

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Antibiotic Therapy Practices Of Dairy Cows And Eventual Impact On Foodstuffs Quality In The Governorate Of Biskra, Algeria.

Mammeri Adel^{1 2*}.

¹Department of Agronomy, University of M'Sila, 028000, Algeria.

²Animals Pathology and Reproduction Control Laboratory (P.A.G.R), Veterinary Institute, University of Constantine 1, El'Khroub, 25100, Algeria.

ABSTRACT

This study aimed to classify the antibiotic therapy modalities practiced by private veterinarians on dairy cows in the governorate of Biskra. The survey concerned 13 private veterinary practitioners localized in 6 municipalities where dairy cattle is developed (Tolga, Ouled Djellal, Sidi Khaled, Doucen, Besbes and Sidi Okba). The questionnaire targeted the classification of antibiotic therapy modalities; the antibiotics of first choice used in common practice to overcome pathologies with special focus on those used in the urogenital sphere and the mammary gland. Non-cumulative classification of the most frequently used antimicrobial agents showed that; Tetracyclines come in first position according to 8/13 of the interviewees, followed by Beta-lactamines (7/13), than, by Sulfamides (5/13). During treatment of udder or urogenital sphere infections; Beta-lactamines were the first choice (9/13), followed by Tetracyclines (6/13), than, by Sulfamides (5/13). None of the interviewed veterinarians uses sensitivity testing before choosing antibiotics, neither calculates animals' weights before administering drugs. Lack of performed diagnostic laboratories in visited veterinary clinics tends to hamper a judicious use of antibiotics and antimicrobials. Therefore, the control of antibiotic residues should be compulsory in foodstuffs to obtain a guarantee on consumers' safety and to preserve the industrial properties of dairy products.

Keywords: survey, antibiotic therapy, cattle, private veterinarians, antibiotic residues, Algeria.

**Corresponding author*

INTRODUCTION

Antibiotics are mainly employed for chemotherapeutic, prophylactic purposes and also used as feed additives to promote growth and improve feed efficiency. However, antibiotic residues in animal products may occur, when administration of drug in extra label fashion and not following of withholding period after treatment [1]. In African countries, antimicrobial residues in foods of animal origin are worrying because of the toxicological risk to consumers and the risk of non-compliance with the regulatory requirements for trade [2]. The residues in milk may lead to allergic reactions in humans and increase the antibiotic resistance of pathogenic bacteria [3]. The issue becomes more relevant on a future perspective because the global use of antimicrobials for food animal production is predicted to increase by 67 % in 2030 [4]. The occurrence of chemical residues in the milk of lactating cows is a matter of public health concern, since dairy products are widely consumed by infants, children and many adults throughout the world. Antibiotics such as Betalactams, Tetracycline, Aminoglycosides (e.g. Streptomycin, Neomycin and Gentamycin), Macrolides (e.g. Erythromycin) and Sulfonamides are the source of residues [5].

The use of antibiotics in dairy cattle for the treatment of diseases such as mastitis has contributed to the presence of residues in dairy products [6]. In some parts of Algeria, antibiotics residues were found in both cow's raw milk [3] and ewe's raw milk [7]. The purpose of this survey is to identify the methods of antibiotic therapy practiced by a sample of private veterinary practitioners in dairy herds reared in the governorate of Biskra.

MATERIALS AND METHODS

ETHICAL APPROVAL

Ethical approval was not needed, since no animal was used in this study

STUDY AREA

The governorate of Biskra is located in Southeast of Algeria, on about 420 km from the capital Algiers, it occupies an area of 21 509.80 km² (Figure -1). It is located between 4 ° 15 'and 6 ° 45' East longitude and between 35 ° 15 'and 33 ° 30' North latitude. Its altitude varies between 29 and 1600 m compared to the level of the Mediterranean [8]. It comprises 12 districts and 33 municipalities, with a population estimated in 2008 to 772 746 inhabitants. It is a large palm trees and pastoral area with a special vocation of small ruminants breeding (sheep, goats), essentially, in extensive breeding system [9]. Currently the governorate of Biskra includes about 260 cattle farmers [10]. According to [11], there are 4995 bovine heads, 942 900 sheep heads, 293 000 goat heads and 5000 camel heads. Small ruminants' flocks are mainly reared in the form of nomadic and semi-nomadic systems. According to [12] census, there is about 52 private veterinary practitioners active on the whole area of the governorate.

SURVEY AIM AND MANAGEMENT

The aim of this study was to know the therapeutic modalities and the most used antibiotics in cattle therapy practiced by private veterinary practitioners, and to estimate their eventual impact on foodstuffs quality according to literature and similar researches.

An interview via questionnaire (Annex 1) was conducted with each veterinarian for a short period while completing the questionnaire. This study concerned 13 private veterinary practitioners (about 25 % of whole active private veterinarians) [12] distributed through 6 municipalities that are characterized by rearing of dairy cattle (Tolga, Ouled Djellal, Sidi Khaled, Doucen, Besbes and Sidi Okba) (Figure-1). The questionnaire targeted the veterinarians' routine activity, the classification of antibiotic therapy modalities, as well as the antibiotics of first choice used in common practice to overcome pathologies, especially those of the urogenital sphere and the mammary gland, because these affections are the most widespread in study area according to personal observations. It also concerned the eventual use of susceptibility testing and weighting type meter before therapy, bovine mastitis frequency and the respect of withdrawal periods after treatment.

RESULTS

Veterinarians' activity

The majority of veterinarians participating in this survey are active in rural areas with a high density of small ruminants and with a lower degree of cattle (Tolga, Ouled Djellal, Sidi Okba, Doucen). Also, the routine activity of veterinarians is essentially related to; sheep, goats and cattle (Table 1), which is very logical in the region of Zibans (Biskra governorate) because it is considered as an important cradle devoted to the breeding of small ruminants in Algeria.

Bovine mastitis frequency in study area

Bovine mastitis is very common in the study area, which generates an intensification of the use of antibiotics to overcome this major scourge of dairy farming. In the majority of cases, a single quarter is infected in the cow, because generally, the farmer realizes early cases of clinical mastitis while milking, otherwise the infection extends to other quarters (Table 1).

Table 1: Global answers of private veterinary practitioners to questionnaire (Annex 1)

Questions' Number*	Answers	(n)
Q1	Tolga	3
	Ouled Djellal	3
	Doucen	3
	Sidi khaled	1
	Besbes	1
	Sidi Okba	2
Q2	1.Sheep -2.Cattle - 2.Goats - 4.Dogs / Cats - 5.Poultry	3
	1.Sheep -2.Goats - 3.Cattle - 4.Dogs / Cats - 5.Poultry	2
	1.Sheep -2.Goats -3.Dogs / Cats - 4.Poultry - 5.Cattle	2
	1.Sheep -2.Goats -3.Dogs / Cats - 4.Cattle - 5.Poultry	1
	1.Cattle - 2.Sheep - 3.Goats - 4.Dogs / Cats - 5.Poultry	1
	Cannot classify	4
Q3	Broad spectrum antibiotics	2
	Intrauterine antibiotics	2
	Hormonotherapy	5
	Do not treat	4
Q4	One or more cases each day	3
	Several cases each week	3
	Several cases each month	5
	Several cases each year	2
Q5	One quarter	7
	Two quarters	4
	More than two quarters	2
Q6	On Figure-2 (%)	13
Q7	On Figure-3 (%)	13
Q8	Never	13
Q9	According to morphological aspect only	7
	According to morphological aspect and age of animal	6
Q10	Often	4
	Sometimes	9

*Questions are detailed on Annex 1.

Annex 1: Questionnaire destined to private veterinary practitioners

- Q1. What is your professional address municipality?
- Q2. Among these animal species, rank those that enter into your routine activity in descending order? : Cattle - Sheep - Goats - Dogs / Cats - Poultry - Others :.....
- Q3. What is the therapeutic protocol often recommended in cases of cows' infertility?
- Q4. Estimate the frequency of bovine clinical mastitis cases during your routine activity?
- Q5. What would be the number of quarters often affected during cases of clinical bovine mastitis?
- Q6. What are the frequently used classes of antibiotics and antimicrobials in your clinic ?
- Q7. What are the frequently used classes of antibiotics and antimicrobials in cases of urogenital sphere and mammary gland pathologies ?.....
- Q8. Do you use a sensitivity testing before using antibiotics? : Often- Sometimes -Never
- Q9. How do you calculate animals' weights before administering drugs? : From morphological aspect - according to age of animal - use a tape measure – Other methods :.....
- Q10. Do breeders respect the recommended withdrawal periods after treatment of cattle ? : Often- Sometimes -Never.

Therapeutic protocols for dominant pathologies

Results showed that the use of broad-spectrum antibiotics and antimicrobial combinations is very common in study area. Non-cumulative classification of the most frequently used antibiotics and antimicrobials in veterinary clinics showed that ; Tetracyclines came in first position according to (8/13) of the interviewees, followed by Beta-lactamines according to (7/13) of them, than, by Sulfamides according to (5/13) of veterinarians. Macrolides were used only by (4/13) of veterinarians, and with lesser degree Aminocyclitol derivatives with only (3/13) of interviewees (Figure -2).

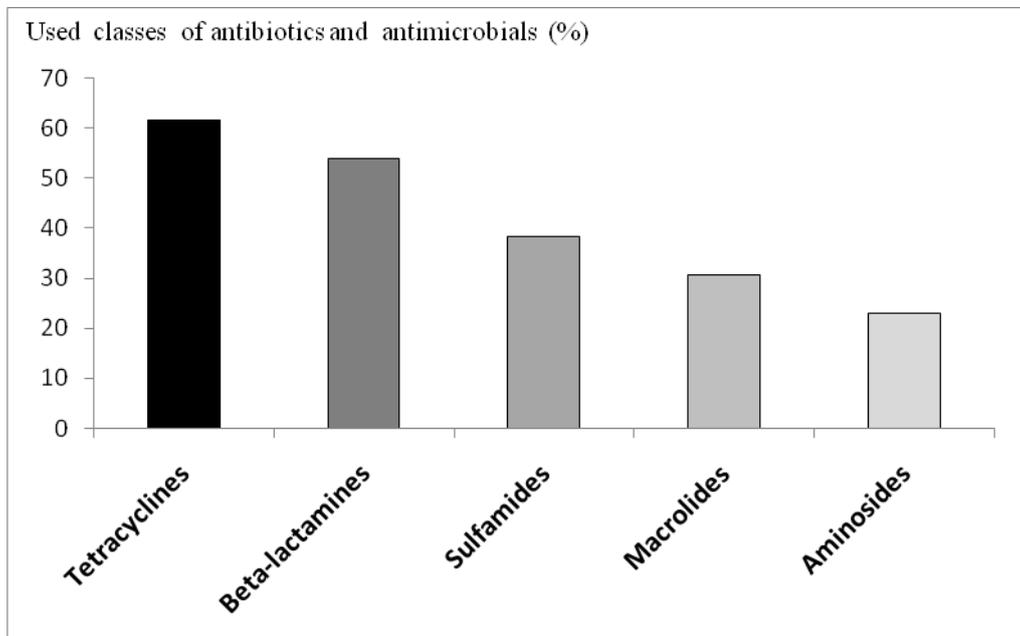


Figure 2: Descendant classification of the frequently used classes of antibiotics and antimicrobials in veterinary clinics according to non-cumulative number of citations

Furthermore, several pharmaceutical substances are used for cases of bovine infertility, but no specific protocols were mentioned (Table 1). During treatment of mammary gland or urogenital sphere infections, with non-cumulative classification; Beta-lactamines were the first choice according to (9/13) of

veterinarians, followed by Tetracyclines with (6/13) of responders, than, by Sulfamides with (5/13) of interviewees. Tylosin were used only by (2/13) of veterinarians (Figure - 3).

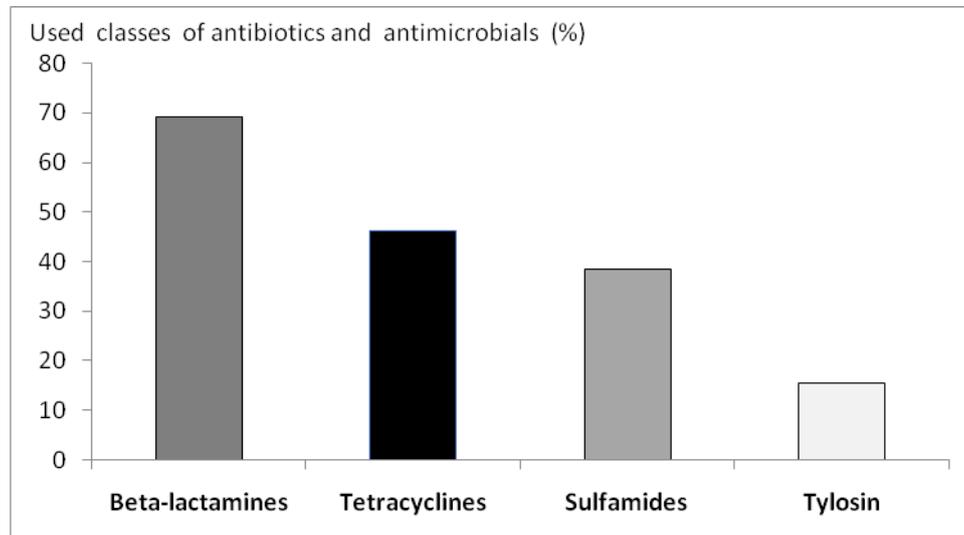


Figure 3: Descendant classification of the frequently used classes of antibiotics and antimicrobials to treat urogenital sphere and mammary gland pathologies according to non-cumulative number of citations

It is remarkable that none of the interviewed veterinarians uses sensitivity testing (antibiogram) before choosing antibiotics. Also, none of surveyed veterinarians calculates animals' weights before administering drugs, but they only take into consideration the morphological aspect and/or age of treated animals. According to our survey, it is not sure that breeders respect the recommended withdrawal periods (waiting time) after treatment of cattle.

DISCUSSION

The majority of veterinarians participating in this survey are active in rural areas characterized with a high density of small ruminants and with a lower degree of cattle. In a survey of 400 residents of rural households in Tebessa (North-East of Algeria) conducted by [13], the results show that the proportion of households that consume fresh liquid (cow, ewe, goat or she-camel) is high, reaching 85.1% ; fresh milk has always been very popular in this area. Industrial milk in rural areas was consumed by only 12.5% of the population. Authors of the same study explained this low consumption of industrial milk by the availability of fresh milk on the one hand and the preference of the population, which has become accustomed to consuming it on the other. By extrapolating these results to our study area, it turns out that the rural populations characterized by its attachment to raw milk, would be more exposed to the risk of consuming residues of antibiotics or even other drugs, than the city populations.

According to our field observations, the most used hormones in dairy farming in study area are prostaglandines (especially $PGF_{2\alpha}$), progesterone and estrogens. [14] reported that it is thought that the great concern about dairy foods hormone content is steroid hormones especially estrogens due to current epidemiological evidence, which indicating most probable effects of them in initiating and provoking of breast and prostate cancers. In addition to the possible impact of naturally-occurring steroid hormones in raw milk [15].

According to [16], reproductive success relies on a complex sequence of actions that involve the interaction of a great number of tissues and physiological events to perform cow's fertility, based primarily on prevention and good management of reproduction. On another part, in the circumstances of the observed lack of veterinary testing laboratories in our study area, practitioners often use broad-spectrum antibiotics which do not seem to be always effective in cases of infertility related to certain insidious microorganisms.

For example [17] reported that when cow's infertility is associated to *Coxiella burnetii*, the percentage of seronegative cows (n=35) after treatment with Oxytetracycline was 52.77 %. Moreover, [18] showed via the

molecular studies (real-time VCR) of cheese from milk of infected animals that the specific sequences of DNA for *Coxiella burnetii* were present despite treatment with Oxytetracycline. [19] suggests that this could be due to the fact that *Coxiella burnetii* induces the expression of multiple anti-apoptotic miRNAs, which likely have a role in inhibiting apoptosis in order to sustain the intracellular replication of the pathogen.

By a similar way, *Brucella* reside within phagocytes of infected hosts to promote their survival, persistence and proliferation [20]. Successful antimicrobial therapy requires eradication of *Brucella* from this intracellular niche by seeking new and improved antimicrobials for brucellosis therapy as well as a method to efficiently evaluate their intracellular efficacy [21]. [22] reported that *Brucella abortus* was found highly sensitive to Gentamicin, Tobramycin and Penicillin G with sensitivity percentage 75, 100 and 100%, respectively. The organism was moderately sensitive against Tetracycline, Chloramphenicol, Rifampicin and Enrofloxacin with sensitivity recorded of 65, 60, 60 and 90%, respectively. However, the organism was weakly sensitive against Streptomycin and Kanamycin 50 and 40%, respectively. The organism confirmed its resistance against the Ampicillin. Nevertheless, since Algerian authorities' follow a detection/slaughter policy toward cattle brucellosis, the treatment of brucellic animals is forbidden and could create new resistant *Brucellae* in human patients.

Also, antibiotics are inefficient in the case of infertility caused by mycotoxins. According to [23], the 5 major mycotoxins causing impairments in the growth and reproductive ability of livestock are aflatoxin, zearalenone, deoxynivalenol, ochratoxin, and ergot. Zearalenone is widely known as an estrogenic mycotoxin and it can induce persistent anovular estrus and irreversible infertility. By returning to our study area, the total lack of performed analysis to detect mycotoxins (as HPLC) is a barrier to conduct a real diagnosis of such related infertility cases. Thus, the anarchic use of antibiotics in such circumstances is rather harmful to animal organism.

Results of our study showed a high incidence of bovine mastitis in study area. Worldwide, mastitis is the most prevalent bacterial disease of dairy cows [24]. Several studies reported the high incidence of mastitis in cattle in Algeria [25; 26]. In a recent study conducted by [27] on cow's mastitis, the incidence of udder infection in cattle appeared to increase with the increase in average daily milk yield and the number of lactations. According to the same study, the rear udder quarters had a higher risk of clinical mastitis incidence compared to the front udder quarters. Stripping and knuckling methods of milking caused more damage to the teat tissues leading to more prone to mastitis. Less hygiene of the farm favoured higher incidence of mastitis in cows. Injury to the udder would make animal more prone to mastitis when compared to animals with healthy udder. [25] reported the association of mastitis with the presence of fungi cells, with a strong frequency of *Trichosporon spp.* followed by *Candida spp.*

For treatment of mastitis in cattle, [26] recommended the screening with California Mastitis Test then the treatment of quarters with subclinical mastitis to limit the clinical mastitis and their consequences. According to [28; 29], in the case of mastitis due to *Candida spp.*, the most effective antifungal agent that can be used is Ketoconazole.

Our study results showed that Tetracyclines and Beta-lactamines are the most used antibiotics, during the whole veterinary activity in clinics, and particularly to treat urogenital sphere and mammary gland pathologies, followed by Sulfamides and Macrolides. Comparatively, in a study done by [30] to detect antibiotic residues in raw milk produced in Freha area (Tizi Ouzou governorate ; Algeria), results showed a strong presence of antibiotic residues in raw milk, with 80 positive samples (46.78%). Most of them contained Penicillin and/or Tetracycline (88.75%), followed by Macrolide and/or Aminoglycoside (12.5%). In the same context but out of Algeria, [31] reported that in Kosovo for the treatment of sick cows are mainly used antibiotics of Betalactams (60.5 % of them), Sulfonamides type, Tetracyclines, Macrolides and Aminoglycosides. According to the same authors, drugs were not given only to sick cattle by their diagnosis, but they were given to healthy cattle too, as a preventative therapy, mainly through intramuscular route. Thus, authors concluded to an abusive use of antibiotics in dairy cattle in Kosovo.

Moreover, it was observed during this present survey that Tetracyclines are largely used in dairy cattle, to prevent respiratory diseases especially. Also, breeders tend to keep antibiotics as a stock and use them without referring to veterinarians' prescriptions. Our field observations are supported by those reported by Boulouf *et al.*, (2014) [3] for the excessive misuse of Tetracyclines in veterinary practice in Algeria. In

addition, during a study conducted by Layada *et al.*, (2016) [32] in Algeria, the most frequently detected antibiotics in cows' milk were : Beta-lactamines, with; Amoxicillin as the most abundant residue in the studied milk, followed by Penicillin (97 %), than by Ampicillin (50 %), in the same study Tetracyclines was present in (88 %) of samples.

According to our field experience in veterinary practice in study region, Beta-lactamines are frequently used to treat mastitis and metritis cases in ruminants, Sulfamides are used too but with lesser degree to the same objective, while Amoxicillin is even used to treat complicated respiratory infections in cattle. Since the obvious lack of diagnostic tools in study area, commonly, veterinary practitioners guide diagnosis in the first time directly to bacterial origins, hence they do a "therapeutic diagnosis" by using one or more antibiotics therapy trials, in case of treatment failure, veterinarians would add other etiologic hypothesis, such as parasitic and/or viral diseases after a considerable period of antibiotic therapy. Remarkably, some veterinarians think they have the option to predict origin of diseases without accomplishing the well-known diagnostic steps. These practitioners are even convinced that long period of practice (considered as experience) allow them such advantage.

Referring to our personal experience in study area, there are some circumstances out of control for veterinary practitioners. On one hand, main breeders are exposed to have a deteriorated psychological state, especially in case of epidemic diseases characterized with high rates of mortality in cattle, so they press on treating veterinarians to accelerate therapy protocol, even without completing a full diagnosis, because a great part of breeders believe that antibiotics are efficient to fight all kinds of animal diseases. On the other hand, respect of therapy period is rather linked to breeders' preferences than to veterinarians' decisions. Mostly, breeders decide to stop treatment after some symptoms of disease disappear, or after a relative recovering of animal that breeders distinguish by return of appetite and/or a part of movement, consequently animal is rather not free germ pathogen yet.

None of veterinarians in our study sample uses susceptibility testing and weighting type meter before beginning therapeutic protocol. Among the most important recommendations cited in the Official Journal of the European Union (2015) [33] , there are : the prescription and dispensation of antimicrobials must be justified by a veterinary diagnosis in accordance with the current status of scientific knowledge; the prescription should be based on a diagnosis made following clinical examination of the animal by the prescribing veterinarian ; where possible, antimicrobial susceptibility testing should be carried out to determine the choice of antimicrobial; a narrow-spectrum antimicrobial should always be the first choice unless prior susceptibility testing -where appropriate supported by relevant epidemiological data- shows that this would be ineffective ; the use of broad-spectrum antimicrobials and antimicrobial combinations should be avoided ; administering medication to an entire herd or flock should be avoided whenever possible ; sick animals should be isolated and treated individually ; the risk of resistance to antimicrobials, increases if such antimicrobials are used. During this present study, it was noticed that personal laboratories in veterinary clinics, are very rare, due mainly to: the high costs of specific equipments of microbiology in comparison to veterinary activity income; to the lack of technical knowledge and familiarity of practitioners with such materials.

Concerning the non respect of waiting time after treatment, findings of this present study are in concordance with other studies in Algeria. For example, Titouche *et al.*, [30], concluded that most of the farmers do not always respect the time delay between the administration of antibiotics and the milk collection in Freha area (Tizi Ouzou governorate). Furthermore, Layada *et al.*, (2016) [32] report the presence of antibiotics in raw and fermented cow's milk collected in Guelma region (East of Algeria) and intended for either direct consumption and/or fermentation was high : 65.5 % of non-conform samples contained authorized residues at levels higher than the (Maximal Residues Limits) MRL, residues without set MRL, or non- authorized residues. Also, Boultif (2015) [34] in a study carried out in Constantine region (East of Algeria), where, after analysis of antibiotic residues by Delvotest, reports that the degree of contamination of milk samples produced locally in Algeria with antimicrobial residues remains very high, compared with that reported in other countries. According to this present study, the surveyed veterinarians reported that breeders insist to preserve the habitual daily income from milk sales as a priority, thus they do not respect waiting time.

The factors favoring the presence of antimicrobial residues in foods of animal origin include : failure to comply with the waiting period after the administration of antimicrobials; failure to consult a veterinarian before using antimicrobials [2]. Also, the widespread and unrestricted usage of different antibiotics in food animals without adequate diagnosis, prescription, and supervision by veterinarians [6]. The eventual impact of all abusive practices done by sampled veterinarians in this present study would be very important on foodstuffs quality, antibiotics-microorganisms interactions' and consumers' health. According to Jayalakshmi *et al.*, (2017) [1], the emergence of drug resistance has been observed following the introduction of each new class of antibiotics and repeated exposure to sublethal dose of antibiotics. However, selection of resistant bacteria in the environment could occur, when antibiotic concentration greater than minimum inhibitory concentration.

Moreover, Mensah *et al.*, (2014) [2] report that main used antimicrobials have potential risks on human health: Tetracyclines could induce drug hypersensitivity syndrome, drug-induced lupus erythematosus such as a rash, anaphylaxis, DRESS syndrome, Sweet's syndrome; Beta-lactamines could produce immediate reactions: urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis, haemolytic anaemia, neutropaenia, eosinophilia, skin rashes, Stevens-Johnson syndrome, Lyell's syndrome. With a lesser degree Sulfamides are known to provoke allergies (with skin rashes), Sweet's syndrome, DRESS syndrome, leucopenia.

In the opposite, Macrolides have rare risks on human health [2]. Among Macrolides, Tylosin is the most used by veterinarians in our study area. Tylosin is a broad-spectrum antibiotic that is restricted to veterinary use. Allergic contact dermatitis caused by Tylosin has been reported in the literature from the farming industry and veterinary medicine [35].

As regards to environmental effects, the highest and most frequently reported concentrations of antibiotic residues in manure belong to the tetracycline group of antibiotics. Tetracyclines (particularly Tetracycline and Chlortetracycline) were found to be more persistent in soils than in manure [1].

As recommendations, [36] insisted on: vaccination of animals, prevention of pathogen entry, and maintenance of general health and hygiene to help in reducing the use of antimicrobials in animals. The use of antimicrobials in farm animals should be under the supervision of veterinary experts. The lag in the discovery or the development of new antimicrobial drugs is worrisome in the face of failing current antimicrobial therapy regimens. Considering the global nature of the antibiotic resistance problem, concerted global efforts are necessary to promote the prudent and responsible use of antibiotics in animals with constant monitoring of resistance development in these systems and the potential transfer of such bacteria throughout the food chain.

CONCLUSION

This present survey revealed that antimicrobials and antibiotics are used anarchically. The broad spectrum antibiotics are misused, in particular Tetracyclines and Beta-lactamines. Breeders tend to use antibiotics without referring to veterinarians. Consequently, the control of antibiotic residues should be recommended in order to control the health risks in both of animals and consumers, and to preserve the industrial potential of dairy products. Also, occupational concerned society (breeders, veterinarians) and consumers should be more aware of potential dangers due to presence of antibiotics in foodstuffs and environment. Furthermore, the systematic use of broad spectrum antibiotics for pathologies eventually due to fungi, mycotoxins, parasites, viruses, without referring to laboratory analysis, is not efficient but rather increases the resistance of some microorganisms to specific antibiotics.

ACKNOWLEDGMENTS

The author acknowledges all veterinarians participating in this survey and both of Mrs. Deroues Kheireddine and Miss Deroues Khadidja for facilitating this study. No fund was received for this study.

REFERENCES

- [1] Jayalakshmi K, Paramasivam M, Sasikala M, Tamilam TV, and Sumithra A.(2017) Review on antibiotic residues in animal products and its impact on environments and human health. Journal of Entomology and Zoology Studies. 5(3): 1446-1451. Available online at www.entemoljournal.com
- [2] Mensah SEP, Koudandé OD, Sanders P, Laurentie M, Mensah GA. and Abiola FA. (2014) Antimicrobial residues in foods of animal origin in Africa: public health risks. Revue scientifique et technique de l'office international des epizooties. 33 (3): 987-996.
- [3] Boultif L, Zeghilet N, Chebira B, Agabou A, Mekroud A. (2014) Validation of a high performance liquid chromatography (HPLC) method for the determination of oxytetracycline residues in milk. Advances in Animal and Veterinary Sciences. 2 (10): 574-581.
- [4] Vishnuraj MR, Kandeepan G, Rao KH, Chand S. and Kumbhar V.(2016) Occurrence, public health hazards and detection methods of antibiotic residues in foods of animal origin: A comprehensive review. Cogent Food & Agriculture. 2 (1): 1235458. On <http://dx.doi.org/10.1080/23311932.2016.1235458>
- [5] Aytensu S, Mamo G, Kebede B. (2016) Review on chemical residues in milk and their public health concern in Ethiopia . Journal of Nutrition and Food Sciences. 6: 524. DOI:10.4172/2155-9600.1000524
- [6] Olatoye IO, Daniel OF, Ishola SA. (2016) Screening of antibiotics and chemical analysis of penicillin residue in fresh milk and traditional dairy products in Oyo state, Nigeria. Veterinary World. 9(9): 948-954.
- [7] Beldjil AAF, Benlahcen K, Guessas B, Aggad H, Kihal M. (2013) Evaluation of microbiological and sanitary quality of ewe's raw milk in Western of Algeria and detection of antibiotic residue by Delvotest. Advances in Environmental Biology. 7(6) : 1027-1033.
- [8] Moussi A. (2012) Analyse systématique et étude bio-écologique de la faune des acridiens (*Orthoptera, Acridomorpha*) de la région de Biskra. Thèse de Doctorat en Sciences Biologiques. Option Biologie Animale. Département de Biologie Animale. Université de Constantine 1. 132 p.
- [9] Direction des Services Agricoles de la wilaya de Biskra (D.S.A) (2010). Monographie de la wilaya de Biskra : Productions agricoles et animales.
- [10] Direction des Services Agricoles de la wilaya de Biskra (D.S.A) (2016). Rapport de statistiques sur les effectifs des éleveurs de bovins et de camelins enregistrés au niveau de wilaya de Biskra.
- [11] Ministère de l'Agriculture et du Développement Rural de l'Algérie (M.A.D.R). (2015) Rapport de statistiques sur les effectifs d'animaux domestiques en Algérie.
- [12] Direction des Services Vétérinaires de la wilaya de Biskra (D.S.V). (2013) Rapport de statistiques sur l'effectif des vétérinaires praticiens privés enregistrés au niveau de wilaya de Biskra.
- [13] Derouiche M, Aissaoui Zitou W, Medjouj NH et Zidoune MN. (2016) Consommation de lait et de produits laitiers en milieu rural de Tébessa, Algérie. Livestock Research and Rural Development. 28 : 5.
- [14] Malekinejad H, Rezabakhsh A. (2015) Hormones in dairy foods and their impact on public health- A narrative review article. Iranian Journal of Public Health. 44(6): 742-758.
- [15] Xueyin Q, Chuanyou S, Nan Z, Songli L, Lu M. and Jiaqi W.(2018) A survey of naturally-occurring steroid hormones in raw milk and the associated health risks in Tangshan City, Hebei Province, China. International Journal of Environmental Research and Public Health.15(1): 38. DOI :10.3390/ijerph15010038
- [16] Alexander COE and Shenming Z. (2017) Causes, prevention and management of infertility in dairy cows. In book: Achieving sustainable production of milk, Volume 3. Burleigh Dodds Science Publishing Limited, Vol. (3): 385-398. DOI: 10.19103/AS.2016.0006.20.
- [17] De biase D, Costagliola A, Del Piero F, Di Palo R, Coronati D, Galiero G, Degli UB, Gabriella LM, Fabbiano A, Davoust B, Raoult D, Paciello O. (2018) *Coxiella burnetii* in infertile dairy cattle with chronic endometritis. Veterinary Pathology. 55, (3): 030098581876037. DOI: 10.1177/0300985818760376.
- [18] Szymańska-Czerwińska M and Krzysztof N. (2012) Evaluation of the effectiveness of Q fever treatment with oxytetracycline. Bulletin of Veterinary Institute in Pulawy. 56: 513-517. DOI: 10.2478/v10213-012-0090-5.
- [19] Jess M. (2017) Uncovering *Coxiella burnetii*'s pathogenicity by elucidating its metabolism and host interactions. MS Biology Thesis. DOI:10.15760/etd.3493.
- [20] Jean C. (2015) The changing nature of the *Brucella*-containing vacuole. Cellular Microbiology. 17, (7).DOI: 10.1111/cmi.12452.

- [21] Michelle WV and William WB. (2008) Establishment of a method for evaluating intracellular antibiotic efficacy in *Brucella abortus*-infected Mono Mac 6 monocytes. Journal of Antimicrobial Chemotherapy. 61 (1): 128-34. DOI:10.1093/jac/dkm433.
- [22] Hussain Abro Shahid HAS, Khan M, Abro R, Leghari R, Rizwana H, Rehman A, Baloach H, Rind M, Yasmin A, Tunio S, Hussain R, Ali S. (2017) Antibiotic susceptibility of *Brucella abortus* isolated from milk and blood samples of cattle. Journal of Basic & Applied Sciences. 13: 8-11. DOI: 10.6000/1927-5129.2017.13.02.
- [23] Yoshitake I. (2000) Infertility caused by zearalenone, an endocrine disrupting substance. JSM Mycotoxins. 50 (2): 119-124. DOI :10.2520/myco1975.50.119.
- [24] Ruegg P. (2017) Minimizing the development of antimicrobial resistance on dairy farms: appropriate use of antibiotics for the treatment of mastitis. In book: Achieving sustainable production of milk. Volume 2 : 117-133. DOI: 10.19103/AS.2016.0005.22.
- [25] Akdouche L, Aissi M, Zenia S, Saadi A. (2014) Yeasts in the mammary environment of the cattle in the region of Sidi Mhammed Ben Ali, Wilaya of Relizane, Algeria. Journal of Microbiology and Antimicrobials. 6: 66-71. DOI: 10.5897/JMA2014.0300.
- [26] Fartas H, Bouzebda Z, Afri F, Khamassi S. (2017) Prevalence and impact of subclinical mastitis on the profitability of dairy cattle in the far east of Algeria. Livestock Research for Rural Development. 29: 9.
- [27] Safeer MS, Venkataramanan R, Serma Saravana Pandian A. (2018) Relationship of risk factors with incidence of mastitis in cows. Journal of Entomology and Zoology Studies. 6 (2): 2397-2402.
- [28] Sonmez M, Erbas G. (2017) Isolation and identification of *Candida spp.* from mastitis cattle milk and determination of antifungal susceptibilities. International Journal of Veterinary Science. 6: 104-107.
- [29] Erbas G, Parin U, Kirkan Ş, Savaşan S, Özavci MV, Tuğba Yüksel H. (2017) Identification of *Candida* strains with nested PCR in bovine mastitis and determination of antifungal susceptibilities. Turkish Journal of Veterinary and Animal Sciences. 41: 757-763. DOI:10.3906/vet-1704-39.
- [30] Titouche Y, Hakem (EX Akam) A, Houali K, Yabrir B, Malki O, Chergui A, Chenouf N, Yahiaoui S, Labiad M, Ghenim H, Kechih-Bounar S, Chirilă F, Nadăș G, and Fiț NI. (2013) Detection of antibiotics residues in raw milk produced in Freha Area (Tizi-Ouzou), Algeria. Bulletin UASVM, Veterinary Medicine, 70(1). Print ISSN 1843-5270; Electronic ISSN 1843-5378.
- [31] Ibraimi Z, Shehi A, Murtezani A, Krasniqi S, Agani Z. (2015) Kosovo's public health damage from abusive use of antibiotics in dairy cattle. Materia Socio Medica. 27 (3) : 149. DOI : 10.5455/msm.2015.27.149-153.
- [32] Layada S, Benouareth D-E, Coucke W and Andjelkovic, M. (2016) Assessment of antibiotic residues in commercial and farm milk collected in the region of Guelma (Algeria). International Journal of Food Contamination. 3 : 19. DOI 10.1186/s40550-016-0042-6.
- [33] Official Journal of the European Union (2015) Guidelines for the prudent use of antimicrobials in veterinary medicine. Commission Notice: (2015/C 299/04). 11.9.2015. 25 p.
- [34] Boultif L. (2015) Détection et quantification des résidus de terramycine et de pénicilline dans le lait de vache par chromatographie liquide haute performance (HPLC)- optimisation des paramètres d'analyse – adaptation des méthodes d'extraction des molécules d'antibiotiques- comparaison de quelques résultats obtenus sur le lait de la région de Constantine et le lait importé (reconstitué). Thèse de Doctorat en Sciences. Option : Hygiène des denrées alimentaires d'origines animales. Université de Constantine 1. 156 p.
- [35] Malaiyandi V, Houle MC, Skotnicki-Grant S. (2012) Airborne allergic contact dermatitis from Tylosin in pharmacy compounders and cross-sensitization to Macrolide antibiotics. Dermatitis. Sep-Oct, 23(5): 227-230. DOI:10.1097/DER.0b013e318262cadd
- [36] Lekshmi M, Ammini P, Kumar S and Manuel F. Varela (2017) The food production environment and the development of antimicrobial resistance in human pathogens of animal origin. Review. Microorganisms. 5 (11). DOI:10.3390/microorganisms5010011- on www.mdpi.com/journal/microorganisms