appears in bacteria that have been sensitive to antibiotics until now, following changes in chromosomal or plasmid genetic equipment, they concern only a few strains of the same species but can spread (Lavigne, 2007).

The acquisition of resistance by bacteria may be related to mutations modifying the antibiotic target, or a metabolic pattern, the mechanisms of acquired resistance are much more numerous (Table 3): decreased permeability, target modification, production of enzymes that inactivate the antibiotic, multiplication of targets that prevent the antibiotic from affecting them all, efflux mechanism, by-pass of the metabolic step targeted by the antibiotic (Pichard, 2002) (Delaere, 2001); There are two types of acquired resistances, a chromosome occurs during a mutation in the bacterial chromosome, it is spontaneous, stable, specific (only one antibiotic or one antibiotic family at a time) and rare, among the antibiotics affected by this type of resistance we can mention: streptomycin and nfampicins; and extra-chromosomal resistance whose support is a plasmid (minichromosome, circular, capable of autonomous replication and propagation from one bacterium to another, by conjugation, transduction or transformation) or a transposon (a "jumping" DNA fragment that can be integrated either into the chromosome or into plasmids, going from one to the other), it is frequent (more than 80% of the acquired resistances) and differs from the first by two main characteristics, the ability of a plasmid to confer resistance to several antibiotics is multi-resistance to several antibiotics from the same or different families, and the ability for a plasmid to transfer from one resistant bacterium to another sensitive one. (Mansouri, 2007)
### Table 3: Mechanisms of bacterial resistance to antibiotics (Sedrati, 2014)

<table>
<thead>
<tr>
<th>Resistance mechanism</th>
<th>Example of an antibiotic</th>
<th>Genetic origin of resistance</th>
<th>Mechanism available to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of permeability</td>
<td>Penicillins</td>
<td>Chromosome</td>
<td><em>Pseudomonas aeruginosa</em> Enteric bacteria</td>
</tr>
<tr>
<td>Inactivation of antibiotics (e.g., penicillinase; modified enzymes methylases, acetylases, such as phosphorylases; others)</td>
<td>Penicillins</td>
<td>Plasmids and chromosome</td>
<td><em>Staphylococcus aureus</em> Enteric bacteria <em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Plasmids and chromosome</td>
<td><em>Staphylococcus aureus</em> Enteric bacteria</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
<td>Plasmids</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Target modification (e.g., RNA polymerase, rifamycin; ribosome, erythromycin and streptomycin; DNA gyrase, quinolones)</td>
<td>Aminoglycosides</td>
<td>Plasmid</td>
<td><em>Staphylococcus aureus</em> Enteric bacteria</td>
</tr>
<tr>
<td></td>
<td>Erythromycine</td>
<td>Chromosome</td>
<td><em>Staphylococcus aureus</em> Enteric bacteria</td>
</tr>
<tr>
<td></td>
<td>Rifamycine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptomycine</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Streptomycine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Norfloxacine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development of resistance of metabolic routes</td>
<td>Sulfamides</td>
<td>Chromosome</td>
<td>Enteric bacteria <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Excretion (pumping out of the cell)</td>
<td>Tetracyclines</td>
<td>Plasmids</td>
<td>Enteric bacteria <em>Staphylococcus aureus</em> Bacillus subtilis <em>Staphylococcus spp.</em></td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
<td>Chromosomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Chromosomes</td>
<td></td>
</tr>
</tbody>
</table>

### B. Changes in the digestive flora of the consumer

Some antibiotic residues that still have antibacterial activity are potentially capable of modifying human intestinal microflora. The presence of antibiotic
residues in food may thus lead to a risk of weakening microbiological barriers and colonisation of the intestine by pathogenic or opportunistic bacteria. (Stoltzer, 2008)

In the digestive tract live billions of saprophytic and commensal bacteria (especially anaerobic bacteria: bacteroids, fusobacterium). The consumption of products containing antibiotic residues (cyclin, sulfonamides) disrupts this intestinal flora; by modifying its composition by selective inhibition; they devastate the normal flora and leave room for pathogenic or opportunistic bacteria such as enterobacteriaceae, pseudomonas, enterococci, staphylococci and yeasts), thus decreasing the pre-established natural immunity. (Stoltz, 2008; Boultif, 2009).

This immune deficiency can lead to certain health problems such as damage to the nervous system, bones, teeth (yellow teeth), liver, blood, as well as the appearance of mutant bacteria resistant to antibiotics, leading to therapeutic failures. (Boultif, 2009). In conclusion, the intestinal ecosystem, together with the immune system, contributes to the host’s defences against microbial attacks. Antibiotics are a major cause of disturbance of this balance, which can then become an entry route for potentially pathogenic bacteria. Since the intestinal flora is an important reservoir of resistance genes, controlling the use of antibiotics is necessary to prevent the spread of these genes. (AFFSA, 2004).

There are other effects on humans due to the presence of residues antibiotics which is the passage of resistant bacteria from animals to humans, zoonotic microorganisms such as Salmonella and Campylobacter can cause disease in humans. The transfer of sensitive zoonotic microorganisms as resistant from animals to humans is becoming a public health problem. There is therefore a risk of selection of a resistant or non-resistant pathogenic bacterium that will be transmitted to humans and lead to the appearance of a pathology or therapeutic failure during antibiotic treatment (Guyonnet, 2004). The administration of fluoroquinolones to poultry causes the development of fluoroquinolone-resistant strains of Campylobacter, a human pathogen, in poultry.

These bacteria are transmitted to humans and contribute significantly to the development of human infections due to fluoroquinolone-resistant Campylobacter strains. Fluoroquinolone-resistant Campylobacter infections pose a risk to human health (Van Vuuren, 2001). Enteric organisms such as E. coli (capable of causing diseases as diverse as urinary tract infections and neonatal meningitis in humans) also pose public health risks (Guyonnet, 2004).

C. Technological problems

The presence of antibiotic residues in milk has negative consequences for the dairy technology used to manufacture fermented products. These harmful consequences result essentially from the partial or total inhibition of the phenomena of bacterial fermentation necessary for the production of many dairy products. The most sensitive products are those in which lactic ferments and flavouring germs are used: yoghurt, sour curd and mixed curd cheeses, cream and mature butters. Among the molecules involved in this inhibition of
fermentation germs are penicillins, streptomycin, chloramphenicol and tetracyclines, as even a small amount of antibiotics is generally sufficient to inhibit these enzymes. (Stoltz, 2008; Akoda, 2004)

4. Ecotoxicological Viewpoint

Antibiotic residues released into the environment without being processed can remain biologically active and present risks to the environment, especially since they can be concentrated in food chains. (Jean-Marie Haguenoer, 2010). It is now accepted that after antibiotic treatment, animals excrete a fraction of the administered dose in their environment: it is present in manure or slurry, as well as in suspended dust before being degraded more or less rapidly in retention pits. Indeed, there are significant differences in half-life time depending on the molecule: tylosin, for example, is degraded much more rapidly than oxytetracycline, which can be detected in the manure of calves treated for 5 months compared to less than 45 days for tylosin. This implies a long persistence of certain antibiotics in the environment, which may then be present in surface waters or rivers. This leads to chemical pollution of the environment, with an action on the microbial flora that may be the same as on the commensal flora, especially since the excreted antibiotics are excreted at doses much lower than the Minimum Inhibitory Concentration. (Chebira, 2009).

5. Conclusion and recommendation

From the abundant international literature, it is clear that antimicrobial drug resistance; is an emerging problem, and that the misuse of antibiotics in human and veterinary medicine contributes to this problem; In Algeria, as a model for this problem, it is necessary, among other things, to focus on remedying its gaps:

- Absence of legislation to promote the prudent and responsible use of antimicrobials in veterinary medicine.
- Lack of Human Resources Veterinary Services capable of identifying recurrent health problems and developing alternative strategies for disease protection or control, thereby reducing the need for antimicrobial use in livestock.
- Insufficient information and training for farmers to communicate the benefits of prudent antimicrobial use and the risks associated with inappropriate use.
- Poor resources resulting in a negative impact on efforts to develop surveillance and monitoring programmes, training strategies, evaluation and authorisation of antimicrobials and actions to combat the distribution and use of illegal or counterfeit products.
- Non-compliance with biosecurity and hygiene measures by farmers.

The uncontrolled use of veterinary drugs, especially antibiotics, is becoming an international priority and shows the essential role that the various socio-economic services should play in ensuring food safety and the accurate assessment of risks to public health and in combating the risks associated with this use. We propose some recommendations that may be the solutions to the previous shortcomings for several reasons:
Continuous monitoring is carried out on the resistance of bacteria naturally present in animals and healthy humans, the fate of these bacteria in the environment and the transfer of bacteria, plasmids or genes between animals and humans.

Pending a total ban on the use of antibiotics as growth promoters, research is needed to offer farmers alternative additives to improve their production and the action of probiotics, bacteria beneficial to human health.

To avoid antibiotic resistance, certain parameters must be set up:

- Compliance with dosages and administration rates;
- Remanence time before placing products of animal origin on the market (milk, meat, eggs);
- Consider regulations prohibiting antibiotic therapy without a veterinary prescription, especially for underdeveloped countries.
- Improve the structures for detecting residues in food of animal origin, all this mainly in poultry farming.

**Conflict Of Interest**
There is no conflict of interest.

**Authors Contribution**
All authors contributed in correcting the article by spending their valuable time and also supported by sharing valuable suggestions in writing an article.

**Reference**


Boultif L (2009). Optimisation des paramètres de détection et de quantification des résidus d’antibiotiques dans le lait par chromatographie liquide haute performance (HPLC). Mémoire de magister en médecine vétérinaire, Option :
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